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Meeting Abstracts

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CIS MEETING ABSTRACTS 2025

Friday Posters

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Brought Back from the Dead: A Case Report on Atypical Hemolytic Uremic Syndrome

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Atypical hemolytic uremic syndrome (aHUS), caused by defects in the alternative complement pathway or its regulatory proteins, is a rare condition that can present in life-threatening episodes, especially when triggered by stressors such as infection or pregnancy. This case underscores the importance of rapid identification and intervention in aHUS, especially in high-risk contexts.

We present a 19-year-old pregnant woman at 37 weeks gestation brought to the ER unresponsive, with agonal breathing and seizures. She had last been seen the day prior and was complaining of abdominal pain. After undergoing emergency C-section for intrauterine fetal demise, she was transferred to the intensive care unit. Physical exam revealed the patient was obtunded with flaccid extremities and absent reflexes. Initial labs showed hyponatremia, leukocytosis, acute kidney injury, severe thrombocytopenia, and microangiopathic hemolytic anemia. Brain imaging suggested anoxic brain injury and EEG showed severe diffuse encephalopathy with no epileptiform discharges. Differential diagnoses included thrombotic thrombocytopenic purpura (TTP); disseminated intravascular coagulation (DIC); aHUS; HELLP (hemolysis, elevated liver enzymes and low platelets); and catastrophic antiphospholipid syndrome. The patient received hemodynamic support, mechanical ventilation, broad-spectrum antibiotics, high-dose corticosteroids, blood transfusions, and plasmapheresis. The patient's clinical status improved significantly within 24 hours, regaining consciousness and reflexes, and was extubated within 72 hours. An ADAMTS13 of 38% ruled out TTP. Given high suspicion for HELLP versus aHUS, she received meningococcal vaccination and penicillin prophylaxis before initiating eculizumab. Genetic testing ultimately confirmed aHUS with two heterozygous gene defects in complement proteins, CD46 and CFHR3-CFHR1. The patient continued eculizumab and later transitioned to ravulizumab for maintenance therapy for 6 months. She returned to her neurological baseline without end-organ damage and received therapy for postpartum depression and contraception counseling for one year.

This case highlights the remarkable recovery that patients with aHUS can experience when treatment is quickly initiated when a high index of suspicion exists. Emphasis on genetic evaluation can provide valuable information regarding probability of relapse or end-stage renal disease. Children should also be tested for complement dysregulation if maternal HUS occurred during pregnancy or postpartum without a clear secondary cause.

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Post-Transplant Chronic Granulomatous Disease Patient Follow-Up: A PIDTC Survey

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Background: Chronic granulomatous disease (CGD) is an inborn error of immunity caused by defects in NADPH oxidase, which causes phagocyte dysfunction. CGD is characterized by recurrent infections and autoimmunity. Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapy. However, data regarding patient satisfaction with post-HSCT state of health and quality of life are lacking.
Methods: A Primary Immune Deficiency Treatment Consortium (PIDTC) working group designed online surveys to assess post-HSCT quality of life and satisfaction with transplantation. Surveys were distributed from November 2023 to March 2024 to all members of the CGD Association of America (CGDAA). Adults who personally underwent or parents of children who underwent HSCT for CGD were asked to participate. Two surveys were offered: one for participants who were 18 years or older and one for parents of patients.
Results: Complete surveys representing 54 unique patients were included for analysis. Forty-four were from parents whose children were a median of 12 years old and a median of 6 years post-transplant. Nine were returned from patients who were a median of 30 years old and a median of 4 years post-transplant (Table 1).

Table 1.

Patient Characteristic Parent survey (n 44)	Number of Participants	Patient Characteristic Patient survey (n 9)	Number of Participants
Gender assigned at birth		**Gender assigned at birth**	
Male (XY)	42	Male (XY)	7
Female (XX)	2	Female (XX)	2
Race (check all that apply)		**Race (check all that apply)**	
White	40	White	8
Asian	5	Asian	1
American Indian or Alaska Native	1	American Indian or Alaska Native	0
Ethnicity		**Ethnicity**	
Hispanic, Latino, or Spanish origin	7	Hispanic, Latino, or Spanish origin	0
Not Hispanic, Latino, or Spanish origin	37	Not Hispanic, Latino, or Spanish origin	9
Prefer not to answer	1	Prefer not to answer	0
Age	**Years**	**Age**	**Years**
Median age at survey	12	Median age at survey	30
Median age at transplant	5	Median age at transplant	29
Median number of years since transplant	6	Median number of years since transplant	4

Seventy-eight percent of patient and parent respondents reported that quality of life was better after transplant and 89% felt that the transplant improved their physical health (Figure 1).

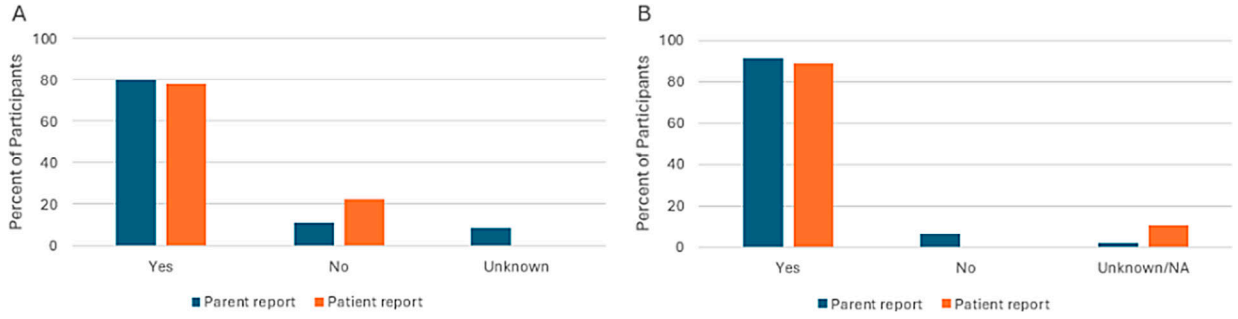

Figure 1. (A) Do you feel quality of life is better now post-transplant than it was pre-transplant? (B) Do you feel that the transplant has been beneficial from a medical perspective?

PROMIS Global Health scoring tool revealed 84% of patients had mental health scores within 1 SE of the mean. Only a few mental health diagnoses were self-reported (Figure 2).

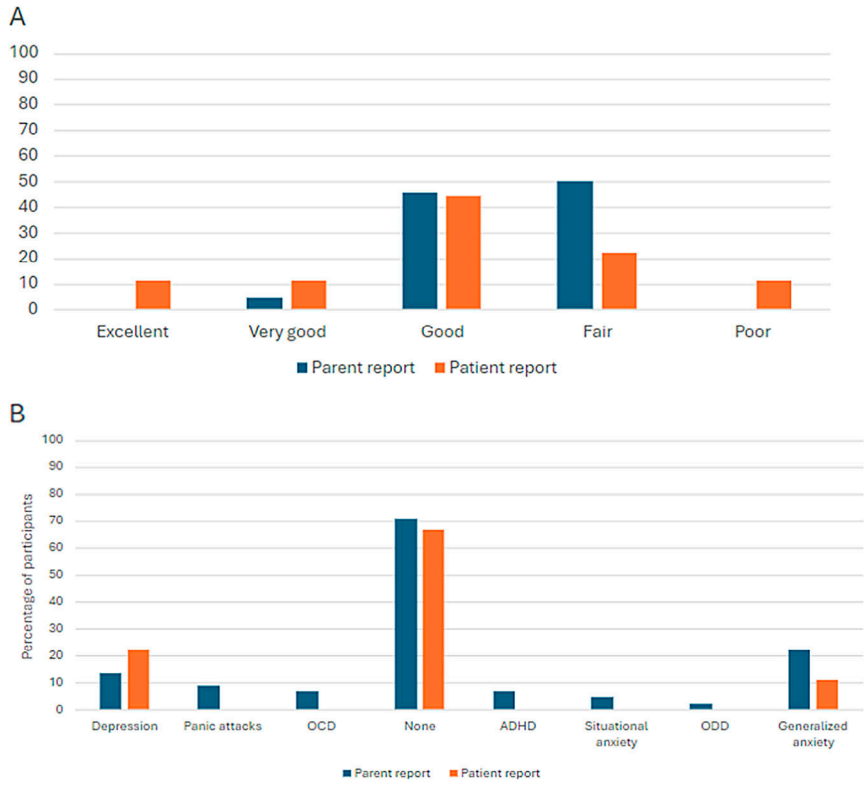

Figure 2. (A) PROMIS Mental Health Report Scores. (B) Mental health condition diagnosed by a physician.

After transplant, there were no self-reported cases of autoimmune disease or malignancy. Three participants were able to conceive children. One respondent used sperm banking; two did not use fertility preservation or treatments.

Discussion: Our data demonstrate that the majority of patients who undergo allogeneic HSCT for definitive treatment of CGD experience improvements in physical and/or mental health and enjoy an improved quality of life after transplant. Overall, this study supports positive outcomes for patients treated with allogeneic HSCT.

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Determining Definitive Therapy Options in Severe Leukocyte Adhesion Deficiency Based on Genetic Mutation, Clinical Presentation, and Risk Stratification

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A 6-year-old male with a history of recurrent stomatitis was admitted for a flare associated with inability to eat. He was noted to be small for age, and the parents reported that he had a long-standing history of recurrent otitis media (with PE tube placement) and poor dentition with tooth loss. There was no history of pneumonia or infections of the skin up to this time; the umbilical cord separated around three weeks of life. Family history was notable for consanguinity (parents are first cousins). On admission, a persistent leukocytosis was noted, and symptoms improved with supportive care. Given the history of poor growth, recurrent stomatitis, and familial consanguinity, a

trio exome was performed, which identified two parentally inherited ITGB2 missense variants associated with LAD type 1 (and previously reported in affected individuals in the literature).

After initiation on antimicrobial prophylaxis, his ear infections resolved and his periodontal disease had improved (but did not resolve). Immune evaluation was unremarkable, and assessment of CD18 expression in neutrophils was undertaken for risk stratification. It was assumed that this patient, given his age and manifestations, would likely have moderate risk. The first two assessments found completely normal CD18 expression (100%) with slight affectation of CD11a in the neutrophils. However, given his more concerning history, samples were sent to two other clinical laboratories. These both noted <2% CD18 expression with variable CD11a and CD11b expression, categorizing him as severe LAD1. This highlights the importance of reliable laboratory assessments in stratification of LAD1 patients.

It has been reported that this specific missense mutation allows for some co-expression of CD11b and CD11c (but not CD11a); this may explain why this patient's clinical course had been somewhat abrogated. However, definitive therapy will likely still be needed.

HLA typing has not been successful in finding him a sibling or matched unrelated donor; given the high morbidity associated with severe LAD1 and with less-than-ideal transplants, this patient is a good candidate for gene therapy once available. In the meanwhile, antimicrobial prophylaxis and appropriate dental and ENT care are essential to keep him healthy.

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The Significant Burden of Infection Among Patients with Warts, Hypogammaglobulinemia, Infections, and Myelokathexis Syndrome: A Patient and Caregiver Survey

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Background: WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome is a rare combined primary immunodeficiency associated with highly variable multisystemic manifestations and increased risk of infections, neoplasm-related comorbidities, end-organ damage, and, in some cases, early death. The published literature describing the clinical disorder and complications are limited. Moreover, there are no published reports describing patient- and caregiver-reported clinical burden of WHIM syndrome. The objective of this patient and caregiver survey is to describe the types of infections and clinical burden among children and adults with WHIM syndrome.

Methods: Individuals with a diagnosis of WHIM syndrome (patients) and any person providing care for a patient (caregiver) were eligible to complete an online survey describing their clinical burden. Caregivers responded for patients less than 18 years of age. Patients currently enrolled in a clinical trial for the treatment of WHIM syndrome, had ever received treatment with a CXCR4 antagonist, or who were not fluent in English were excluded.

Results: Twenty patients with WHIM syndrome had survey data collected (<18 years of age, n = 5; ≥18 years of age, n = 15). Among adult patients, 7 were female, 5 were male, 1 was non-binary, and 2 were transgender; all children were male. Infection burden in the past 3 months included high rates of eye infection (80% of children and 33% of adults), oral infection (53% of adults), and HPV (80% of children and 67% of adults) (Figure). As expected, high rates of respiratory infection were also reported (80% of children and 93% of adults). Sixty percent (12/20) of patients (60% of pediatrics <18 years of age; 73% of patients ≥18 years of age) experienced at least 1 infection requiring medical treatment in the last 3 months. Of those, 25% (5/20) reported receiving care at a hospital overnight due to infection.

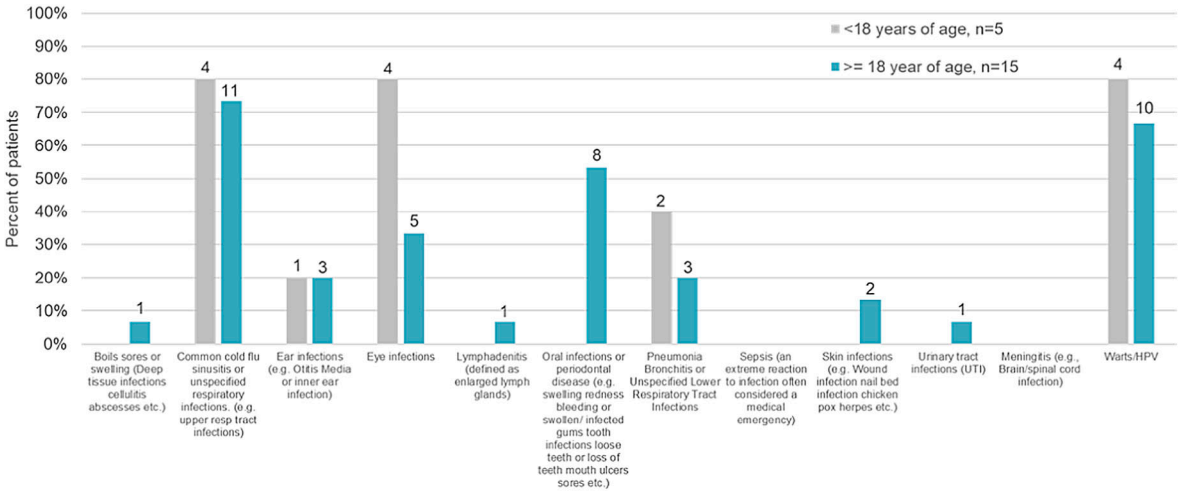

Figure. Patient-reported infections (past 3 months).

Conclusions: This is the first ever report on the day-to-day infection burden of WHIM syndrome from a patient perspective. The frequency and severity of infections requiring medical care and hospitalization underscores the urgency to proactively treat patients with WHIM syndrome.

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Follicular Helper T Cell Dysfunction in 22q11.2 Deletion Syndrome Segregates with Impaired B Cell Maturation and Recurrent Infections

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Purpose: 22q11.2 deletion syndrome has been primarily described as a disorder of T cell production secondary to thymic hypoplasia. However, there is great complexity in the clinical picture with infections, autoimmunity, and inflammation occurring. Emerging evidence suggests that qualitative T cell dysfunction occurs, and the goal of this study was to utilize single-cell RNA-seq to better define altered gene expression patterns that might inform on the processes associated with recurrent infections.
Methods: We utilized single-cell RNA-seq to define distinct populations in 22q11.2 deletion syndrome and controls as well as within a subcohort of patients with 22q11.2 deletion syndrome and recurrent infections.
Results: The subcohort of patients with recurrent infections had a higher number of follicular helper T cells (Tfh) and a lower number of class-switched memory B cells (Figure 1). When we analyzed differentially expressed genes, we identified a strong signature of type I interferons across all cell types. Within the T cell compartment and particularly within the Tfh, we noted a strong senescence signature (Figure 2). Nearly every effect observed in T cells was most altered in the patients with recurrent infection. B cells had a less mature composition particularly in those with recurrent infections.

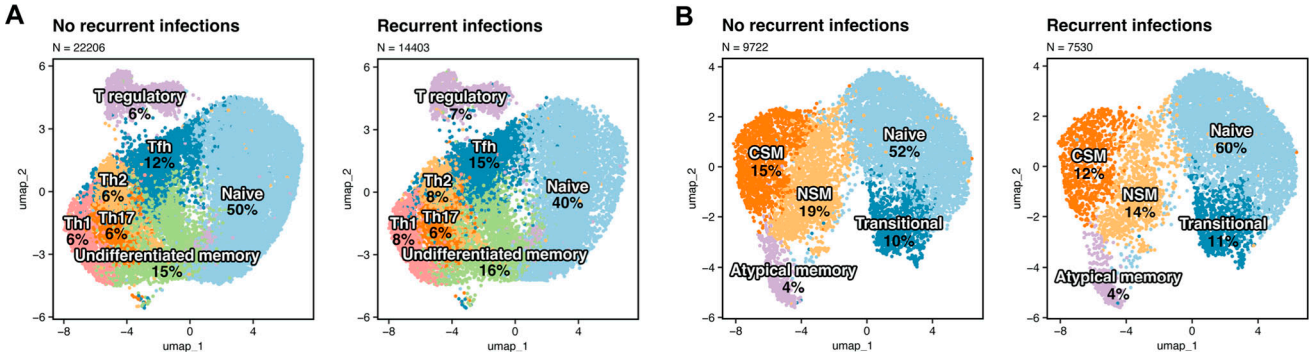

Figure 1. Subcohort of 22q11.2 DS patients with recurrent infections had a higher number of Tfh cells (1A), and a lower number of class-switched memory B cells (1B) compared to patients without recurrent infections.

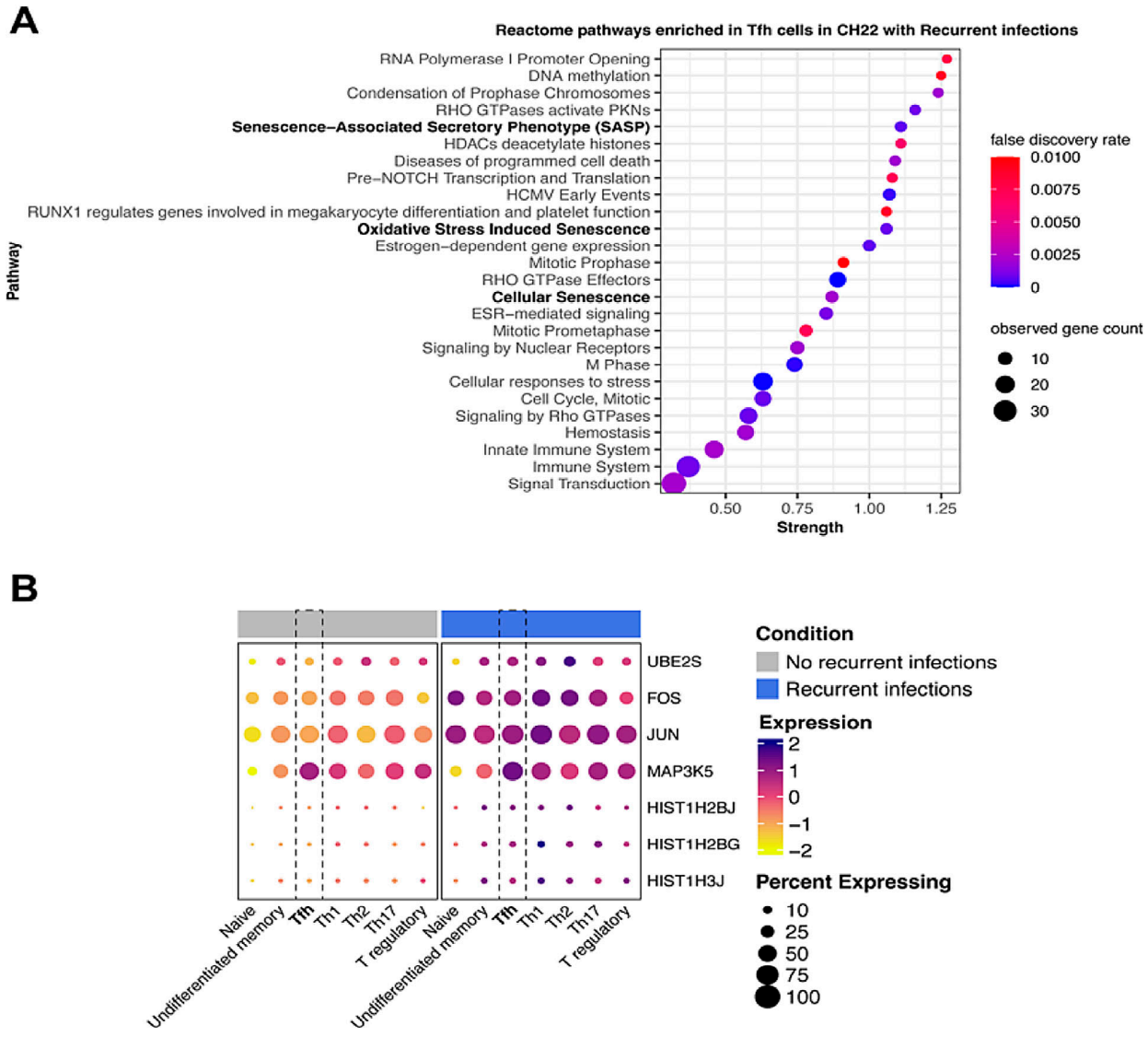

Figure 2. Differentially expressed modules within the Tfh cells. 2A) The Reactome modules are displayed comparing differentially expressed genes in Tfh in patient with recurrent infection vs. those without. We noted three senescence modules (bolded) and multiple RHO GTPase modules. 2B) We combined the three senescence modules and portrayed the expression according to whether the patients had a history of recurrent infections. In this dotplot, the highest expression levels were seen in the patients with recurrent infections across all T cell subsets.

Conclusions: While the total T cell numbers can often normalize in patients with 22q11.2 deletion syndrome, the subcohort with recurrent infections had a lower number of class-switched memory B cells despite having a higher number of Tfh cells, suggesting a compensatory increase. Our data indicate significantly altered function as defined by differentially expressed genes and aligned with what is known about T cell senescence. This would be expected to impact T cell function and may account for ongoing symptoms, reduced B cell maturation, and possibly the risk of immune dysregulation.

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Primary and Safety Outcomes of a Phase 3 Open-Label, Single-Arm, 12-Week Study of Treatment with PI3Kδ Inhibitor Leniolisib in Pediatric Patients Aged 4–11 Years with Activated PI3Kδ Syndrome (APDS)

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Leniolisib is an FDA-approved PI3Kδ inhibitor used to treat activated phosphoinositide 3-kinase delta syndrome (APDS) in patients aged ≥12 years who weigh ≥45 kg. Pediatric patients aged 4 to 11 years with APDS were enrolled in a two-part, prospective, open-label, single-arm, international study to evaluate the safety and efficacy of leniolisib (NCT05438407).

Here we report safety and efficacy outcomes following the completion of 12 weeks of leniolisib treatment (part 1). Twenty-six patients were screened; 21 patients enrolled across the United States, France, and Japan (Table 1). Leniolisib was administered orally twice daily (BID) as tablets in 10- and 30-mg strengths, with doses ranging from 20 to 70 mg BID based on weight. Co-primary outcomes were change from baseline (CFB) at 12 weeks in log10-transformed sum of product of diameters (SPD) of index lymph nodes and normalization of naïve B cells. Additional outcomes included changes in spleen volume and quantitative immunoglobulin (Ig) levels, including IgM.

Table 1. **Patient demographics and baseline characteristics.**

Patient Characteristic (N=21)	**Value**
Age at time of study, median (range), y	7.0 (4-11)
Sex, male to female, n	13:8
Self-identified race, n (%)	
White	9 (42.9)
Asian	4 (19.0)
Other	1 (4.8)
Not reported/unknown/missing	7 (33.3)
Self-identified ethnicity, n (%)	
Hispanic	3 (14.3)
Non-Hispanic	12 (57.1)
Not reported	6 (28.6)
Weight at baseline, median (range), kg	23.9 (15.4-44.5)
Time since APDS diagnosis, median (range), mo	32.9 (2.2-142.2)

Table 1. **Patient demographics and baseline characteristics. (*Continued*)**

Patient Characteristic (N=21)	**Value**
APDS variant distribution, n (%)	
PIK3CD	17 (81.0)
PIK3R1	4 (19.0)

APDS, activated phosphoinositide 3-kinase delta syndrome; PIK3CD, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1.

Both primary end points improved from baseline after 12 weeks of treatment with leniolisib across all dose levels. Mean CFB of log10-transformed SPD reduced by -0.1956 (n = 19). Mean CFB of naïve B cells (CD19+CD27-CD10-) from total B cells was 33.3% (SD, 13.1; n = 11). Mean CFB of spleen log10 volume reduced was -0.1222 (n = 21). Mean Ig levels (n = 14) changed from baseline after 12 weeks of leniolisib treatment: IgM, 2.7 g/L to 1.6 g/L; IgG, 10.1 g/L to 11.1 g/L; and IgA, 0.88 g/L to 0.83 g/L. Leniolisib was well tolerated (Table 2). Twenty patients had treatment-emergent adverse events (AEs). All were grades 1 or 2; none were serious. Five patients had treatment-related AEs, including headache, palpitations, abdominal pain, diarrhea, nausea, pruritus, fatigue, decreased neutrophil count, and increased aspartate aminotransferase. No AEs led to discontinuation of study drug treatment.

Table 2. **Summary of Treatment-Emergent Adverse Events.**

Adverse Events Category	**Total No. of Patients, n (%)**
Any TEAE	20 (95.2)
Grade 1	20 (95.2)
Grade 2	8 (38.1)
Grade 3	0
Grade 4	0
Grade 5	0
Any study treatment-related TEAE	5 (23.8)
Leading to discontinuation of study treatment	0
Leading to death	0
Any serious TEAE	0

TEAE, treatment-emergent adverse event.

Overall, leniolisib was well tolerated, reduced lymphoproliferation, and improved normalization of naïve B cells, meeting the co-primary end points. All 21 patients completed part 1, and 20 transitioned to the 1-year treatment extension (one patient discontinued due to social reasons).

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Patients with Genetic Immune Diseases in the Hematologist's Waiting Room

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Uncomplicated autoimmune cytopenias in children can present emergently but usually respond to first- or second-line treatment (steroids, immunoglobulin replacement therapy, and +/- rituximab) without long-term sequelae. In contrast, refractory cytopenias of childhood requiring repeated cycles of multi-agent immunosuppressive therapy constitute severe and debilitating conditions with significant long-term morbidity and compromise in quality of life. Genetic immune diseases causing global immune dysregulation are often associated with refractory cytopenias (AIHA, ITP, Evans syndrome, less frequently AIN, and aplastic anemia) along with other autoimmune manifestations (colitis, lung disease, vitiligo, alopecia, etc.) and, collectively, heighten suspicion for a primary immune dysregulation syndrome and prompt a comprehensive immunological and genetic evaluation.

Here we report our experience with a cohort of pediatric and young adult patients with presumed autoimmune cytopenia, referred to our interdisciplinary hemato-immunology clinic after failing multiple lines of immunosuppressive therapy in which isolated recalcitrant cytopenias were the only presenting symptom. More than half of these patients had an underlying genetic diagnosis [18/32; 56%], of which 77% (14/18) predisposed them to autoimmunity or autoinflammation. In patients with genetic forms of immune dysregulation, only one hematopoietic lineage was affected in 23% (6/26 patients). Importantly, all patients in whom targeted treatments addressing the underlying immunopathology could be identified responded significantly more favorably to therapy compared with patients who received broad immunosuppression with a combination of steroids and second-line agents (steroids, MMF, 6MP, azathioprine, cyclosporine, and tacrolimus).

Our experience highlights that genetic causes of immune/inflammatory dysregulation should be considered even in patients with isolated therapy-refractory cytopenia affecting only one hematopoietic lineage. A comprehensive immune workup and genetic screening is of paramount importance in cases of refractory cytopenia, as findings carry prognostic significance and influence treatment choices; targeted therapies should be explored whenever available. Those with an identified monogenic disease experienced significant benefit from targeted therapies and tolerated them well. The successful management of these complex conditions is facilitated by establishing multidisciplinary teams, underscoring their pivotal role in comprehensive care.

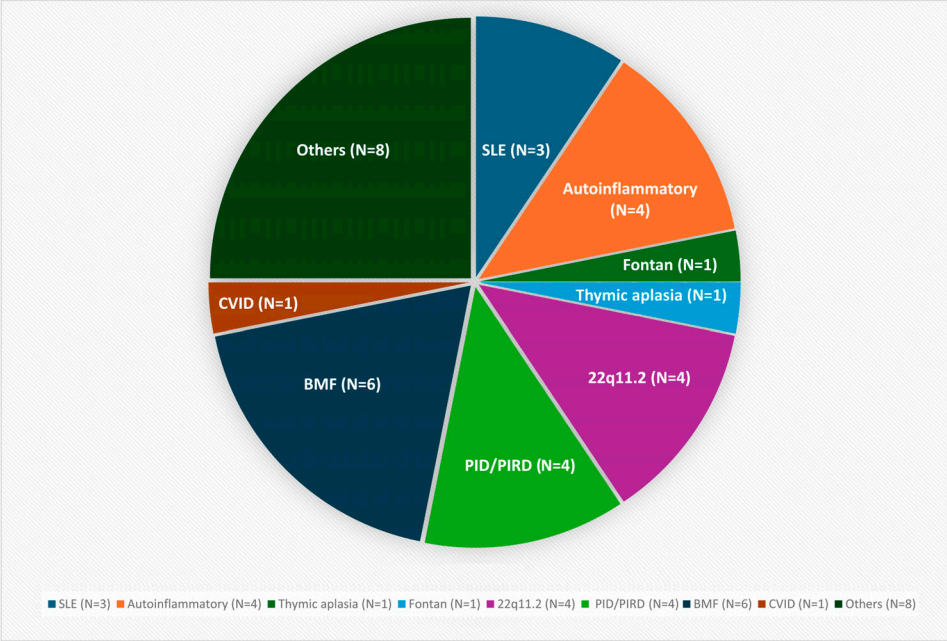

Figure 1. Underlying genetic diseases in our cohort of pediatric and young adult patients with presumed autoimmune cytopenia.

Table 1. **Characteristics of patients with an underlying PIRD or PID assessed at our immunology-hematology clinic.**

Patients	Age at diagnosis	Gender	Clinical	Diagnosis	Hematology	Genetic variants	Treatment and response to therapy
Rheumatology							
Pat #1	14 yo	Female	Arthralgia	SLE without any underlying PID/ monogenic disease	ITP and Coombs positive AHAI	PID Invitae panel (PID): no pathogenic variant	Plaquenil, transfusions, steroids, rituximab (Reaction to Rituximab) then sirolimus. On sirolimus for 2 years, then slow taper. In remission on 1 mg/day of sirolimus
Pat #2	15 yo	Female	Fatigue	SLE without any underlying PID/ monogenic disease	Warm AIHA plus ITP	Negative WES trio	History of steroid, s/p 4 doses of rituximab. In remission, on hydrochloroquine
Pat #3	5 yo	Male	Arthralgia, fatigue	SLE without any underlying PID/ monogenic disease	Chronic refractory ITP	PID panel: VUS in **TNFRSF6B c.364C>T (p.His122Tyr)**, reported to be associated with juvenile arthritis, autoimmune cytopenia and SLE	Multiple courses of steroids, transfusions, IVIG, on Promacta 75 mg/day
Bone marrow failure							
Pat #4	2 yo	Female	Fatigue	Myelodysplastic syndrome	Combs positive warm AHAI and ITP	PID panel: no pathogenic variant	Multiple courses of steroids, transfusions, IVIG, rituximab, HSCT: Allogeneic 5/10 mismatched maternal haploidentical peripheral blood stem cells
Pat #5	Birth	Male	Microcephaly, short stature, lower limb asymmetry, developmental delay	AR Schwachman-Diamond syndrome	Bone marrow failure, aplastic anemia	WES trio: **homozygous c.544>T (p.R182) pathogenic variant in DNAJC21**, each inherited from one parent	Transfusions for a Hgb < 7 and platelets <10k. HSCT: Paternal haploidentical peripheral blood stem cells
Pat #6	7 yo	Female	Polydactyly	Aplastic anemia	Coombs positive aplastic anemia	PID panel: **PMM2 [c.703G>T (p.Glu235*)]**, **likely pathogenic**; PMM2 is associated with AR congenital disorder of glycosylation	Transfusions for a Hgb < 7 and platelets <10k; s/p ATG) and started on cyclosporine and Eltrombopag. She is stable on Cyclosporine, Elthrombopag, prednisone taper
Pat #7	3 yo	Male	Disseminated pseudomonal infection with ecthyma gangrenosum/Jeune syndrome/fat pancreas	AR Schwachman-Diamond syndrome	Pancytopenia	WES trio: **Compound heterozygous with 2 pathogenic variants** in the SBDS gene - **SBDS (c.258+2T>C; GT / c.184A>T; p.Lys62*),** inherited respectively from father and mother	Transfusions for a Hgb < 7 and platelets <10k. HSCT has been considered

Table 1. **Characteristics of patients with an underlying PIRD or PID assessed at our immunology-hematology clinic. (*Continued*)**

Patients	Age at diagnosis	Gender	Clinical	Diagnosis	Hematology	Genetic variants	Treatment and response to therapy
Pat #8	29 yo	Male	Recurrent bacterial infections in the first few months of life. Short stature, gingivitis, multiple mouth ulcers	G6PC3 LOF	Congenital neutropenia and thrombocytopenia	PID panel: **homozygous variant in the G6PC3 gene, Exon 1, c210del (p.Phel71Serfs*46)**, each inherited from one parent	Received prolonged therapy with steroids and G-CSF (neupogen). In remission on SGLT2 inhibitor (Jardiance 10 mg per day)
Pat #9	10 yo	Male	Recurrent epistaxis	Fanconi Anemia	Neutropenia, thrombocytopenia, and macrocytic anemia	PID panel: one pathogenic variant and one variant of uncertain significance identified in FANCA. **FANCA: c.987_990del (p.His330Alafx*4)** inherited from mother, and one VUS c.2222+8C>T(intronic) inherited from father	Stable on Promacta, currently been evaluated for HSCT
PID/PIRD							
Pat #10	2 yo	Female	Fatigue	AD NFkb1	ITP and neutropenia, immunodeficiency/ humoral defect)	PID panel: **AD NFkb1 [NFkB1 c.418-427del (pLeu.140Phefs*3)]**, inherited from father	IVIG q4 wks. In remission on Sirolimus 0.5 mg/day and Promacta 25 mg/day)
Pat #11	7 yo	Female	No clinical symptom	AD NFkb1	Severe neutropenia	PID panel: **AD NFkb1 [NFkB1 c.418-427del (pLeu.140Phefs*3)]**, inherited from father	Sirolimus (1 mg/day)- partial remission
Pat #12	11 yo	Female	No clinical symptom	AD NFkb1	Neutropenia	PID panel: **AD NFkb1 [NFkB1 c.418-427del (pLeu.140Phefs*3)]**, inherited from father	-
Pat #13	1 yo	Male	Bloody discharge from eyes	X-linked MAGT1	ITP and Coombs positive AHAI	PID panel: **likely pathogenic variant in the MAGT1 gene: deletion exon 2-10**	Steroid taper, sirolimus has been considered
Auto-inflammatory							
Pat #14	16 yo	Male	Fatigue, short stature	SPENCDI	AHAI, ITP	WES trio: **biallelic compound heterozygous pathogenic variants** in the **ACP5 gene (c.325G>A, p.Gly109Arg/c.526C>T, p.Arg176*)** inherited from mother and father respectively	Stable on ruxolitinib 5mg-0mg-5mg per day
Pat #15	4 yo	Female	Fatigue, short stature, speech delay	SPENCDI	AHAI, ITP	PID panel: **biallelic compound heterozygous variants** in the **ACP5 gene (c.733C>T, p.Gln245*/ c.611G>A, p.Gly204Asp)**, inherited respectively from mother and father	Unstable on ruxolitinib. Anifrolumab (Saphnelo) been considered
Pat #16	10 yo	Female	Fatigue, short stature, speech delay	SPENCDI	AHAI, ITP	PID panel: **homogonous pathogenic variant** in the **ACP5 gene, c.643G>A (p.Gly215Arg)**. Parents not tested	Deceased due to non-adherence: s/p steroids, Rituximab, and ruxolitinib

Table 1. **Characteristics of patients with an underlying PIRD or PID assessed at our immunology-hematology clinic. (*Continued*)**

Patients	Age at diagnosis	Gender	Clinical	Diagnosis	Hematology	Genetic variants	Treatment and response to therapy
Pat #17	2 yo	Female	Fatigue, short stature, developmental delay	C terminal CDC42 mutation	Severe thrombocytopenia and anemia	WES trio: ***De novo* likely pathogenic in the CDC42 gene c.563G>A;p.C188Y**	Received multiple transfusions, in remission on Anakinra 4mg/kg/day
Partial DiGeorge							
Pat #18	2 months	Male	Cardiac defect	Partial DiGeorge	Pancytopenia; DAT+, cold agglutinin+	**22q11.2 deletion** (FISH), TBX1 gene mutation, consistent with known DiGeorge syndrome	Received multiple transfusions, steroids; On sirolimus 1.8 mg, he is doing well
Pat #19	16 yo	Male	Speech/language delay, cardiac defect	Partial DiGeorge	Pancytopenia, hx of epistaxis	**22q11.2 deletion** (FISH), TBX1 gene mutation, consistent with known DiGeorge syndrome	Received steroids; On sirolimus 2 mg, stable Plat, WBC and Hb count, doing well
Pat #20	8 yo	Male	Developmental delay, cardiac defect	Partial DiGeorge	Chronic refractory ITP	**22q11.2 deletion** (FISH), TBX1 gene mutation, consistent with known DiGeorge syndrome	Received steroids; IVIG and on sirolimus 0.5mg, he is doing well
Pat #21	6yo	Female	Developmental delay, chronic lung disease, oral food aversion, cardiac defect, intermittent fever, cytopenia, fatigue	Partial DiGeorge	Hx of neutropenia with positive DAT, chronic thrombocytopenia and anemia	**22q11.2 deletion** (FISH), TBX1 gene mutation, consistent with known DiGeorge syndrome; WES trio: VUS in JAK2 gene: c.1279T>C (pCys427Arg) inherited from father (asymptomatic)?	Received IVIG, considering adding ruxolitinib
Thymic aplasia							
Pat #22	2 yo	Male	Dysmorphic faces, ear anomalies, hearing loss, branchial defects, and skeletal and vertebral anomalies	Thymic aplasia	Refractory AHAI 6 months after receiving post cultured thymus tissue transplant	PID panel: **homozygous variant in the PAX1 gene**: c.509C>A (p.Pro170His), each inherited from one parent	Received Rituximab (x4), plasmapheresis (x5), Abatacept (x4 weekly doses), IVIg q weekly
Others							
Pat #23	18 yo	Male	No clinical symptom	CVID	Severe ITP	WES trio: negative	Steroids, rituximab, IVIG q 4 weeks/Plat ~10,000
Pat #24	17 yo	Female	Depression	Fontan	Evans syndrome with severe ITP	PID panel: negative	Steroids, sirolimus in remission

AD: autosomal dominant; AIHA: Autoimmune hemolytic anemia; AR: Autosomal recessive; G6PC3: CVID: common variable immunodeficiency; Glucose 6 phosphatase catalytic subunit-3 deficiency; ITP: idiopathic thrombocytopenia; IVIG: immunoglobulin replacement therapy; HSCT: Hematopoietic stem cell transplant; MAGT1: Magnesium transporter 1; NFkb1: Nuclear factor NF-kappa-B p105 subunit 1; PID: Primary immunodeficiency; PMM2: Perpetual motion machine of the second kind; SGLT2: Sodium-glucose cotransporter-2 (SGLT2) inhibitors; SLE: Systemic lupus erythematosus; TBX1: T-box transcription factor 1; VUS: Variant of unknown significance; WES: Whole-exome sequencing.

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Lymphoma in Patients with Activated Phosphoinositide 3-kinase δ Syndrome Enrolled in Targeted PI3Kδ Inhibitor (Leniolisib) Clinical Trial

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Hyperactivation of phosphoinositide 3-kinase δ (PI3Kδ) due to gain-of-function variants in catalytic domain gene PIK3CD or loss-of-regulatory-function variants in PIK3R1 leads to activated PI3Kδ syndrome (APDS1/APDS2). APDS manifests as immunodeficiency, cytopenia, lymphoproliferation, and increased risk of lymphoma. Leniolisib, a selective PI3Kδ inhibitor, addresses hyperactive signaling, but long-term data on the risk of subsequent lymphoma development are not available. We present two cases of lymphoma in patients with APDS1 and APDS2, respectively, while on leniolisib.

The first case is a 20-year-old Saudi female with APDS1 (NM_005026.5(PIK3CD), c.1574A>G, p.Glu525Gly) and a maternal history of lymphoma who experienced recurrent infections, splenomegaly, and EBV+ lymphoproliferative disease. She initially received mycophenolate mofetil and sirolimus before enrolling in a leniolisib Phase III trial (NCT02435173) in March 2020. After 85 days in the placebo arm, she transitioned to leniolisib during open-label extension. Adherence challenges, including customs-related issues, complicated her treatment. In June 2022, she developed stage IV CHL and received ABVD chemotherapy. Following remission, she underwent haploidentical stem cell transplantation but died from sepsis and acute respiratory failure in June 2023.

The second case is a 25-year-old male with APDS2 (NM_181523.3(PIK3R1), c.1425+1G>T, del434-475) and chronic colitis who presented with massive hematochezia and small bowel obstruction from lymphocyte aggregation in December 2020. He enrolled in the leniolisib trial in March 2021 and transitioned to the commercial drug after Day 115, following FDA approval. In June 2024, he had a sigmoidoscopy for recurrent hematochezia with biopsy demonstrating crypt destructive colitis with cryptitis and crypt abscesses. In September 2024, he developed retroperitoneal lymphadenopathy, recurrent hematochezia, and weight loss. Biopsy revealed CD20+MUM1+EBV-DLBCL. He died from hemorrhagic shock and septicemia before lymphoma treatment could begin.

These cases represent the first reported instances of lymphoma in APDS patients enrolled in the leniolisib Phase III trial. Diligent treatment adherence and lifelong lymphoma surveillance are critical. The emergence of resistance mechanisms in APDS, including co-optation of non-PI3K pathways like FAS-FASL defects, may contribute. Comprehensive genetic sequencing of germline and somatic tumor tissue may uncover alternate mechanisms of lymphomagenesis. Therapeutic strategies targeting more than one signaling pathway in APDS patients might improve prognosis.

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Allogeneic Hematopoietic Stem Cell Transplant Restores Naïve T Cell Immune Reconstitution in Infants with SCID Phenotype due to EXTL3 Deficiency

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Background: EXTL3 deficiency is associated with a neuro-immuno-skeletal dysplasia syndrome due to defective heparan sulfate synthesis. Patients can present with a SCID phenotype from inability to generate early T cell progenitors in the bone marrow and impaired thymopoiesis due to defective thymic epithelial cell differentiation. There are limited data on the success of allogeneic hematopoietic stem cell transplantation (HSCT) in patients with SCID phenotype due to EXTL3 deficiency. We hypothesized that allogeneic HSCT can restore naïve T cell immune reconstitution in patients with SCID phenotype due to EXTL3 deficiency despite defective thymopoiesis.
Methods: We report our single center retrospective analysis of two patients who underwent allogeneic HSCT for SCID phenotype due to EXTL3 deficiency.
Results: Two infants were referred to our center due to abnormal TRECs on newborn screening and were found to have T-, B+, NK+ SCID phenotype (Table 1). Both had skeletal dysplasia, and genetic testing showed biallelic mutations in EXTL3 gene (Table 1). Artificial thymic organoid differentiation assay was suggestive of a thymic defect in patient 1 (Figure 1). Patient 2 developed Omenn syndrome that required treatment with anti-thymocyte globulin. Additional clinical details and transplant characteristics are shown in Table 1. Both patients underwent unrelated donor cord blood transplant with reduced intensity conditioning that included fludarabine, melphalan, and

thiotepa without serotherapy. Both tolerated conditioning well without excess toxicity. Patient 1 engrafted on day +14 and patient 2 on day +13 post-HSCT. Both engrafted with full donor chimerism and experienced engraftment syndrome with brief oxygen requirement. Patient 2 experienced grade I acute skin GVHD that was treated with topical steroids. None of the patients developed chronic GVHD. At last follow-up (3 years post-HSCT in patient 1 and 2 years post-HSCT in patient 2), both patients had excellent T cell and B cell immune reconstitution with normal CD4+ naïve T cell counts (Table 2). Both were off IgG replacement and demonstrated protective vaccine titers. Both patients continue to have significant neurodevelopmental delay.

Table 1. **Patient and transplant characteristics.**

	Patient 1	**Patient 2**
Age at presentation	4 weeks	10 days
Gender	Female	Male
Race	Caucasian	African American
Gene variant	c.1006C>T, (p.Pro336Ser)	c.1609C>T, (p.Arg537Cys)
	Heterozygous (Paternal)	Heterozygous
	c.1040G>A, (p.Gly347Asp)	c.2506A>G (p.Met836Val)
	Heterozygous (Maternal)	Heterozygous
Lymphocyte subsets	CD3: 27, CD4:25, CD8:0, CD19: 1398, CD16/56: 170 cells/µL	CD3: 16, CD4:0, CD8:11, CD19: 1409, CD16/56:467 cells/µL
	CD4 naïve T cells: 6%	CD4 naïve T cells: NR
Skeletal abnormalities	Clinodactyly	Platyspondyly, broadening of the tufts of the distal phalanges of the middle, ring, and small fingers
Neurodevelopmental abnormalities	Yes	Yes
Maternal engraftment	No	No
Omen Syndrome	No	Yes
Pre-transplant infections	No	Staphylococcus Aureus Bacteriemia
		Staphylococcus Epidermis Bacteriemia
Transplant characteristics		
Age at transplant	3 months	5 months
HLA match	10/10 HLA	8/10 HLA
Stem cell source	Cord	Cord
TNC count	49.5 x 10x7 TNC/kg	14.25 x 10x7 TNC/kg
CD34 count	19.6 x 10x5 CD34/kg	12.7x10x5 CD34/kg
Conditioning regimen*	RIC	RIC
GVHD prophylaxis	CSA/MMF	CSA/MMF
Neutrophil engraftment	Day 14	Day 13
Platelet engraftment	Day 40	Day 27
Transplant complications		
Engraftment Syndrome	Yes	Yes
Acute GVHD	No	Yes, skin (mild)
Chronic GVHD	No	No
Infections	Right upper lobe pneumonia	Pseudomonas aeruginosa bacteriemia
Seizure	No	Yes

*RIC regimen: Fludarabine 1 mg/kg/dose IV for 5 day (days -8 to -4), Melphalan 4.7 mg/kg/dose once at day -3, Thiotepa 200 mg/m2/dose once at day -2.

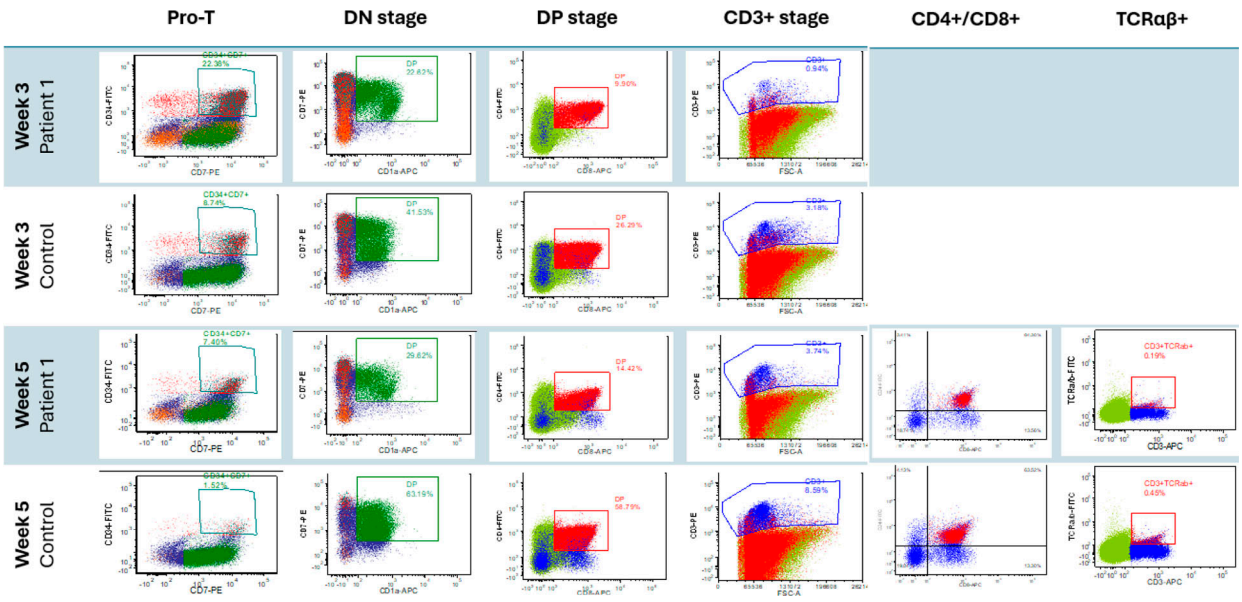

Figure 1. Artificial thymic organoid differentiation assay for patient 1. *Control: Cord Blood, CD34+.

Table 2. **Immune reconstitution at last follow-up post-transplant.**

	Patient 1 (3 yrs. post HSCT)	**Patient 2 (2 yrs. post HSCT)**
Donor chimerism (%)	100% myeloid 99% T cell	100% donor
Absolute CD3+ T cells (cells/mcL)	2653	3691
Absolute CD4+ T cells (cells/mcL)	1771	2251
Naïve CD4+ T cells (%)	68.2	69.2
Absolute CD4 naïve T cells	1204	1553
Absolute CD8+ T cells (cells/mcL)	707	987
Absolute NK cells (cells/mcL)	560	538
Absolute B cells (cells/mcL)	1063	1371
IgG (mg/dL)	728	974
IgM (mg/dL)	71.8	154
IgA (mg/dL)	66.3	166

Conclusion: Our experience suggests that allogeneic HSCT is well tolerated, restores naïve T cell immune reconstitution, and is a potential curative approach for the SCID phenotype in EXTL3 deficiency despite defective thymopoiesis.

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Familial Cohort with Novel IRF2BP2 Variant and Autoimmunity

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We present a 16-month-old previous term male with recurrent infections starting at 3 months of age. Parents reported recurrent infections, including 2 episodes of RSV and 8 episodes of otitis media by 6 months of age, requiring tympanostomy tubes—with persistent drainage for months afterward. He was up-to-date with vaccines. Family history was significant for autoimmunity. Mother and great maternal aunt have systemic lupus erythematosus diagnosed in adulthood. The mother also has Sjögren's disease and had recurrent otitis media during childhood. The maternal grandmother has hypothyroidism, rheumatoid arthritis, Raynaud's, lichen planopilaris, irritable bowel syndrome, monoclonal gammopathy of undetermined significance, and breast cancer. She was also diagnosed with common variable immunodeficiency (CVID) at age 50.

Initial immune evaluation was unremarkable with normal T, B, and NK cell counts, B cell subpopulations, immunoglobulin levels, and protective titers to diphtheria and tetanus. Genetic testing via commercial genetic panel for inborn errors of immunity revealed a missense variant of uncertain significance in IRF2BP2 in exon 1 c.794C>T (p.Ala265Val). The gnomAD database (v4.1) shows a population frequency of 0.00001799 for the variant. The variant has an AlphaMissense score of 0.08059, categorizing it as likely benign, and a CADD score of 14.7. Other variants in the vicinity of this variant have been categorized as likely benign or of uncertain significance in ClinVar. Parental testing revealed that the variant was maternally inherited. Extended investigation confirmed that the variant is present in the maternal grandmother.

Because impaired regulatory T cell function has been reported in IRF2BP2 deficiency, Foxp3 expression in T cells was tested in the patient and was normal. Increased type 1 interferon signature has also been described; type 1 interferon activity was normal in this patient. IRF2BP2 mutations have also been associated with STAT1 hyperactivity; however, STAT1 functional testing was normal for our patient.

IRF2BP2 was initially associated with CVID with the phenotype expanding further to include autoimmunity and immune dysregulation. Our patient does not currently have features of CVID or autoimmunity; however, the family history is significant for both. He will require careful lifetime monitoring for both of these conditions.

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Toll-like Receptor 3 Defect in a Patient with Autoimmune Encephalitis Following HHV-6 Encephalitis

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Introduction: Toll-like receptors play an important role in innate immunity. The toll-like receptor 3 (TLR3) genes encodes a transmembrane protein that recognizes dsRNA and helps eradicate viral infections through the activation of NF-kappaB and production of type I interferons.

Case Description: The patient is a 13-year-old girl with Rubinstein-Taybi syndrome (RSTS) who presented at 8 years old for first-time generalized tonic-clonic (GTC) seizure. Workup was notable for cerebral spinal fluid (CSF) positive for HHV-6, which was of unknown clinical significance; she was discharged on an anti-epileptic. At 10 years old, she experienced another GTC seizure with CSF that was again positive for HHV-6. It was felt that this detection of HHV-6 was a latent infection and that influenza A was possibly driving her encephalitis given positive nasopharyngeal PCR testing. Given prolonged symptoms, an autoimmune encephalitis panel was obtained, which was positive for glial fibrillary acidic protein (GFAP) antibodies. She improved with intravenous immunoglobulin and steroids. Since her GFAP autoimmune encephalitis, she has experienced recurrent sinopulmonary infections. Initial immunologic workup showed a mildly decreased IgA and a decreased percentage of isotype-switched (IgM-/IgD-) memory B cells, which is not unexpected in patients with RSTS due to B cell maturation defects. Her pneumococcal titers were non-protective, but family deferred revaccination. Genetic testing showed a heterozygous variant in TLR3 (c.1234C>G (p.Leu412Val)).

Discussion: Genetic testing showed a heterozygous variant in TLR3 (c.1234C>G (p.Leu412Val)) not previously reported in the literature to be associated with TLR3-related conditions. The genotype-phenotype relationship identified between the patient's TLR3 variant is immunodeficiency 83 (IMD83), which is associated with an increased susceptibility to severe viral infections, including herpes simplex virus (HSV), varicella zoster virus, and influenza A virus. IMD83 has been associated with HSV encephalitis due to impaired TLR3-dependent interferon production in central nervous system cells. While there appears to be no clear association between IMD83 and autoimmune encephalitis, TLR3 defects have been associated with autoimmune predisposition, given that appropriate endosomal

expression of TLR3 may prevent activation by host nucleic acids and the development of autoimmunity. This case highlights the importance of monitoring patients with TLR3 defects for both viral and autoimmune encephalitis.

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Clinical Implications of ZNFX1 Mutation in Interferonopathy: A Case Study

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Interferonopathies are complex inborn errors of immunity characterized by dysregulation of interferon signaling pathways. They lead to excessive immune responses and systemic inflammation. This case report describes an infant with cytopenia and severe viral illness presented as hemophagocytic lymphohistiocytosis (HLH)-like features caused by a mutation in the ZNFX1 gene, a significant cause of type 1 interferonopathy.

Case Scenario: This case study presents a unique instance of a ZNFX1-related interferonopathy in a 6-month-old boy, a nonidentical twin, with a novel homozygous mutation (c.1928G>A, p.Trp643X) identified following cytomegalovirus infection. The patient exhibited classic HLH features, including recurrent fevers, pancytopenia, elevated inflammatory markers, and high serum ferritin levels. The mutation in ZNFX1, a critical gene encoding a helicase protein integral to viral infection recognition, disrupted normal interferon regulation and immune response mechanisms. Genetic testing revealed autosomal recessive inheritance, with both parents heterozygous for a ZNFX1 gene variant. And no mutation was detected in his twin brother. Treatment options employed included steroids, intravenous immunoglobulin (IVIG), and Anakinra, an IL-1 receptor antagonist. Despite these interventions and plans for hematopoietic stem cell transplantation, the patient developed a severe CMV infection, and he died before transplantation.

Conclusion: This case underscores the importance of genetic evaluation in diagnosing complex immunological disorders, highlighting the need for comprehensive management and early intervention in ZNFX1-related interferonopathies. The findings contribute to the growing understanding of genetic factors underlying immune dysregulation and provide insights into potential therapeutic approaches for similar pediatric immunological conditions.

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Demographic and Clinical Characteristics of People with Activated Phosphoinositide 3-Kinase Delta Syndrome in the APDS Characterization and Clinical Outcomes Immunologic Registry

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Activated phosphoinositide 3-kinase delta syndrome (APDS) is a rare disorder with autosomal dominant inheritance pattern that leads to immune deficiency and dysregulation. As APDS was first characterized in 2013, there are gaps in knowledge related to the demographic and clinical characteristics of patients affected by APDS. The APDS-CHOIR registry was constructed to provide increased visibility into this population. Here we present baseline characteristics of APDS-CHOIR enrollees through October 2024.

Participants qualifying for the study were required to have a genetically confirmed pathogenic variant in PIK3CD or PIK3R1. Data from electronic health records (EHR) were entered directly by participating sites and includes demographic data, comorbidities, infection history, lab results, and transplant history. Diagnostic and screening procedures ordered by treating physicians were collected to understand healthcare resource utilization of this population (Figure 1).

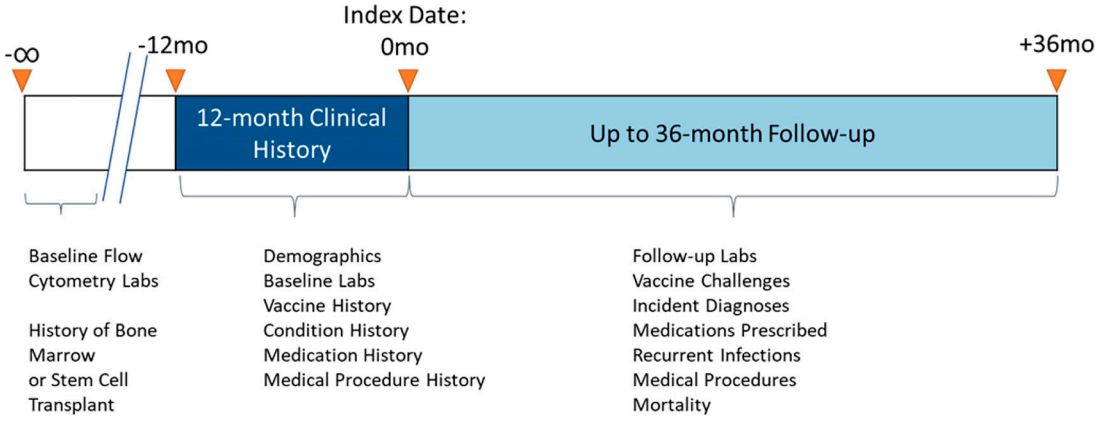

Figure 1. Study schematic.

Currently, 41 participants have been enrolled across the U.S. (Figure 2). The median age at enrollment was 21 years (range 4-70) with majority female (63%) gender and white race (68%). Participants were diagnosed with APDS a median of 2 years prior to the enrollment date, with 39% diagnosed within 1 year prior to the index date. Most patients have PIK3CD pathogenic variant (76%). Medicaid was the most common payer type (41%), followed by commercial payer (29%). The most common clinical manifestations of disease reported are infections (80%), lymph node abnormalities (76%), respiratory issues (76%), gastrointestinal issues (63%), and splenomegaly (63%); these are most common in both pediatric and adult patients (Figure 3). At or prior to enrollment, 10 (24%) had been prescribed leniolisib, 9 (22%) mTOR inhibitors (sirolimus or everolimus), and 26 (63%) IVIG therapy. Bone marrow or stem cell transplants were identified in 6 patients prior to enrollment.

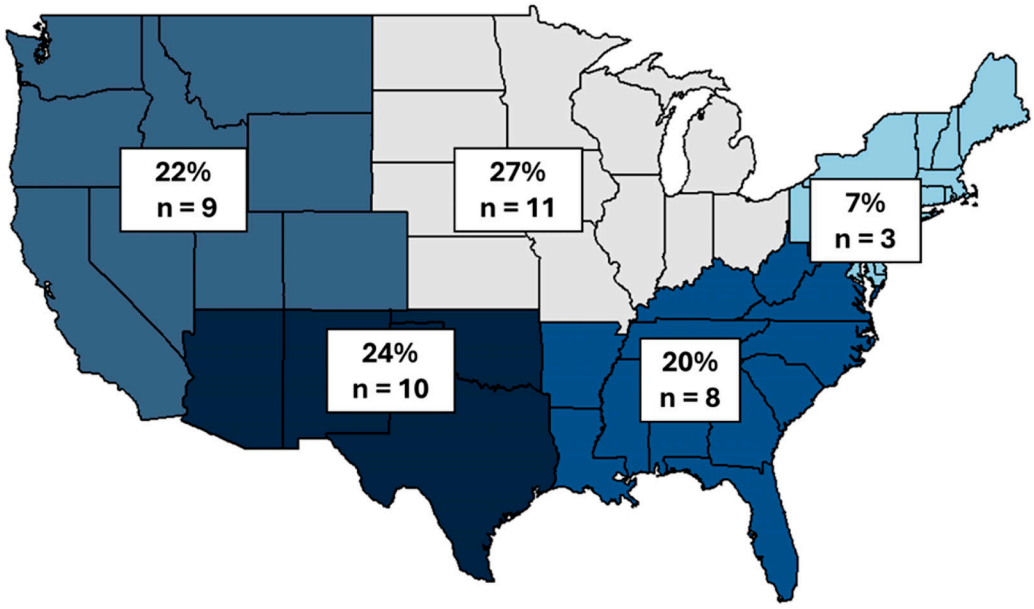

Figure 2. U.S. map of enrollment.

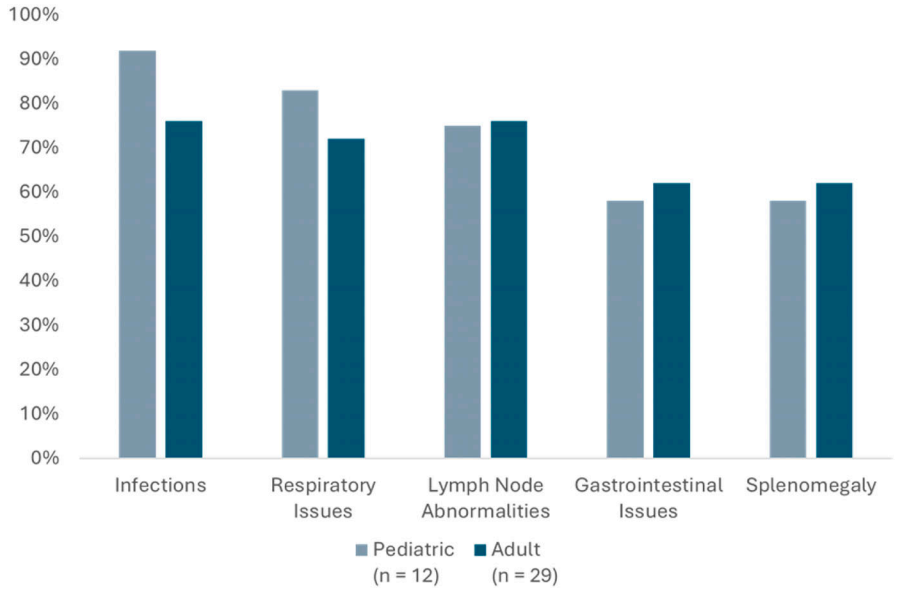

Figure 3. Most frequent medical conditions for pediatric and adult patients.

The real-world data from the APDS-CHOIR registry allow for the versatile phenotyping of patients with APDS and documentation of their clinical care. The longitudinal observational nature of this registry will provide insights into the evolving clinical manifestations of patients with APDS and responses to treatments over time in this rare-disease population.

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SEPTIN6-Related Congenital Neutropenia and B Cell Deficiency

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Septins, a highly conserved family of GTP-binding, filament-forming proteins, serve as scaffolds and diffusion barriers in various cellular processes. SEPTIN6 is involved in hematopoiesis, assisting in cell division and cytokinesis. We present the second reported case of SEPTIN6-related disease with X-linked congenital neutropenia, tetraploid precursors, and multinucleated myeloid cells associated with the unique finding of B cell deficiency and abnormal initial NBS.

A full-term male infant with uncomplicated delivery screened positive on NBS for SCID. Labs showed moderate T cell deficiency (CD3+ 548 cells/μL) enumerated as 90% CD45RA+, persistent profound B cell deficiency (CD19+ 8 cells/μL), and severe neutropenia (ANC < 200). NK cells were normal in range. ADA testing was also normal. Repeat TRECs and T cell quantitation normalized by 2 months. Given absent circulating B cells (CD19+ < 1%), immunoglobulin replacement was started. Peripheral smear showed decreased neutrophils with intermittently abnormal multi-lobation and normal granulation. Anti-neutrophil antibodies were negative. Bone marrow (BM) biopsy at 2 months was normocellular with maturing trilineage hematopoiesis with hypersegmentation of myeloid forms (neutrophils, monocytes, and eosinophils), neutropenia, and decreased lymphoid cells. Neutropenia was unresponsive to G-CSF and vitamin B12 supplementation. At 4 months, BM showed enlarged, hypersegmented myeloid cells (up to 80% tetraploidy), absent B cells (<1%), and rare CD79a+ cells (plasma cells). A primary immunodeficiency genetic panel returned negative. Research trio whole genome sequencing identified an X-linked maternally inherited variant in SEPT6 c.1282T>A (p.*428Lysext*9). Sequential BMs identified increased reticular fibrosis, trisomy 8 without overt dysplasia, and markedly decreased PAX5+CD20+ B cells (<<1%) with continued rare CD79a+ cells

(<1%) morphologically similar to plasma cells; a matched-related donor BM transplant resulted in full donor chimerism and no acute or chronic GVHD 3 years post-transplant. Maternal cells demonstrated skewed X-inactivation at the SEPTIN6 locus. Mechanistic studies, including RNA-seq on BM and B cell development assays, explore the role of SEPTIN6 in B cell development.

Overall, we identified a novel germline defect in SEPTIN6 in a male with congenital neutropenia, B cell aplasia, and rare plasma cells. We present the case, successful transplant outcome, and remarkable similarity to the initial report of SEPTIN6-related disease.

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A Case for Early Genetic Testing in an Infant with Recurrent Infections Concerning for Primary Immunodeficiency

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Common variable immunodeficiency (CVID) is a rare diagnosis characterized by low levels of serum IgG, low serum IgA and/or IgM, and failure to produce specific protective antibody titers. This condition can present clinically as recurrent infections and/or inflammatory and hematologic complications. CVID is a complex condition that may not have a singular genetic cause; however, multiple genes have been implicated. Correlation between genetic testing, clinical presentation, and laboratory findings is vital in guiding diagnosis and treatment. We present a single case of an infant with recurrent infections, low IgG, and a pathogenic variant on genetic testing associated with CVID.

A 7-month-old female born at 35 weeks with a complex medical history, including 14q partial deletion syndrome, was admitted to the ICU for respiratory failure and sepsis from methicillin-susceptible *Staphylococcus aureus* pneumonia. Her hospital course was complicated by recurrent bacterial infections, including ventilator-associated pneumonia, bacteremia, cystitis, and tracheitis. The patient had persistently low absolute counts in B cells (513 cells/μL), T cells (1,538 cells/μL), and natural killer cells (151 cells/μL) as well as low IgG levels (158 mg/dL) concerning for immunodeficiency. Serum levels of IgA (28 mg/dL) and IgM (72 mg/dL) were normal. *Streptococcus pneumoniae* IgG antibodies demonstrated adequate immunity for 22 of the 23 serotypes. Tetanus and diphtheria toxoid IgG antibodies were protective. Genetic testing revealed a heterozygous, pathogenic variant in the CR2 gene, which is associated with autosomal recessive CVID caused by CD21 deficiency. The patient was started on intravenous immunoglobulin G (IVIG) infusions with subsequent improvement in recurrent infections.

Although our patient had normal IgA, IgM, and polysaccharide and protein vaccine responses, she was found to have a pathogenic gene variant associated with autosomal recessive CVID in the setting of low IgG and responded clinically to treatment with IVIG. It is unclear if the patient will eventually develop the clinical and laboratory findings of CVID, given this autosomal recessive genetic variant. However, this case suggests a role for early genetic testing in patients who present with recurrent infections, as it may help to guide compassionate treatment decisions and further understanding of the patient's disease process.

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Hyper IgD Syndrome: A Complex Case of Recurrent Fevers, Abdominal Pain, and Atypical Skin Rash

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Background: Hyper immunoglobulin D syndrome (HIDS), also known as mevalonate kinase deficiency, is a rare autosomal recessive autoinflammatory disorder caused by mutations in the MVK gene, characterized by recurrent fevers, abdominal pain, and elevated serum IgD levels.

Case Presentation: We report the case of a 5-year-old Saudi boy with history of recurrent fever, abdominal pain, and hyperpigmented skin lesions. He started to have recurrent fever episodes with abdominal pain at 4 months of age. His past medical history was notable for failure to thrive and congenital atrioventricular block. His past medical history was notable for failure to thrive and congenital

atrioventricular block. Physical examination revealed abdominal distension and multiple hyperpigmented spots on the lower extremities but no lymphadenopathy or organomegaly. His height and weight were below the 3rd and 10th percentiles for age, respectively. Laboratory investigations showed leukocytosis with lymphocytosis. The patient also had thrombocytosis (666 × 10^3/μL) and elevated inflammatory markers, including ESR (68 mm/h), CRP (15.6 mg/dL), and serum amyloid A (45.1 mg/L). A CT scan demonstrated thickening of the terminal ileum, cecum, and ascending colon with mucosal hyperenhancement. However, stool calprotectin was negative, and a lower GI endoscopy was unremarkable. Skin biopsy showed increased basal cell pigmentation and melanocytes consistent with café-au-lait spot. Whole-exome sequencing revealed a homozygous missense pathogenic variant (c.1129G>A; p.Val377Ile) in the MVK gene, consistent with a diagnosis of HIDS. The patient was initially treated with an interleukin-1 inhibitor (anakinra) and colchicine. However, he continued to experience recurrent fever and abdominal pain. Due to concerns about compliance with daily anakinra injections, treatment was switched to canakinumab. After starting canakinumab, the patient showed significant clinical improvement, with resolution of symptoms and normalization of inflammatory markers.

Conclusion: This case highlights the diagnostic complexity and therapeutic challenges of HIDS. Café-au-lait spots are typically associated with genetic disorders, such as neurofibromatosis, Legius syndrome, and Noonan syndrome but have not been previously reported in HIDS. While this association cannot be established based on a single case, this report may inspire further research into this potential link.

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Expanding the Allelic Spectrum of TCN2: A Case Report on Transcobalamin II Deficiency

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Introduction: Transcobalamin II deficiency is a rare autosomal recessive disorder classified as an inborn error of immunity. Transcobalamin II is a plasma protein essential for the absorption, transport, and cellular utilization of vitamin B12. Its deficiency leads to diverse clinical manifestations, including gastrointestinal disturbances, failure to thrive, megaloblastic anemia, pancytopenia, agammaglobulinemia, neurological impairments, metabolic abnormalities, and recurrent infections. According to Orphanet and PubMed, fewer than 50 cases have been reported globally, suggesting a prevalence of less than 1 in 1,000,000.

Materials and Methods: Genomic DNA was extracted from peripheral blood leukocytes using phenol-chloroform extraction. Whole-exome sequencing was performed on a DNBSEQ-G50 (MGI, China) using the Exome Capture V5 Probe Set (MGI, China). Secondary data processing of FASTQ files was performed using ZLIMS (MGI, China), and tertiary analysis involved the Annovar software, followed by variant filtering. Detected variants were evaluated using the Varsome software. Clinically significant variants were confirmed by Sanger sequencing on a 3500 Genetic Analyzer (Thermo Scientific, USA).

Results: Two novel heterozygous variants in the TCN2 gene (NM_000355.3) were identified, neither reported in the gnomAD Exomes database. These included a splice-site variant c.1223-2 A>G (VarSome classification: likely pathogenic) and a coding region variant c.154C>T, p.Pro52Ser (VarSome classification: uncertain significance). The compound heterozygous genotype was consistent with the patient's clinical presentation.

The patient was first admitted at age five with an acute anemic crisis (hemoglobin 49 g/L), required erythrocyte transfusion. Subsequent evaluations revealed persistent megaloblastic anemia, hyperbilirubinemia, and mild splenomegaly. Bone marrow analyses excluded myelodysplastic syndrome and hematologic malignancies. Iron and folate therapies were ineffective; however, cyanocobalamin normalized hemoglobin levels (130 g/L) and reduced splenomegaly. Mild intellectual impairment was noted during follow-up.

Conclusion: Transcobalamin II deficiency typically manifests in early childhood with symptoms such as developmental delays, hypotonia, diarrhea, pallor, anemia, pancytopenia, and agammaglobulinemia. This case contributes to the understanding of the condition, expands the allelic spectrum of TCN2, and supports the optimization of treatment strategies for this rare condition.

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Primary Intestinal Lymphangiectasia as a Cause of Combined Immunodeficiency

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Primary intestinal lymphangiectasia (PIL, also referred to as Waldmann's disease) is a rare disorder characterized by the dilation of intestinal lymphatic vessels, resulting in lymph loss. We present the case of a previously healthy eleven-year-old male, referred to immunology after recurrent Cryptosporidium infections, raising concerns about primary or secondary immunodeficiency. Clinical immunophenotyping revealed combined immunodeficiency, with severe hypogammaglobulinemia (total IgG: 212 mg/dL) and T cell lymphopenia (CD4+ count: 172 cells/μL; CD8+ count: 208 cells/μL). Clinical symptoms included peripheral edema, fatigue, chronic diarrhea, bloating, and abdominal pain. Extensive genetic testing, including a primary immunodeficiency panel and research-based whole-exome sequencing, did not identify a plausible causative variant. After initiating treatment with subcutaneous immunoglobulin and trimethoprim/sulfamethoxazole prophylaxis, immune parameters remained suboptimal (total IgG: 515 mg/dL; CD4+ count: 150 cells/μL; CD8+ count: 153 cells/μL). Stool samples collected by the patient's gastroenterologist for persistent abdominal symptoms showed intestinal inflammation and suspected protein-losing enteropathy. The diagnosis of PIL was confirmed via esophagogastroduodenoscopy with biopsies. Dietary strategies were implemented, consisting of a low-fat diet (12 g/day), high-protein intake (75–125 g/day), and supplementation with ADEK vitamins and medium-chain triglyceride oil. This intervention resulted in improvement in antibody levels, with total IgG levels rising to 1114 mg/dL, although T cell lymphopenia remained at similar levels. In this report, we discuss the clinical course of this patient and provide an overview of the published literature regarding clinical manifestations and diagnostic laboratory values of immunodeficiency associated with PIL. We conclude that PIL should be considered as a cause of combined immunodeficiency or hypogammaglobulinemia in the absence of an alternative explanation in both adult and pediatric patients.

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A Case of Recurrent Hemophagocytic Lymphohistiocytosis-like Episodes in a Patient with XIAP Deficiency

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A 14-year-old male with Crohn's disease since age 9, refractory to multiple treatments, was referred to immunology for evaluation of primary immunodeficiency. He had no history of recurrent infections and no family history of immunodeficiency, autoimmunity, or consanguinity. Evaluation demonstrated an absolute lymphocyte count of 900, normal lymphocyte subset percentages, but a low absolute CD3 count of 558, CD4 count of 373, and CD8 count of 130. Proliferation to mitogens and antigens showed decreased proliferation to concanavalin and phytohemagglutinin. Immunoglobulins and specific antibodies were normal. A neutrophil oxidative burst was normal. An inflammatory bowel disease (IBD) genetic panel demonstrated a hemizygous pathogenic variant in XIAP c.1141C>T (p.Arg381*), creating a premature translation stop signal resulting in an absent/disrupted protein product. X-linked proliferative disorder 2 (XLP2) was diagnosed. Further workup demonstrated mild anemia, no other cytopenia, normal ferritin, normal fibrinogen, and negative EBV serology. The possibility of hematopoietic stem cell transplant (HSCT) was discussed but deferred due to social considerations.

A month after diagnosis, he was hospitalized for hypovolemic shock in the setting of norovirus colitis, with laboratory evidence of anemia and elevated inflammatory markers. He had elevated ferritin >10,000; elevated CD163; sIL2R 1,705; CXCL9 43,167; IL-18 57,094; normal NK cell function, and CD107a. CRP, ferritin, and liver function improved on broad-spectrum antibiotics, and he did not meet criteria or undergo treatment for HLH. Within the following 6 months he was hospitalized three times with fever, arthralgia, and HLH-like laboratory findings, without meeting HLH criteria. Considering these episodes and his poor IBD control, he was started on 150 mg canakinumab monthly for HLH-like episodes and chronic inflammation. He remained free of such episodes for a year but was then

hospitalized again with severe arthralgia, fevers, and increased ostomy output despite IL-1 blockade, with CXCL9 7,388; IL-18 53,437; IL-1b 185.3; and sIL2R 1,387. All cultures were negative. Concerned he may have developed antibodies to canakinumab, he was trialed on anakinra, which resolved his fever and symptoms. He was discharged on rilonacept and has remained fever- and symptom-free since. Discussions regarding HSCT remain ongoing.

This case highlights the importance of targeted pharmaceutical therapies, such as anti-IL-1, in managing complex inflammatory conditions like XLP2.

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The Many Sides of RIPK1

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Introduction: RIPK1 is a key regulator for mediating inflammatory signaling and cell death. This includes apoptosis, necroptosis, and innate immune signaling. Given these important functions of RIPK1, abnormalities in its pathway can lead to immune deficiency and/or autoinflammatory disease, with autosomal dominant cleavage-resistant RIPK1-induced autoinflammatory (CRIA) disease associated with RIPK1 gene mutations.
Case: A 15-year-old female with a history of recurrent lymphadenitis and infections since early childhood was referred to immunology during an admission for recurrent fevers of unknown origin, night sweats, and lymphadenopathy. Previous infections included bacterial sinusitis and pneumonia, bronchitis, otitis media, and skin and soft tissue infections. Additionally, she had nonspecific gastrointestinal symptoms, including abdominal pain and intermittent diarrhea, that were attributed to irritable bowel syndrome. For seven years, she was seen by multiple subspecialties without a unifying diagnosis. She had an extensive workup, which ruled out rheumatologic disorders, ongoing chronic infection, and malignancy. Workup showed CBC with mild thrombocytosis, normal immunoglobulin levels, elevated inflammatory markers (both ESR and CRP), and elevated B cells on flow cytometry (later normalized). She had a normal bone marrow biopsy. CT chest/abdomen/pelvis showed prominence of abdominal lymph nodes and several cervical and occipital lymph nodes. Her left neck lymph node was biopsied, with pathology showing reactive follicular and parafollicular hyperplasia and no evidence of lympho-proliferative disorder or changes on flow cytometry. After her extensive workup, genetic testing was pursued and the patient was found to have a heterozygous RIPK1 variant (c.82T>C (p.Phe28Leu)), classified as of unknown significance, but in silico analysis suggesting the variant to likely be disruptive.
Discussion: The patient's clinical and immunological phenotype, with increased inflammatory markers, regular prolonged fevers, lymphadenopathy, ulcers, and GI symptoms, has features that overlap with CRIA. The patient was trialed on colchicine; however, she had limited response. This particular RIPK1 variant has not been described as pathogenic, but her presentation warrants further functional evaluation and a possible treatment trial with an IL-6R or IL-1 blocker.

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Papillon-Lefèvre Syndrome Presenting with Early-Onset Psoriasis and Osteomyelitis

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Background: Papillon-Lefèvre syndrome (OMIM #245000) is a rare autosomal recessive genodermatosis caused by mutations in the cathepsin C gene (CTSC). CTSC encodes the lysosomal protease cathepsin C, which is highly expressed in white blood cells. Defects in CTSC typically lead to early-onset hyperkeratosis and periodontitis, resulting in premature tooth loss.
Case Presentation: We report the case of an 8-year-old boy with a history of early-onset psoriasis diagnosed in infancy, for which he has been receiving adalimumab 20 mg every other week. The patient presented to our clinic with complaints of swelling and pain in the

right knee over the past few weeks, accompanied by intermittent fever that improved with paracetamol. On physical examination, a severe psoriatic rash was noted on the extremities (hands, feet, elbows, and knees), accompanied by dystrophic nails. Significant swelling and a flexion contracture of the right knee joint were observed. The patient was started on prednisolone (0.5 mg/kg PO) with a tapering plan over one month, methotrexate (7.5 mg SC weekly), and folic acid (1 mg PO daily). Despite this, the swelling worsened and fever persisted. He was subsequently admitted for further evaluation. Laboratory tests revealed a WBC count of 13.2, hemoglobin of 10.7, platelet count of 464, and ESR of 78. Ultrasound imaging identified two oval-shaped hypoechoic masses in the lower right thigh. MRI of the knee revealed a large collection surrounding the distal femur (Brodie abscess) with involvement of the growth plate and epiphysis, along with bone marrow edema suggestive of osteomyelitis. Blood cultures were negative; however, abscess fluid cultures grew methicillin-resistant *Staphylococcus aureus*. Whole-exome sequencing revealed a likely pathogenic homozygous variant in the CTSC gene (c.899G>A; p.Gly300Asp), consistent with a diagnosis of Papillon-Lefèvre syndrome. This variant has been reported in the literature as causative of Papillon-Lefèvre syndrome.

Conclusion: Early-onset, difficult-to-treat psoriasis should prompt a consideration of genetic testing, particularly in patients with a history of unusual infections. The management of Papillon-Lefèvre syndrome requires a multidisciplinary approach, involving pediatricians, dermatologists, immunologists, dentists, and surgical team. Early diagnosis provides an opportunity for aggressive management of periodontitis, potentially reducing the risk of premature tooth loss

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Successful Management of Netherton Syndrome Using IVIG and Dupilumab: A Case Report

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Background: Netherton syndrome (NS) is a rare autosomal recessive genodermatosis caused by mutations in the SPINK5 gene, characterized by congenital ichthyosis, trichorrhexis invaginata (bamboo hair), and severe atopy. NS disrupts skin barrier function and immune regulation, leading to significant clinical and immunological complications.

Case Presentation: We report the case of a 7-month-old Saudi boy with NS, confirmed by genetic analysis revealing a homozygous splice site mutation in SPINK5 (c.1302+5G>C). Clinical features included generalized erythema, scaling, pruritus, and hallmark trichorrhexis invaginata. The patient experienced frequent cutaneous infections and elevated serum IgE levels. At the age of 18 months, he was started on intravenous immunoglobulin replacement therapy (IVIG) 500 mg/kg every 4 weeks due to frequent cutaneous infections, which required multiple antibiotics and hospital admissions. At six years of age, dupilumab (300 mg every 4 weeks) was added as an adjunct therapy to reduce skin inflammation and improve skin barrier function prior to food reintroduction. The patient demonstrated substantial clinical benefits, with marked relief from pruritus and chronic itching. Relieving the itch helped improve his sleep quality, playtime, focus, and overall quality of life. Additionally, the patient exhibited notable hair growth, with longer strands that resisted immediate breakage. Serologically, total serum IgE levels decreased from 1078 IU/mL to 55.8 IU/mL (reference range: 25–449.7 IU/mL) following dupilumab therapy. Additionally, food-specific IgE antibodies showed improvement.

Conclusion: NS is a complex disorder requiring a comprehensive approach to management. Comprehensive treatment strategies incorporating IVIG and dupilumab can significantly improve patient outcomes and quality of life.

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Parental Knowledge and Attitudes Toward Expanded Newborn Screening to Include SCID Screening in Saudi Arabia: A Cross-Sectional Study

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Introduction: Severe combined immunodeficiency (SCID) newborn screening (NBS) has been successfully implemented in various countries using T cell receptor excision circles (TRECs) in dried blood spots. This innovative approach not only facilitates early diagnosis but also mitigates the risk of complications associated with live vaccines, such as the oral poliovirus vaccine and BCG, which can potentially cause disseminated infection in susceptible individuals. The prevalence of SCID in Saudi Arabia is likely to be elevated given the high rate of consanguinity, which further suggests the importance of including it to the NBS program.
Methodology: This descriptive cross-sectional study utilized a validated questionnaire to evaluate knowledge and attitudes regarding the expansion of NBS. The study included Saudi parents aged 18 and above, each with at least one child. A total of 242 parents completed the self-administered questionnaire. Parental knowledge of NBS was assessed using 12 true/false questions, with a score of 60% (7 out of 12), indicating sufficient knowledge. Attitudes were measured using a 12-item questionnaire on a 5-point Likert scale, with responses categorized as agree, uncertain, or disagree.
Results: The results revealed that 76.9% of parents had poor knowledge about NBS. Parents in healthcare occupations were associated with better knowledge ($p < 0.001$). Regarding SCID, 72.3% of parents lacked prior knowledge about the condition. Prior knowledge of SCID was associated with gender, educational level, and occupation, ($p = 0.007$, $p = 0.004$, and $p < 0.001$, respectively). Despite this knowledge gap, 82.2% of parents wanted their children to undergo NBS, although 48.8% expressed anxiety about potential positive screening results. A significant majority (87.6%) supported screening for SCID when it becomes available. Furthermore, while 86% indicated that the government should cover the costs of expanded screening, 69.4% expressed a willingness to pay out of pocket for the test.
Conclusion: This study reveals a significant knowledge gap among Saudi parents regarding NBS and SCID. However, the majority of parents express a desire for their children to undergo NBS and demonstrate strong support for the implementation of SCID screening, should it become available.

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The Role of IFNAR1 and IFNAR2 Genes in Antiviral Immunity: Two Case Reports

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Introduction: The study of inborn errors of immunity (IEI) has made a crucial contribution to understanding the regulatory and effector mechanisms of immunity. Here we present 2 cases involving variants in the IFNAR1 and IFNAR2 genes, both associated with increased susceptibility to severe viral infections. Clinical presentation, history of deceased siblings, and parental consanguinity suggested a potential genetic etiology.
Case 1: 7-year-old female with consanguineous parents (first cousins). Bilateral sensorineural deafness after severe case of chickenpox at age 1. At age 3, acute hepatitis and stroke after yellow fever vaccine (YFV). Two deceased siblings, one from diarrhea of unknown etiology and the other from acute liver failure after YFV. Blood counts, immunoglobulins, lymphocyte subpopulations, and vaccine response were normal. Immunodeficiency (PID) panel without candidate variants. Whole-genome sequencing (WGS) revealed a homozygous 8-kb deletion (exons 3–5) in the IFNAR1 gene. IDP panel did not yet include the IFNAR1/2 genes.
Case 2: 14-year-old female, consanguineous parents (first cousins). Suspected hemophagocytic lymphohistiocytosis (HLH) after MMR vaccination at age 1, viral meningitis at 20 months, chickenpox at age 3, and disseminated herpes at age 4, with corneal ulcer and bilateral visual loss. Normal blood count, immunoglobulins, lymphocyte immunophenotyping, and vaccine response. Normal NK cell cytotoxic activity. HLH panel and Exome with no candidate variants. WGS revealed a homozygous missense variant (c.840+1G>T) in a splicing region following exon 8 in the IFNAR2 gene.

Conclusion: The impact of variants in these genes and their effects on the type I IFN signaling pathway have been more widely studied in recent years, particularly after COVID-19 pandemic. The presented cases highlight the importance of expanding the investigation of IEI in patients with infectious complications involving a restricted pattern of microorganisms, especially those with a family history and consanguinity. Reanalysis of molecular data, in light of ongoing advances in genetic research, is crucial. Early and accurate diagnosis is essential for optimizing patient care.

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Autologous Lentiviral Vector LVFOXP3 CD4 T Cells for IPEX Syndrome

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A first-in-human (FIH) Phase 1 clinical trial with a novel regulatory T (Treg) cell therapy product to treat IPEX syndrome is ongoing (NCT05241444) at our center. We administer autologous engineered CD4LVFOXP3 Treg-like cells, lentiviral vector (LV)-transduced CD4+ T cells expressing wild-type human FOXP3.

Primary objectives include feasibility and safety. Our secondary objective is to assess the impact of CD4LVFOXP3 infusion on clinical manifestations. The study is a 2 + 4 dose escalation trial design with 3 doses in two different age cohorts. A total of six patients have been treated. The first two patients in the >12-year-old cohort received the lowest dose (1×10^6/kg) and the second two received the intermediate dose (3×10^6/kg). Two patients <12 yrs of age received the intermediate dose. Feasibility of GMP manufacturing of high-purity CD4LVFOXP3 cells was met. There have been no safety concerns. CD4LVFOXP3 expresses membrane tNGFR (CD271) from the same LV construct that expresses the FOXP3 cDNA, facilitating ex vivo purification during manufacturing and

in vivo traceability. Pharmacokinetics shows that CD4LVFOXP3 are detectable in blood and tissue; their phenotypic and functional stability has been confirmed at the single-cell level by CITEseq on the drug substance and ex vivo. We found that CD4LVFOXP3 maintain the T helper subsets' heterogeneity of the parental cells but express the transgene FOXP3-lv and Treg marker genes, including CCR4, CTLA4, and IL2RA and low IL7R. There was lower expression of the inflammatory cytokines IL17A, IL17F, IL22, IL15, IFNg, constrained TCR clone expansion, and cycling status. More intriguingly, we found that the most dominant subset of CD4 LV-FOXP3 cells have stem cell memory features, most likely derived from naïve CD4+ T cells. We also found that CD4LVFOXP3 cells can survive over one year in small proportion. Thus, these findings reveal that CD4LVFOXP3 products preserve their Treg-like signatures, maintain their stemness from naïve cells, and keep their identity in vivo.

Successful completion of this trial will address a significant unmet medical need while also providing proof of safety and feasibility of this novel therapy. These data could expand the application of autologous CD4LVFOXP3 to additional autoimmune disorders.

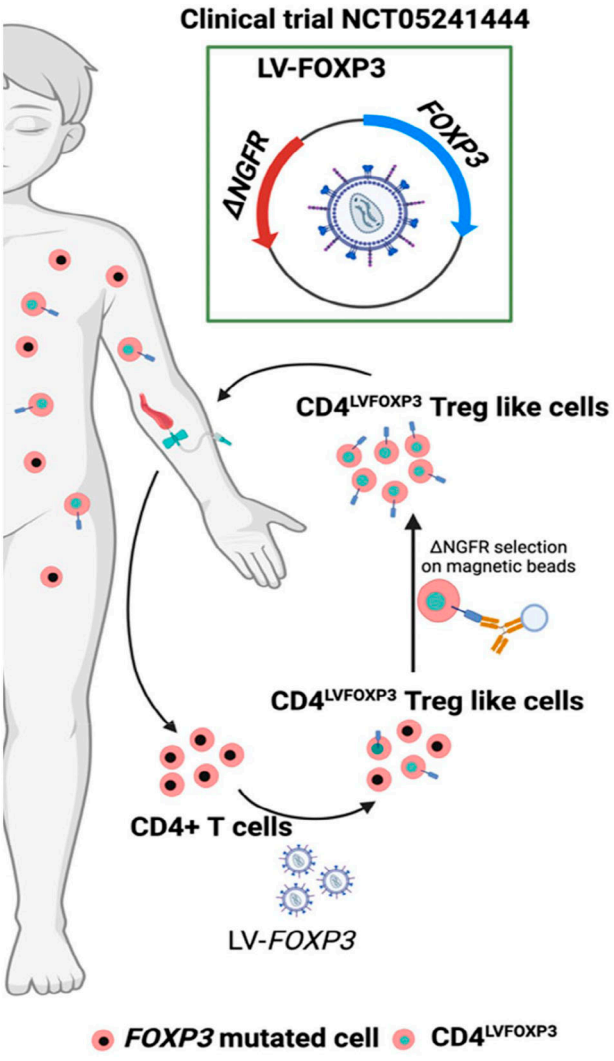

Figure 1. Features of 20 CCSs with persistent cytopenia (A), cumulative incidence of autoimmune phenomena (B), and lymphocyte subpopulations (C).

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Persistent Cytopenia After Cancer Treatment Reveals Underlying Inborn Errors of Immunity in Childhood Cancer Survivors: A Monocentric Italian Case Series

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Background: Inborn errors of immunity (IEI) are often associated with higher cancer risks, especially lymphoma, and genetic predispositions underlie many hematologic malignancies. Cytopenias following cancer treatment may occur sporadically or persist due to incomplete immune reconstitution. Recent findings suggest these abnormalities may indicate a previously undiagnosed IEI. Data on the prevalence and long-term follow-up of cytopenias in childhood cancer survivors (CCSs) remain limited.

Aim: To evaluate the prevalence of persistent cytopenias (PCs) in a cohort of CCSs followed at our late effects clinic (IRCCS Giannina Gaslini) and describe their clinical, immunologic, and genetic characteristics.

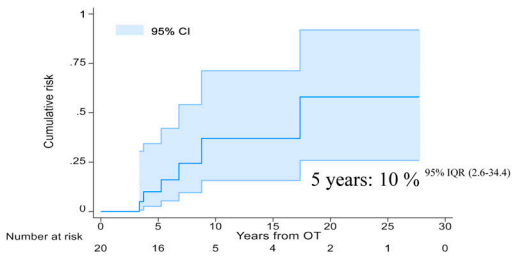
Materials and Methods: PCs were defined as those lasting over 12 months post-treatment or starting 6-12 months post-treatment and lasting over a year. CNS tumor survivors and those treated with allogenic marrow transplantation were excluded. Immunological and genetic analysis (NGS of 162 IEI genes or WES) were performed in patients with PC.

Results: Twenty (2.7%) out of 751 eligible CCSs (including 304 hematologic malignancies) showed PC, which was more common in patients with hematologic malignancies history ($p < 0.00001$). Patient characteristics and PC type are shown in Figure 1A. During follow-up, 6/20 patients developed autoimmune signs (10% incidence at 5 years, Figure 1B) at a median of 6.0 years post-treatment, 3/20 showed concomitant benign lymphoproliferation (EBV related in 1 case). Peripheral lymphocyte subsets revealed decreased B-memory and T-regulatory cells, increased activated δγ/HLADR+ T cells and B-naïve cells, and a shift to memory T cells (Figure 1C).

A

Gender, n (%)	
Males	15 (75)
Females	5 (25)
Age at cancer diagnosis, years, median (IQR)	9.9 (3.9-12.7)
Cancer diagnosis, n (%)	
Hematological malignancies	13 (65)
Lymphoblastic Leukemia	4
Myeloid Leukemia	1
Hodgkin Lymphoma	4
Non Hodgkin Lymphoma	3
Histiocytosis	1
Non-Hematological malignancies	7 (35)
Neuroblastoma	4
Ewing Sarcoma	1
Schwannoma	1
Nephroma	1
Treatment, n (%)	
Only Chemotherapy	11 (55)
Chemotherapy + Radiotherapy	5 (25)
Only Surgery	4 (20)
Monoclonal antibody only (Rituximab)	2 (10)
Cytopenia, n (%)	
Persistent since EoT	8 (40)
Onset after EoT	12 (60)*
Type of cytopenia, n	
Leukopenia	9
Neutropenia	14
Autoimmune (AIN)	3
Idiopathic (IN)	6
AIN/IN diagnosis in progress	5
Lymphocytopenia	6
Monocytopenia	6
Trombocytopenia	8
Anemia	0
*Median time after EoT years (min-max)	2.6 (1.3-8.2)
Median follow-up time after EoT, years (IQR) (min-max)	6.8 (5.2-11.8) (3.7-27.7)

B



C

	% Low values*	% Normal values*	% High values*
CD3+ (T cells)	16	79	5
CD3+CD4+ (Helper)	21	79	0
CD3+CD4+CD45RA (Naive T Helper)	**71**	29	0
CD3+CD4+CD45RO (Memory T Helper)	0	29	**71**
CD3+CD8+ (Suppressor)	21	74	5
CD3CD4CD25brCD45RA+ (T regulatory)	**95**	5	0
gamma/delta T lymphocytes	16	31	**53**
CD3HLADR+	10	42	**48**
CD19+ (B cells)	16	74	10
CD3-CD56+CD16+ (NK cells)	10	90	0
CD19CD27+ (Memory)^	**95**	5	0
CD27-CD10+-CD38+-IgD+ (Naive B)^	0	21	**79**
CD27+IgD+IgM+ (Marginal Zone B)^	**79**	14	7
CD27+IgD-IgM- (Switched Memory B)^	**57**	43	0
CD27-IgD- (Double negative B)^	0	57	**43**

*Ranges according to ages and to literature *(Morbach H et al, Clin Exper immunol 2021, van Gent et al Clinical Immunology 2008)*
**performed in 14/20*

Figure 1. Features of 20 CCSs with persistent cytopenia (A), cumulative incidence of autoimmune phenomena (B), and lymphocyte subpopulations (C).

12/20 patients were screened by genetic analysis, which in 6/12 (50%) of them showed pathogenic variants in TNFRSF13B, MAGT1, ITK, CEBPA, AIRE, and SAMD9 genes, related to auto/dysimmunity. 3/6 further developed subsequent neoplasms (SNs) (lymphomas, sarcoma, and giant-cell carcinoma).

Conclusions: In our cohort, the prevalence of PC following cancer treatment is overall low but higher in CCSs treated for hematologic malignancies, a finding consistent with the literature. PC may suggest underlying IEI, especially when associated with features like autoimmunity, peculiar immunophenotype, and lymphoproliferation. Careful and prolonged follow-up is necessary for the potential development of autoimmunity and SNs. Further studies are needed to confirm these findings and broaden their application to all CCSs with post-treatment immunologic abnormalities.

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CXCR5 as a Therapeutic Target in Autoimmune Diseases: Insights from Sjögren's Syndrome

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Introduction: CXCR5, a chemokine receptor expressed on B cell and T follicular helper (Tfh) cell, is associated with autoantibody-mediated pathogenesis in multiple autoimmune and chronic inflammatory disorders (I&I) such as SLE, RA, MS, IBD, and Sjögren's syndrome (SS). The interaction between CXCR5 and its ligand CXCL13 and subsequent formation of ectopic germinal centers have been shown to be key to disease progression. Despite its pivotal role in the CXCR5/CXCL13 signaling axis, CXCR5 remains underexplored as a therapeutic target. In this study, we hypothesize that selective depletion of pathogenic CXCR5+ B and Tfh cells is a promising treatment approach for I&I disorders associated with production of autoantibodies targeting self-antigens.

Methods: We developed HFB100204, an afucosylated anti-CXCR5 antibody designed to deplete pathogenic CXCR5+ cells through ADCC while blocking CXCL13-dependent signaling. As a case study, we leveraged HiFiBiO Therapeutics' translational single-cell platform to profile CXCR5+ immune cells in SS patients at different disease stages and evaluated CXCR5+ cell depletion by HFB100204 in vitro and in vivo.

Results: CXCR5 expression was found to be selectively enriched in autoreactive B cells and hyperactive Tfh cells in SS as the disease progresses. Distinct CXCR5+ B cells populations previously linked to autoreactive phenotypes were overrepresented in SS patients in advanced disease stages. HFB100204 demonstrated robust depletion of CXCR5+ B and Tfh cells in vitro. Notably, HFB100204 selectively depletes CXCR5+ B cells more potently than rituximab and ianalumab from human PBMCs. In vivo, HFB100204 effectively reduced CXCR5+ B and Tfh cells in blood and spleen of hCXCR5-knockin mice, suggesting that this intervention has the potential to disrupt pathological B-Tfh interactions, thus preventing autoantibody formation.

Conclusion: This study underscores the therapeutic potential of targeting the CXCR5/CXCL13 axis for I&I. Using SS as an example, we show that at a single-cell level, CXCR5 is critical for the disease progression. HFB100204 effectively depletes pathogenic CXCR5+ immune cells, including B cells and Tfh cells, offering a novel strategy for autoimmune diseases. These findings support CXCR5 as an innovative therapeutic target, addressing critical unmet needs in autoimmune disease management.

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Clinical and Analytical Validation of a NOD2 Functional Test for XIAP/XLP2 Diagnosis

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Most pathogenic variants in the BIRC4/XIAP gene lead to absent or very low XIAP protein expression distinguishable via protein staining, but missense variants may allow expression of reduced or normal levels of XIAP. Thus, normal protein levels alone cannot fully exclude possible XIAP deficiency. As such, an assay examining function is needed to complement XIAP protein expression. We present clinical and analytical validation data of a NOD2 stimulation assay for the diagnosis of XIAP functional deficiency.

Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized whole blood. Cells were stimulated for 2 h with either LPS as a positive control (signaling is independent of XIAP) or L18-MDP, which signals through NOD2 and requires XIAP for normal signaling. Cells were stained for viability and lineage markers before being fixed and permeabilized, followed by staining for TNF-α and IL-8. Results were acquired on a BD FACSLyric flow cytometer. The increase in TNF-α and IL-8 levels (delta) was calculated for LPS and MDP stimulations by subtracting levels found in untreated cells (Figure 1A).

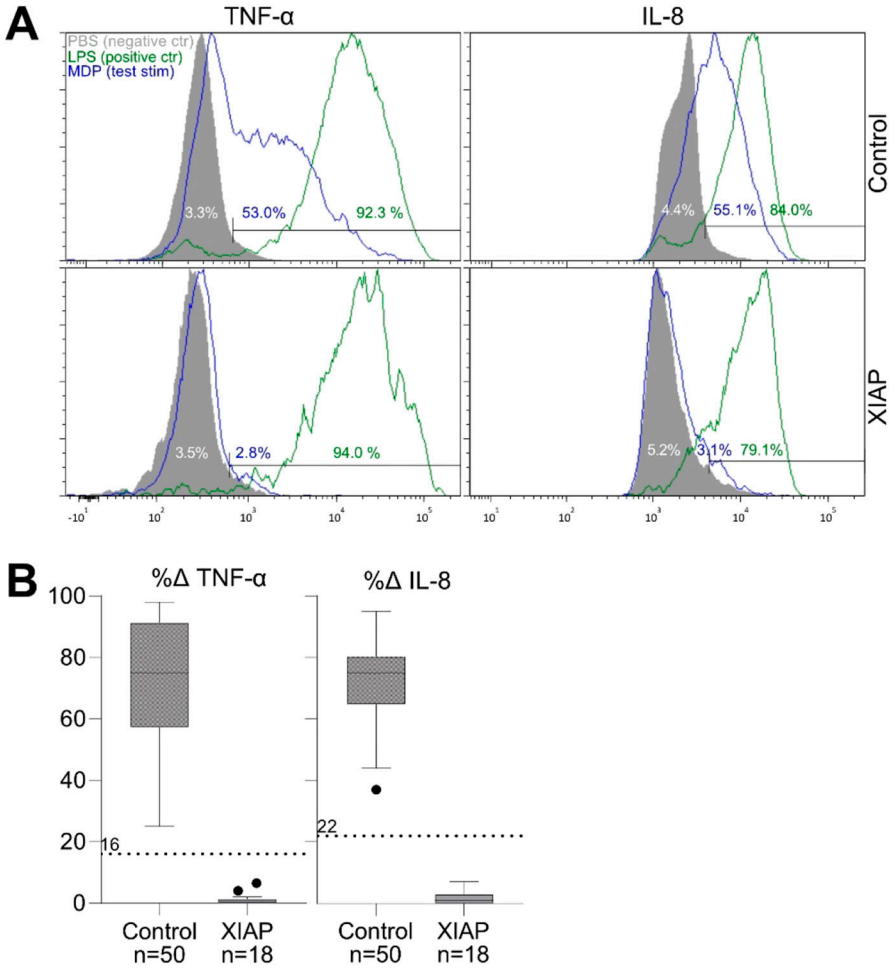

Figure 1. Functional characterization of an XIAP deficiency cohort. (A) Histograms depict monocyte responses to either PBS for mock stimulation, LPS as a positive control, and MDP as the test stimulation. Shown for a healthy adult and an XIAP patient bearing c.1141C>T, p.Arg381Ter. Percent positive cells gated displayed above each marker for both TNF-α and IL-8. (B) Tukey box plots comparing control and patient NOD2 functional readouts. Dotted lines represent calculated cutoffs to obtain 100% accuracy by ROC analysis.

A total of 19 male patients were collected, of which there were 4 sets of siblings. Age at sampling ranged between 1 month and 56 years old. For controls, we ran 50 samples between 9 and 69 years of age. XIAP expression was normal in 11% of this cohort. All patients had defective TNF-α and IL-8 upregulation upon MDP stimulation (Figure 1B). The results were reproducible upon patent resampling over several years. No trends in age or sex were noted among controls.

Our data demonstrate the importance of a functional NOD2 assay for the functional confirmation of XIAP deficiency. LPS stimulation produces robust TNF-α and IL-8 response, while response to MDP in XIAP-deficient cases is close to null. The test returned excellent accuracy and typically requires only 4-6 mL whole blood.

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Mavorixafor Inhibits Pathogenic Cxcr4 Signaling and Function in T Lymphocytes from Patients with WHIM Syndrome in vitro

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WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome is a rare, combined, primary immunodeficiency, and chronic neutropenic disorder predominantly caused by autosomal dominant gain-of-function (GOF) variants of the chemokine receptor CXCR4, resulting in impaired receptor internalization, hyperactive signaling, and enhanced chemotaxis to CXCL12. This signaling dysregulation underlies the clinical and hematologic manifestations of WHIM syndrome, such as enhanced bone marrow leukocyte retention. While effects of CXCR4 antagonists on GOF signaling in cells from individuals with WHIM syndrome have been reported, comprehensive analyses from larger patient cohorts are lacking. We assessed CXCR4 molecular functions in T lymphocytes from individuals with WHIM syndrome enrolled in the mavorixafor phase 3 trial (NCT03995108) and evaluated the potential of mavorixafor, an oral CXCR4 antagonist, to counteract molecular GOF phenotypes in vitro. For this, we first investigated the most conserved hallmark of CXCR4 GOF variants, impaired CXCR4 receptor internalization, in primary T lymphocytes from peripheral blood mononuclear cells collected pre dose. Second, ligand-induced CXCR4 signaling and chemotaxis of expanded T lymphocytes were assessed after in vitro pretreatment with mavorixafor or control. T lymphocytes from patients with WHIM syndrome showed defective receptor internalization and hyperactive signaling, including enhanced CXCL12-induced calcium flux, increased ERK, and prolonged AKT phosphorylation, consistent with enhanced chemotaxis observed in a CXCL12 gradient. Pretreatment with mavorixafor in vitro inhibited CXCL12-induced hyperactive signaling and migration of T lymphocytes. This study represents the first comprehensive characterization of CXCR4 GOF phenotypes in T lymphocytes from a large cohort of individuals with WHIM syndrome. The correction of underlying molecular defects may be linked to improved leukocyte mobilization observed in participants in the mavorixafor WHIM syndrome phase 3 trial.

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Selective JAK Inhibition Ameliorates Aire Deficiency–Driven Autoimmunity

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Background: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal recessive monogenic autoimmune disease caused by deficiency in the autoimmune regulator (AIRE) gene that manifests with multiple life-threatening autoimmune manifestations. Deficiency in AIRE results in self-reactive T cells that escape into the periphery and infiltrate organs causing injury. We recently showed that APECED is an interferon-gammopathy, as deletion of IFNg or treatment with the FDA-approved JAK1/2 inhibitor, ruxolitinib, improved autoimmunity in Aire KO mice and APECED patients.
Methods: We aimed to evaluate the efficacy of selective JAK1, JAK2, and JAK3 inhibitors relative to that of ruxolitinib to delineate the mechanistic roles of the different Janus kinase pathways in the context of APECED. Aire KO mice underwent treatment with three selective JAK inhibitors: JAK1i (itacitinib), JAK2i (CEP-33779), and JAK3i (ritlecitinib). To evaluate the efficacy of these JAK inhibitors in ameliorating autoimmunity, we performed ELISA, qPCR, immunoblot, flow cytometric, and histological analyses.
Results: JAK1-, JAK2-, and JAK3-selective inhibitors significantly decreased the accumulation of pathogenic CD4 and CD8 T cells in Aire KO mouse lungs at levels comparable with ruxolitinib. Ruxolitinib and JAK1- and JAK2-selective inhibitors resulted in more pronounced

decreases in IFNg and Cxcl9 transcripts and levels of STAT1 and pSTAT1 by immunoblot analyses relative to the JAK3-selective inhibitor in Aire KO mouse lung. Concordantly, ruxolitinib and JAK1- and JAK2-selective inhibitors exhibited greater efficacy in ameliorating tissue injury in autoimmunity-affected organs as assessed by histological analysis compared with the JAK3-selective inhibitor in Aire KO mice.
Conclusion: We show that JAK1- and JAK2-selective inhibition led to a similarly effective amelioration of IFNg-driven inflammation and tissue injury compared with the JAK1/2 inhibitor, ruxolitinib, in Aire KO mice. By contrast, although JAK3 inhibition markedly decreased lymphocytic accumulation in Aire KO mice, it appeared less effective in reducing IFNg-driven inflammation and tissue injury compared with all other tested JAK inhibitors. Our study sheds light on the differential roles of JAK inhibitors in the context of APECED-associated autoimmunity and informs future work that may help develop more selective JAK inhibitor-based treatments in APECED patients with the goal to achieve maximal efficacy and long-term safety.

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Vedolizumab Treatment in Adults with Inflammatory Gastrointestinal Disorders and Underlying Immunodeficiency

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Background: Noninfectious gut inflammation is a common manifestation of inborn errors of immunity (IEI) and can affect various segments of the gastrointestinal tract. Vedolizumab, which selectively blocks leukocyte trafficking to the gut, is approved for treatment of inflammatory bowel disease; however, there is lack of data regarding safety and efficacy in IEI. We aim to describe the experience of patients with gut inflammation related to IEI treated with vedolizumab.
Material and Methods: 4 patients >18 years old with humoral or combined immunodeficiency and gut inflammation treated with vedolizumab (weeks 0, 2, and 6, and then every 8 weeks) at a tertiary center. Clinical improvement was defined as a reduction in diarrhea reported by patients with weight gain and/or improvement of malabsorption.
Results: Case 1: 37-year-old man, combined immunodeficiency with dysregulation due to TRAF3 haploinsufficiency. He had a long-standing enteropathy with duodenal, ileal, and colonic involvement and was corticosteroids dependent. He started vedolizumab, achieving good symptomatic control. After one year of treatment, mild endoscopic activity was observed, so he added a low dose of corticosteroids, resulting in clinical improvement.
Case 2: 23-year-old man, combined immunodeficiency with dysregulation, WES negative. He presented chronic diarrhea, weight loss, and malabsorption requiring hospitalizations in context of complete villous atrophy with poor response to corticosteroids. A clear clinical response was observed after induction with 3 doses of vedolizumab.
Case 3: 49-year-old woman, CVID with autoimmune hepatitis and chronic severe colitis refractory to topical and oral corticosteroids and azathioprine. She received four doses of vedolizumab without clinical improvement, eventually developing extensive pancolitis due to CMV. She is being considered for a subsequent treatment line with ustekinumab.
Case 4: 51-year-old woman, persistent agammaglobulinemia after rituximab treatment for immune thrombocytopenia and multiple other autoimmune manifestations, WES pending. Chronic diarrhea with complete villous atrophy refractory to corticosteroids. After 5 doses of vedolizumab, she exhibited clinical and endoscopic improvement and remained free of atrophy for two years. After this period, partial villous atrophy recurred.
Conclusion: We observed a more favorable and sustained effect of vedolizumab on duodenal atrophy compared with colitis, emerging as a safe option for patients with immunodeficiency and enteropathy.

Table 1. **Clinical and immunological features.**

	Case 1	Case 2	Case 3	Case 4
Age of first symptoms (years)	15	1	38	26
Age of first gastrointestinal symptoms (years)	17	19	38	29

Table 1. **Clinical and immunological features. (*Continued*)**

	Case 1	**Case 2**	**Case 3**	**Case 4**
Extraintestinal clinical features	Recurrent RTI, warts, penile intraepithelial neoplasia, polyarthritis	Recurrent RTI, bronchiectasis, HSM, portal hypertension, Hodgkin lymphoma, short stature	Autoimmune hepatitis, esophageal candidiasis, recurrent RTI	ITP, splenectomy, thyroiditis, vitiligo, alopecia areata, CMV pneumonia, severe COVID-19
Immunoglobulin levels				
IgG (800-1700 mg/dL)	673	<200	370	<200
IgA (70-400 mg/dL)	57	<4	36	<4
IgM (50-300 mg/dL)	32	8	19	<10
IgE (0.1-100 UI/mL)	2		<0.1	<0.1
Antipneumococcal response	Absent	Poor response	Poor response	Absent
Lymphocyte subsets (cel/uL)				
CD19+ (110-570 cel/uL)	515 (22%)	8 (0.9%)	3 (0.3%)	1 (1%)
CD4+ (530-1300 cel/uL)	196 (28%)	123 (14%)	281 (36%)	358 (42%)
CD8+ (330-920 cel/uL)	413 (59%)	687 (86%)	337 (43%)	275 (32%)
CD56+ (70-597 cel/uL)	70 (3%)	75 (8.4%)	181 (21%)	221 (26%)

HSM: hepatosplenomegaly. RTI: respiratory tract infection.

Table 2. **Endoscopic and biopsy findings before and after treatment with vedolizumab.**

	Findings before treatment	**Findings after treatment**
Case 1	Duodenum: complete villous atrophy (Marsh IIIc). Active duodenitis	Duodenum: absence of villous atrophy. Active duodenitis
	Ileum: follicular hyperplasia, chronic ileitis	Ileum: follicular hyperplasia
	Colon: chronic active colitis	Colon: absence of inflammatory activity
		Rectum: focal active colitis
	Calprotectin: 2065 ug/g	Calprotectin: 838 ug/g
Case 2	Duodenum: complete villous atrophy (Marsh IIIc). Intraepithelial lymphocytosis >25%, absence of plasmocytes	Pending results
Case 3	Duodenum: absence of villous atrophy and lymphocytosis	Colon: severe active colitis, with viral inclusions
	Ileum: follicular hyperplasia, active ileitis	
	Colon: severe active chronic colitis, increased apoptosis and absence of plasmocytes	
	Calprotectin: 371 ug/g	
Case 4	Duodenum: complete villous atrophy (Marsh IIIc). Intraepithelial lymphocytosis >30%	Duodenum: absence of villous atrophy and lymphocytosis
	Ileum: follicular hyperplasia	
	Colon: absence of inflammatory activity	Colon: absence of inflammatory activity
	Calprotectin*: 332 ug/g	Calprotectin: 203 ug/g

*Normal range: 5-45 ug/g

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Defining an Activated PI3K-delta Syndrome-like Endotype Within Broader Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) is the most common symptomatic inborn error of immunity in the world. While the autoimmune and end-organ lympho-infiltrative complications that occur in patients with CVID continue to drive high morbidity and mortality, we lack available FDA-approved therapeutics to treat these noninfectious CVID-related complications. Previously, we used unbiased network clustering of noninfectious autoimmune and end-organ lympho-infiltrative complications to define a high-risk CVID patient endotype. Here, we asked whether this high-risk CVID patient endotype overlaps with the clinical spectrum of activated PI3K-delta syndrome (APDS), a rare inborn error of immunity that can clinically present as CVID and has an existing FDA-approved immunomodulator for disease management. Data including patient demographics, ICD-10 coded immunodeficiency diagnoses, ICD-10 coded noninfectious disease complications, and detailed immunophenotype were extracted from existing registry and research databases of 983 patients with predominantly antibody deficiency (PAD), which included 423 patients with CVID, and compared with 46 patients with APDS. Unbiased network clustering of noninfectious disease complications alone was sufficient to cluster APDS patients with high-risk CVID and PAD patient cohorts. Specifically, APDS patients clustered tightly with CVID patients with clinical evidence of splenomegaly, lymphadenopathy, autoimmune cytopenias, interstitial lung disease, liver disease, and gut lumen disease resembling celiac disease. Using the criterion of two or more autoimmune and end-organ lympho-infiltrative complications, we identified that 74% (N = 314) of CVID patients and 28% (N = 274) of PAD patients exhibited an 'APDS-like' phenotype. Future directions include overlapping patient immunophenotypes to determine how this impacts clinical clustering. Together, these data demonstrate that a significant proportion of CVID patients assessed at major tertiary care centers exhibit a spectrum of noninfectious autoimmune and end-organ lympho-infiltrative disease that closely resembles those observed in APDS and suggest a possible shared pathophysiology which may have therapeutic implications.

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Digging in the DIRT Since 2018: Form, Function, and Findings of a Complex Immune Dysregulation Program

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Inflammation and immune disturbance are common to the pathology of most diseases. Clinical understanding and ability to interrogate immune function lag far behind the rising number of available immune-directed therapies. Historically, diagnosis and management of patients with complex immune dysregulation is often siloed by specialty and inefficient. Building from a successful hemophagocytic lymphohistiocytosis response team, we describe our experience implementing a comprehensive, multidisciplinary dysregulated immunity response team (DIRT, colloquially) to improve the care of children with severe, recalcitrant, or otherwise complex immune dysregulation disorders.

With seed support through a competitive internal mechanism, The Children's Hospital of Philadelphia Immune Dysregulation Program (IDP) commenced in 2018, graduating to an established program in 2021. With coordination by dedicated administrators and highly specialized nurse practitioners, the IDP now staffs a year-round inpatient consultation service and four outpatient clinics per month. Inpatient service is staffed by IDP infectious disease, immunology, rheumatology, hematology, or oncology specialists. Preparation for outpatient visits is tailored to individual patient needs and includes triage, prior authorization (for testing), medical record review, and determination of which IDP specialists are needed (as above and/or gastroenterology, hepatology, dermatology, neurology, and pulmonology). In Fiscal Year '24, the IDP staffed 187 outpatient visits and 90 inpatient consultations. 36% of IDP patients traveled from >20 states outside PA/NJ and internationally.

Additional clinical accomplishments include establishment of an in-house, rapid turn-around, clinical plasma cytokine panel; a weekly "office hours" external patient discussion; a widely attended weekly case teleconference; three institutional guidance documents (MIS-C, HLH, and antimicrobial prophylaxis); contributions to three international consensus guideline projects; and treatment of nine patients on single-patient investigational new drug protocols. Research accomplishments include enrollment of >325 subjects in a biobank/registry protocol and publication of eight primary manuscripts. Education/training accomplishments include establishment of an immune dysregulation elective, conducting a yearly 10+-part "Fellows Immunology Course," hosting seven Immune Dysregulation Symposia, and receiving the first "Physician Scientist Training Program in Immune Dysregulation" award (T32AI170501). An integrated, multidisciplinary IDP is a feasible and sustainable approach to meeting the growing clinical, educational, and research challenges posed by caring for patients with complex immune dysregulation.

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Anti-Vedolizumab Abrogates False-Positive Allogeneic T and B Cell Flow Cytometry Crossmatches in Solid Organ Transplantation

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Aim: Vedolizumab is a humanized monoclonal antibody that binds to α4β7 integrin expressed on most leukocytes and is used for treatment of inflammatory bowel disease. The objective of this study was to assess the effect of recombinant anti-vedolizumab treatment in vitro on allogeneic T and B cell flow cytometry crossmatches (FCXM) in solid organ transplantation.
Methods: Serum samples from kidney transplant recipients that received parenteral therapeutic vedolizumab monoclonal antibody injection 5 days prior to collection were used in the study. All serum samples were tested for the presence of HLA donor-specific antibodies (DSA) by Luminex single antigen beads assay (Thermo Fisher-One lambda). FCXM were performed using surrogate lymphocytes and sera were treated with heat inactivation (HI, 56°C for 30 mins), dithiothreitol (DTT, 5 mM at 37°C for 15 mins), and inhibitory anti-idiotypic recombinant anti-vedolizumab antibodies (HCA292, Bio-Rad, at 0.1, 0.05, and 0.025 mg/ml at room temperature for 30 min).
Results: Parenteral administration of therapeutic vedolizumab monoclonal antibodies caused false-positive allogeneic T and B cell FCXM in the absence of HLA DSA. HI and DTT treatment of sera had no effect on the false-positive T and B cell FCXM. However, recombinant anti-vedolizumab antibodies successfully abrogated the false-positive T and B cell FCXM at 0.1 mg/ml and 0.05 mg/ml concentrations (Table 1). Anti-vedolizumab antibodies at 0.1 mg/ml concentration had no effect on the negative and positive crossmatch control serum.

Table 1.

Serum treatment	Flow cytometry crossmatch	
	T cell	B cell
Heat inactivation	positive	positive
DTT	positive	positive
Anti-vedoluzimab 0.1mg/ml	negative	negative
Anti-vedoluzimab 0.05mg/ml	negative	negative
Anti-vedoluzimab 0.025mg/ml	positive	positive

Conclusions: This is the first report showing that therapeutic administration of vedolizumab monoclonal antibodies cause false-positive T and B cell FCXM in absence of HLA DSA, which can preclude from proceeding with allogeneic transplantation. In addition, recombinant anti-vedolizumab antibodies abrogated false-positive allogeneic T and B cell FCXM.

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Germline Mutation Leading to a Pathogenic STAT3 Gain of Function

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Introduction: A STAT3 gain-of-function (GOF) mutation leads to enhanced STAT3 signaling, leading to generalized autoimmunity caused by impaired regulatory T cell development and enhanced Th17 cell function. It is characterized by fevers, lymphoproliferation, recurrent infections, hypogammaglobulinemia, low IgE levels, and multiorgan autoimmunity, including type 1 diabetes and enteropathy.
Case Description: An 11-year-old male with a history of recurrent otitis media and asthma presented with two weeks of intermittent umbilical pain, non-bloody nonbilious diarrhea, and emesis. On physical exam he was afebrile, had splenomegaly (13.8 cm), and generalized lymphadenopathy. Infectious and oncologic evaluation was negative, including a cervical lymph node biopsy. Immune workup was notable for hypogammaglobulinemia, including IgG 457 [568-1490 mg/dL], IgA 28 [58-358 mg/dL], IgM 30 [48-226 mg/dL], IgE 4 [≤100 KU/L], unprotected vaccine titers, and CD4+ lymphopenia to 504 [650-1500 cell/μL]. Given his profound lymphadenopathy, autoimmune lymphoproliferative syndrome (ALPS) screening was pursued, which revealed an increased double-negative T cell population; however, caspase-10, FAS, and FASLG gene sequencing were normal. Whole-exome sequencing revealed a pathogenic, dominant, and heterozygous GOF mutation in STAT3 (variant c.2144C>T [p.Pro715Leu]). Of note, family history of this child's 43-year-old father was positive for autoimmune lung (with a partial lung resection), intestinal, and liver disease, followed since childhood as "idiopathic" multiorgan disease. The father's genetic screening returned positive with the same GOF mutation in STAT3.
Discussion: This case highlights the need to consider STAT3 GOF in patients with multiorgan autoimmune disease, lymphadenopathy, hypogammaglobulinemia with specific antibody deficiency, and T cell lymphopenia with low serum IgE levels. Low serum IgE levels in patients can be a simple and cost-effective way to distinguish between STAT3 GOF versus loss of function, seen in Job Disease.

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Dissecting the HLH Immune Synapse: Critical Roles for Termination, Cytokine Intensity, and Target Cell Death

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome arising in many contexts. Its underlying mechanisms are often unclear, but defective granule-mediated cytotoxicity (familial HLH) and excess IL-18 (macrophage activation syndrome, MAS) provide important and complementary clues. Mounting evidence suggests the various genetic, infectious, malignancy-associated, and rheumatic causes of HLH all converge on cytotoxic T lymphocyte (CTL) hyperactivation and overproduction of IFNγ. Current clinical guidance emphasizes the need to address multiple HLH contributors but is challenging without a more functional mechanistic framework.

Methods: We developed an in vitro system to simultaneously quantify how multiple parameters of the murine CTL immune synapse (CTL-IS) responded to various HLH-related stimuli or specific cell death pathway inhibitors. We defined IS duration in CTL/target cell dyads as the time between CTL Ca++ flux and target cell PI uptake by live-cell microscopy. We also measured cytokine levels longitudinally in co-culture supernatants. We assessed the effects of cell death inhibition on HLH in vivo in Il18tg and Prf1-/- mice infected with LCMV(Armstrong).

Results: Perforin haploinsufficiency prolonged IS duration and increased IFNγ production, demonstrating the system's sensitivity. Target cell death resistance (immortalization or caspase inhibition) similarly prolonged CTL-IS duration and cytokine production, substantiating "Impaired IS Termination" as a category of HLH contributors. By contrast, strong CTL activation, via TCR or IL-18 signaling, increased IFNγ secretion but accelerated target cell death. This pattern, which we call "CTL Cytokine Production Intensity," has been observed in CART IS and may represent a distinct category of HLH contributors. Surprisingly, IL-18 exposure drove some CTL-IS to terminate, even in the absence of perforin, via a morphologically inflammatory form of cell death inhibitable by blocking necroptosis. In vivo, RIPK1 inhibition ameliorated virus-triggered HLH in Il18tg but not Prfl-/- mice.

Conclusions: By quantifying CTL-IS duration, cytokine production, and mode of cell death, we modeled multiple HLH contributors and their interactions and identified three HLH mechanistic categories: impaired IS termination, intense CTL cytokine production, and inflammatory target cell death. Integrating the inputs and outcomes of a hyperinflammatory CTL-IS may provide a useful framework for understanding, predicting, or treating HLH in its many forms.

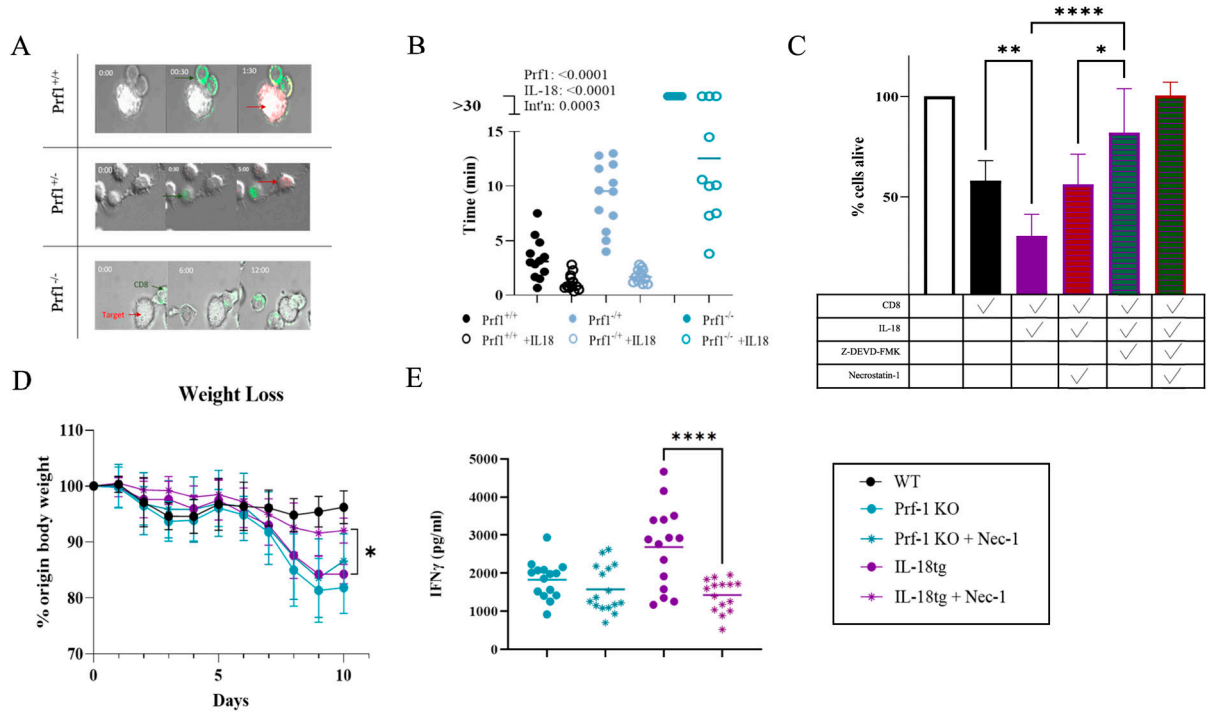

Figure. HLH contributors fall into three mechanistic categories: impaired IS termination, CTL cytokine production intensity, and inflammatory target cell death. (A) Still images from live cell microscopy of the CTL-IS. Green = Ca^{++} flux (fluo-4); red = target cell death (PI). (B) CTL-IS duration by *Prf1* genotype with and without exogenous IL-18. (C) In vitro target cell death assay with IL-18, caspase-3/7 inhibition (Z-DEVD-FMK), and necroptosis inhibition (necrostatin-1). (D) Weight loss and plasma IFNg (Day 10) following LCMV Armstrong infection of the indicated mice with and without inhibition of necroptosis (Nec-1).

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A Cdc42 C-terminal Mutation Associated with Life-Threatening Hyperinflammation in Humans Is Well-Tolerated in Mice

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Primary immune disorders offer important pathoetiologic insights into human immune dysfunction. Often, studying pathogenic human mutations in murine systems provides an excellent system for probing those mechanisms. Recently, multiple groups found that de novo arginine-to-cysteine missense mutations at position 186 of the human cell division cycle (CDC42) gene, near its C terminus, were associated with a life-threatening hyperinflammatory disorder called NOCARH (neonatal onset of pancytopenia, autoinflammation, rash, and episodes of hemophagocytic lymphohistiocytosis (HLH). NOCARH patients demonstrate excessive activation and expansion of macrophages and CD8+ T lymphocytes. In vitro, human CDC42^cterm mutants drove cell-intrinsic hyperactivation of the pyrin inflammasome. To better understand the immunobiology of NOCARH, we used CRISPR-Cas9 editing of C57Bl/6 mouse embryos to introduce the R186C transition in murine Cdc42, which is amino acid identical to human. We were successful in generating founders harboring mosaic R186C and R186F alleles, and these alleles transmitted to the germline of offspring upon breeding to wild-type mice. Both R186C and R186F heterozygous and homozygous mice appeared viable, fertile, and were similar to wild-type littermates in growth and development. Mice harboring the mutated alleles (even in homozygosity) also responded to transient LCMV infection similarly to WT. In vitro, activation of the pyrin inflammasome in bone marrow–derived macrophages (BMDM) was unaffected by the presence of Cdc42^R186C. However, murine pyrin lacks a B30.2 domain present in humans, and this domain is the site of many classical Familial Mediterranean Fever mutations. However, BMDM pyrin activation was unaffected by Cdc42 genotype even in cells from mice also expressing a humanized mouse pyrin allele (Mefv^B30.2). Murine express an alternative Cdc42 transcript in CNS tissues that utilizes an alternative exon 6 and therefore would not contain the engineered mutation. However, we found no change in the low expression of this alternative transcript in blood cells even in Cdc42^R186C homozygous mice. These data suggest critical differences in the regulation mouse and human CDC42 that, if understood, could identify novel ways of regulating CDC42^cterm-driven inflammation in NOCARH patients.

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X-Linked CGD Carrier State in a Down Syndrome Girl

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Introduction: Cutaneous infections are a common concern in individuals with Down syndrome, who often present with recurrent skin lesions such as folliculitis, furunculosis, and impetigo. Similarly, carriers of hemizygous variants in the CYBB gene, associated with X-linked chronic granulomatous disease (CGD), may also be more susceptible to skin infections. This case describes a female patient with both conditions, contributing to her vulnerability to recurrent skin infections.

Case Description: A 10-year-old girl with trisomy 21 was referred for immunological evaluation due to recurrent furuncles and abscesses in the axillary and inguinal regions, requiring frequent antibiotic treatments. Laboratory investigations showed normal neutrophil counts, as well as normal levels of T, B, and NK lymphocyte subpopulations, serum immunoglobulins, and antibody responses to vaccine antigens. A dihydrorhodamine (DHR) assay was performed with abnormal results. The histogram analysis revealed a bimodal pattern, consistent with a carrier status for X-linked CGD, and a second test confirmed this finding, with similar results. Genetic testing (NGS sequencing) identified a heterozygous deletion of 31 genes on the X chromosome (Xp21.1-p11.4), including CYBB.
Conclusion: Mutations in the CYBB gene cause X-linked CGD, the most common form of this phagocyte dysfunction. Female carriers can be identified by the bimodal pattern observed in the DHR assay. Although often asymptomatic, female carriers who present with a low percentage of neutrophils with normal superoxide production may present with a CGD-like phenotype, showing infectious, inflammatory, and autoimmune manifestations. The identification of carrier status in this girl with Down syndrome was crucial for managing and preventing further infections. Additionally, this finding allows for monitoring other possible complications and holds particular significance for genetic counseling.

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Hematologic and Clinical Characteristics Distinguishing Persistent and Transient Idiopathic T Cell Lymphopenia

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Objective: Newborn TREC screening has identified infants with idiopathic T cell lymphopenia (TCL) with no known associated genetic factors. By convention, lymphopenia resolves by 12 months of age in transient TCL. We aim to characterize demographic, laboratory, maternal and perinatal health characteristics that differentiate infants with transient vs. persistent idiopathic TCL.
Methods: A single-center retrospective analysis was performed on patients born from September 2010 through August 2021. Chart review was performed through August 2022 on 53 eligible infants with abnormal TREC screening at corrected gestational age 37 weeks or greater. Descriptive statistics were calculated for initial TREC levels and T cell lymphocyte counts at initial referral. Two-sample t-tests and Wilcoxon rank-sum tests were used to assess continuous data. Fisher's exact test assessed associations between transient and persistent TCL patients and selected health characteristics and risk factors of both mother and baby.
Results: When comparing the percentage of CD3 cells out of total lymphocytes, transient TCL babies demonstrated higher percentages than persistent TCL babies (61.1 +/- 13.4% and 48.5 +/- 14.6%, p = 0.002). Absolute CD3 levels were higher in transient compared with persistent (2011.5 +/- 678.7 cells/μL vs 1279.5 +/- 539.6 cells/μL, p < 0.0001). Percent of CD4 of total lymphocytes were higher in transient compared with persistent TCL babies (42.7 +/- 12.6% vs 34.5 +/- 12.1%, p = 0.02), in addition to percent of CD8 of total lymphocytes (17.5 +/- 6.0 % vs 13.1 +/- 5.1%, p = 0.006). Absolute lymphocyte counts on a concurrent CBC sample were also higher in transient (4.2 +/- 1.4 K/μL vs 3.1 +/- 1.2 K μL, p = 0.005) than persistent TCL subjects. Moreover, transient TCL patients were less likely to be on any medications or supplements compared with their persistent counterparts: 18/25 (72%) of those taking medications were persistent compared with 10/28 (35%) transient subjects (p = 0.013). No other statistically significant associations were discovered.
Discussion: Babies with idiopathic TCL show distinct hematologic characteristics on initial screening that could predict duration of lymphopenia. The use of medications is associated with longer duration of disease; however, the reasons for this are unclear.

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FOXI3 Variant Associated with Persistent T Cell Lymphopenia

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FOXI3 is a transcription factor essential for pharyngeal arch development, with certain variants linked to autosomal dominant craniofacial microsomia. Emerging evidence implicates specific FOXI3 mutations in thymic hypoplasia and lymphopenia, akin to 2p11.2 deletions involving the FOXI3 locus.

We describe a full-term female infant identified through newborn screening with low TREC levels, subsequently referred for immunologic evaluation. She demonstrated a low absolute number of TREC copies, moderately decreased CD4 (~600 cells/μL), and CD8 (~200 cells/μL) T cell counts with preserved functional responses. Additional findings included mild hypogammaglobulinemia and mild B cell lymphopenia age-appropriate class-switched memory B cells. Genetic analysis revealed a missense variant of uncertain significance in FOXI3 (c.512T>C and p.Ile171Thr) within the DNA-binding domain, alongside variants in DNAAF4 (heterozygous frameshift) and G6PD (pathogenic). Cytogenomic studies were unremarkable.

We propose FOXI3 haploinsufficiency as a potential mechanism underlying her T cell lymphopenia. At 20 months of age, she remains clinically stable on trimethoprim-sulfamethoxazole prophylaxis without significant infections, and live viral vaccines have been withheld.

This case highlights the potential role of FOXI3 in thymic function and T cell development. The long-term prognosis remains uncertain, underscoring the need for further biochemical and functional studies to clarify the pathogenicity of FOXI3 variants and optimize clinical management strategies.

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A Hyperferritinemia Screen to Aid Differentiation of Hyperinflammatory Disorders

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High ferritin is an important and sensitive biomarker for the diverse and deadly group of cytokine storm syndromes grouped together under the term hemophagocytic lymphohistiocytosis. Early identification of the syndrome and its contributors are critical to guiding targeted treatments and preventing immunopathology, morbidity, and mortality. Unfortunately, we lack specific diagnostic biomarkers, which complicates etiologic workup and delays targeted intervention. Through implementing a hyperferritinemia alert system, we hoped to identify what diagnoses are associated with hyperferritinemic, collect the earliest samples for research purposes, and test these samples for relevant biomarkers. We instituted an alert system at UPMC Children's from June 1st, 2017, to June 30th, 2019, wherein serum ferritin >1000 ng/mL triggered via real-time chart review and biobanking of remnant samples from willing patients deemed to have "inflammatory hyperferritinemia (IHF)" (Figure 1). From consenting patients, we extracted relevant clinical data; retrospectively classified patients by etiology into infectious, rheumatic, or immune dysregulation; measured certain serum biomarkers (total IL-18, IL-18-binding protein, and CXCL9); and subjected a subgroup of samples to a 96-analyte O-link biomarker screen. The alert system identified 181 patients with hyperferritinemia, 30.5% of which had IHF (Figure 2A). Of the IHF patients, the majority had infection, followed by immune dysregulation, with the least common cause being rheumatic—all Still's (Figure 2A). Highly elevated total IL-18 levels were distinctive to Still's with or without MAS compared with other IHF, whereas CXCL9 did not differentiate IHF subcategories (Figure 2C). Other lab values—triglycerides, AST, platelets, and fibrinogen—did not differentiate different causes of IHF. Principal component analysis of a 96-analyte biomarker screen showed distributed elevation of proteins associated with T cell activation and IFNγ activity (e.g. granzyme B and CXCL9) in all IHF samples compared with healthy controls. Samples from patients with hyperferritinemic sepsis were distinctively lower in proteins involved in vessel homeostasis (e.g. ANGPT-1 and VEGFR-2) compared with other IHF subgroups and healthy controls (Figure 3). This IHF study proved a variety of diagnoses are associated with hyperferritinemia, enabled early sample collection, validated prior observations about the specificity of IL-18, expanded our understanding of IHF heterogeneity, and suggested a unique hyperferritinemic sepsis signature.

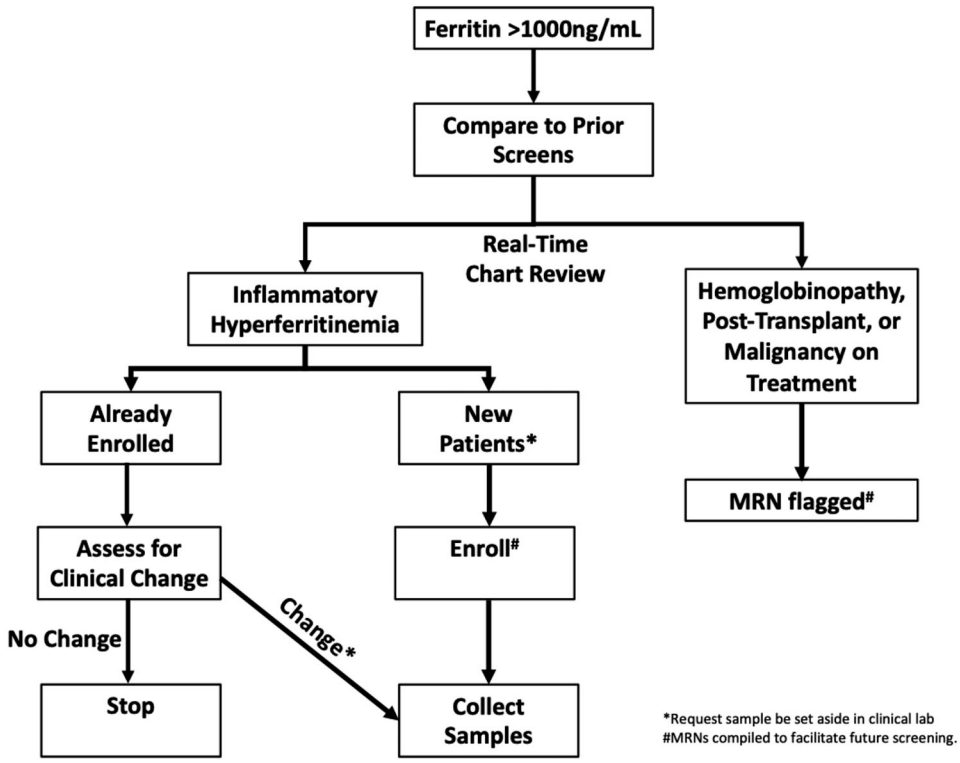

Figure 1. Steps in the hyperferritinemia screening protocol.

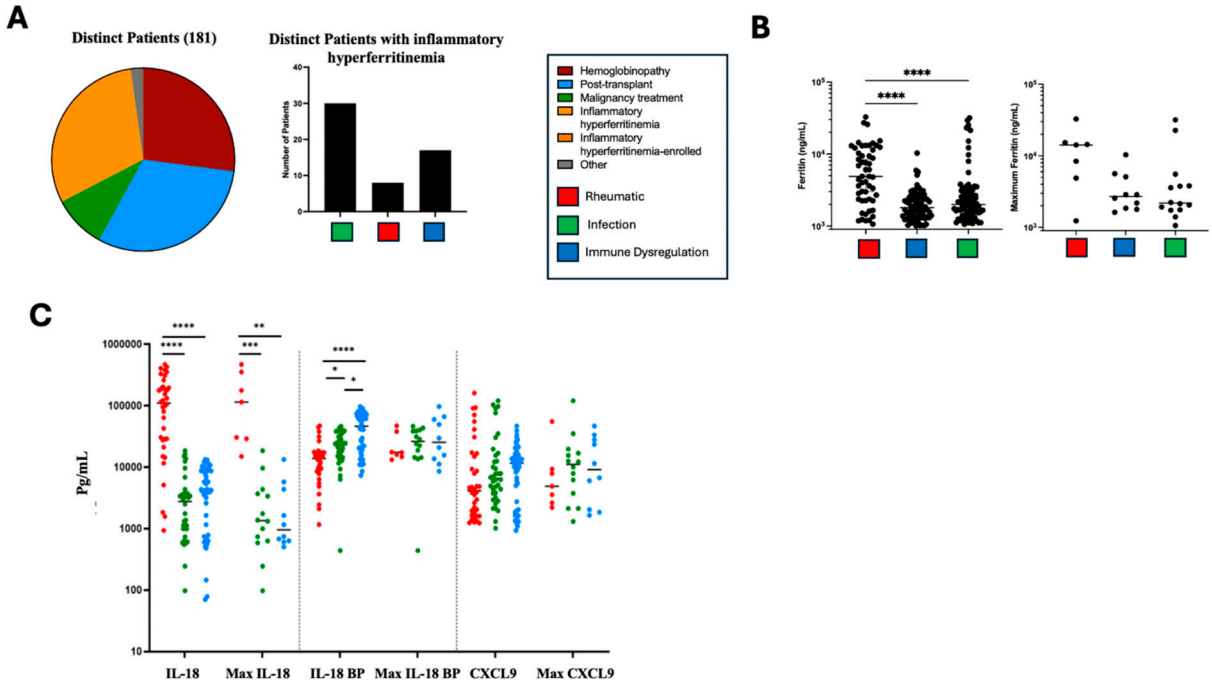

Figure 2. Clinical diagnosis and laboratory characteristics of patients with positive ferritin screens. A. Distribution of distinct patients triggering alerts by disease category and bar graphs display the number of distinct patients representing inflammatory hyperferritinemia subgroup. B. Distribution of ferritin values and maximum ferritin value per distinct patient by subgroup of inflammatory hyperferritinemia. C. IL-18, IL-18BP, and CXCL9 levels by subgroup of inflammatory hyperferritinemia. Patients with rheumatic disease have significantly higher IL-18 levels ($P < 0.001$ for both) and significantly lower IL-18BP levels ($P < 0.05$, $P < 0.0001$, respectively) compared with those with infection or immune dysregulation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ Kruskal-Wallis with Dunn's post-test; only comparisons with $p < 0.05$.

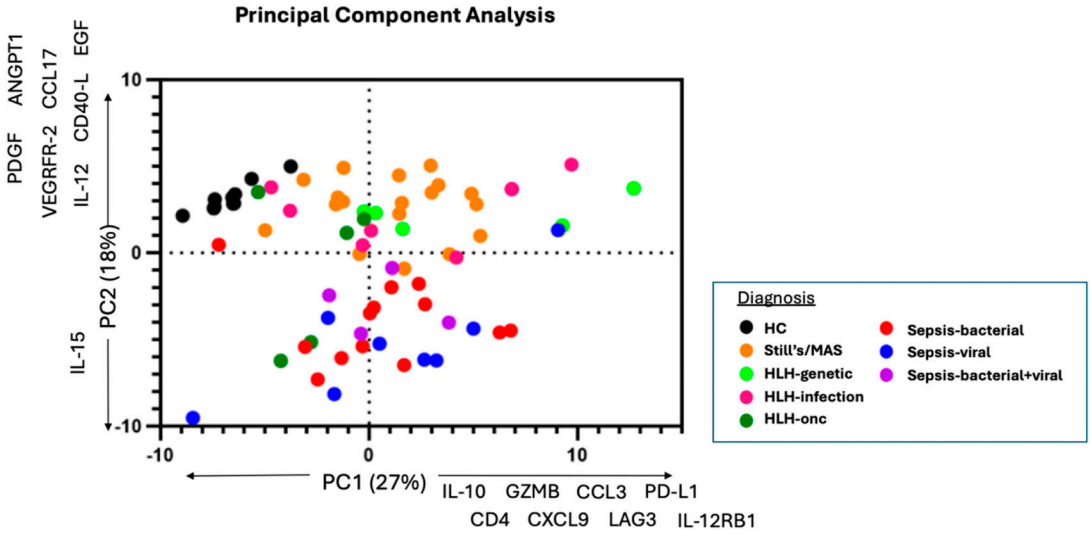

Figure 3. Biomarker screen using Olink. Principal component analysis shows unsupervised clustering of analyte NPX values with PC1 accounting for 27% of the variability and PC2 accounting for 18%. The analytes with the highest absolute value contribution to PC loading are listed on their respective axes. PC1 separate hyperferritinemic samples from healthy controls. PC2 separate hyperferritinemic sepsis samples from all other hyperferritinemic samples and healthy controls. Abbreviations: PDGF = PDGF subunit B.

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Novel Physiology and Imaging Approaches for Enhanced Detection of Lung Disease in Common Variable Immunodeficiency

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Background: Common variable immunodeficiency (CVID) is an inborn error of immunity (IEI) characterized by hypogammaglobulinemia and impaired specific antibody responses. This fundamental crippling of immunity predisposes affected individuals to respiratory infections, inflammation, and malignancy, all of which contribute to CVID-associated lung disease. Early detection and treatment of lung disease in individuals with CVID is crucial for reducing both morbidity and mortality. However, existing diagnostic techniques carry limitations, ranging from the radiation exposure associated with computed tomography (CT) to the insensitivity of pulmonary function tests (PFTs).

Objectives: We aimed to assess the feasibility and sensitivity of novel lung monitoring tools (multiple breath washout [MBW] and hyperpolarized 129-xenon magnetic resonance imaging [XeMRI]) in individuals with CVID and known lung disease, compared with CT and PFTs.

Methods: MBW and XeMRI tests were performed during a single visit, and CT scan and PFT results were abstracted from clinical documentation within 3 months of the study visit. The MBW test assesses the gas clearing efficiency of the lungs by measuring the rate of clearance of a tracer gas over repeated cycles of free breathing (primary outcome is the lung clearance index [LCI], where a higher value reflects abnormal pulmonary physiology). XeMRI measures regional lung ventilation and gas exchange using hyperpolarized xenon gas as a contrast agent. Ventilation defect percent (VDP) serves as a whole-lung measure of ventilation inhomogeneity.

Results: We describe a cohort of five individuals with CVID and known lung disease, defined as bronchiectasis or interstitial lung disease on CT scan. Only one was classified as abnormal based on pulmonary function tests (PFTs). In contrast, 4/5 (80%) individuals were identified as abnormal through the MBW test; all five participants exhibited an abnormal VDP (Table 1).

Table 1. **CVID participant clinical info and lung function data compared with thresholds of normal. HC = healthy control; BE = bronchiectasis; ILD = interstitial lung disease; FVC = forced vital capacity; FEV_1 = forced vital capacity in one second; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for carbon monoxide; LCI = lung clearance index; VDP = ventilation defect percent. PFT and MBW z-scores are calculated using the reference equations from the Global Lung Function Initiative. Abnormal results are considered z-scores: <-1.65 (for PFTs) and >1.65 (for MBW). A VDP greater than 1% is considered abnormal, based on a threshold set in previous work.**

CVID Participant Data, Compared to Thresholds of Normal					
Participant	**1**	**2**	**3**	**4**	**5**
Clinical Info					
Age	35	22	34	38	56
Sex	Male	Male	Male	Male	Male
Lung Disease	BE/ILD	BE	ILD	ILD	BE
PFTs $_{z\text{-score}}$					
FVC	0.04	0.62	-2.60*	0.57	1.60
FEV1	1.37	0.98	-3.27*	-0.29	1.18
TLC	-1.33	0.28	n/a	0.44	1.10
DLCO	-0.34	-0.01	-5.26*	-0.28	-0.01
MBW $_{z\text{-score}}$					
LCI	1.88*	1.27	7.71*	1.92*	1.95*
XeMRI					
VDP (%)	1.82*	1.93*	6.26*	1.88*	1.92*

*denotes above/below the threshold of normal.

Conclusions: These findings illustrate that MBW and XeMRI can detect lung pathology in CVID patients overlooked by standard PFTs and without the radiation risk of CT scans. These novel modalities may, in the future, offer additional screening tools for clinicians to monitor for lung disease in this high-risk population, potentially providing an opportunity for earlier diagnosis and treatment.

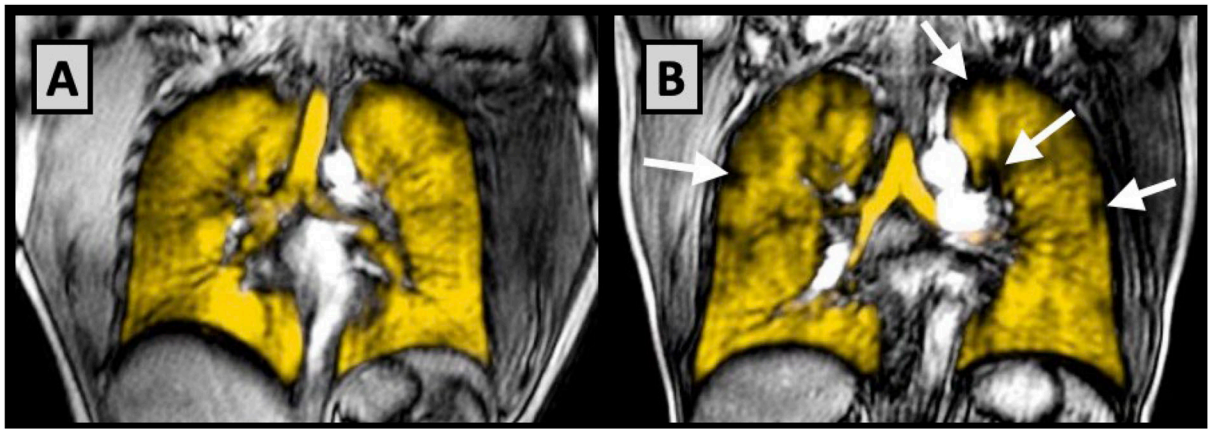

Figure 1. Representative images of ventilation from hyperpolarized xenon MRI. Yellow colored image is the xenon MRI signal overlaid on top of the structural MRI proton image. (A) A healthy 32-year-old participant (VDP = 0.37%) and (B) CVID participant 1 with CT-diagnosed interstitial lung disease and bronchiectasis (VDP = 1.82%). Arrows indicate regions of defective ventilation.

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Biallelic DUOX2 Variants and the Link to Very Early-Onset IBD

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Introduction: Very early-onset inflammatory bowel disease (VEO-IBD) involves children less than 6 years of age presenting with IBD. These patients are more likely to have inborn errors of immunity. We present a child with VEO-IBD, found to have compound heterozygous variants in the DUOX2 gene that expands on the rare association of VEO-IBD with DUOX2 insufficiency.

Case Description: A 5-year-old male presented with six months of watery diarrhea, with labs notable for thrombocytosis, elevated CRP, and fecal calprotectin to 1430 [ref ≤ 49 µg/g]. Endoscopy and colonoscopy with biopsy revealed intraepithelial lymphocytosis in the duodenum, eosinophilic infiltrate in the stomach, esophagitis without eosinophilia, and chronic active ileitis with eosinophils of 65/hpf in the terminal ileum, consistent with a diagnosis of Crohn's disease. The patient underwent immune phenotyping given his young age, which revealed elevated sIL2R, IL-17, IL-5, IL-13, IL-10, and IL-6, T cell lymphocytosis, and a normal neutrophil oxidative burst. Targeted genetic sequencing revealed two heterozygous variants in the DUOX2 gene: one maternally inherited likely pathogenic splice site variant, c.2922-14_2925del; and one paternally inherited variant of uncertain significance (VUS), c.1528C>T (p.Arg510Trp). The VUS is within the peroxidase-like region of the gene, which plays a crucial role in enzyme function, has a high CADD score of 25, and has a GnomAD allelic frequency of only 0.001%, suggesting possible pathogenicity. The patient is currently doing well on infliximab, with interval normalization of his cytokines.

Discussion: The DUOX2 gene encodes for dual NADPH oxidase (DUOX), which is responsible for the release of hydrogen peroxide as part of the innate immune defense of gut epithelial cells. In mice, DUOX2 has been shown to play an integral role in maintaining immune homeostasis in the gut biome, with knockout models showing elevated IL-17C levels in the ileum. There are few reported cases describing the association of compound heterozygous variants in DUOX2 in patients with VEO-IBD, with this being the fourth patient, to the best of our knowledge. This case highlights the importance of further research to better understand the role of this gene in the development of inflammatory bowel disease.

Table 1.

Diagnostics	Value
Cytokine panel	IL-2 <2.1 (ref range ≤ 2.1)
	IL-2R 2259.3 (ref range 175.3 - 858.2)
	IL-12 <1.9 (ref range ≤ 1.9)
	INF- γ <4.2 (ref range ≤ 4.2)
	IL-4 <2.2 (ref range ≤ 2.2)
	IL-5 19.1 (ref range ≤ 2.1)
	IL-10 11.1 (ref range ≤ 2.8)
	IL-13 2.5 (ref range ≤ 2.3)
	IL-17 5.5 (ref range ≤ 5.5)
	IL-1β <6.5 (ref range ≤ 6.7)
	IL-6 6.3 (ref range ≤ 2.0)
	TNF-α 2.5 (ref range ≤ 7.2)
Immunoglobulins	IgA – 69 (ref range 21 – 144)
	IgE – 4680 (ref range 2 – 524)
	IgG – 734 (498 – 1332)
	IgM – 82 (ref range 31 – 63)

Table 1. **(*Continued*)**

Diagnostics	Value
Lymphocyte subset panel	Absolute CD3 3080 (ref range 1400 – 3700)
	Absolute CD4 1969 (ref range 700 – 2200)
	Absolute CD8 876 (ref range 490 – 1300)
	Absolute CD45RA 1505 (ref range 430 – 1500)
	Absolute CD45RO 652 (ref range 220 – 660)
	Absolute HLADR 660 (ref range 50 – 180)
	Absolute CD19 594 (ref range 390 – 1400)
	Absolute CD20 552 (ref range)
	Absolute NK 170 (ref range 130 – 720)
EGD/Colonoscopy	Duodenum - Intraepithelial lymphocytosis
	Esophagus mid and distal – esophagitis up to 2 eos/hpf
	Esophagus upper – esophagitis up to 1 eos/hpf
	Chronic active ileitis with eosinophils (up to 65/hpf)
Neutrophil oxidative burst	Normal granulocyte dihydrohodamine fluorescence suggesting normal NADPH oxidase activity
Primary immunodeficiency panel	1. *DUOX2*
	a. c.2922-14_2925del (splice site). Het. Likely pathogenic. GnomAD AC 99. CADD 31.
	b. c.1528C>T (p.Arg510Trp). Het. VUS. GnomAD AC 3. CADD 25. Peroxidase-like region (mediates peroxidase activity).
	2. *FOXI3*
	a. c.713G>A (p.Arg238Gln). Het. VUS. GnomAD AC 3. CADD 28.8. Associated with T cell lymphopenia. Not clinically relevant.
	3. *MS4A1*
	a. c.352A>C (p.Ile118Leu). Het. VUS. CADD 17.01. Conflicting in silico prediction models. GnomAD AC 71. Associated with CVID. Not clinically relevant.
	4. *POLD1*
	a. c.520C>T (p.Arg174Trp). Het. VUS. Associated with AD mandibular hypoplasia, deafness, progeroid features and lipodystrophy and AR T cell immunodeficiency. GnomAD AC 12. Not clinically relevant.

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Trisomy 21 Promotes an Inflammatory Hyperresponsiveness in the Brain and Modulates Transcriptional Regulation in a Cell Type–Specific Manner

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Patients with type I interferonopathies, a collection of disorders leading to elevated levels of type I interferon (IFN), have a neuropathological hallmark of basal ganglia calcification thought to result from persistent IFN-dependent inflammation. Similar calcification patterns have been detected in Down syndrome (DS) individuals as young as one year of age and worsens over time, implying that the underlying mechanism begins early and progresses throughout development. Neuropathological studies have identified many patterns of abnormal development in DS brains, including hypocellularity, defective oligodendrocyte differentiation and function, and, of particular interest to us, elevated astrocyte counts and altered microglial morphological phenotypes. We hypothesize that the type I IFN receptor, encoded by IFNAR1/2, which is triplicated in DS as it is on chromosome 21, creates a pro-inflammatory environment that results in calcification, altered development, and disorganization of the fetal brain. Recently, it has been shown that there is a population of basally IFN-I–responsive microglia that express interferon-stimulated genes (ISGs) in

the developing brain of mice; this population can expand in response to developmental trauma, and similar microglia have been implicated in Alzheimer's pathophysiology in both mice and humans. It is possible that DS brains have an expanded population of these microglia and/or other populations of CNS cells with heightened type I IFN responsiveness, even in the absence of acute stressors.

To evaluate causes and effects of inflammation during development in DS, we have generated hiPSCs from patients and typical controls and have used them to generate astrocytes and microglia. We have shown that DS astrocytes are hyperresponsive to stimulation with IFN-α2b and have further conducted bulk RNA sequencing on fibroblasts, astrocytes, and microglia with or without IFN stimulation. We have found that the transcriptional signature in fibroblasts and astrocytes differs greatly between DS and CT as well as between cell types. Microglia depict a less robustly altered transcriptome. Further, IFN-α2b treatment produces a predictable, dose-dependent increase in expression of ISGs that is more pronounced in DS. Overall, our results indicate that IFN-signaling in the DS brain can result in dramatic transcriptional dysregulation in a cell type–specific manner.

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Determining the Genetic Drivers of Diffuse Large B Cell Lymphoma 30 Years After Gamma Retroviral Gene Therapy for Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency

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In 1993, a newborn with adenosine deaminase–deficient severe combined immunodeficiency (ADA-SCID) received investigational gene therapy with autologous cord blood cells transduced with a gammaretroviral ADA vector infused without conditioning (PMCID: PMC3013367). Low-level engraftment ensued, but without clinical benefit, and the patient was maintained on chronic ADA enzyme replacement therapy. At age 30 years, they developed diffuse large B cell lymphoma (DLBCL) that has been studied to determine whether insertional mutagenesis contributed to clonal proliferation.

ADA-SCID was diagnosed prenatally due to a positive family history; cord blood was harvested at delivery and transduced with LASN gammaretroviral vector, with cells reinfused at four days of age. The patient received IVIG until age 19 years and ADA enzyme replacement therapy (ERT, Adagen followed by Revcovi) for 27 years, when they chose to discontinue treatment. At 30 years, they resumed ERT, but presented with pancytopenia, sepsis, liver and lung granulomas, cholestasis, and lymphadenopathy. To address persistent lymphopenia, ERT was increased, but signs of hemophagocytic lymphohistiocytosis ensued, after which metastatic DLBCL was diagnosed. Despite remission with chemotherapy, the patient developed multiorgan dysfunction, elected hospice care and died within a few months.

At 5 years of age, the patient had maintained detectable gene marking in 1% of PBMC, 0.01-0.1% of monocytes and granulocytes, 1% of T cells, and 0.1% of B cells (PMCID: PMC3777239). With the recent diagnosis, analysis of bone marrow and lymph node, both with high proportions of malignant cells, revealed low transgene copy number (0.05 and 0.11/cell, respectively). Insertion site sequencing showed no vector incorporation near genes previously implicated in malignancy in gene therapies. Capture-based next-generation sequencing of 529 cancer genes revealed pathogenic mutations in ARID1A, NFKBIE, GNA13, and DUSP2, all associated with DLBCL, but not found among the patient's insertion sites. Thus, our patient's lymphoma was not a result of insertional mutagenesis but could reflect an intrinsic cancer diathesis in ADA deficiency and/or defective immune surveillance, recurrent infections, and impaired organ function. Patients with ADA-SCID require long-term monitoring for immune status and malignancy regardless of whether primary treatment is with chronic enzyme replacement, allogeneic transplantation, or gene therapy.

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Serial Management of Anti-Interferon-γ Autoantibodies: Lessons Learned

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Introduction: Loss of interferon-γ (IFN-γ) function through the development of neutralizing autoantibodies results in a late-onset immunodeficiency characterized by disseminated opportunistic infection. While rare, there is a higher prevalence in patients of Southeast Asian ancestry. Treatment is aimed at B cell depletion; however, relapse is common. Here we describe two cases of anti–IFN-γ autoantibody-associated immunodeficiency.

Case Descriptions: Patient 1: A 42-year-old female originally from Laos presented with a 30-lb weight loss and fatigue over the course of 8 months. Cultures grew *Mycobacterium hassiacum*. Testing by National Jewish was positive for anti–IFN-γ autoantibody via ELISA and for IFN-γ neutralizing ability via pSTAT1 phosphorylation. Autoantibodies were treated with rituximab 375 mg/m^2 weekly for 4 weeks. She had subsequent negative autoantibody levels for 6 months until positive autoantibodies were again detected. She was treated with an additional 3 rituximab 375 mg weekly infusions and maintained remission for an additional 15 months until autoantibody levels were again positive without associated symptoms or infection (see table for timeline). She is currently undergoing additional 4 rituximab infusions.

Table

Patient 1: Timeline of Response to Treatment

	Time from treatment initiation	Autoantibody Status	CD19 level (cells/uL)
375mg/m2 x4 doses →	0 month	Positive	166
	1 month	----------	<1
375mg/m2 x3 doses →	3 months	Negative	<1
	6 months	Positive	245
	12 months	----------	<1
	18 months	Negative	108
	21 months	Positive	314

Patient 2: A 59-year-old female originally from Laos who presented for an immunodeficiency workup with a history of disseminated *Mycobacterium avium* infection, with pulmonary, lymph node, and parotid gland involvement. Anti–IFN-γ autoantibody testing from National Jewish was positive. She was treated with rituximab 375 mg/m^2 weekly for 4 weeks. Autoantibody levels were negative 3 months later, and she has maintained remission since by serial monitoring.

Discussion: In our experience, anti–IFN-γ autoantibody-associated secondary immunodeficiency should be suspected in middle-aged patients with disseminated opportunistic infection, especially women of Southeast Asian ancestry. Rituximab rapidly depletes autoantibody levels; however, maintenance of remission is variable. The average duration of response in patient 1 was 10.5 months compared with persistent remission in patient 2. Thus, serial monitoring with autoantibody levels, markers of inflammation, and symptom assessments should be performed with consideration for repeated doses of rituximab.

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Preserved CD8+ T Cells, Severe Viral Infections, Profound Immune Dysregulation, and Variable Expressivity in a Kindred with Novel, Homozygous Pathogenic ZAP70 Splice-Site Variants

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Few studies have assessed hypomorphic variants in ZAP70, leading to profound, late-onset combined immunodeficiency.

A previously healthy 21-year-old man presented with primary EBV B cell lymphoproliferative disease (LPD). He developed hemophagocytic lymphohistiocytosis treated with rituximab, although EBV LPD rapidly relapsed. He subsequently underwent matched, unrelated donor hematopoietic cell transplantation complicated by fatal hepatic sinusoidal obstructive syndrome.

The family history included profound immune dysregulation in his younger sister, characterized by juvenile systemic lupus erythematosus/juvenile idiopathic arthritis overlap diagnosed at 7 years of age, HPV+ warts, and EBV viremia. She failed therapy with methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, rituximab, tofacitinib, abatacept, tocilizumab, and adalimumab. After NIH evaluation, she was confirmed to be HLA:B27-positive and had a marked clinical response to ustekinumab without loss of viral control. Maternal history included epidermodysplasia verruciformis, recurrent infectious rectovaginal fistulas, and lymphocytic colitis.

Whole-exome sequencing (WES) revealed novel homozygous, splice-site variants in ZAP70 (c.1623+5G>A) in all 3 affected family members. WES homology was consistent with founder effect without consanguinity, although the mother and father were fourth cousins. cDNA analysis of patient cells confirmed aberrant splicing between exons 12 and 13 (Figure 1).

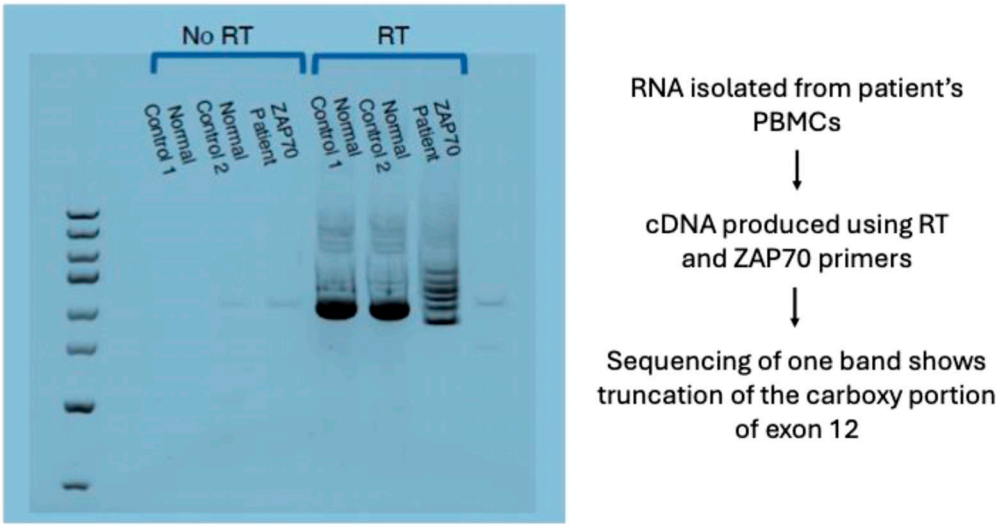

Figure 1. cDNA generated from RNA of the proband, his affected sister, and his affected mother confirmed aberrant splicing at Exon 12 and Exon 13 of *ZAP70*, consistent with the homozygous, splice-site variant found on whole-exome sequencing.

All affected family members had CD4 lymphopenia, although CD8 central and effector memory T cells were relatively preserved. Naïve CD4+ and CD8+ T cells were nearly absent in the proband and his sister. Assays in cells from all affected individuals showed reduced ZAP70-dependent T cell receptor stimulation (Figure 2) and decreased T cell proliferation to mitogens. Maternal lymphocyte phenotyping showed increased NK cells with strong cytolytic function, which may have contributed to her relatively mild phenotype. Markedly increased phospho-S6 and PD-1 expression in CD8 cells as well as increased CD4+ and CD8+ TIGIT and PD-1 double-positive cells were consistent with immune dysregulation and T cell exhaustion.

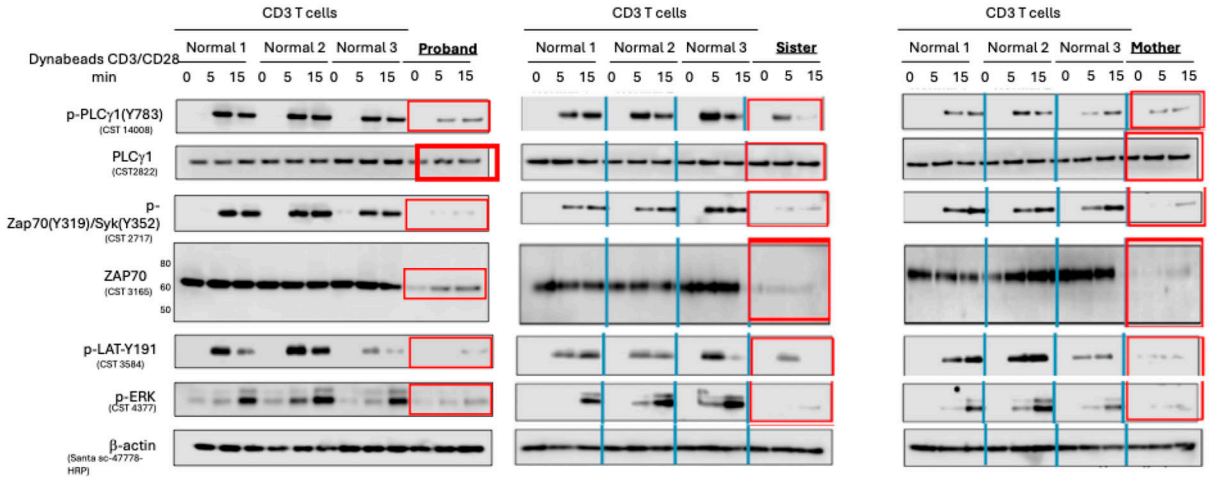

Figure 2. T cells from the proband, his affected sister, and his affected mother showed decreased total ZAP70 protein as well as decreased ZAP70 signaling (phospho-ZAP70, phospho-LAT, and phospho-ERK).

Here we present a 3-member kindred with variable expressivity of a novel homozygous, hypomorphic, splice-site variant in ZAP70. While all family members suffered from severe viral infections, they also presented with multiple features not typically associated with ZAP70 deficiency, including late-onset CID, profound immune dysregulation, and relative preservation of total and memory CD8+ T cell populations.

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Prolonged Neonatal Hypogammaglobulinemia Secondary to Maternal B Cell–Depleting Therapy

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Rituximab is an anti-CD20 monoclonal antibody commonly used as a disease-modifying antirheumatic drug for multiple autoimmune conditions. Rituximab crosses the placenta and has been associated with transient B cell lymphopenia, hypogammaglobulinemia, and decreased response to vaccines in infants exposed in utero. While transient effects of rituximab have been reported in infancy, most affected infants are asymptomatic, and there are no reports on its effects beyond the first year of life. We present the case of an infant with in utero rituximab exposure, who developed persistent secondary hypogammaglobulinemia and recurrent sinopulmonary infections, necessitating immunoglobulin replacement (IVIG) therapy.

Case: The patient was a full-term male infant born to a mother with mixed connective tissue disease and systemic lupus erythematosus. The patient's mother received rituximab, azathioprine, and hydroxychloroquine during pregnancy. The patient initially presented at 5 weeks of age for evaluation of absent T cell receptor excision circles on newborn screening. Immunophenotyping demonstrated mild T cell lymphopenia, absent B cells, and low IgA and IgM at 2 mg/dl and <4 mg/dl, respectively. IgG was normal (332 mg/dl). He had normal naive and memory T cell proportions and proliferations to mitogens. By 6 months of age, the patient had developed recurrent sinopulmonary infections. While T and B cell numbers were normal, switched memory B cells were entirely absent, and unswitched memory B cell percentages were low. IgG, IgA, and IgM were low at <40 mg/dl, <4 mg/dl, and 3 mg/dl, respectively, and pneumococcal and tetanus IgG levels

were non-protective despite complete primary immunization series. IVIG was initiated, and the patient has remained stable on monthly IVIG therapy. Re-evaluation at 16 months demonstrated ongoing low IgM, IgA, and a persistently low percentage of switched memory B cells. **Conclusion:** A full-term infant with in utero rituximab exposure had persistent secondary immune deficiency with prolonged suppression of production of immunoglobulins and switched memory B cells. Contrary to prior reports, maternal rituximab therapy may have resulted in prolonged effects on the developing neonatal immune system beyond the first year of life. This highlights the importance of ongoing monitoring of immune status, including B cell phenotyping in patients with in utero rituximab exposure.

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Transcriptomic Artificial Intelligence Identifies Novel Lymphocyte Signatures Diagnostic for Primary Immunodeficiencies

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This study applied machine learning (ML) and deep learning methods to analyze features of the whole blood transcriptome and mucosal microbiome of patients with primary immunodeficiency (PID). The aim was to better understand disease mechanisms and further develop an effective diagnostic test for PID (referred to as PrimDx) based on blood gene expression. Early diagnosis of PID is crucial, as delays in diagnosis are associated with increased morbidity and mortality. Whole blood RNA and buccal swabs for microbial DNA were collected from patients with a range of antibody deficiencies (n = 62, age 2–67, 32 female) and age- and sex-matched healthy controls (n = 71). RNA sequencing was used to characterize the blood transcriptome of each participant, detecting and measuring over 15,000 genes. ML approaches were applied iteratively to training (70%) and blinded test sets (30%). The diagnostic accuracy to identify PID for the eight models tested ranged from 85% to 95%, with Deep Neural Networks achieving the highest accuracy of 95% and an F1 score of 95% (ROC 99%). Feature selection with the least absolute shrinkage and selection operator (LASSO) identified 13 key genes as significant predictive features, most of which are not well characterized but show expression restricted to lymphocytes. To investigate PID links to the microbiome, ML models were also applied to 16S rRNA profiles of the mucosal microbiome, achieving diagnostic accuracy between 57-78% for PID, with the highest performance observed for Random Forest and LightGBM models, which achieved 78% accuracy and F1 score of 82% (ROC 82%).

In conclusion, a diagnostic (PrimDx) based on whole blood transcriptomic data combined with a predictive algorithm demonstrated high accuracy in identifying PID patients. PrimDx has the potential to support early diagnosis of PID, enabling timely treatment and improved patient outcomes. Features of the mucosal microbiome had predictive power for diagnosing PID, indicating immune function links to the microbiome. Current studies underway are expanding the transcriptome reference database for improving prediction models and investigating the 13 key predictive genes to enhance the effectiveness and accessibility of this diagnostic approach.

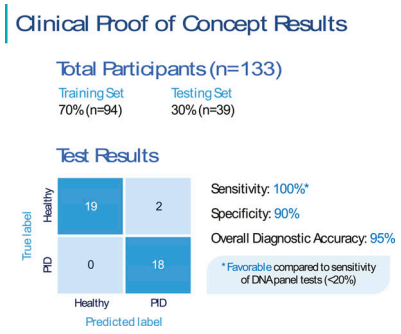

Figure 1.

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Experience with T Cell–Depleted Allogeneic HSCT for Refractory sJIA Associated with Lung Disease

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Background: A subset of patients with systemic juvenile idiopathic arthritis (sJIA) develop sJIA-associated lung disease (sJIA-LD). Allogeneic hematopoietic stem cell transplant (HSCT) is a treatment option for patients with refractory sJIA and can ameliorate associated lung disease. Infusion of T-replete grafts into sJIA-LD patients who have a high background of preexisting systemic and pulmonary inflammation may contribute to risks of inflammatory complications or graft versus host disease following allogeneic HSCT. We hypothesized that a T cell–depleted approach would achieve durable engraftment while minimizing the risks of GVHD, pulmonary complications, and TRM.

Methods: We report our single-center retrospective analysis of 4 pediatric patients with sJIA-LD who underwent allogeneic HSCT with reduced intensity conditioning (RIC) with alemtuzumab (days 14-12), fludarabine (150 mg/2 over days -8 to -4), melphalan (140 mg/m^2 on day -3), and thiotepa (200 mg/m^2 on day -2) and received either a CD34+-selected (n = 3) or TCR-αβ–depleted (n = 1) peripheral blood stem cell product.

Results: Patient and transplant characteristics are shown in Table 1. All patients had highly refractory disease and were heavily pretreated with a median of 8 (6-12) lines of sJIA-directed therapy. At the time of HSCT, three patients required respiratory support (supplemental O_2 in n = 2, overnight BiPAP with supplemental O_2 in n = 1).

Table 1. **Transplant characteristics**

Pt	Age at BMT	Age at sJIA diagnosis	Age at diagnosis of ILD	Baseline IL-18 pg/ml	HLA match	Stem cell source	T-cell depletion	Complications post HSCT	Donor chimerism (last FU)	Il-18 pg/ml (last FU)
1	8 yrs.	11 mos.	6 yrs.	34,000	#1 10/10 MUD	PBSC	#1 HSCT TCR Alpha Beta Depleted	Secondary graft failure day+43	na	na
1	8 yrs.				#2 Haplo 5/10 (Father)	Bone Marrow	#2 Post HCT Cytoxan	Engraftment syndrome	100% (3 years)	247
2	10 yrs.	1 yr.	2 yrs	56,000	9/10 MUD	PBSC	CD34 selection	No	100% (2 years)	620
3	9 yrs.	6 yrs.	7 yrs.	50,984	9/10 MUD	PBSC	CD34 selection	Cerebral venous sinus thrombosis BK viremia	100% (1 year)	670
4	7 yrs.	1.5 yrs.	4 yrs,.	126,000	10/10 MUD	PBSC	CD34 selection	None	100% (6 months)	1900

All patients engrafted with >95% donor chimerism (range, 9-10 days post-HSCT). One patient experienced secondary graft failure on day +43 requiring a second HSCT with a haploidentical parental donor and post-transplant cyclophosphamide (Table 1). Second HSCT was complicated by grade 1 (skin) acute GVHD. None of the other patients developed acute or chronic GVHD or significant pulmonary complications. All had significant improvement in their pulmonary status and were able to discontinue their respiratory support (Figure 1). At a median follow up of 19.8 months (range, 6-36 months), all patients have 100% donor chimerism. None of the patients have had relapse of their sJIA. IL-18 levels declined post-HSCT to near normal levels in all patients (Table 1).

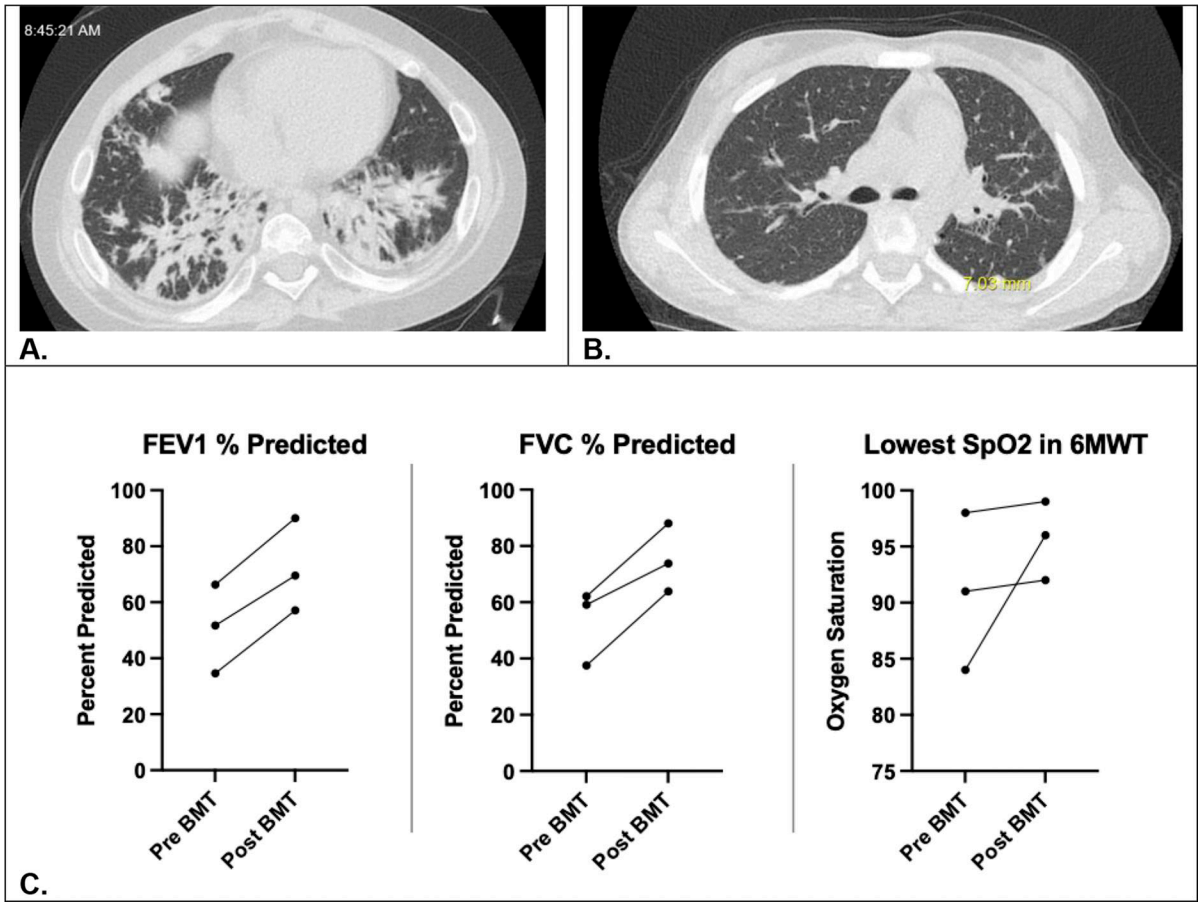

Figure 1. Progress of pulmonary disease pre- and post-HSCT. High-resolution CT chest images of patient #1 pre- (A) and 2.5 years post- (B) HSCT. (C) This shows percent predicted FEV1 and FVC and lowest SpO2 in 6-minute walk test for patients #1-3 (patient 4 unable to reliably perform spirometry).

Conclusions: Our experience suggests that allogeneic HSCT with a T cell–depleted approach for patients with sJIA-LD offers durable engraftment with low risk of GVHD, pulmonary complications, and TRM.

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Genome-Wide Association Study Identifies Novel Variant Associated with Susceptibility to Pediatric Tuberculosis

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Introduction: RNA signatures and T cell activation responses to *Mycobacterium tuberculosis* (Mtb) have demonstrated good diagnostic and prognostic performance in adults. To further evaluate the implementation of these novel assays in children, we hypothesized that host genetic variation is associated with susceptibility to pediatric tuberculosis disease and blood biomarker expression.
Methods: We used a case-control study with a 12–36-mo prospective observation period to examine susceptibility to tuberculosis in children aged 2 mo to 5 yr with household Mtb exposure in Worcester, South Africa. Low-pass whole-genome sequencing followed by imputation was completed for 219 cases and 207 controls. A GWAS was performed to assess for association between genetic variants and

susceptibility to tuberculosis disease. Lead genetic variants were subsequently evaluated for their effect on BCG-induced innate and adaptive immune responses. Whole blood collected from an independent cohort of 189 BCG-vaccinated 10-week-old South African infants was stimulated with BCG or media and examined with flow cytometry to measure cell surface-marker and cytokine expression.
Results: We identified a genome-wide significant variant rs4600676 (p = 4.5e-08) associated with increased susceptibility to pediatric tuberculosis. rs4600676 maps to a noncoding region of DNA and is positionally nearest genes GPR45 and TGFBAP1, suggesting it may regulate cytokine signaling. We identified an additional 25 lead genetic variants across 24 risk loci mapping to 55 genes at a prespecified suggestive significance level (p < 1e-05) associated with susceptibility to pediatric tuberculosis. MAGMA gene-set analysis of these suggestive variants revealed enrichment for chemokine receptor binding (p = 6.2e-06) and IRAK4-TLR2/4 deficiency (p = 2.2e-05). Six lead variants were associated with BCG-induced immune responses (p < 0.05). Specifically, rs34925982 maps to the T cell–inhibiting gene ILDR2, is associated with decreased BCG-induced T cell responses (p = 0.007), and increased susceptibility to childhood tuberculosis (p = 4.1e-06).
Conclusion: We identified a genome-wide significant variant associated with increased susceptibility to pediatric tuberculosis as well as an additional 26 variants suggestive of an association with tuberculosis susceptibility. These findings identify potential immunoregulatory mechanisms involved in host responses to tuberculosis that can be leveraged for therapeutic intervention. Future work will associate genetic variants with Mtb-induced RNA signatures and T cell activation responses to understand how performance of these assays may vary across populations.

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Complement Factor I Deficiency Presenting as Pseudomonas Septic Arthritis

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Complement factor I (CFI) is a serine protease that inactivates complement C3b and C4b in the presence of cofactors. Complete CFI deficiency leads to a secondary complement deficiency due to uncontrolled amplification of C3 cleavage leading to a severe C3 deficiency. CFI deficiency can lead to severe infections particularly with encapsulated organisms early in life in addition to atypical HUS and autoimmune diseases.

Here, we present a case of a previously healthy 13-month-old girl who developed pseudomonas septic arthritis and was found to have CFI deficiency. She first presented with acute onset right knee swelling and refusal to walk without any inciting trigger. Her only prior infection was one episode of acute otitis media. She underwent intraoperative irrigation and debridement of the knee and cultures subsequently grew *Pseudomonas aeruginosa*. She completed a course of antibiotics with cefepime followed by oral levofloxacin with clinical improvement. Immunologic laboratory evaluation revealed low CH50 on three samples 3 months apart (16.1, 31.1, and 16.4 U/mL) with low C3 (53 mg/dL) and normal C4. She also had unremarkable DHR, quantitative immunoglobulins, lymphocyte enumeration, mitogen response, vaccine titers after completing immunization series, red blood cell pitting, and TLR assay. Genetic testing was then performed that revealed a pathogenic homozygous mutation (c.80_81del, p.Asp27Alafs*18) consistent with a diagnosis of autosomal recessive CFI deficiency.

Management recommendations included hypervaccination with the conjugated pneumococcal vaccine and meningococcal (MenACWY and MenB) vaccines and consideration of prophylactic antibiotics. The clinical phenotype in CFI deficiency is driven by the CFI variant; some heterozygous variants lead to atypical HUS and age-related macular degeneration, while other homozygous variants are associated with neuroinflammation, glomerulonephritis, or autoimmunity. Our patient's variant results in a premature translational stop signal and has been associated with infection and recurrent IgA vasculitis. Further understanding the risks associated with different variants may help guide patient care and screening. This case highlights the importance of noting and further evaluating a decreased but nonzero CH50 in a patient with a severe sentinel infection for complement pathway deficiencies in addition to using a personalized medicine approach for care and other disease manifestation screening.

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Clinical Response Among Participants with Warts in the Phase 3 Trial, Mavorixafor, an Oral CXCR4 Antagonist, for Treatment of Patients with WHIM Syndrome

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Background: Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome, a rare, combined primary immunodeficiency disorder caused by hyperactive CXCR4 signaling, leads to impaired leukocyte egress from bone marrow into peripheral blood. Among the variable multisystem manifestations, individuals are highly susceptible to recalcitrant warts. Plerixafor, an injectable CXCR4 antagonist, has shown improvement in warts in WHIM syndrome; however, the question remains whether CXCR4 antagonism shows a wart benefit in this population. Mavorixafor, an orally available reversible CXCR4 antagonist, demonstrated clinical efficacy in participants with WHIM syndrome in the 4WHIM phase 3 trial (NCT03995108). Here, we report the positive wart effect from chronic oral mavorixafor treatment in this post hoc analysis of participants enrolled in the study.

Methods: 4WHIM included a 52-week randomized, double-blind, placebo-controlled period (RCP) with an ongoing open-label mavorixafor-only extension (OLE); participants were aged ≥12 years with WHIM syndrome ± history of baseline warts. Local dermatologists reviewed 23 wart regions, and adjudicators reviewed 3 target wart regions. Wart assessments included Clinical Global Impression of Severity (CGI-S; 1 = no warts to 5 = very severe warts) and Clinical Global Impression of Change (CGI-C; +1 = worsening to -2 = complete resolution) scores (Figure); only CGI-S was used for this analysis. Change from baseline to week 52 (end of RCP) and to the end of the OLE year 1 (week 104) were analyzed.

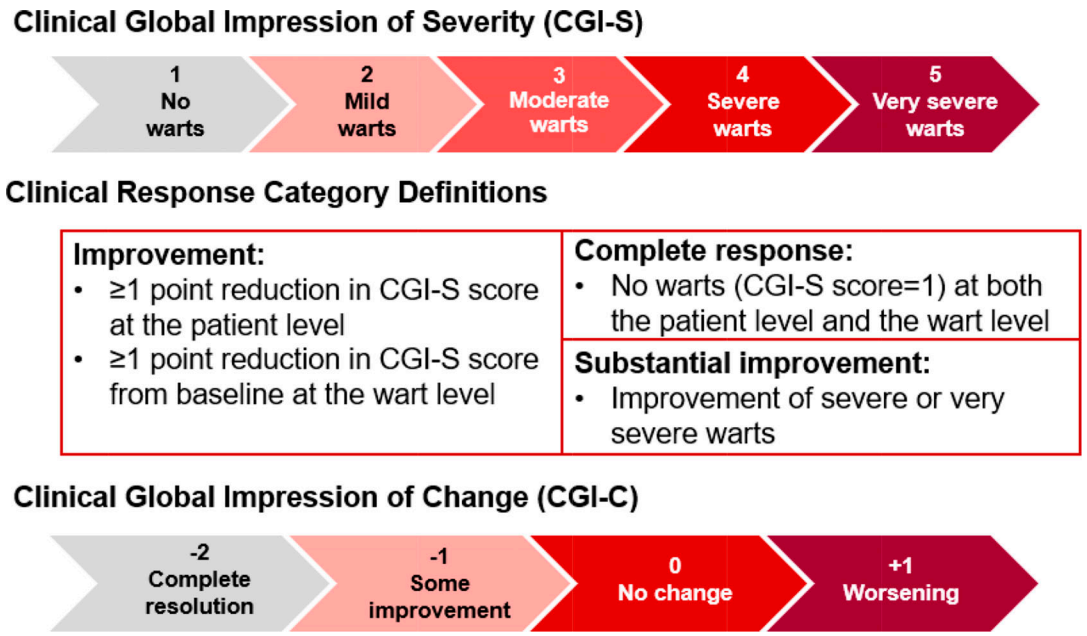

Figure. Clinical assessment tools and response definitions.

Results: Fifteen participants completed 2 years of the trial and had 70 defined wart areas, which were followed for 2 years. Despite a history of warts, no participants in the mavorixafor group had worsening warts during the RCP compared with 2/9 (22.2%) participants in the placebo group. After 2 years of mavorixafor treatment, 4 (66.7%) participants showed improvement and 2 (33.3%) achieved complete remission. Of participants in the RCP placebo group who transitioned to mavorixafor in the OLE, 3 (33.3%) had improvement and

2 (22.2%) experienced complete remission during RCP, whereas 6 (75.0%) participants showed improvement and 4 (50.0%) experienced complete remission during OLE.

Conclusions: Two-year treatment with chronic oral mavorixafor was associated with marked clinical improvement in wart severity, providing further evidence that CXCR4 antagonism leads to wart improvement in patients with WHIM syndrome.

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Quality Control of Target Region Coverage in Whole-Exome Sequencing: An Important Step in Data Analysis

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Introduction: Whole-exome sequencing (WES) has gained significant traction as a tool for both scientific research and clinical practice in diagnosing genetic disorders. Despite its high informativeness, the method is not without limitations. Moreover, target regions may exhibit incomplete coverage or lack coverage entirely. A clear understanding of the completeness of exonic region coverage in genes selected for analysis is crucial when interpreting WES data.

Materials and Methods: This study included WES data from 71 patients, generated using the DNBSEQ-G50 genetic analyzer (MGI, China) and the Exome Capture V5 Probe Set (MGI, China) for DNA library preparation. Secondary data processing was performed using the ZLIMS software platform (MGI, China). The quality of sequencing results was assessed based on the exonic regions of 662 genes associated with the clinical manifestations of primary immunodeficiency. Coverage statistics were calculated using the bedtools software package (v2.27.1). Target regions for the analysis were extracted from the MGI Exome Capture V5 BED file corresponding to the Human hg19/hg37 genomic assembly.

Results: Among the genes associated with primary immunodeficiency, 339 regions within 210 genes (31% of the total gene list) exhibited coverage of fewer than 30 nucleotides. Additionally, 224 exons in 183 genes were entirely uncovered across all samples (n = 71). The absence of coverage was partially attributed to the exclusion of certain region coordinates in the BED file integrated into the ZLIMS system, which resulted in the exclusion of these regions from downstream analyses. Other contributing factors to the absence of coverage remain unresolved due to the proprietary nature of the system.

Conclusion: Our data analysis demonstrates that the significant number of regions with low coverage necessitates careful consideration of the potential for both false-positive and false-negative results. However, even with good statistical parameters, it is important to remember the rule that the results of WES should not be used as a basis for excluding a clinical diagnosis. Our study highlights that identifying clinically significant variants may be limited not only by the inherent technical constraints of WES but also by deficiencies in the software solutions used for data processing. Even high-cost commercial data processing tools may contain critical flaws.

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Addition of Thiotepa to Alemtuzumab, Fludarabine, and Melphalan Reduced-Intensity Conditioning Reduces Secondary Graft Failure in Allogeneic HSCT for Inborn Errors of Immunity

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Introduction: Alemtuzumab, fludarabine, and melphalan reduced-intensity conditioning (RIC) regimen is associated with a high incidence of mixed chimerism and secondary graft failure in patients undergoing allogeneic hematopoietic stem cell transplant (HSCT) for inborn errors of immunity (IEI). We hypothesized that addition of thiotepa to this regimen would reduce secondary graft failure without increasing toxicity in children and young adults undergoing allogenic HSCT for IEI.

Methods: We retrospectively reviewed charts of patients undergoing allogenic HSCT for IEI who received alemtuzumab (starting on day -14), fludarabine (150 mg/m^2 or 5 mg/kg over days -8 to -4), and melphalan (140 mg/m^2 or 4.7 mg/kg on day -3) containing RIC regimen with the addition of thiotepa (200 mg/m^2 on day -2). Mixed chimerism and low-level mixed chimerism were defined as whole blood donor chimerism <95% and <50%, respectively, on two consecutive measures within a 2-week period.

Results: Thirty-one patients underwent allogeneic HSCT at a median age of 1.7 years (0.3-21 yrs). Patient demographics are outlined in Table 1. All patients engrafted at a median of 12 days (range, 8-17 days). The incidence of mixed chimerism was 0% (0/31), 20% (5/25), and 46% (7/15) upon engraftment at day +100 and one-year post-HSCT, respectively. Incidence of low-level mixed chimerism was 0% (0/25) and 6.6% (1/15) at day +100 and one-year post-HSCT, respectively. Three (9.6%) patients required a secondary intervention (2 CD34 selected boost and 1 second HSCT). Two (6.4%) patients developed sinusoidal obstruction syndrome, and 11 (35%) patients developed thrombotic microangiopathy. Six (19%) patients developed grade I-II skin GVHD, with none developing grade III-IV GVHD. One (3.2%) patient developed limited chronic GVHD. Thirteen of 31 (42%) patients had viral reactivation requiring treatment, with CMV (54%), EBV (54%), and adenovirus (15%) being the most common. Twenty-six (84%) patients are surviving at median follow-up of 10 months (range 2m-4y 2m) post-HSCT.

Table 1. **Patient demographics (n = 31).**

Median age at transplant (range)	**1y 8m (4m-21y 11m)**
Median Follow up (range)	**10 m (2m-4y 2m)**
Gender	
Male	19 (61%)
Female	12 (39%)
Diagnosis	
HLH	19 (61%)
sJIA	5 (16%)
XLP	1 (3.2%)
XIAP	1 (3.2%)
LRBA deficiency	1 (3.2%)
XMEN	1 (3.2%)
SCID	1 (3.2%)
Griscelli	1 (3.2%)
Early onset IBD	1 (3.2%)
Donor Relationship	
Related	21 (68%)
Unrelated	10 (32%)
HLA Match	
10/10	21 (68%)
9/10	6 (19%)
7/10	1 (3%)
6/10	3 (10%)
Stem cell source	
BM	23 (74%)
PBSCs, CD34 selected	5 (16%)
PBSCs, alpha beta depleted	3 (10%)
GVHD prophylaxis	
CSA/MMF	11 (35.5%)

Table 1. **Patient demographics (n = 31). (*Continued*)**

Median age at transplant (range)	**1y 8m (4m-21y 11m)**
Median Follow up (range)	**10 m (2m-4y 2m)**
CSA/MMF/Abatacept	10 (32%)
CD34 selection	5 (16%)
Alpha-beta T cell depletion	3 (10%)
CSA/MMF/PT-Cy	2 (6.5%)

Conclusion: Addition of thiotepa to a RIC regimen containing fludarabine, alemtuzumab, and melphalan reduces secondary graft failure without increasing toxicity in children and young adults undergoing allogenic HSCT for IEI. Longer duration of follow-up is needed to assess durability of donor chimerism.

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Idiopathic CD4+ Lymphocytopenia Is Associated with Alterations of the Gut Microbiome

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Background: Idiopathic CD4 lymphocytopenia (ICL) is a rare immunodeficiency disorder characterized by low circulating CD4+ T cells (<300 cells/μl) in the absence of HIV or any other immunosuppressive condition or therapy. Patients with ICL have high risk of serious opportunistic infections and malignancies. Gut microbiota dysbiosis has previously been associated with immune deficiencies and altered responses to immune therapies. We hypothesized that patients with ICL would exhibit unique gut microbiome communities compared with healthy household contacts (HC).
Methods: Shotgun metagenomic sequencing was performed to measure gut microbiome diversity in rectal swabs from patients with ICL (n = 55, median CD4 88 cells/μl) ICL and HC (n = 19). Taxonomic annotations of short reads were performed against the NCBI reference genomic database (RefSeq), and abundance was estimated via read counts. Viral content was estimated from quality assessed full-length viral sequences contained within de novo assembled contigs. Permutational analysis of variance (PERMANOVA) tests were performed based on the Bray–Curtis distance matrix to assess microbial contrasts between groups.
Results: ICL group was further stratified to no (n = 30), single (n = 13), or multi (n = 12) antimicrobial use. Gut microbiomes of ICL were significantly different from HC with respect to bacterial (p = 0.042) and eukaryotic (p = 0.011) composition. Bacterial variability within ICL communities tended to be higher than intragroup variability of HC (p = 0.002), especially with respect to Clostridia and Bacteroidia classes. ICL patients on multiple antimicrobial medications were found to have distinct bacterial communities from ICL patients on single or no antimicrobial medications (p = 0.027 and 0.018, respectively) with relative depletion of Gammaproteobacteria. ICL had a significantly higher relative abundance of bacterial pathogens than HC, even after controlling for antibiotic use. ICL viral communities did not differ significantly from HC; however, the presence of human papillomavirus (HPV) diseases, a common ICL comorbidity, was a significant contributor to variation in both bacterial (p = 0.026) and viral community composition (p = 0.004), especially in more severe HPV cases refractory to surgical/medical management.
Conclusions: People with ICL have alterations in gut microbiota composition, diversity, and community stability regardless of antimicrobial use. Further investigation of metabolomic signatures may provide additional context for the potential role of microbiome changes in ICL comorbidities.

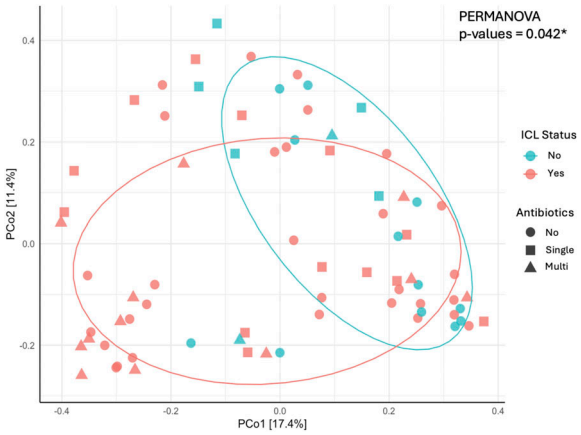

Figure. PCoA with bay distances for ICL status and antibiotic use for bacterial diversity.

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Never Say Never—Delayed and Unusual Presentations of XLA in Two Patients with a Kinase-Domain Variant

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Background: X-linked agammaglobulinemia (XLA) is caused by pathogenic variants in Bruton tyrosine kinase (BTK), causing arrest of B cell development and immunoglobulin production. Patients typically present in infancy or early childhood with recurrent infections, notably bacterial sinopulmonary and gastrointestinal infections. Older presentations are infrequently described, and their cause remains unclear.
Objective: We describe two unrelated patients who presented with late-onset XLA and unusual manifestations, both harboring the same variant in the kinase domain.
Clinical Case Descriptions: Patient 1 was diagnosed at age 17 after experiencing multiple sinopulmonary infections. He subsequently developed several difficult-to-treat autoimmune/inflammatory complications, including recurrent fevers with adenopathy, seronegative tenosynovitis, immune thrombocytopenic purpura, liver nodular regenerative hyperplasia (NRH), portal hypertension, and widespread granuloma annular-like lesions. After failing multiple immunosuppressive medications, he experienced some improvement on tofacitinib. Patient 2 was diagnosed at age 54, following a less extensive infectious history, including a pneumonia (age 8) requiring intravenous antibiotics and bacteremia secondary to trauma (age 38). He also has a likely NRH, pending biopsy.
Laboratory Investigations: Patient 1 had absent B cells and complete agammaglobulinemia with residual IgM. Patient 2 had near-absent B cells, with surprisingly normal total IgG and IgA and low IgM. He mounted an abnormally low pneumococcal titer despite boosting. Both patients underwent extensive genetic testing, revealing only the pathogenic BTK variant: c.1574G>A (p.Arg525Gln).
Discussion: Adult-onset XLA is rare and can present clinically as "CVID." Interestingly, most late cases described to date had absent B cells, suggesting a likely decline in B cells over time. Our patients both harbored a known variant affecting Arg525 of the kinase domain. This variant has been previously reported in classical, early onset XLA. However, it has also been described in patients presenting later with CVID. This variant is expected to abrogate the catalytic kinase activity due to loss of substrate recognition. It is unclear if phenotypic variability relates to the variant itself or to a polygenic effect. We suggest clinicians maintain suspicion for XLA in patients presenting with absent B cells at any age, while the best management strategies for autoimmune/inflammatory manifestations remain to be determined.

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Study of Genome-Wide DNA Methylation Profile in a Large Cohort of Patients with 22q11.2 Deletion Syndrome

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22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion syndrome in humans. The clinical phenotype is variable among different patients, also when they come from the same family, suggesting that nongenetic factors may be implicated in the pathogenesis. Recently, a specific episignature was defined for patients affected with 22q11.2DS. However, it has not been yet clarified whether these changes may reflect the variability of the phenotype observed among different patients.

The study is aimed at defining genome-wide DNA methylation profiling in a large cohort of patients, including 63 carrying a deletion on the 22q11.2 chromosome and 5 with clinical features of DGS in whom genetic analysis did not reveal any alteration on the chromosome 22 (DGS-like). Among patients with 22q11.2 deletion, 12 were identified through FISH, suggesting that the deletion includes the proximal region, but information on the extension of the deletion is not available. For the remaining 51 patients, 38 carried the typical A-D deletion, 3 carried an A-B deletion, 7 carried a C-D deletion, while 3 patients carried a deletion downstream the DGS region. The analysis included 20 familial cases from 8 kindred.

By selecting the 160 previously published differentially methylated CpG probes (DMPs), we were able to distinguish a specific methylation profile in the group of 38 patients carrying the typical A-D deletion, in the 3 patients carrying the A-B deletion, and in those diagnosed with FISH. On the contrary, the 7 patients carrying the distal C-D deletion, the 3 patients carrying a deletion downstream the DGS region and the DGS-like clustered with the controls. When the analysis was extended to a larger number of DMPs, we observed a gradient among typical deletion, distal deletions, DGS-like, and controls. Interestingly, most of the DMPs were found in the DGS region on the non-deleted allele. Hierarchical clustering also revealed similarities among affected and unaffected members of the different families, suggesting that epigenetic modifications may be partially inherited.

These data showed a gradient of DMPs among typical deletion, distal deletions, DGS-like, and controls. This may suggest a correlation between the severity of the clinical phenotype and the degree of DNA methylation.

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Distinctive Genome-Wide DNA Methylation Profiling in a Cohort of Patients with Known Pathogenic STAT1 Gain-of-Function Variants

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Background: High throughput sequencing techniques are very effective tools to achieve a timely genetic definition of inborn errors of immunity (IEIs). However, they often reveal variants of uncertain significance (VUS), and in some cases, the identification of a causative genetic alteration may be hampered by technical issues. Recent studies suggest that genome-wide DNA methylation profiling on blood

samples may represent an effective tool for reassessing the pathogenic role of VUS in a defined set of disease-causing genes and to increase the diagnostic yield in unresolved cases.

Aim: The aim of the study is to define the genome-wide DNA methylation profiling in a cohort of patients with known pathogenic STAT1 gain-of-function (GOF) variants.

Methods: As proof of principle, genome-wide DNA methylation profiling was evaluated on 11 patients carrying 7 different known pathogenic STAT1 GOF variants.

Results: We compared the DNA methylation profile (β-values) between all cases with GOF variants in STAT1 and age- and sex-matched controls. Through hierarchical clustering, we were able to differentiate the patients' and controls' groups. In total, 2356 differentially methylated CpG probes (DMPs) were identified. Among these, 75 DMPs (64% hypomethylated and 36% hypermethylated) were in genes regulated by STAT1 and 58 DMPs (60% hypomethylated and 40% hypermethylated) were in genes regulated by STAT3. Using the genes covered by the 2356 DMPs, we performed KEGG pathway enrichment analysis revealing genes implicated in antiviral response to CMV and HPV but also genes implicated in cancer, cellular senescence, and thyroid hormone signaling.

Conclusions: These preliminary data suggest that patients with different STAT1 GOF variants display a distinctive genome-wide DNA methylation profile. Further data on a larger cohort of patients are necessary to validate these results and to define whether this technique is effective in assessing the pathogenicity of VUS. If confirmed, this study may be extended to other different IEIs.

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Genome-Wide DNA Methylation Profiling Led to the Identification of a Novel ZNF699 Mutation in a Patient with DEGCAGS Syndrome and Severe B Cell Depletion

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Background: DEGCAGS syndrome is an autosomal recessive disorder characterized by developmental delay and dysmorphic features caused by biallelic ZNF699 variants. Immunodeficiency is reported in a significant number of affected patients. A specific DNA methylation profile has been recently described for this syndrome.

Objective: To describe the immunological features in a patient with DEGCAGS syndrome in whom diagnosis was suggested by the study of DNA methylation profiling.

Methods: CGH-array, whole exome, clinical exome, and Sanger sequencing were used to define the genetic diagnosis. DNA methylation was used to assess the pathogenic role of a heterozygous de novo VUS in ADNP gene identified through clinical exome.

Results: DNA methylation profile ruled out a pathogenic role of the VUS in ADNP gene and suggested a diagnosis of DEGCAGS syndrome, subsequently confirmed through Sanger sequencing, which revealed the homozygous missense c.153C>A variant in ZNF699 gene. Immunological studies revealed a never described before significant reduction of CD4+CD45RA+ naïve T cells (12%) and CD19+ B cells (2%, 33.2 cells/μL) associated with impaired T cell proliferation and recurrent and severe lung infections, suggesting a diagnosis of TlowB-NK+ combined immunodeficiency (CID). Despite severe B cell depletion, immunoglobulin levels and specific antibody responses were normal.

Conclusion: This report offers for the first time an in-depth characterization of the immunological features in DEGCAGS syndrome and suggests that biallelic loss-of-function ZNF699 variants may represent an additional cause of syndromic CID. The diagnosis was supported by the study of DNA methylation episignature that represents an additional powerful tool to increase the diagnostic yield in unresolved cases.

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Determining Molecular Mechanisms of SPI1-Mutated CVID

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Previous work in our group described a novel cause of agammaglobulinemia (lack of circulating B cells) in certain patients due to heterozygous mutations in the SPI1 gene, which encodes transcription factor SPI1, also known as PU.1. Recently, we identified common variable immunodeficiency (CVID) patients with similar heterozygous mutations in the SPI1 gene. These patients possessed circulating B cells but lacked antibody titers and class-switched memory B cells. We were interested in understanding what the B cell subsets present in these patients look like relative to their healthy counterparts and the trends in their expression profiles at both the protein and transcript levels to better understand what is causing the spectrum of disease severity.

We compared the transcripts of circulating B cells in the blood of an SPI1-mutated CVID patient and an age/sex matched healthy donor. We showed the appearance of a novel early transitional B cell population, an expansion of CD21loTBEThi B cells, and a stark decrease in mature naïve B cells. This confirmed our suspicion that there are key differences observable as soon as patient B cells enter circulation due to decreased SPI1 dosage. Upon thorough analysis of immunophenotyping data from our other SPI1 CVID patients in the cohort, we saw that all patients at the protein level showed a similar increase in transitional and CD21loTBEThi B cells, as well as a decrease in mature naïve B cells. Finally, we revisited bulk RNAseq data from three previously created isogenic pro B cell lines, edited to have normal SPI1 expression, monoallelic SPI1 expression, or no SPI1 expression. We saw a significant increase in TBET gene expression with decreasing SPI1 gene expression in each line, which was confirmed by flow cytometry that showed an increase in TBET correlating with the loss of SPI1 at the protein level. This suggested an inverse relationship between SPI1 and TBET, potentially explaining the developmental roadblock in the transitional B cells of SPI1 CVID patients.

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Challenging the Paradigm: Severe Rheumatoid Arthritis and Anti-TNF Failure in an X-Linked Agammaglobulinemia Patient

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Background: X-linked agammaglobulinemia (XLA) is a rare inherited immunodeficiency disorder caused by a mutation of the Bruton tyrosine kinase (BTK) gene on the X chromosome. It is characterized by absent B cells and recurrent infections. Autoimmune manifestations in XLA, such as rheumatoid arthritis (RA), are uncommon and poorly understood [1, 2].
Case Presentation: We report a case of a 56-year-old male with XLA, diagnosed at age 5, and chronic seronegative erosive polyarthritis who failed anti-TNF therapy with adalimumab (Hadlima), despite the absence of circulating B cells. He fulfills the 2010 ACR/EULAR classification criteria for RA with ongoing disease activity in small and large joints. After treatment failure with adalimumab, he was switched to upadacitinib (JAK1 inhibitor) with significant improvement and resolution of his synovitis.
Investigations: A primary immunodeficiency gene panel was performed, and the results were consistent with an XLA diagnosis, revealing a likely pathogenic mutation on the BTK gene (c.1932C>G and p.Phe644Leu). The investigations concord with agammaglobulinemia, including absent circulating B cells on flow cytometry (Figure 1, Tables 4, 6). Additionally, a rheumatologic workup was conducted and showed results supportive of seronegative arthritis (Table 7).

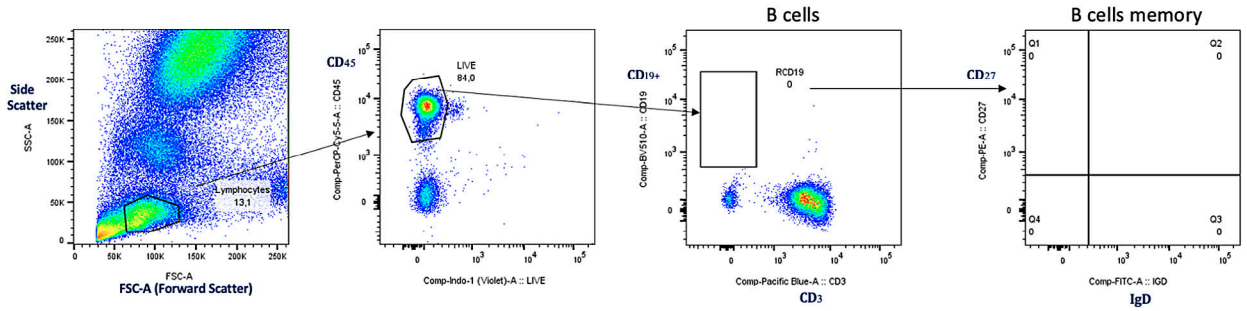

Figure 1. Flow cytometry.

Table 1. **Naïve and memory T cell subsets (% and cells/cu mm).**

Subpopulation	% of CD4 Lymphocytes	Cells/cu mm	Reference Range (%)	Reference Range (Cells/cu mm)	% of CD8 Lymphocytes	Cells/cu mm	Reference Range (%)	Reference Range (Cells/cu mm)
Effector Memory (CD45RA-CCR7-)	21%	77	[9–32]	[28–92]	17%	107	[6–32]	[48–180]
Central Memory (CD45RA-CCR7+)	17%	62	[12–39]	[28–62]	2%	12	[1–8]	[1–8]
Naïve (CD45RA+CCR7+)	59%	220	[28–62]	[42–121]	2%	15	[11–47]	[30–148]
TEMRA (CD45RA+CCR7-)	4%	17	[1–16]	[8–47]	79%	505	[27–64]	[230–640]

Table 2. **T cell subsets (% and cells/cu mm).**

Subpopulation	% of Lymphocytes	Cells/cu mm	Reference Range (%)	Reference Range (Cells/cu mm)
Total T Cells	97%	1038	[65–80]	[805–1606]
B Cells	0%	0	[7–16]	[97–270]
T-Helper (CD4+) Cells	35%	375	[34–52]	[474–1009]
T-Suppressor (CD8+) Cells	60%	642	[18–34]	[208–635]
NK Cells	3%	32	[6–23]	[83–372]
CD4/CD8 Ratio	0.6	-	[1.0]	-

Table 3. **T cell activation markers.**

Marker	% of CD4 Lymphocytes	Cells/cu mm	Reference Range (%)	Reference Range (Cells/cu mm)
Total CD28+ on CD3+CD4+	54%	203	[90–100]	[432–934]
Total CD28- on CD3+CD4+	46%	173	[0–10]	[1–71]
Total CD28+ on CD3+CD8+	3%	19	[54–86]	[134–413]
Total CD28- on CD3+CD8+	96%	616	[14–46]	[6–290]

Table 4. **Memory B cells.**

Subpopulation	% of B Cells	Cells/cu mm	Reference Range (%)	Reference Range (Cells/cu mm)
CD27+IgD- (Memory)	0%	0	[11–33]	[10–73]
CD27+IgD+ (Memory IgD+)	0%	0	[7–24]	[10–46]
CD27-IgD- (DN)	0%	0	[1–10]	[4–15]
CD27-IgD+ (Naive)	0%	0	[42–71]	[44–158]

Table 5. **Genetic investigations.**

Gene	Zygosity	Protein Function / Association	Chromosome	cDNA Change	Protein Change	Variant Classification
BTK	Hemizygous	X-linked recessive agammaglobulinemia (XLA)	X chromosome	c.1932C>G	p.Phe644Leu	Likely Pathogenic
C2	Heterozygous	Complement component 2 (C2) deficiency	Chromosome 6	c.841_849+19del (Splice site)		Pathogenic
NJOD2	Heterozygous	Autosomal dominant Blau Syndrome, associated with an increased risk of Crohn's disease	Chromosome 16	c.2722G>C	p.Gly908Arg	Increased Risk Allele

Table 6. **Laboratory investigations.**

Parameter	Value	Reference Range
IMM profile		
IgG	9.52 g/L	[7.00-15.00]
IgA	< 0.10 g/L	[0.80-4.00]
IgM	< 0.20 g/L	[0.50-3.00]
Complete Blood Count		
White Blood Cell	6.20 x 10^9 g/L	[4.50-11.00]
Relative Neutrophil	62%	[40-70]
Relative Lymphocyte	18%	[22-44]
Relative Monocyte	18%	[2-10]
Relative Eosinophil	1%	[0-4]
Relative Basophil	1%	[0-2]
Absolute Neutrophil	3.83 x 10^9 g/L	[1.8-7.70]
Absolute Lymphocyte	1.08 x 10^9 g/L	[1,00-4.80]
Absolute Monocyte	1.15 x 10^9 g/L	[0.00-0.80]
Absolute Eosinophil	0.03 x 10^9 g/L	[0.00-0.45]
Absolute Basophil	0.06 x 10^9 g/L	[0.00-0.22]

Table 7. **Rheumatology workup.**

Parameter	Value
Cyclic Citrullinated Peptide (CCP)	Negative (-)
Rheumatoid Factor (RF)	Negative (-)
Antinuclear Antibodies (ANA)	Negative (-)
Complement Components 3 and 4 (C3/C4)	Normal
Creatine Kinase (CK)	Normal
Uric Acid	333
Anti-neuronal Antibodies	Negative (-)
Anti-Neutrophil Cytoplasmic Antibodies (ANCA)	Negative (-)
Anti-Double-Stranded DNA Antibodies (dsDNA)	Negative (-)
Anti-Cardiolipin Antibodies (aCL)	Negative (-)

Discussion: The failure of an anti-TNF inhibitor is unusual in this case, as this patient's XLA results in no circulating B cells. It is unexpected for a patient with no functioning B cells to develop autoimmunity and anti-TNF treatment failure, as it is most often due to antibody development. Furthermore, although the role of T cells is not fully established with regard to RA, it is thought that they are involved in chronic inflammatory responses [3, 4]. There have been some recorded cases in the literature of RA in XLA patients, although the sample size of XLA patients is too small to draw a definitive conclusion [3].

Conclusion: This case raises questions about the mechanisms underlying treatment resistance in B cell–deficient patients and highlights a rare and complex presentation of autoimmune RA and anti-TNF treatment failure in a patient with XLA. These findings underline the need for further investigation into immune dysregulation in XLA and the implications for autoimmune disease development and treatment response [3].

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A Nationwide Analysis of Temporal Trends and Outcomes in Hospitalized Patients with Predominantly Antibody Deficiency (PAD) Using the National Inpatient Sample (NIS)

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Rationale: Predominantly antibody deficiency (PAD) is associated with increased susceptibility to infections and chronic complications, yet we lack population-level data on its impact on hospitalization outcomes in the United States. We conducted a nationwide analysis to evaluate healthcare utilization, mortality, and discharge patterns among PAD patients compared with other hospitalized patients.

Methods: We performed a cross-sectional analysis from 2017 to 2020 using the National Inpatient Sample (NIS), part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality. ICD-10 codes were used to identify PAD-associated admissions and assess hospitalization outcomes, including total hospital costs, length of stay, discharge disposition, and in-hospital mortality, as well as temporal trends in these outcomes.

Results: We identified 36,276 PAD-associated admissions and 27,783,886 non-PAD–associated admissions from 2017 to 2020. Patients with PAD-associated admissions were older (mean age 54.9 vs. 49.9 years), predominantly female (57.2% vs. 55.9%), and predominantly white (81.1% vs. 62.2%). Patients with PAD had hospitalizations that were associated with higher total costs ($33,305 vs. $13,193, $p < 0.0001$) and longer length of stay (8.8 vs. 4.7 days, $p < 0.0001$) compared with non-PAD hospitalizations. PAD-associated admissions were less frequently discharged home routinely (59.9% vs. 67.7%, $p < 0.0001$) and more likely to require home health care (20.6% vs. 13.0%, $p < 0.0001$) or transfer to other facilities (13.1% vs. 13.7%, $p < 0.0001$). PAD-associated admissions had significantly higher in-hospital mortality rates (3.8% vs. 2.2%, $p < 0.0001$). Temporal analysis revealed worsening trends for PAD-associated hospitalizations over time. Total hospital costs increased significantly from $30,224 in 2017 to $40,458 in 2020 ($p < 0.0001$). The length of stay increased from 8.7 days in 2017 to 9.5 days in 2020 ($p = 0.0001$). Discharge to home health care became more frequent over time (19.2% in 2017 to 23.3% in 2020), while in-hospital mortality rose from 3.8% in 2017 to 4.5% in 2020 ($p = 0.0025$).

Conclusions: Patients with PAD had increased healthcare utilization and worse outcomes, including longer and more costly hospitalizations, and increased in-hospital mortality. These outcomes worsened in 2020, potentially reflecting the impact of COVID-19. Further investigation is warranted to identify underlying drivers and develop targeted strategies to improve outcomes in patients with PAD.

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Perforin-Deficient Hemophagocytic Lymphohistiocytosis (HLH) Presenting as Recurrent Shock in a Previously Healthy 13-Year-Old Girl

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HLH is a systemic hyperinflammatory syndrome characterized by the inappropriate overactivation of T cells, NK cells, and macrophages, leading to infiltration and damage of multiple organs. Familial forms caused by genetic defects in granule-mediated cytotoxicity often present in infancy or early childhood and are fatal without treatment. Herein, we describe a previously healthy 13-year-old female with a delayed, indolent presentation of familial hemophagocytic lymphohistiocytosis type 2 (FHL2) due to perforin deficiency.

The patient had no significant past medical history and presented with 1 week of high fevers, a petechial rash, and pancytopenia progressing to fluid-refractory shock requiring multiple vasopressors.

Her initial labs and exam demonstrated splenomegaly, pancytopenia (platelets 13,000, hemoglobin 8.0 g/dL, and ANC 770 cells/μL), triglycerides of 200 mg/dL, ferritin of 1,036 ng/ml, and sIL2R of 10,806 U/ml. Bone marrow biopsy revealed hemophagocytosis with hypocellular marrow (40%). Although these labs are consistent with HLH, they are nonspecific and could also be consistent with an infectious or oncologic etiology, which were highest on our differential.

She was initially treated with broad-spectrum antibiotics, platelet and pRBC transfusions, and a single stress dose of hydrocortisone while she underwent extensive infectious, oncologic, and metabolic workups. Her condition stabilized, and after a week of clinical stability without further treatment, she was prepped for discharge.

Unfortunately, her discharge was delayed by recrudescence of fever, pancytopenia, and hypotension. Further workup at this time revealed reduced NK activity and absent perforin staining (Figure 1). Whole-genome sequencing confirmed a diagnosis of perforin deficiency with compound heterozygous likely pathogenic variants in PRF1: a paternally inherited c.695G>A (p.Arg232His) variant and a maternally inherited c.1337A>C (p.Gln446Pro) (Figure 2). She was started on steroids and ruxolitinib for HLH-directed therapy and demonstrated rapid clinical improvement. She ultimately underwent a matched sibling donor hematopoietic stem cell transplant and remains in good clinical condition 6 months later with full donor chimerism and emerging immune reconstitution.

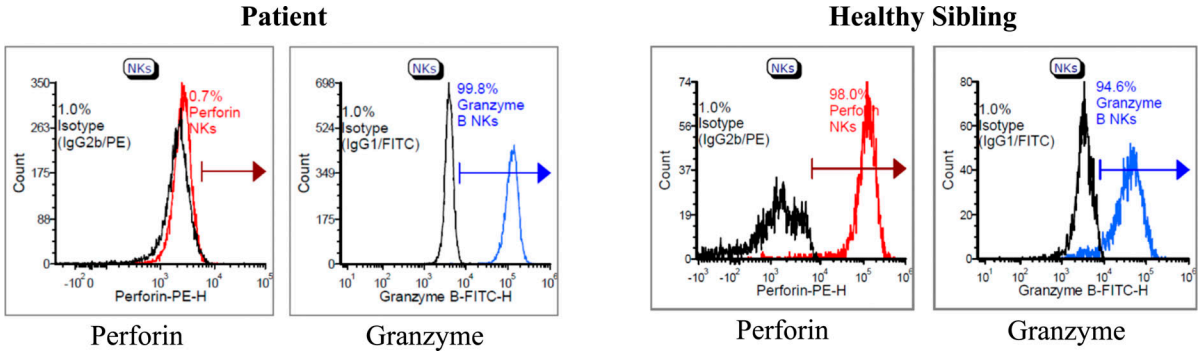

Figure 1. Perforin and granzyme flow cytometry of patient and healthy sibling.

Causative Variant(s) in Disease Genes Associated with Reported Phenotype:

Gene	Disease	Mode of Inheritance	Variant	Zygosity	Inherited From	Classification
PRF1	PRF1-related hemophagocytic lymphohistiocytosis	Autosomal Recessive	c.695 G>A p.(R232H)	Heterozygous	Father	Likely Pathogenic
PRF1	PRF1-related hemophagocytic lymphohistiocytosis	Autosomal Recessive	c.1337 A>C p.(Q446P)	Heterozygous	Mother	Likely Pathogenic

Figure 2. Whole-genome sequencing results.

Though typically presenting in infancy, later presentations of familial HLH are possible and can include atypical features. Providers should retain a high index of suspicion.

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Autoimmune Manifestations as Initial Presentation of NFKB-1 Mutation

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NFKB1 plays a role in the regulation of the innate immune system, adaptive immune system, and inflammation through the canonical NFKB pathway, and therefore dysregulation in this pathway can lead to both immunodeficiency and immune dysregulation. Most commonly, NKFB1 deficiency is associated with both hypogammaglobulinemia and CVID-like phenotypes with loss-of-function mutations in NFKB1 reported to be the most common monogenetic cause of CVID.

We present the case of a patient who presented with symptomatic immune-mediated thrombocytopenia and was subsequently found to have immunodeficiency in his labs, which led to the diagnosis of his NFKB1 deficiency, an inborn error of immunity. This case highlights that patients who present with severe and refractory autoimmune presentations may benefit from an immunology evaluation. A diagnosis of CVID not only places individuals at a higher risk of infection but also at an increased rate of lymphomas, gastrointestinal symptoms, granulomas, lymphadenopathy, and autoimmune phenomena. While previously primary immunodeficiency disorders were thought to present primarily with infections, we know now that noninfectious clinical manifestations can be the initial clinical presentation of an inborn error of immunity and these noninfectious manifestations increase associated morbidity and mortality. Therefore, it is crucial to recognize and evaluate these patients early to allow for appropriate treatment, counseling, and improved outcomes.

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A Presentation of X-Linked Agammaglobulinemia with Normal Immunoglobulin Levels

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Introduction: X-linked agammaglobulinemia (XLA) is an inborn error of immunity caused by loss-of-function variants in Bruton's tyrosine kinase (BTK) on the X chromosome. This defect disrupts B cell development, resulting in low or undetectable immunoglobulin levels. Rarely, patients may present with atypical features, including normal immunoglobulin levels. We report a case of XLA with normal immunoglobulin levels.
Case Description: A 12-year-old male with a history of asthma and a maternal half-brother with XLA was admitted to the hospital for an asthma exacerbation in the setting of pneumonia. He had recently been hospitalized within the past month for similar symptoms and was treated with antibiotics for pneumonia. His infection history was unremarkable until the age of 12, when he began to experience frequent upper respiratory infections in the months leading up to his presenting illness. An immunologic evaluation was performed that revealed the following immunoglobulin (Ig) levels: IgG 572 mg/dL, IgA 184 mg/dL, and IgM 50 mg/dL. Lymphocyte subsets were performed showing a CD3 count of 1,041 cells/μL (93%), a CD4 count of 688 cells/μL (59%), a CD8 count of 359 (31%), CD16 and CD56 counts of 58 cells/μL (5%), and a CD19 count of 3 cells/μL (0%). Specific antibodies to streptococcus pneumoniae, measles, mumps, and varicella were not protective. His antibody levels to diphtheria and tetanus were equivocal, but antibodies to rubella were protective. After resolution of his acute infection, examination in clinic was notable for presence of tonsillar tissue and small palpable submandibular and cervical lymphadenopathy. Repeat immunoglobulins revealed an IgG 802 mg/dL, IgA 271 mg/dL, and IgM 44 mg/dL. Next-generation sequencing revealed a hemizygous pathogenic mutation in BTK (c.82C>T and pArg28Cys).
Discussion: XLA typically manifests with severe hypogammaglobulinemia and absent mature B cells in peripheral blood. However, this case highlights an atypical presentation with normal total immunoglobulin levels. A review of the existing literature reveals that atypical presentations are rare but have been increasingly described as a manifestation of this disease. Clinicians should recognize the significant phenotypic and immunologic variability with XLA and consider the diagnosis in patients with recurrent infections, poor specific antibodies, but normal total immunoglobulin levels.

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Validation of a Clinical NGS Panel for Detecting Somatic Variants in 69 Inborn Errors of Immunity Genes

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Nearly 500 genes underlie primary immunodeficiencies (PID). Yet, many patients have no pathogenic variants reported after testing by germline sequencing. Some of these cases will be caused by somatic variants in the inborn errors of immunity genes, increasingly recognized as an important cause of immunodeficiency. However, detecting these somatic variants is challenging. Typically, whole exome and whole genome do not sequence deeply enough to detect variants with low allele fractions. Furthermore, the relevant immunity genes mostly do not overlap with existing targeted cancer genetic panels. Thus, in collaboration with members from the NICER Consortium, we designed a somatic NGS genetic panel to fill this gap in clinical testing by targeting a large number of inborn errors of immunity genes at a sufficiently high read depth with a speedy turnaround time to meet the testing needs of some of the sickest patients in the hospital. Here we describe our clinical validation of this NGS genetic panel. The test targets 69 genes, requires 60 ng of DNA, aims for ~5,000x average read depth and sensitivity down to 2% variant allele fraction, with a turnaround time of 5 days.

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cAMP-Modulated Inflammatory Disease in MAGIS Syndrome

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G protein-coupled receptors (GPCRs) are heterotrimeric protein complexes (composed of α, β, and γ subunits) that mediate cellular responses to a variety of environmental cues. Of the Gα subunits, the Gαi/o family contains inhibitory isoforms of the Gα subunit that have been shown to inhibit adenyl cyclase's production of the secondary messenger cyclic adenosine monophosphate (cAMP). Our lab has recently shown that patients with activating mutations in Gαi2, encoded by GNAI2, suppress production of cAMP and develop MAGIS syndrome (defined by Midline malformations of the brain, Anterior hypopituitarism, Growth retardation, Immunodeficiency/immunodysregulation, and Skeletal abnormalities) [1]. Since phosphodiesterase-4 (PDE-4) inhibitors such as roflumilast reduce cAMP breakdown, we hypothesized that treatment to increase cAMP levels might improve disease. We explored this possibility in a 36-year-old woman with MAGIS syndrome whose disease manifests in recurrent infections, autoimmunity, and increased inflammation, as demonstrated by leukocytosis in the setting of enteropathic arthritis (characterized by tenosynovitis in multiple joints in the setting of chronic colitis). Additionally, she has type 1 diabetes mellitus, as well as severe mixed hyperlipidemia and hypertriglyceridemia, possibly related to her growth hormone deficiency. After starting roflumilast, weekly scoring using the Patient-Reported Outcomes Measurement Information System (PROMIS) showed increased physical function. This was consistent with the patient's self-report of decreased joint pain and objective measures of improved joint and tendon disease as documented by sequential ultrasounds. Leukocytosis normalized and histological findings from sequential colonoscopies showed decreased active colitis. Additionally, her triglyceride, cholesterol, and hemoglobin A1C levels improved. These observations suggest that the suppressed cAMP might contribute to inflammatory disease in MAGIS, and if so, targeted therapy to normalize cAMP might be beneficial in some patients.

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Refractory Hepatocellular Carcinoma in a Patient with CVID

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We report the case of a 47-year-old female with common variable immunodeficiency (CVID) who developed refractory and fatal hepatocellular carcinoma (HCC). She was diagnosed with CVID at age 32 and maintained on subcutaneous IgG replacement. Her medical history was complicated with chronic giardia-induced enteropathy and chronic atrophic gastritis leading to gastric cancer at age 42, for which she underwent a distal gastrectomy. A commercial genetic panel test for inborn errors of immunity involving 207 genes was not diagnostic at the time of her initial CVID diagnosis. Attempts for whole-exome sequencing were unsuccessful due to insurance limitations.

At age 47, she presented with a suspected liver hematoma bleed, which was managed by embolization. Subsequent imaging revealed a liver mass, confirmed as HCC via biopsy. Histological analysis ruled out metastasis from her previous gastric cancer. She had no history of elevated liver functions tests, negative testing for hepatitis B and C, and no evidence of nodular regenerative hyperplasia. She received immunotherapy with druvalumab and tremelimumab followed by Y-90 radio embolization. She did not respond well; lenvatinib was trialed, but she developed malignant ascites, hepatic encephalopathy, and passed away at the age of 48.

HCC in the context of CVID has been reported only once before, in a 50-year-old male with no previously known liver disease and no hepatitis. He also experienced rapid progression and death. This case highlights the aggressive nature of HCC in patients with CVID and underscores the need for further research to understand the underlying mechanisms and develop effective treatments.

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A Novel Homozygous LCK Variant in the SH2 Domain: Understanding Null vs. Hypomorphic LCK Mutations and Immune Dysregulation

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Background: The lymphocyte-specific protein tyrosine kinase (LCK) is a critical proximal component of T cell receptor (TCR)–mediated signaling. LCK deficiency leads to combined immunodeficiency (CID), but patients with null versus hypomorphic mutations present with varying degrees of immune dysregulation, suggesting a differential impact of such mutations on T cell development and function. Although expressed by B and NK cells, how distinct LCK mutations affect their phenotype and functions and immune dysregulation is not well understood. Here, we report the immunological and clinical impact of novel null and previously described hypomorphic LCK mutations.

Methods: To determine the consequences of the novel LCK p.Gly190fs*31 variant, we performed mass cytometry (CyTOF)–based immune phenotypic and functional profiling of peripheral blood mononuclear cells. T cell proliferation responses and NK cell phenotype and function were also assessed.

Results: A novel homozygous variant in LCK (p.Gly190fs31) was identified in a child born to consanguineous parents, presenting with recurrent viral and fungal infections. The immunological phenotype included T lymphopenia with a skewed memory phenotype, decreased T cell proliferation to PHA and absent to anti-CD3 stimulation, decreased isotype-switched B cells and concomitant hypogammaglobulinemia. p.Gly190fs31 variant led to nonsense-mediated mRNA decay, absent protein expression, and impaired LCK-mediated TCR signal transduction. Similarly to the previously described homozygous null p.C465R and hypomorphic P440S mutations, surface CD4 expression was diminished in the patients and heterozygous parents (and CD8 to a lesser extent). Additionally, CD21lo B cells were expanded in the P440S patient only, which has been associated with other monogenic disorders of immune dysregulation. Further, NK cell function was affected in patients with null mutations only, suggesting the more severe phenotype can be attributed to T and NK cell dysfunction while in the hypomorphic mutation T cell defects dominate microbial susceptibility risk.

Conclusions: Our results shed light on the LCK-mediated signaling threshold requirement for T, B, and NK cell development and differentiation—and most importantly, downstream immune dysregulation complications. These data could be leveraged to identify null vs. hypomorphic defects in rare CID/immune dysregulation due to proximal TCR signaling and to design chimeric antigen receptor cellular therapies applicable to autoimmune disorders and malignancies.

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Malignancies and Cryptococcal Infection in a Patient with Ataxia-Telangiectasia

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Ataxia-telangiectasia (A-T) is an inborn error of immunity caused by mutations in the A-T-mutated (ATM) gene, involved in coordinating cellular signaling pathways in response to DNA double-stranded breaks and oxidative stress. This results in immunodeficiency, neurodegeneration, and increased risk of malignancies. The most prevalent types of malignancy in A-T patients are leukemia and lymphoma, but multiple primary hematologic malignancies are uncommon. While A-T results in combined immunodeficiency with frequent bacterial sinopulmonary infections, opportunistic infections are very rare, and cryptococcal infections have not been reported. We present the case of a 5-year-old girl diagnosed with T cell acute lymphoblastic leukemia at the age of 2. She was referred to immunology due to severe lymphopenia and infections complicating her chemotherapy course and was diagnosed with A-T. After 1 year of remission, she presented with back pain, and a bone marrow biopsy confirmed a new CD20+CD19+ mature large B cell lymphoma. She received chemotherapy per ANHL1131 Group C1 with rituximab and successfully achieved remission. She was maintained on immunoglobulin replacement therapy and PJP prophylaxis. She remained significantly T and B cell lymphopenic (Table 1) and developed respiratory insufficiency with persistent rhinovirus/enterovirus requiring O_2 supplementation. Eight months after completion of her B cell chemotherapy, she returned to the hospital for acute worsening respiratory status. Despite antibiotics, her respiratory status worsened, prompting further workup with an expanded differential including interstitial lung disease, bronchiectasis, and opportunistic infections. A bronchoalveolar lavage was performed, with fungal cultures growing Cryptococcus (Figure 1). Serum cryptococcal antigen (CrAg) resulted positive; however, lumbar puncture reported a normal opening pressure with negative cerebrospinal fluid CrAg. Fluconazole was not effective, so she was treated with amphotericin B and flucytosine for two weeks, followed by fluconazole maintenance therapy.

Table 1. **Lymphocyte characterization**

Component	
Reference range in cells per cubic millimeter	
Total T Cells (CD3 Avg)	758
1,400 – 3,700	
Total Suppressor Cells (CD8)	316
490 – 1,300	
Total Helper Cells (CD4)	236
700 – 2,200	
Helper-Suppressor Ratio	0.75
Total B Cells (CD19)	186
390 – 1,400	
Total NK Cells (CD16/CD56)	852
130 – 720	

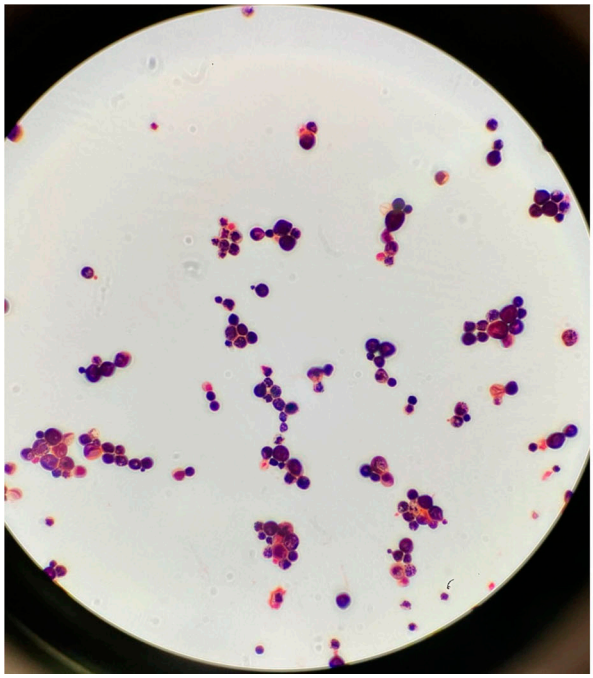

Figure 1. Microscopic and macroscopic images of *Cryptococcus* on fungal culture from bronchoalveolar lavage.

We report a case of a 5-year-old girl with A-T diagnosed after almost a complete course of chemotherapy with numerous imaging studies, possibly contributing to a second malignancy. In addition, we report the first case of cryptococcal pneumonia in a patient with A-T. For patients with A-T and a history of malignancy, opportunistic infections such as cryptococcus should be considered.

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Successful Treatment of Refractory Disseminated Coccidioidomycosis with Adjunctive Interferon-γ

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Background: Coccidioidomycosis (CM) is an infection caused by the *Coccidioides* ssp., which are endemic to the southwestern United States and Mexico. Most cases of CM are asymptomatic or cause mild respiratory illness, but 1% progress to extrapulmonary multi-organ dissemination, which can be severe or even fatal. When standard antifungal treatment regimens are inadequate, immunomodulatory interventions may be required. Here we present a case of refractory disseminated CM (DCM) that achieved remission with the addition of recombinant IFNγ.
Case Presentation: A previously healthy 19-year-old African American male was referred to the NIH with refractory DCM, complicated by a paraspinal phlegmon and a T10 compression fracture. His infection failed to respond to treatment with itraconazole and amphotericin B. The patient had no history of recurrent or severe infections and no family history of immune deficiency or autoimmunity. He lived for a year in Arizona prior to diagnosis, where he was likely exposed to the pathogen. CT imaging revealed severe disseminated infection in the lungs and pleural space, with lytic lesions in several thoracic spine vertebrae, as well as a pathologic T10 fracture. Lung biopsies and serum testing confirmed DCM without secondary infection. Upon admission, the patient's CRP was elevated (65.3 mg/l). Despite initiating treatment with amphotericin B, caspofungin, and posaconazole, the infection continued to progress. Amphotericin B

was discontinued due to side effects, and IFNγ therapy was initiated subcutaneously at 50 mcg/m 2-3 times weekly. The patient showed rapid improvement and was discharged on posaconazole and IFNγ alone, with reduced pain and normalizing CRP levels (2.2 mg/L) within one month. A follow-up CT scan at two months showed a marked reduction in measurable disease.

Discussion: We present a case where adjunctive IFNγ led to successful and significant symptom improvement when no other treatments were effective. Treating DCM with IFNγ could be effective in enhancing immune responses in treatment-resistant cases, leading to improved clearance of refractory fungal infections, even in patients with no clearly defined immunodeficiency.

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Clinical Outcome and Quality of Life in Patients with ARPC1B Deficiency Managed Conservatively or with Allogeneic Hematopoietic Stem Cell Transplantation

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Background: ARPC1B deficiency leads to a combined immunodeficiency characterized by early clinical onset, recurrent infections, and platelet abnormalities with bleeding tendency. Although most patients with ARPC1B mutations tolerate transplant conditioning, with a high rate of immunodeficiency resolution, there is a lack of studies comparing the clinical outcome and quality of life of patients undergoing transplantation or treated conservatively. The aim of the study is to compare ARPC1B patients managed conservatively and with HSCT assessing clinical outcome and quality of life.

Methods: The study was approved by ESID, EBMT, and CIS inborn error working parties. The inclusion criteria are patients with ARPC1B deficiency genetically confirmed and treated conservatively or with HSCT. Clinical data including symptoms, genetics, IDDA 2.1 score at last follow-up, and HSCT-related features were collected by local physicians and anonymized. Patients included in the study completed age-related quality of life questionnaires: PedsQL 4.0 and SDQ for children and SF 12 for adults, respectively.

Results: Thirteen centers from nine countries have been involved, collecting data from 20 patients. Clinical onset was early in all patients (median age 1 month [0-36]). The most frequent homozygous variant was c.311G>C (20%). Eight out of the 20 patients (40%) received allo-HSCT at a median age of 8.8 years [0.76-16.2]. The main clinical features are summarized in Table 1. At last available follow-up, 17 out of 20 patients are alive (85%), with 3 out of 8 patients dead after transplant. The median age at follow-up was 10.41 (1.58-36) for non-transplanted

and 14.85 years (0.83-22.2) for transplanted patients. At the time of writing, 10 out of 17 patients (58.8%) had completed the QoL questionnaire (8/12 not transplanted, 2/5 transplanted). Preliminary results from the quality of life questionnaires are highlighted in Figure 1A-B.

Table 1.

	HSCT		No-HSCT		Total n
	n=8	100%	n=12	%	n=20 (100)
Infections	8	100	11	92	19 (95%)
Recurrent AOM	4	50	9	75	13 (65%)
URTI	5	62.5	3	25	8 (40%)
LRTI	5	62.5	6	50	11 (55%)
Sepsis	3	37.5	0	0	6 (30%)
CNS infections	0	0	1	8	3 (15%)
Skin infections	6	75	9	75	15 (75%)
Severe Warts	2	25	4	33	6 (30%)
Acute/Chronic CMV	2	25	4	33	7 (35%)
Bleeding	3	37.5	8	67	11 (55%)
Enterorrhagia	3	37.5	7	58	10 (50%)
Recurrent epistaxis	0	0	2	17	2 (10%)
ITP	3	37.5	3	25	6 (30%)
Severe eczema	6	75	8	67	14 (70%)
Skin vasculitis	2	25	5	42	7 (35%)
Arthritis	2	25	4	33	6 (30%)
Lymphoproliferation	2	25	1	8	3 (15%)
IBD-like	2	25	4	33	6 (30%)
Last follow-up IDDA 2.1 score	32.9 [4.1-174]		33.9 [6.9-66]		32.9 [4.1-174]

HSCT: Hematopoietic Stem Cell Transplantation; **AOM**: Acute Otitis Media; **URTI**: Upper Respiratory Tract Infection; **LRTI**: Lower Respiratory Tract Infection; **CNS**: Central Nervous System; **CMV**: Cytomegalovirus; **ITP**: Immune Thrombocytopenic Purpura; **IBD**: Inflammatory Bowel Disease; **IDDA**: Inflammatory Disease Damage Assessment

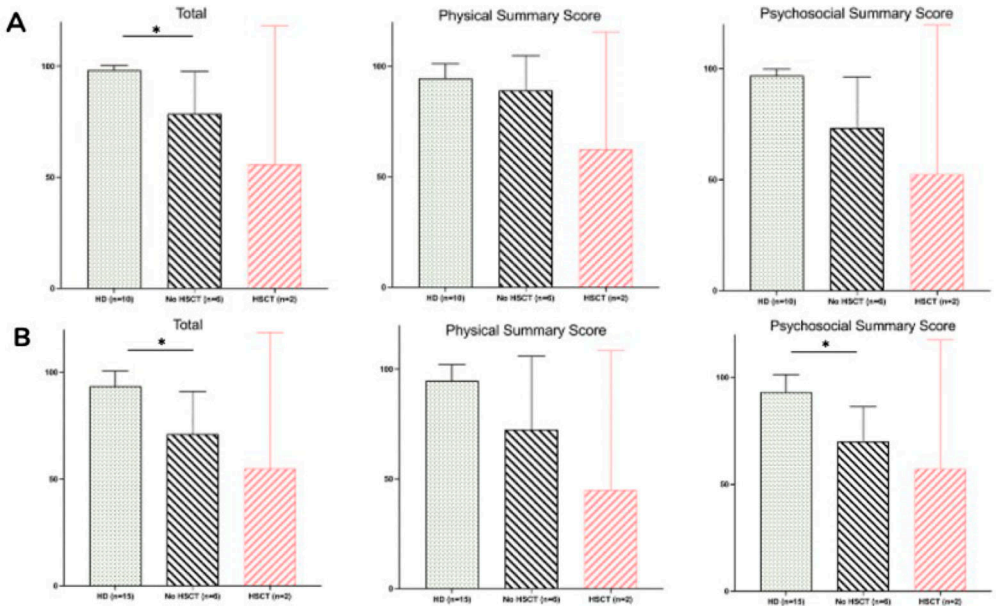

Figure 1. Patient (A) and proxy (B) PedsQL 4.0 scales scores of pediatric patients with ARPC1B deficiency. Scores are compared with children with healthy pediatric population.

Conclusion: Preliminary results confirm that HSCT in ARPC1B deficiency is feasible and effective. Even if preliminary, QoL was significantly reduced in patients treated conservatively compared with healthy donors. Notably, there is a marked reduction in the frequency of bleeding, eczema, and autoimmune/autoinflammatory symptoms in the HSCT group. More data are needed to determine its impact on patient outcomes and quality of life.

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Long-Term Viral Presence in Monocytes Correlates with Dysregulation of Innate Immunity in Patients with SARS-CoV-2–Related Multisystem Inflammatory Syndrome in Children

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Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a severe postinfectious complication associated with SARS-CoV-2. Although the crucial pathogenic role of the monocyte compartment is known, information regarding the mechanisms and maintenance of the inflammatory trigger is lacking. Genetic variants in the OAS/RNase L pathway, involved in viral double-stranded RNA (dsRNA) sensing and the modulation of inflammatory responses, have been identified in patients with MIS-C. We conducted a comprehensive analysis, including the study of NLRP3 inflammasome activation, blood biomarkers, and autoantibodies, as well as transcriptomic and proteomic profiling.
Methods: Peripheral blood mononuclear cells (PBMCs), plasma, and RNA samples from MIS-C patients were analyzed. PBMCs were stimulated with lipopolysaccharide (LPS) and adenosine triphosphate (ATP), and inflammatory responses were quantified using enzyme-linked immunosorbent assay (ELISA), flow cytometry, and Imaging Flow Cytometry (IFC). Apoptosis was assessed via annexin V staining. Type I interferon (IFN) signatures were measured using qPCR. Pro-inflammatory cytokines were evaluated using an automated ELISA system (ELLA). RNA sequencing (RNA-seq) data were analyzed through bioinformatics pipelines, including gene set enrichment analysis (GSEA), while proteomics data were processed using weighted gene coexpression network analysis (WGCNA).
Results: We found a monocyte exhaustion phenotype, demonstrated by reduced inflammasome activation in response to stimuli and an associated lack of IL-1β secretion (Figure 1A-B). Intriguingly, dsRNA was detected in monocytes from MIS-C patients even during follow-up, suggesting a long-lasting viral presence that could drive sustained immune activation (Figure 1C-D). Blood biomarker profiling, bulk RNA-seq, and proteomic analyses revealed a signature characterized by the activation of genes involved in antiviral response, systemic inflammation, oxidative stress, and coagulation pathways. Additionally, we observed anti-IL1RA autoantibodies in 40-50% of patients, consistent with previous reports.

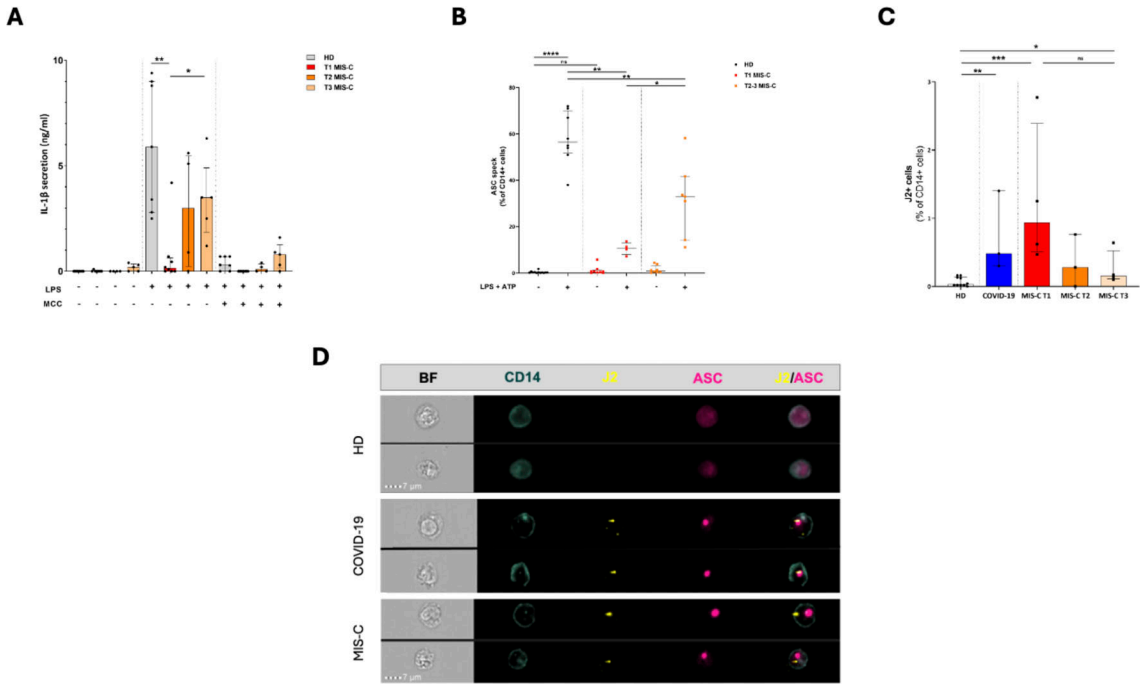

Figure 1. (A) In vitro inflammatory cytokine secretion by MIS-C patients' PBMCs (T1: 0 to 10 days from onset, T2: 10 to 30 days from onset, and T3: over 30 days from onset) of as measured in culture supernatant after 18 hours with or without stimulation with the indicated stimuli. The NLRP3 blocker MCC950 inhibited secretion, indicating that secretion of IL-1β is dependent on the NLRP3 inflammasome. (B) Percentages of spontaneous and after ASC specks detection in monocytes (*left*) and after stimulation (LPS+ATP, *right*) from controls (HD), MIS-C patients in acute stage (T1), and during follow-up (T2-3) by flow cytometry. Representative imaging flow cytometry images and analysis (C, D) of monocytes from HD, patients with COVID-19 (*blue*), and MIS-C patients (T1: *red*, T2: *orange*, T3: *light orange*) stained for dsRNA (anti-J2 antibodies) and ASC. ASC, apoptosis-associated speck-like protein containing a CARD; HD, healthy donors; IQR, interquartile range; MCC, MCC950 NLRP3 inhibitor. Data are expressed as median ± IQR. *P < .05, **P < .01, ***P < .005, ****P < .001 as assessed by Mann–Whitney t test.

Conclusion: Our findings underscore the multifaceted nature of immune dysregulation in MIS-C, encompassing monocyte exhaustion, persistence of intramonocytic dsRNA, autoantibody formation, and a distinct transcriptomic and proteomic signature. This study provides insights into the underlying mechanisms driving sustained inflammation in post-COVID syndromes.

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Newborn Screening for Inborn Errors of Immunity via Whole-Genome Sequencing: A Pilot Study

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Newborn screening by T cell receptor excision circle (TREC) measurement has transformed the care of severe combined immunodeficiency disease (SCID) by identifying babies and intervening prior to symptoms and/or infection. Many other inborn errors of immunity (IEI) could be managed similarly but cannot be identified by the TREC screen. The Genomic Uniform-screening Against Rare Disease In All Newborns (GUARDIAN) study was initiated with the aim of expanded genome-based newborn screening for actionable diseases across disciplines—including an expanded and evolving list of IEI—within a diverse population of newborns. Out of the first ~10,000 asymptomatic newborns screened, four possible IEI were identified, none of whom had abnormalities on the standard TREC screen. These included

1) a male with hemizygous IL2RG c.664 C>A p.R222S—previously reported in 2 patients with atypical X-SCID. He had a CD3 count of 1319 (polyclonal, 63% naïve), B cell count of 704, and NK cell count of 2792 cells/μL with normal proliferation to phytohemagglutinin, but markedly decreased IL-2– and IL-7–induced pSTAT5 activation. He underwent successful haploidentical stem cell transplantation; 2) a male with compound heterozygous variants in ADA (c.454C>A p.L152M—reported in SCID, and c.548C>A p.A183D—a variant of uncertain significance [VUS]). Despite normal percentages and numbers of naïve and memory CD4 and CD8 T cells, recent thymic emigrants, B cells, and NK cells, his RBC ADA activity level was 0 with a modest elevation in dAXP—consistent with ADA-deficient combined immunodeficiency associated with a delayed onset presentation. Therapeutic intervention is under consideration; 3) a female with compound heterozygous C9 variants (- c.346 C>T p.R116* - pathogenic and c.1511 A>T p. E504V - VUS). Complement studies showed low normal C9 function and low normal CH50 indicating minimal risk for terminal complement deficiency-associated infection; and 4) a female with heterozygous STAT1 c. 181del p. L61Cfs*23 that is being evaluated now. These cases illustrate the potential for expanded genome-based newborn screening to identify newborns with medically actionable IEI at frequencies likely much higher than standard TREC screening. They also highlight the importance of efficient laboratory immunophenotying, VUS assessment, genetic counseling, and, when indicated, prompt management.

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Population Pharmacokinetic Modeling and Simulation of Immune Globulin Intravenous (Human), 10% Liquid in Pediatric and Adult Patients with Primary Immune Deficiency Disorders

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Background: Immune globulin intravenous (human), 10% liquid (IVIG) (BIVIGAM®) is approved for use in patients with primary immunodeficiency disorders (PIDD). To support a post-marketing requirement for pharmacokinetic (PK)-focused assessments in pediatric patients aged 2-16 years, a model-informed drug development approach was used to increase number of patients to improve estimation of factors affecting drug exposure and evaluate application of allometry for this plasma-derived therapeutic.
Objectives: 1) Characterize total immunoglobulin G (IgG) PK of BIVIGAM® in children and adolescents with PIDD using a population PK (PPK) modeling approach; 2) Quantify the impact of age or body weight on the PKs of IVIG; and 3) Compare simulated exposure of BIVIGAM® between pediatric and adult subjects to support supplemental PK and efficacy.
Methods: A PPK model was developed using pooled adult and pediatric data from 2 studies in 79 subjects (phase 3 study Nabi-7101 [NCT00538915; n = 63] and phase 4 study 994 [NCT03164967; n = 16]) with 3, 9, 13, and 54 subjects in age-groups of 2 to <6 years, 6 to <12 years, 12 to 16 years, and >16 years, respectively. Covariate analysis evaluated associations between age and body weight with IgG clearance. Fixed and estimated allometry were used to simulate and conservatively extrapolate therapeutic efficacy.
Results: Serum IgG PK of IVIG following intravenous infusion was well characterized using a 2-compartment model, based on 1243 IgG concentrations, with body weight confirmed as the sole covariate affecting total IgG clearance and volumes of distribution. Model-based clearance values when estimating allometric exponents were comparable across age-group categories (Table 1). Simulations performed for every 4-week dosing cycles for both model types (Figure 1) suggested ≥90% of subjects would achieve ≥5 g/L trough levels (minimum recommended level) for a mid-range dose of 500 mg/kg every 4 weeks.

Table 1. **Distribution of post hoc clearance values (dL/day/kg) for estimated and fixed allometric exponents models**

Estimated Allometry				**Fixed Allometry**	
Age Group	**N**	**Mean**	**CV(%)**	**Mean**	**CV(%)**
2 to <6 years	3	0.0149	6.7	0.0185	22.2
6 to <12 years	9	0.0146	15.8	0.0165	27.9
12 to ≤16 years	13	0.0137	21.2	0.0143	24.5
>16 years	54	0.0145	24.8	0.0147	25.2

Abbreviations: CL=clearance; CV=coefficient of variation; N=number of subjects with available information.

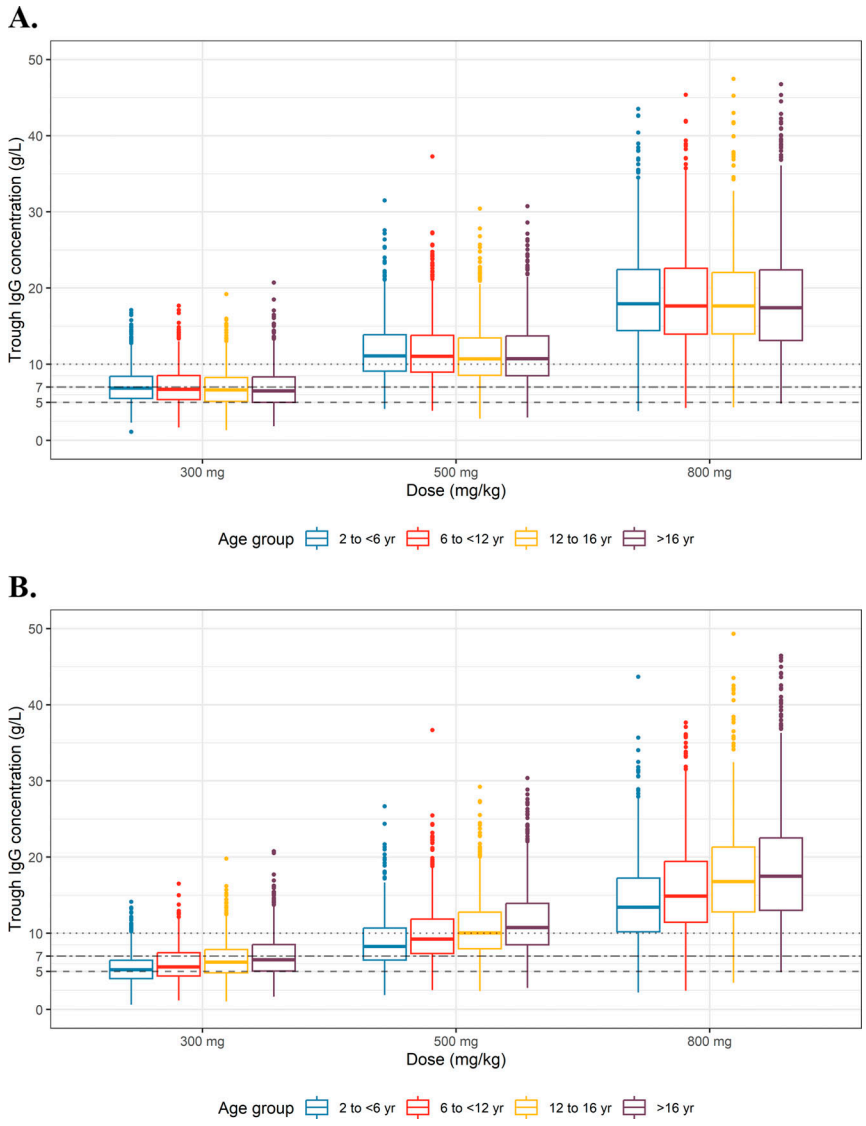

Figure 1. Simulated total trough IgG concentration following 4-week cycles of BIVIGAM® for (A) estimated and (B) fixed allometric exponents models. Note: The box starts in the quartile (25%) and ends in the third quartile (75%) of trough concentration in each age-group. The solid line in each box represents the median of trough concentration in each age-group. The dots represent the subjects with trough concentration more than 1.5 × IQR from the closest edge of the box. Abbreviations: IgG = immunoglobulin G; IQR = interquartile range.

Conclusions: Simulation from models with estimated and fixed allometric predicted trough IgG levels for a virtual population of 1000 subjects across pediatric age-groups with the recommended BIVIGAM® dosage of 300 to 800 mg/kg and confirmed clinically acceptable trough IgG levels (~7 g/L) would be achieved to support dosing recommendations for patients ≥2 years of age with PIDD.

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Baby's First Test: Importance of the Newborn Screen in the Diagnosis of SCID

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Introduction: Severe combined immunodeficiency (SCID) is defined as the inability of hematopoietic stem cells to differentiate into mature T cells, with or without B and natural killer (NK) cells. The most common genes involved include IL2RG, RAG1/RAG2, and ADA. The estimated incidence of SCID in the United States is 1 in 58,000 live births, but with the inclusion of SCID on the newborn screen (NBS), initiated between 2010 and 2018, survival has improved significantly through early identification and intervention. If intervention is performed before 3.5 months of age, survival increases to 94% compared with after 3.5 months of age with a survival rate of 70%.

Case Presentation: A 7-month-old female was admitted for acute respiratory failure secondary to bocavirus infection. The development of leukopenia, deteriorating clinical status, and lack of a completed NBS prompted a workup for an inborn error of immunity. Quantitative immunoglobulins were undetectable with low lymphocyte counts (Table 1). Flow cytometry showed markedly decreased B cells and T cells but retained NK cells, consistent with T-B-NK+SCID and concerning for RAG1-mutated SCID. A genetic panel revealed two pathogenic variants in RAG1:(c.1682G>A, a missense variant, and c.2487_2488delinsTT, a nonsense variant) (Table 2), confirming as autosomal recessive SCID. With improvement of respiratory status, intravenous immunoglobulin (IVIG) and anti-fungal and *Mycobacterium avium* complex prophylaxis were initiated. She continues monthly IVIG, prophylactic antibiotics and antifungals, and clinical monitoring while waiting for allogeneic hematopoietic stem cell transplant (HSCT). A pretransplant chest computed tomography scan revealed pulmonary nodules. At one year of age, she awaits HSCT, delayed for treatment of presumed fungal infection.

Table 1. **Lymphocyte count.**

	Absolute Count (mm^3)	**Reference Range[7] (mm^3)**	**Percentage (%) of total lymphocytes (unless otherwise noted)**
Absolute Lymphocyte Count	264	3,400 - 9,000	
CD3	140	1,900 - 5,900	53.1
CD4	122	1,400 - 4,300	46% of CD3
CD8	10	500 - 1,700	3.8% of CD3
CD19	<1	610 - 2,600	0.05
CD16/56	119	160 - 950	45.2
CD45RA of CD4	6	396-3,111	5.1% of CD4
CD45RA of CD8	2	264-1,421	14.9% of CD8
CD3 RA/RO	0.1		

Table 2. ***RAG1* variants description.**

	Variant 1	**Variant 2**
Sequence Change	c.1682G>A	c.2487_2488delinsTT
Amino Acid Change	p.Arg561His	p.Arg829_Lys830delinsSer*
Classification	Pathogenic	Pathogenic
Zygosity	Heterozygous	Heterozygous
Type of Variant	Missense	Non-sense
GnomAD Frequency	0.003%	Absent
ClinVar	5 entries- Likely pathogenic/pathogenic (Variation ID: 13143)	5 entries- pathogenic (Variation ID: 1034220)
Experimental Studies	Shown affects RAG1 function	Not applicable
Other Evidence	- Observed in other individuals with SCID[8,10] - Other variants that disrupt p.Arg561 amino acid residue have been determined pathogenic	Observed in other individuals with SCID

Discussion: Newborn screening would likely have prompted earlier diagnosis and treatment of this patient, including reverse isolation, antimicrobial prophylaxis, and earlier preparation for transplant. This patient's survival and long-term immune reconstitution may be impaired given that HSCT was not able to be performed before 3.5 months of age.
Conclusion: This case demonstrates the necessity of newborn screening, prompt confirmatory testing, including genetic panels, immune function testing, and HSCT in the diagnosis and management of SCID. With public skepticism of medical interventions rising, it emphasizes advocating for continued education and utilization of the NBS among providers and the public.

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Leniolisib Treatment of Childhood-Onset Lupus Nephritis in Activated PI3K-Delta Syndrome Illustrates Precision Medicine in Pediatric Autoimmunity

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Background: Constitutively active PI3Kδ, as occurs in patients with activated PI3K-delta syndrome (APDS) 1, results in disturbed immune cell development and function leading to microbial susceptibility and immune dysregulation. Leniolisib, a novel, orally FDA-approved bioavailable small molecule inhibitor, was engineered to selectively target PI3Kδ signaling. Leniolisib was shown to partially reconstitute lymphocyte subsets and decrease lymphoproliferation as measured by reduced spleen size and lymphadenopathy. However, its effect in other immune dysregulation manifestations has not been studied.
Methods: We evaluated the patient's peripheral blood by flow cytometry and kidney biopsies by spatial single-cell transcriptomics and proteomics to track LN progression during treatment with leniolisib.
Results: The patient presented at age 10 yo with recurrent sinopulmonary infections and significant bronchiectasis. She developed class IV LN at age 14 yo with autoantibodies to dsDNA, RNP, SSA, and Smith. She was treated with corticosteroids, cyclophosphamide, mycophenolate, hydroxychloroquine, and tacrolimus with suboptimal renal response and infectious complications. She was also treated with rituximab, but early B cell repopulation (with plasmablast skewing) persisted with LN flares. The frequency of her peripheral CD21lo B cells, plasmablasts, CD8 T effector memory, exhausted (PD1+), and senescent (CD57hi) cell subpopulations decreased after three doses of rituximab, with some clinical improvement in renal function, but remained clinically tenuous. She started leniolisib in April 2023, three years after her initial renal biopsy, with marked improvement and weaning of immunomodulation. Multiplexed ion beam imaging (MIBI) demonstrated that the CD45+ leukocytes in the patient's kidney biopsy had a significant increase in the CD8 T cells and M1 macrophages compared with other 30 cLN patients' biopsies, based on single-cell antibody panel in situ immune profiling. These data were further confirmed by spatial transcriptomic data. These tissue-specific findings are consistent with the genetic immunopathology of the patient, particularly the increased CD8 T cellular effector phenotype, which drives the immune infiltrate and renal disease in the APDS patient.
Conclusions: This report illustrates the criticality of understanding the underlying disease mechanism to guide pathway and patient specific therapy in autoimmunity. Further, it demonstrates the therapeutic effect leniolisib for the treatment of APDS-related immune dysregulation complications beyond splenomegaly and lymphadenopathy.

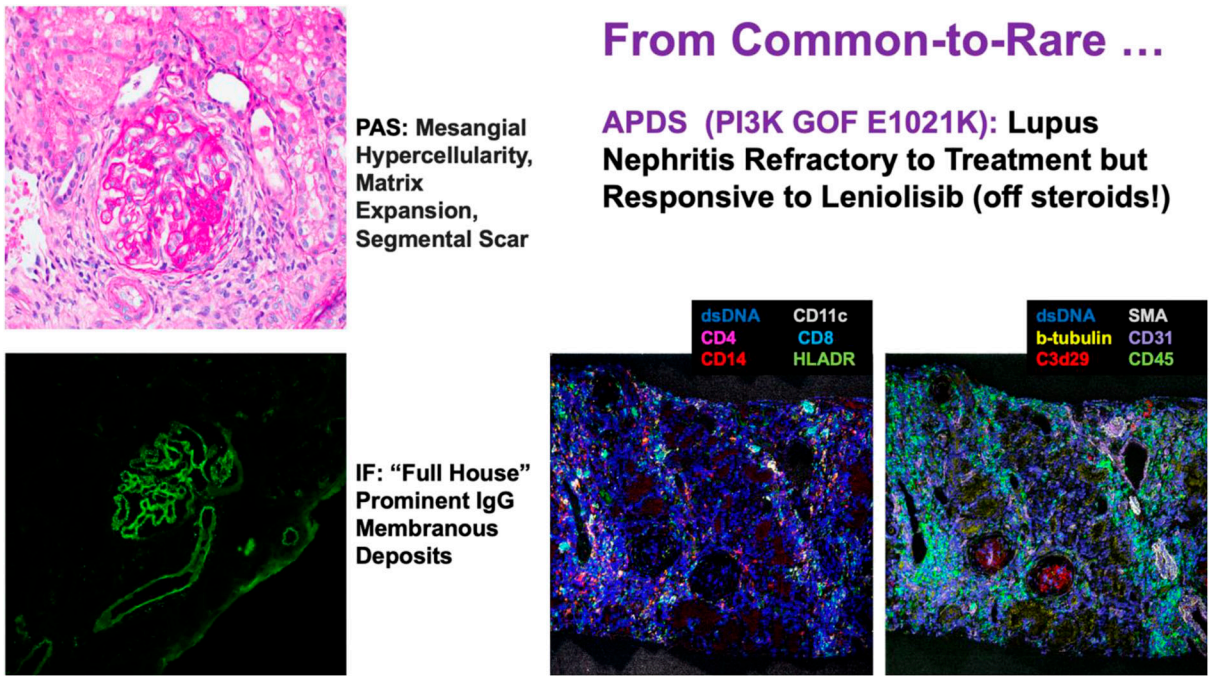

Figure 1.

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FOXN1 Deficiency Associated to Severe Viral Infections and Anti–IFN-α/-ω Neutralizing Antibodies

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The patient, a male from Mexico born to unrelated parents, presented at 20 days old with erythematous macules, scaly plaques, generalized alopecia, purulent otorrhea, cervical lymphadenopathy, hepatomegaly, and eosinophilia. At 4 months, he developed meningitis without an identified pathogen, anemia, and lymphocytosis, treated with broad-spectrum antibiotics. Immunoglobulin levels were IgG 790, IgM 110, IgA 324, and IgE 14.3 mg/dL. A thymus ultrasound showed hypoplasia (1.6 × 0.8 mm).

At 1 year, he experienced gastrointestinal infection and autoimmune thrombocytopenic purpura (platelets 15 x 10^3), which resolved with immunosuppressants. He missed medical follow-ups for 7 years. At 8, he suffered community-acquired pneumonia requiring antibiotics and oxygen therapy, with a recurrence six months later. At 9, dental caries and molluscum contagiosum were noted. At 10, he was hospitalized for severe varicella and pneumonia, treated with acyclovir, ceftriaxone, and vancomycin.

Lymphocyte counts revealed CD3+ 808, CD4+ 428, CD8+ 380, CD19+ 333, and CD16+56+ 974 cells/µL. Lung CT showed fungal infection; *Aspergillus montevidensis* was identified in bronchoalveolar fluid culture, with antigen measurement of 0.94 IDO. He improved with voriconazole, caspofungin, and posaconazole. Nail onychodystrophy was noted during hospitalization.

Severe infections prompted evaluation for immune disorders. Genetic testing identified a heterozygous pathogenic FOXN1 variant (c.1448_1451del, p.Ala483Glyfs*66). Given the link between thymic defects and type I interferon autoantibodies, these were measured due to suspected immune dysfunction.

Interferon-alpha and omega autoantibodies were detected in the patient's plasma using Bio-Plex (Luminex). Neutralizing capacity was confirmed in vitro via STAT-1 phosphorylation assays. The patient's STAT-1 response to IFN-alpha 2 and IFN-omega was significantly reduced, indicating neutralization, even at high IFN concentrations, while IFN-beta remained unaffected.

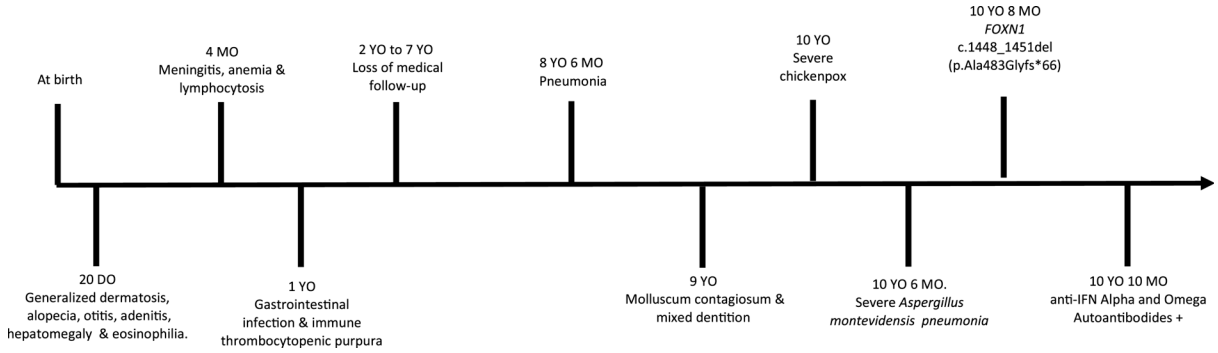

Figure 1.

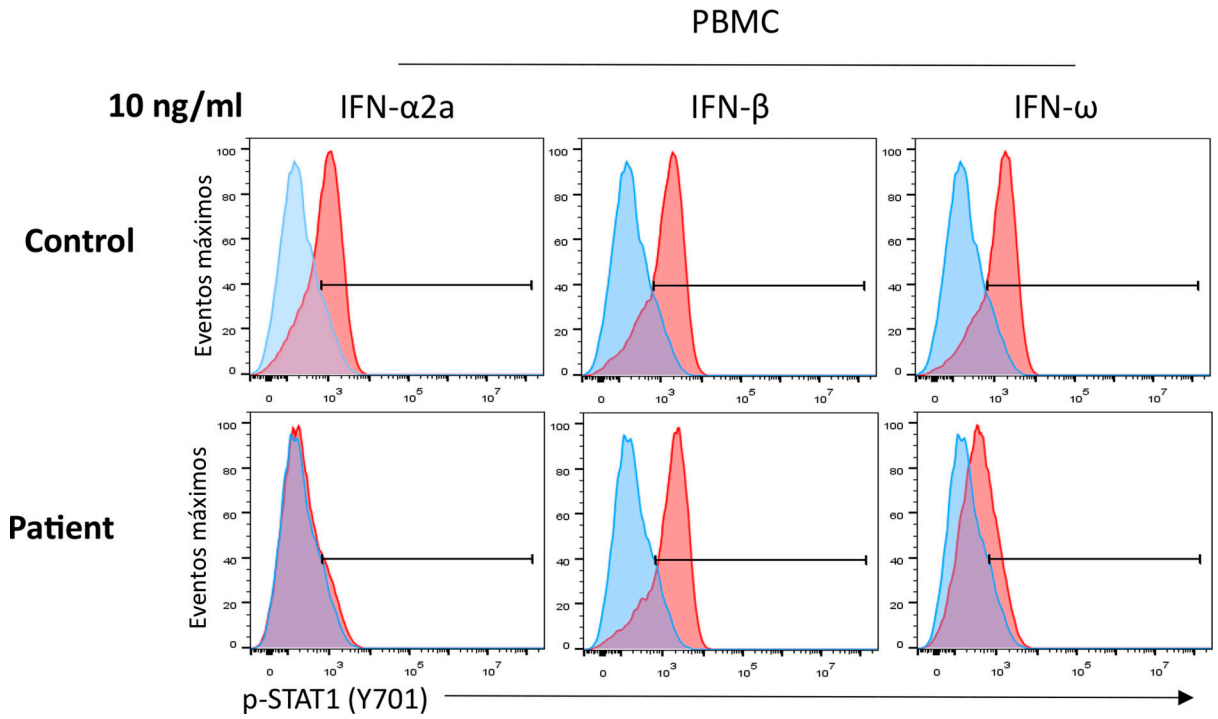

Figure 2. Phosphorylation of STAT-1 (p-STAT1) tyrosine 701 (Y701).

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Chronic Pulmonary and Systemic Inflammatory Manifestations Associated with Interstitial Lung Disease in Patients with Common Variable Immunodeficiency

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Rationale: Interstitial (diffuse) lung disease (ILD) in common variable immunodeficiency (CVID) patients significantly impacts their quality of life and survival. We aimed to identify phenotypic characteristics associated with ILD in a large U.S. cohort of CVID patients.
Methods: We conducted a cross-sectional analysis of 1,470 CVID cases in the USIDNET registry. The primary outcome was physician-diagnosed ILD. Clinical characteristics were compared using chi-square or Wilcoxon–Mann–Whitney tests. Logistic regression evaluated associations between respiratory comorbidities, immunological features, extrapulmonary autoimmunity, and ILD.
Results: There were 103 CVID patients with known ILD (7%). Their median age was 47 years (IQR 25) compared with 50 years (IQR 38) in the non-ILD group, with a similar sex distribution, predominantly female (62.1% vs. 61%). Most ILD patients were asymptomatic for chronic respiratory symptoms, but dyspnea (15.5% vs. 3.6%, $p < 0.001$) and weight loss (14.6% vs. 7.1%, $p = 0.007$) were the most frequent symptoms. ILD patients had lower serum IgA levels (7 mg/dL vs. 29 mg/dL, $p < 0.001$) and CD3+, CD4+, CD8+, and CD19+ lymphocyte counts ($p < 0.01$). Chronic respiratory comorbidities associated with ILD included lung granulomas/multiple nodules (OR 16.75, 95% CI 9.23-30.39, $p < 0.0001$) and bronchiectasis (OR 3.1, 95% CI 1.9-5.1, $p < 0.0001$) independent of age. In contrast, upper airway inflammatory conditions and lower airway diseases (e.g., asthma and COPD) were not significantly associated. CVID patients with extrapulmonary immune dysregulation, including hepatosplenomegaly (OR 6.29, 95% CI 4.16-9.51, $p < 0.0001$), cytopenias (OR 3.9, 95% CI 2.59-5.88, $p < 0.0001$), inflammatory GI disease (OR 1.76, 95% CI 1.18-2.65, $p = 0.006$), and autoimmune endocrine disorders (OR 1.69, 95% CI 1.06-2.69, $p = 0.028$) also had an increased likelihood of ILD. No significant associations were observed between ILD and autoimmune skin or rheumatologic diseases.
Conclusions: CVID patients with ILD feature a severe phenotype characterized by a higher frequency of bronchiectasis, lung granulomas/nodules, reduced IgA, and T and B cells, as well as non-pulmonary immune dysregulation, particularly hematologic, GI, and endocrine manifestations. These findings highlight the need for targeted monitoring of lung disease in patients with these complications. Despite limitations (risk of recall/selection/attrition bias), our study provides valuable clinical insights into ILD in CVID patients and motivates further research into this highly relevant clinical problem.

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Association of the CD45 C77G Polymorphism with Development of Autoimmune Disease and Transplant-Related Outcomes

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Introduction: The CD45 C77G (SNP# rs17612648) polymorphism is present in ~3% of individuals of European ancestry, impairs formation of the CD45RO isoform, and has been controversial regarding its association with autoimmune disease.
Methods: We analyzed clinical samples from 2019 to 2022 in the UAB Cellular Immunobiology Laboratory, identifying patients with the characteristic flow cytometry pattern for this polymorphism.
Results: We identified 23 pediatric females (PF) and 22 pediatric males (PM) with C77G, compared with 817 PF and 1,057 PM with C77C. Similarly, we identified 38 adult females (AF) and 10 adult males (AM) with C77G, compared with 1,001 AF and 314 AM with C77C. The frequency of adults with C77G analyzed in our lab was significantly greater than that of the general Alabama population ($p = 0.0025$). While the frequency of AF with C77G was greater than PF with C77G ($p = 0.0051$), it was comparable with AF with C77C relative to male counterparts ($p = 0.7314$).

Autoimmune conditions or serologic markers (positive ANA or RF) were present in 33% (15/45) of pediatric and 52% (25/48) of adult C77G patients. Pediatric C77G patients with autoimmunity had significantly more hematological/oncological comorbidities (3/15, 20%; $p = 0.0321$) and history of organ transplant (6/15, 40%; $p = 0.0035$) compared with pediatric C77G patients without autoimmunity (0/30, 0% and 1/30, 3%, respectively). Three pediatric C77G autoimmune patients had received hematopoietic stem cell transplant (HSCT) for aplastic anemia or leukemia, with two developing severe graft-versus-host disease (alloimmunity) and the other developing Graves' disease requiring thyroidectomy. Additional pediatric C77G patients with autoimmunity include two thymic transplant recipients that developed complications during the T cell reconstitution period (one with transverse myelitis, the other with macrophage activation syndrome and autoimmune hemolytic anemia). Adult autoimmune and non-autoimmune C77G populations did not differ in overall comorbidities, and no adult C77G patient had a history of hematopoietic cell or solid organ transplantation.

Conclusions: The presence of the CD45 C77G polymorphism in pediatric patients with autoimmune/alloimmune disease, particularly following HSCT or thymic transplant, suggests a potential role for this variant in influencing T cell maturation within the thymus and in predisposing for autoimmunity.

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A Three-Year-Old Male with an Intronic BTK Variant of Uncertain Significance

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A three-year-old male presented to the allergy and immunology clinic after a recent admission for pneumococcal sepsis. His infectious history was significant for several episodes of acute otitis media, and he was fully immunized. Evaluation demonstrated pan-hypogammaglobulinemia (immunoglobulin [Ig]G—230 mg/dL, IgA—<5 mg/dL, and IgM—<5 mg/dL), absent pneumococcal, tetanus, and diphtheria titers. Lymphocyte enumeration showed near-absent CD19+ B cells (20 cells/μL, 0%), mildly elevated CD3+ T cells (5763 cells/μL), and normal NK cells (267 cells/μL). Further inquiry into family history was notable for a 5-year-old brother with several episodes of community-acquired pneumonia and acute otitis media. Immunophenotyping in the sibling revealed pan-hypogammaglobulinemia (IgG—336 mg/dL, IgA—<5 mg/dL, and IgM—33 mg/dL) and near absent CD19+ B cells (4 cells/μL, 0%) as well. Intracellular BTK protein expression via flow cytometry in the index patient was decreased in monocytes (mean fluorescent intensity [MFI] 1.06) as compared with a healthy control (MFI 5.91). Given these findings, genetic testing was pursued. Single-gene sequencing (to 20 flanking intronic nucleotides) of BTK by Laboratory Corporation of America (labcorp®) demonstrated a synonymous variant, c.1899C>T, which was interpreted as benign. An inborn errors of immunity/primary immunodeficiency panel was then sent to Prevention Genetics notable for a hemizygous intronic variant of uncertain significance in BTK, c.1567-23A>C. This variant was not reported in ClinVar and was not predicted to significantly impact splicing of the BTK gene based on available prediction programs. However, it was absent in gnomAD and is mentioned in one previously published patient in a cohort of those with X-linked agammaglobulinemia. Genetic testing in the older sibling is still pending. With the addition of phenotypic and functional data, the suggested reclassification of the BTK variant is likely pathogenic.

XLA typically presents in the first year of life with recurrent infections, low to absent immunoglobulins, and B cells. We describe two siblings with pan-hypogammaglobulinemia, near-absent B cells, and abnormal BTK expression. Initial single-gene sequencing failed to detect the likely culprit BTK intronic variant, which was later noted on repeat testing.

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Evaluating the Role of Genetic Testing for Inborn Errors of Immunity in Pediatric Patients with Very Early-Onset and Early-Onset Inflammatory Bowel Disease

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Introduction: The incidence of inflammatory bowel disease (IBD) has significantly increased in developing countries over the last decade with a rising prevalence among the pediatric population. Very early-onset IBD (VEOIBD), defined as IBD in children younger than 6 years, requires a comprehensive diagnostic approach including clinical history, physical examination, laboratory tests, endoscopy, and genetic evaluation. Literature indicates that 8–20% of pediatric patients diagnosed with VEOIBD have identifiable genetic causes, often involving monogenic mutations related to inborn errors of immunity (IEI), namely those that play a role in intestinal barrier function, innate and adaptive immunity, and autoinflammatory disorders. Identifying these mutations can offer insights into potential therapeutic targets. This

study examines our cohort of VEOIBD and early-onset IBD patients referred to the Stanford immunology clinic, with a focus on the prevalence of monogenic diseases and their clinical implications.

Results: Among the 31 pediatric patients referred for immunologic evaluation at Stanford, targeted genetic testing for primary immune deficiency revealed pathogenic mutations in 7 patients (22%). These included mutations in DUOX2, NOD2, CTLA4 (2), CARD11, and NEMO (Table I). The median age of IBD onset was 6.25 years, with a slight female predominance. Crohn's disease was more prevalent than ulcerative colitis in this VEOIBD cohort. As a note, one 11-year-old female diagnosed with Crohn's was found to be a carrier for LRBA, inherited from her asymptomatic mother. Patients with identified monogenic causes showed significant improvement with targeted therapies, such as abatacept for CTLA-4 haploinsufficiency.

Table 1.

Patient	Gender	Age of Onset IBD-like Symptoms (year)	UC/Crohn's	Pathogenic Mutation
A	Male	1	Crohn's	DUOX2
B	Male	1.5	GVHD vs NEMO colitis/Crohn's	NEMO
C	Female	11	Combined	CTLA4
D	Female	1	Crohn's	CTLA4
E	Female	11	Crohn's	NOD2
F	Male	6-6.5	UC	AS20
G	Female	11	Crohn's	NOD2
Other:				
H	Female	11	Crohn's	Carrier for LRBA

Discussion: Predicting which patients have an underlying monogenic disease remains challenging, emphasizing the importance of genetic evaluation.

Conclusion: Genetic screening plays a crucial role in the management of VEOIBD, providing insights and guiding treatment decision. Targeted therapies should be considered whenever available. The effective management of these complex conditions relies on multi-disciplinary teams, underscoring their pivotal role in comprehensive care.

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A Heterozygous Mutation in the BLM Gene Identified in a Pediatric Patient with an Inborn Error of Immunity

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Bloom syndrome is an autosomal recessive disease caused by loss-of-function mutations in the BLM gene. Mutations in this gene cause deformations in the DNA helicase protein, which is functional in DNA repair. DNA repair is known to have an important role in the development of antigen receptors on B and T cells; therefore, DNA repair disturbances may lead to immunodeficiency. However, the cause of immunodeficiency in Bloom syndrome is still undergoing investigation. This case involves a one-year-old with an inborn error of immunity which was associated with a heterozygous mutation in the BLM gene. This patient presented with recurrent infections, febrile seizures, and failure to meet developmental milestones. He was found to have CD8 deficiency and eosinophilic gastroenteritis, prompting further investigation. Lymphocyte enumeration included CD3 (54%), CD3 absolute (2,576), CD3+CD4+ (41%), CD3+CD4+ absolute (1,956), CD3+CD8+ (10%) (low), CD3+CD8+ absolute (477) (low), CD4/CD8 ratio (4.10) (high), CD3+CD4-CD8- (2%), CD3-CD16+CD56+ (11%), CD3-CD16+CD56+ absolute (525), CD19 (35%), and CD19 absolute (1,670). IgG, IgA, and IgM were within normal limits. Genetic testing of 429 genes depicted a heterozygous mutation in the BLM gene (c.2193+1_2193+9del). Poor antibody response to primary polysaccharide vaccines was noted, and this patient was instructed to receive gamma globulin subcutaneously. The mutation causes a disruption of a splice site in intron 9 of the BLM gene. This results in exon 9 being skipped, and the development of a premature termination codon causes nonsense-mediated mRNA decay. The protein encoded by the BLM gene is an ATP and Mg2+-dependent DNA helicase that works

to correct DNA when it is damaged and helps regulate any problems that may occur at the replication fork. Cellularly, patients with Bloom syndrome develop breaks in the chromosome, a high sister chromatid exchange, a slower replication fork due to the activation of the ATM–Chk2–γH2AX pathway, increased blockages of replication forks and anaphase bridges, and additional micronuclei in cells. Further studies will need to be conducted to understand the true ramifications of Bloom syndrome on immunodeficiency in children.

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Delayed Diagnosis in X-Linked Agammaglobulinemia and Its Relationship to the Occurrence of Mutations in the Bruton Tyrosine Kinase Catalytic Domain

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Background: Bruton tyrosine kinase (BTK) is a protein-coding gene crucial for B cell development. It is found on Xq21.3-Xq22 of the long arm of the X chromosome and belongs to the Tec family of cytoplasmic protein tyrosine kinases consisting of 5 structural domains: PH, TH, Src3, Src2, and TK. Pathogenic variants in the BTK gene can fully or partially block B cell development. BTK has been linked to various antibody deficiencies beyond agammaglobulinemia, including CVID. In hypomorphic BTK variants, there are detectable B cells in the periphery that may result in variable levels of serum immunoglobulins and clinical phenotype.
Objective: Investigate the impact of a missense pathogenic hypomorphic BTK variant (p.Arg525Gln) observed in a large kindred.
Results: We plan to assess by flow cytometry BTK protein expression in specific B cell subsets in hypomorphic XLA patients in this kindred. The flow cytometry revealed a uniformly reduced BTK expression in B cells (B cells evaluation is limited by low cell counts). BTK expression was decreased with an unexpected bimodal distribution in monocytes. Since both patients were male, XXY syndrome was initially considered but deemed less likely. The unexpected monocyte expression pattern in the current patient suggests possible somatic mosaicism or other genetic factors, or the two peaks are related to BTK protein degradation, and this may differ in specific cellular compartments or change with age, warranting further investigation.
Conclusions: This highlights the challenges of diagnosing hypomorphic XLA, especially in patients with detectable B cell counts and atypical BTK expression. Flow cytometric analysis of two patients with BTK mutations identified bimodal mosaic patterns of BTK expression in monocytes. This bimodal expression pattern may reflect cellular mosaicism like in mothers who are obligate carriers of XLA. BTK biology with hypomorphic variants remains incompletely understood, particularly how these variants affect B cell development and result in milder antibody deficiency phenotypes, warranting further investigation. This emphasizes the importance of genetic screening in kindreds with XLA and the need for increased awareness of partial XLA among healthcare providers to ensure timely diagnosis and treatment.

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Unmasking NCF1 Gene Defects: Atypical Presentations of p47phox Deficiency in Chronic Granulomatous Disease

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Introduction: Mutations in NCF1 encodes phagocytic nicotinamide adenine phosphate (NADPH) p47-phox protein, which accounts for 23% of chronic granulomatous disease (CGD), a rare inherited inborn error of immunity (IEI). NCF1 has 2 pseudogenes near its

chromosomal locus 7q11.23. Reciprocal crossover between functional genes and pseudogenes in high frequency can obscure DNA interpretation, thereby complicating diagnosis, especially in atypical presentations.

Case 1: A 4-year-old male from Saudi Arabia with recurrent *Rhizopus* skin infections had oxidative burst assay with a broad peak of intermediate granulocyte dihydrorhodamine (DHR) fluorescence and an abnormal population, suggesting AR CGD. Genetic CGD panel identified no variants in known CGD genes. Gene ratios revealed his defect was not found in the common ΔGT region at the start of exon 2. The variant found in NCF1 was c.579 G>A, p. Trp193X, a previously reported pathogenic variant in the NCF1 gene. Western blot showed absent p47 protein, thus confirming NCF1-deficient CGD.

Case 2: A 5-year-old female with a history of congenital heart block and recurrent mucosal aphthous ulcers presented with recurrent fevers. Labs showed low NK counts and elevated sIL-2 receptor but normal lymphocyte counts, immunoglobulins, cytokines, and CXCL9. Lip biopsy suggested orofacial Crohn disease. Whole-exome sequencing was negative. Neutrophil oxidative burst assay showed normal and abnormal granulocyte DHR fluorescence populations of stimulated granulocytes, suggesting the carrier state of CGD. Genetic testing and flow confirmed a ΔGT deletion in p47phox/NCF1 gene.

Discussion/Conclusion: Mutations in genes encoding components of phagocyte NADPH oxidase manifests as CGD. Dinucleotide deletion in NCF1 exon 2 pseudogenes leads to frameshift alterations. This can cause premature stop codons, which replace authentic NCF1. This variation in the ratio of functional genes to pseudogenes can result in masking of CGD on routine testing. Non-ΔGT mutations occur in ∼20% of p47phox patients. Sanger sequencing is sometimes not sufficient to determine the underlying defect in NCF1 due to the extensive sequence homology of NCF1 with pseudogenes. With atypical presentations of CGD as described here, a high index of suspicion is needed in order to broaden workup when evaluating patients with clinical manifestations that suggest possible IEI.

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EBV Susceptibility Associated with RECQL4 Deficiency

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Topic: Novel Genetic Etiologies of PIDs

Preliminary data from this work were accepted and presented as an oral communication at the 21st biennial ESID meeting (October 2024).

Background: Epstein-Barr virus (EBV) is an oncogenic virus. Mostly asymptomatic, primary infection may be complicated by nonmalignant, malignant proliferations, and hemophagocytic lymphohistiocytosis. Infection resolution requires an appropriate cytotoxic T cell response, which depends on sustained T cell expansion. Several inherited EBV susceptibilities are associated with a high risk of complicated infection, which are often characterized by defective T cell expansion.

Methods: Four patients with EBV-related diseases and one with severe CMV were analyzed by whole-exome sequencing, in whom six deleterious biallelic compound heterozygous variants were identified in RECQL4. These mutations are predicted to be highly damaging and absent in exome public databases. RECQL4 is a DNA helicase involved in DNA replication initiation and DNA repair. Patients with RECQL4 variants have been previously reported with several autosomal recessive syndromes associated with poikiloderma and an increased risk of cancer. Few rare cases were also reported with immunodeficiency but no EBV-related diseases. An additional patient carrier of a homozygous null variant in RECQL4 presenting severe combined immunodeficiency and a severe RECQL4-related syndrome was studied.

Results: We showed that RECQL4 is upregulated in activated control T cells upon TCR-CD3 activation. In HEK cells, transiently overexpressed RECQL4 variants of the patients result in a reduced or absent RECQL4 expression. In activated T cells from patients, RECQL4 expression is strongly reduced or absent, and T cells exhibit a proliferation defect and an increased activation-induced apoptosis. In Jurkat T cell line, 3 different shRNA-targeting RECQL4 decrease its expression and induce a cell cycle blockade, proliferation arrest, and an

increased apoptosis. Similarly in control T cells, silencing RECQL4 results in an expansion disadvantage and an increased apoptosis in the infected cells.

Conclusion: RECQL4 deficiency is associated with impaired T cell expansion that may underlie EBV susceptibility in patients.

Late-Breaking Abstract

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HMGCS1 Deficiency Is a Novel Immunometabolic Autoinflammatory Disease with Progressive Myositis

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The mevalonate kinase (MVK) pathway is an essential metabolic pathway for sterol and isoprenoid synthesis. Non-sterol isoprenoids have critical biological functions in the post-translational modifications of numerous signaling molecules via prenylation, including inflammasomes. A defect in prenylation impacts protein trafficking and localization and increases proinflammatory cytokine production. Deficiency of the enzymes in the MVK pathway is known to cause systemic autoinflammatory diseases with a broad spectrum of clinical manifestations. Anticholesterol drug statins, which block the second enzyme in this pathway, HMG-CoA reductase, can lead to muscle inflammation.

We report biallelic loss-of-function variants in the HMGCS1 gene, which encodes for the first enzyme in the MVK pathway, in four patients from three unrelated families who presented with recurrent fever, arthritis, abdominal pain, and progressive myositis. Three patients were homozygous for a rare variant, c.265C>T (p.Arg89Trp), predicted to be deleterious by multiple algorithms. One patient was homozygous for the novel c.572G>C (p.Arg191Pro) variant classified as VUS. The enzyme activity of both mutant HMGCS1 proteins was decreased, suggesting a deleterious effect on the protein function. Preliminary results showed that these missense variants do not affect protein expression or dimerization, which is critical for protein activity. The PBMCs from patients and CRISPR/cas9–edited HMGSC1-deficient cells showed a defect in prenylation, confirming the involvement of the MVK pathway.

HMGCS1-deficient cells displayed an elevated level of IL-1β and IL-18 in response to stimulation with Pam3CSK4 and IFNγ, indicating that HMGCS1 deficiency led to inflammasome activation, which was independent of NLRP3 but was dependent on pyrin. UMAP analysis of peripheral blood single-cell RNA sequencing identified two major cell clusters: NK cells and monocytes. The most differentially upregulated pathways include oxygen/CO_2 transport genes, cell death genes, and NF-κB signaling. Intracellular cytokine staining identified a significant increase of IL-1 β, IL-6, and IFNγ in all monocyte subsets of affected patients compared with unaffected relatives. RNA sequencing of frozen muscle tissues detected strong type I and II IFN signatures. Treatment with a JAK inhibitor ameliorated systemic and muscle inflammation in two patients. Further studies are in progress to understand the spectrum of immune dysregulation associated with the HMGCS1 deficiency.

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Norovirus Infection at the NIH Clinical Center from 2010 to 2023: A Comparative Analysis of Acute vs. Chronic Norovirus Infection with a Focus on Inborn Errors of Immunity

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Rationale: Chronic norovirus infection (CNI) is a significant cause of morbidity and mortality in immunocompromised patients. We sought to determine clinical and virologic features associated with CNI with an emphasis on IEI.
Methods: Norovirus-positive stool samples from 88 patients at the NIH Clinical Center from 2010 to 2023. Longitudinal clinical and virologic data were collected.
Results: Forty-eight patients had CNI; 23 had acute norovirus infection (ANI); 17 patients were unclassifiable. Eighty-three percent of CNI patients had an underlying diagnosis of IEI, including CID (N = 23), CVID (N = 11), and SCID (N = 6). The majority with ANI had hematologic disorders (48%); only 5 (21%) had CVID, CID, or SCID. Mortality in the CNI cohort was 38%. More than half of CNI patients had nutritional defects, including electrolyte abnormalities and hypovitaminosis; 20% required TPN. GII.4 was the predominant norovirus genotype among all patients, although diverse genotype I and II viruses were represented. Gastrointestinal coinfections during CNI infection were prevalent (50%); the most common being enteropathogenic *E. coli* (N = 12) and *C. difficile* (N = 12).

Seventy-seven percent of CNI patients had chronic liver disease, including both cholestatic (N = 18) and hepatocellular (N = 14) patterns. Thirty-three percent (N = 16) of CNI patients had a diagnosis of nodular regenerative hyperplasia (NRH). Only 35% of patients with ANI had chronic liver disease.

Twelve patients with CNI eventually cleared norovirus (median duration of 688 days versus 18 days for ANI). Eight patients cleared in the setting of definitive immune reconstitution, specifically HSCT or gene therapy. Three patients cleared in the setting of immunomodulatory therapy for concurrent IEI-related enteropathy treated with ustekinumab, abatacept, and/or JAK inhibitors. No patient cleared after traditional CNI therapies, including nitazoxanide, ribavirin, or immunoglobulin (PO or IV).
Conclusions: CNI patients were nutritionally compromised with high mortality and a high prevalence of liver disease. IEI with adaptive defects were disproportionately represented in CNI. Common CNI treatments were not effective. CNI consistently resolved with definitive immune reconstitution; some patients cleared infection with immunomodulatory therapy for enteropathy, suggesting a new treatment strategy to be explored in future studies. To our knowledge, this is the largest cohort of CNI with a focus on IEI analyzed to date.

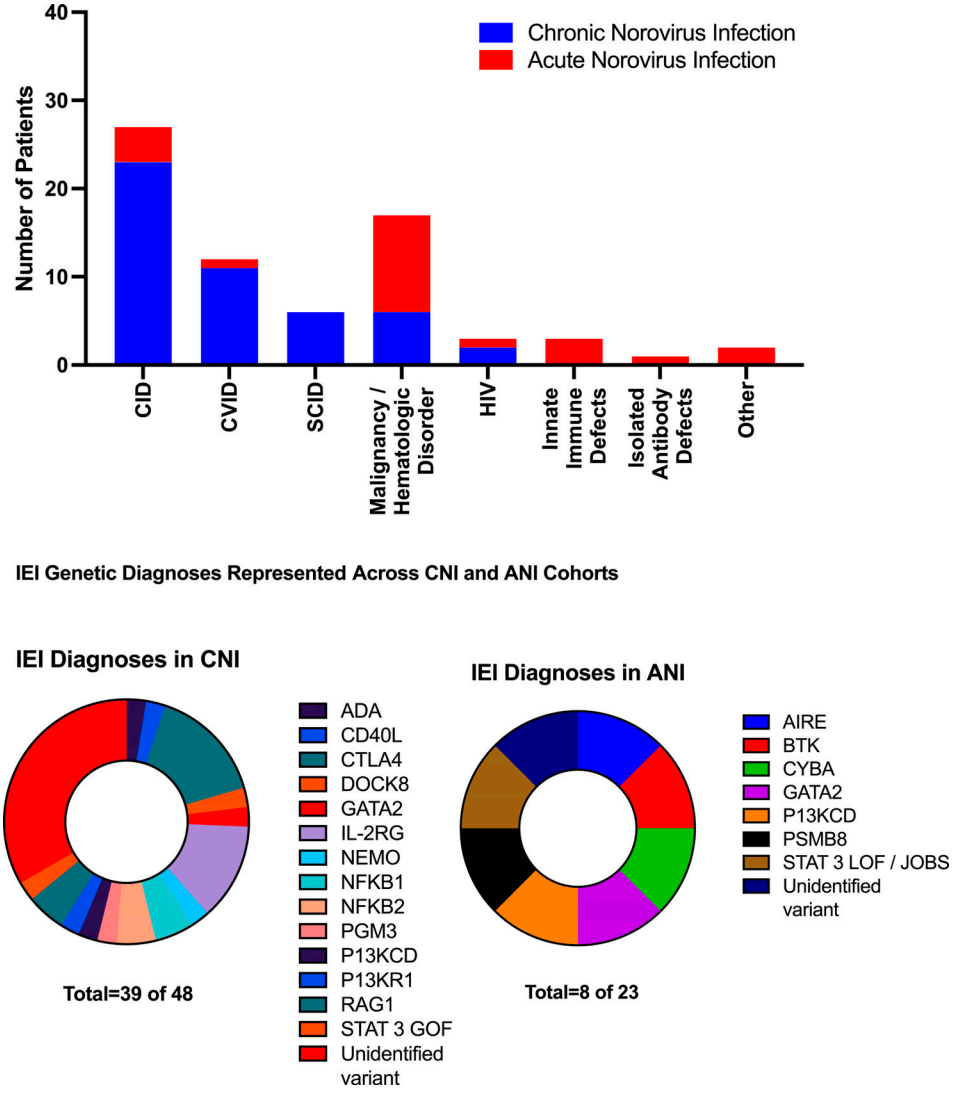

Figure 1. Category of underlying diagnosis.

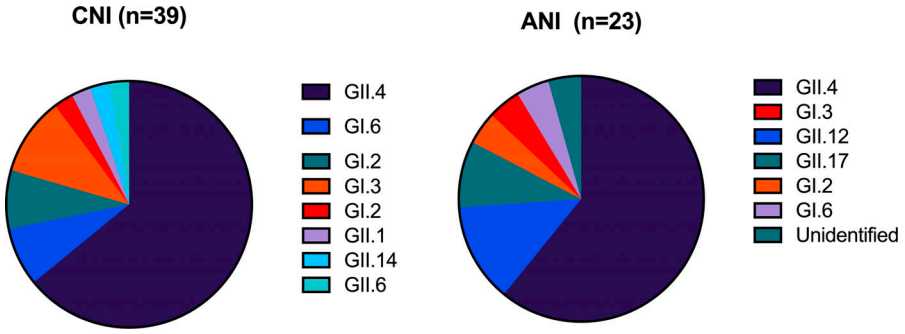

Figure 2. Norovirus genotypes represented across cohorts.

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Functional Overlap of Inborn Errors of Metabolism and Immunity Genes Identifies CD4+ T Cell immunometabolic Requirements

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During the past decade, it has become increasingly apparent that cellular metabolism plays a critical role in the function and regulation of the immune system. Immune cell utilization of specific metabolic pathways influences immune function and can be pharmacologically targeted to alter immune outcomes. The importance of immune cell metabolism and function is further demonstrated by the development of primary immunodeficiencies in patients deficient in certain metabolic pathways. Inborn errors of immunity (IEI) and metabolism (IEM) are Mendelian diseases in which complex phenotypes and patient rarity can limit comprehensive clinical descriptions. Few genes are assigned to both IEM and IEI, but the varied and intensive immunometabolic demands of immune cells suggest greater functional overlap may exist. We applied pooled CRISPR screens to test IEM-associated genes for immunologic roles and IEI-associated genes for metabolic effects in CD4+ T cells and found considerable crossover. Screens of IEM-associated genes showed N-linked glycosylation and the de novo hexosamine biosynthetic enzyme, GFAT (Gfpt1), are critical for CD4+ T cell function. Interestingly, Gfpt1-deficient TH1 cells were more affected than TH17 cells and demonstrated a greater rate of de novo UDP-GlcNAc synthesis. Likewise, screens of IEI-associated genes indicated that the transcription factor BCL11B promotes CD4+ T cell mitochondrial activity and MCL1 expression necessary to prevent metabolic stress. These data illustrate a high degree of functional overlap of IEM and IEI genes and suggest immunometabolic mechanisms for a previously underappreciated set of these disorders.

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Precision Alemtuzumab Dosing Results in Day 0 Target Range Achievement in 80% of IEI Patients and Minimizes Risks of GVHD, Clinically Significant Mixed Chimerism, and Secondary Graft Failure

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Introduction: Reduced intensity and reduced toxicity conditioning regimens offer low rates of toxicities and superior survival for patients with inborn errors of immunity undergoing allogeneic HCT. However, these approaches can be associated with increased rates of mixed chimerism and secondary graft loss. Day 0 alemtuzumab levels of 0.15-0.9 µg/mL minimize the risks of acute GVHD, clinically significant mixed chimerism, and secondary graft failure. We hypothesized that model-informed precision dosing of alemtuzumab with therapeutic concentration intervention (precision alemtuzumab dosing) could achieve target Day 0 alemtuzumab levels of 0.15-0.9 ug/mL in >80% of patients.
Methods: Prospectively enrolled patients were given model-informed initial alemtuzumab dosing of 10 mg/m^2 divided over Days -14 to -12. Alemtuzumab levels were measured through Day -5 or -4. Individual PK profiles were estimated using MW/Pharm software (version 2.4) based on our previously reported population PK model. Patients who were projected to clear alemtuzumab by Day 0 to <0.15 ug/mL were given additional model-informed individualized "top-up" alemtuzumab dosing on Day -3 or -2 (Figure 1).

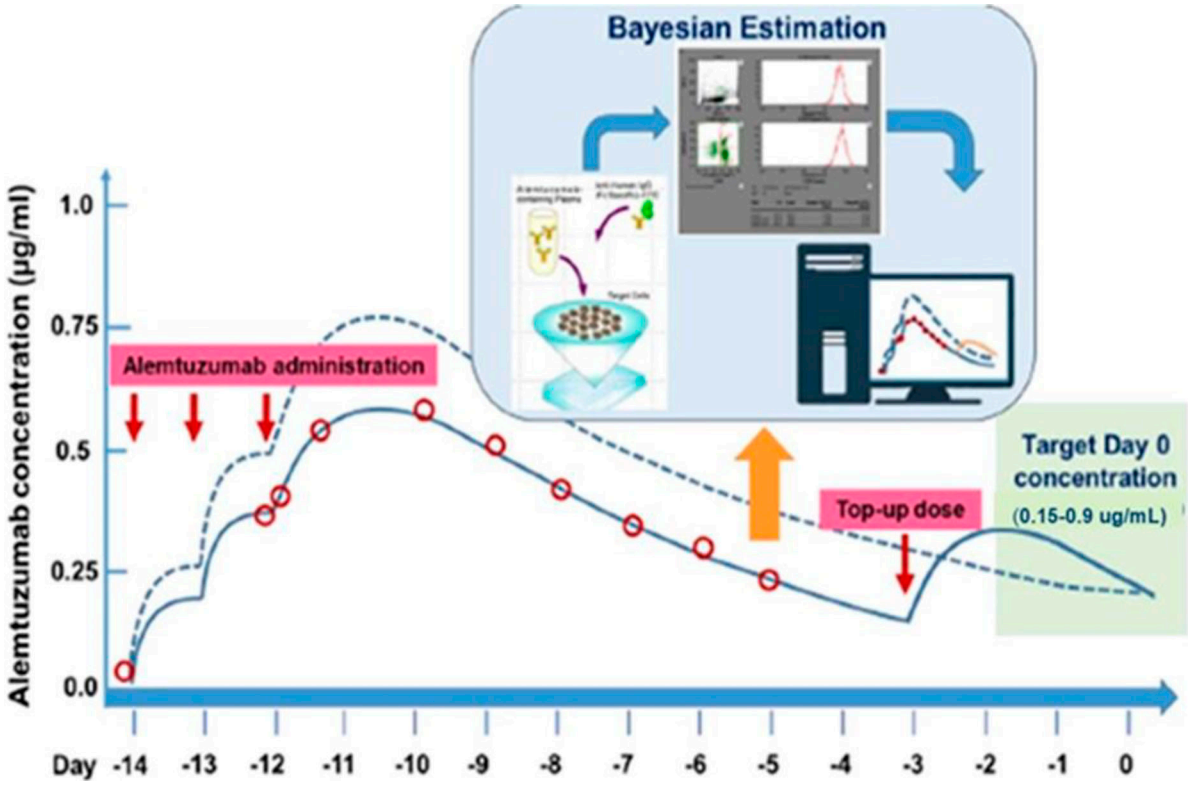

Figure 1.

Results: Twenty patients of median age 1.5 years (range 3 months-23 years) were treated. The underlying diagnoses included HLH (n = 10), sJIA (n = 5), WAS (n = 2), XMEN (n = 1), CGD (n = 1), and SCID (n = 1). Sixteen patients received fludarabine, melphalan, and thiotepa, and 4 patients received busulfan and fludarabine in addition to alemtuzumab. Sixteen patients (80%) achieved Day 0 alemtuzumab levels within the optimal therapeutic range of 0.15-0.9 µg/mL. Fifteen patients were evaluable for Day +100 outcomes. One patient developed acute grade I GVHD. Six patients (40%) experienced mixed chimerism, predominantly in the T cell lineage as is typical of alemtuzumab-containing RTC preparative regimens. Five of these patients maintained myeloid chimerism >97% and one patient who had reactivated HLH during conditioning experienced clinically significant mixed chimerism in all lineages and subsequent secondary graft failure. **Conclusion:** Precision alemtuzumab dosing is feasible and results in target range achievement in 80% of patients compared with only approximately 25% of patients treated with standard-of-care alemtuzumab dosing regimens. Use as part of reduced toxicity conditioning approaches appears to result in low rates of acute GVHD, clinically significant mixed chimerism, and secondary graft failure at Day +100.

Friday Lightning Posters

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Validation of an Interferon Type I Score Test on the Nanostring nCounter Platform

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Type I interferons have wide-ranging impact on the immune system in response to viruses, bacteria, and parasites. However, excessive and uncontrolled levels could lead to various autoimmunity and autoinflammatory conditions, a subset of which have been linked to monogenetic mutations in a growing number of genes and termed type I interferonopathies (monogenic autoinflammatory diseases). The

gold standard for diagnosis remains genetically determining a disease-causing mutation, but the IFN signature has emerged as a useful and relatively rapid diagnostic screening tool. Traditionally performed by RT-PCR, more recent RNA-hybridization technologies promise to significantly improve patient diagnosis.

The Nanostring nCounter platform was selected as it can be multiplexed and directly quantifies the number of RNA transcripts without the need for prior reverse transcription and amplification, avoiding bias. Mirroring previous NIH studies, 29 genes associated with the IFN I pathway were picked. For clinical accuracy, we reanalyzed samples previously tested on a similar platform at NIH and recruited known affected patients locally that were freshly collected into PAXgene tubes. On the other hand, target oligos were synthesized for the entire panel and pooled for analytical validation.

Scores obtained from 16 patients and 9 controls through NIH highly correlated between centers. Reference ranges were estimated from 82 individuals aged 1-69 years old. We found scores do not trend with either age or sex, thus not requiring brackets. An ROC comparing heathy controls against 31 known patients pooled from both NIH and local sources returned a 99% accuracy for type I interferonopathies (Figure 1). Using the pooled oligos, precision studies were preformed, including repeatability, reproducibility, interlot, instrument linearity, and inter-operator. Additionally, whole blood samples were used to test for sample stability and processed sample stability, all giving results within acceptable bias or variation.

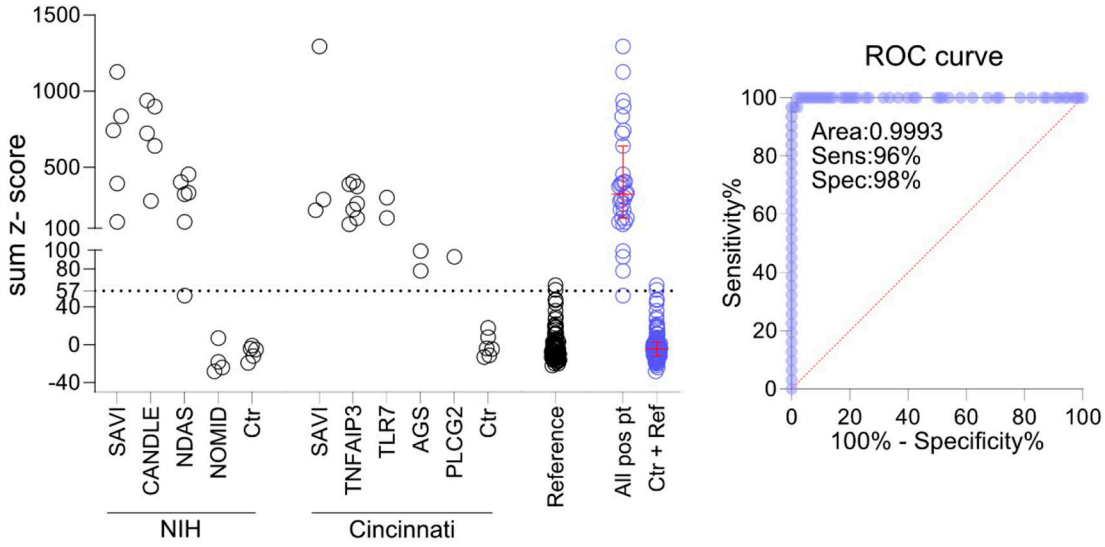

Figure 1. Type I interferon scores of patients with known elevated or normal levels performed at Cincinnati Children's. Positive samples from NIH and Cincinnati were pooled (n = 31) and compared against all controls (n = 98), as shown as blue open circles in an ROC curve (right plot). Red horizontal lines represent median and interquartile range. Dotted black horizontal line represents the 97.5th percentile of the reference cohort.

We report data on both analytical and clinical validation of an interferon score test using the Nanostring nCounter platform performed at the Cincinnati Children's Hospital Diagnostic Immunology Laboratory. This shall soon be the first clinically available test in North America for the diagnosis and treatment monitoring of various interferon-mediated diseases.

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Two- to Six-Year Clinical Outcomes Prior to Treatment with Cultured Thymus Tissue Implantation in Children with Congenital Athymia

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Background: Congenital athymia (CA), a T cell immunodeficiency due to absent thymus development during embryogenesis, results in profound T cell lymphopenia and defective self-tolerance unless treated with cultured tissue thymus implantation (CTTI). Prior to national newborn screening (NBS) for T cell deficiency, the majority of infants with CA died by 3 years of age. There has not been an assessment of CA clinical outcomes since NBS implementation.

Methods: Duke is the only center in the United States performing CTTI. Prior to 2021 FDA approval of Rethymic®, there was a hiatus in CTTI. This single-center retrospective analysis of infants referred to Duke between 2018 and 2022 assessed survival and incidence of infectious and autoimmune outcomes prior to CTTI. Inclusion criteria included an abnormal NBS, T cell negative, B cell and NK cell positive lymphocyte enumeration, and naïve T counts <50 cells/μL. Data were collected from review of referral information and the EMR. Data were stored in a secure REDCap® database with data transfer through protected analytics computing.

Results: Sixty-three infants were eligible. 22q11.2 deletion syndrome was most common (36%), followed by maternal diabetes (24%), CHARGE syndrome (24%), PAX1 (5%), TBX1 (5%), TP63 (1.5%), or EXTL3 (1.5%). Disrupted pharyngeal arch syndromic features were evident in 93% of cases. Autoimmunity was the most prevalent comorbidity (51%), including thyroid disease, autoimmune cytopenia, and/or autologous GVHD, defined as rash, lymphadenopathy, and/or eosinophilia. Median day of life (DOL) onset for autoimmunity was 127 (min-max 9-1468). Despite prophylaxis for most infants, infections were common with SARS-CoV-2 (17%), adenovirus (10%), HHV-6 (8%), norovirus (8%), EBV (5%), CMV (3%), *Mycobacterium avium* (5%), and *Pneumocystis* (5%). Clinical outcomes included: 36 (57%) successfully received CTTI at median DOL 965, 6 (9.5%) experienced spontaneous T cell reconstitution (naïve T cells >100 cells/mm^3 by median DOL 1359 (1214-2284), and 20 (32%) died at median DOL 362 (71-2068).

Conclusion: Despite early diagnosis and prophylaxis, mortality remains high in CA without CTTI. Prior to definitive therapy, the risk of autoimmunity and community-acquired infection remains high. Spontaneous T cell recovery occurs in <10% of CA. Taken together, early implementation of CTTI with appropriate isolation and prophylaxis is the optimal management of CA.

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Unravelling Enigmatic IgE-Expressing B Cells by Studying Patients with Monogenic Atopic Disorders

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Deleterious allergen-specific IgE responses underlie atopic disease. Defining the nature of IgE memory has fundamental clinical implications in the era of cytokine-targeting biologic therapies. Current dogma holds that signaling through the IgE BCR enforces either apoptosis or plasmablast differentiation upon IgE+ B cells. A subset of IgG1+ memory B cells (MBC2s) has been proposed to undergo sequential IgE switching and plasmablast differentiation to maintain serum IgE in atopic individuals. Interestingly, even in patients who respond to biologic therapies targeting Th2 cytokines, IgE levels fall substantially but can continue to persist at elevated levels. Moreover, disease recurrence can follow cessation of treatment, suggesting an ongoing need for continual therapy.

To address these uncertainties, we examined circulating B cells in patients with IEI associated with atopy, as well as disease controls. Our cohort included patients with dominant negative (DN) variants in STAT3 or IL6ST, GOF variants in STAT6 and STAT1, biallelic LOF variants in DOCK8 or ZNF341, and individuals with severe atopic dermatitis.

An optimized highly sensitive flow cytometric assay to detect intracellular IgE revealed discrete populations of IgE+ B cells that corresponded to either memory-type B cells (IgElo CD27+ Ki67-) or plasmablasts (IgEhi CD27+ CD38+ Ki67+). scRNAseq and BCR (scVDJseq) analyses verified the expression of productive IGHE transcripts in putative IgE+ B cells. While present at extremely low frequencies in healthy donors, IgE+ B cells were greatly enriched in individuals with STAT3 hyper IgE syndrome.

Regardless of donor genotype, the phenotype and transcriptional profile of IgE+ B cells resembled that of IgG1+ MBC2s. IgE+ B cells were neither clonally expanded nor related to B cells of other Ig isotypes. Crucially, IgE+ B cells downregulate SYK, suggesting a mechanism to avoid BCR-induced apoptosis identified in murine studies. A broad range of SHM in IgE+ B cells suggested several developmental trajectories and provided evidence of selection pressure in IgE+ B cells comparable with other switched isotypes. Interestingly, IgE+ B cells survived IL-4R/IL-13R blockade in some STAT3 HIES patients.

These data elucidate the phenotype of human IgE+ B cells and suggest approaches which may further reveal their ontogeny and pathological relevance.

Saturday Lightning Posters

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Endophilin-A2 Deficiency Impairs Antibody Production in Humans

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Endophilin A2, the sole endophilin A family member expressed in hematopoietic cells, regulates various aspects of membrane dynamics, including autophagy and endocytosis. Recent studies in rodents highlight the essential role of endophilin A2 in modulating immune responses. Here we report a homozygous frameshift variant in the SH3GL1 gene (NM_003025.3:c.427delC; p.Leu143Serfs*9), detected by whole-exome sequencing in a 14-year-old boy with predominantly antibody deficiency. The patient, who is issued from a consanguineous Lebanese family, has presented since the age of 18 months with recurrent respiratory tract infections, low peripheral B cell counts, and pan-hypogammaglobulinemia, with no history of opportunistic infections. This defect is associated with decrease in switched memory B cells development, impaired in vitro B cell proliferation, and diminished in vitro IgG production. The detected variant in SH3GL1 segregates with the disease in the family and abolishes the expression of the protein in the patient's peripheral blood. Interestingly, endophilin A2–deficient Sh3gl1-/- mice have been reported to present defects in germinal center B cell responses and in the production of high-affinity IgG. Our data suggest that endophilin A2 deficiency impairs antibody production in humans. Reporting further cases with mutations in SH3GL1 is needed to better characterize the inborn error of immunity linked to this gene.

Reference

Mehawej, C., et al. 2025. *J. Clin. Immunol.* https://doi.org/10.1007/s10875-024-01827-1

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Dissecting the Glycolytic Requirements of Human T cells via G6PC3 Deficiency

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Glucose metabolism is thought to play a pivotal role in proper activation and differentiation of T cells and in sustaining T cell effector functions. However, the glycolytic requirements of T cells in vivo in humans remain elusive, in part, due to the impossibility of prolonged inhibition of glycolysis. We tackle this limitation by studying glucose-6-phosphatase catalytic subunit 3 (G6PC3) deficiency, which is a rare

immunometabolic disorder that causes intracellular accumulation of the metabolite 1,5-anhydroglucitol-6-phosphate (1,5-AG6P) in immune cells. This accumulation is known to prompt cell death in neutrophils by inhibiting glycolysis. However, neutrophil-independent clinical phenotypes have been reported in some G6PC3-deficient patients, suggesting a broader immunodeficiency.

When treated with 1,5-anhydroglucitol (1,5-AG), the precursor to 1,5-AG6P, prior to extracellular flux assays, G6PC3 CRISPR/Cas9 knockout Jurkat T cells exhibited impaired glycolytic activities. This finding indicates that the 1,5-AG6P accumulation resulting from G6PC3 deficiency alters T cell metabolism. We then performed Single-Cell ENergetIc metabolism by profiling Translation inHibition (SCENITH) analysis on primary T cells from G6PC3-deficient patients, and we confirmed that patient T cells have markedly reduced glycolytic capacity when compared with cells from healthy donors. This metabolic defect is particularly noticeable in CD4+ and CD8+ effector memory T cells. Moreover, in-depth immunophenotyping by cytometry by time of flight (CyTOF) showed that G6PC3-deficient patients display lower frequencies of naïve T cells with a concomitant increase in the effector memory T cell and TEMRA proportions in both CD4+ and CD8+ compartments. Within the CD4+ T cells, patients also have an increased frequency of TH2/TH17 (CD4+CD45RA-CXCR3-) cells and indications of impaired thymic function. Furthermore, our data reveal that memory T cells from G6PC3-deficient patients exhibited elevated PD-1 expression. CD3/CD28 stimulation induces a significantly greater upregulation of PD-1 expression in CD4+ and CD8+ T cells from patients than those from healthy donors. An integrative analysis of scRNA-seq and scTCR-seq data shed light on the potential mechanisms underlying these observations.

Collectively, these findings demonstrate that T cells from G6PC3-deficient patients reflect how impaired glycolysis profoundly impacts human T cell activation, differentiation, and function in previously unrecognized ways.

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DOCK8 Deficiency: Extended Clinical Phenotypes and the Impact of Somatic Reversions

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Introduction: DOCK8 deficiency is a rare combined immunodeficiency characterized by atopy, recurrent oto-sinopulmonary infections, viral skin infections, and malignancy. Mortality is approximately 50% by age 20 without curative hematopoietic cell transplantation (HCT). We clinically phenotyped our cohort and assessed whether somatic reversions in lymphocytes impacted clinical severity.
Methods: We reviewed the clinical characteristics, laboratory studies, and outcomes of 59 patients with DOCK8 deficiency evaluated at the NIH Clinical Center. Twenty-one anti-cytokine autoantibodies were screened using a multiplex particle-based assay. Somatic reversions restoring DOCK8 protein expression in lymphocytes were assessed by flow cytometry in 49 patients.
Results: The median age at initial evaluation was 10 years (range 0.5-42), with 54% female. The most common clinical findings were sinopulmonary infections (96.6%), recurrent or chronic viral skin infections (96.6%), and eczema (93.2%). End-organ damage included bronchiectasis (44.1%), liver disease (primarily *Cryptosporidium*-related) (28.1%), and vasculopathy (17.9%). Malignancies (27.1%) included squamous cell carcinoma (13.6%) and lymphoma (23.7%). Laboratory findings showed elevated serum IgE (87.9%), low serum IgM (62.1%), and lymphopenia-affecting CD4 (64.9%), CD8 (43.9%), and NK cells (52.6%). The overall survival was 64% (age of death 7-45 years; median 18). Forty-five patients (76.3%) underwent HCT with a survival rate of 75.6%; 14 (23.7%) did not undergo HCT with a survival rate of 21.4%. Neutralizing autoantibodies against type I/II interferons were not detected in 57 patients. Forty-nine patients were assessed for lymphocyte somatic reversions; 23 had reversions in lymphocytes, while 26 either did not have reversions or had mutations (e.g., large homozygous

deletions) that could not be reverted. Patients with reversions had milder eczema, an increased incidence of warts, older age at HCT, and less CD8 lymphopenia; other clinical features, including malignancy and mortality did not differ from those without reversions.
Conclusions: DOCK8 deficiency is associated with a high incidence of morbidity and mortality by early adulthood without curative HCT. Neutralizing autoantibodies against type I/II interferon were not present despite a high burden of viral infections. Somatic reversions were common but did not preclude life-threatening complications, including malignancy.

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Evaluating Transition and Survival in Adolescents and Young Adults with Inborn Errors of Immunity

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Background: Despite advancements in early diagnosis and treatment of patients with inborn errors of immunity (IEI), transitioning from pediatric to adult care remains challenging, with significant barriers contributing to patients being lost to follow-up (LTF). This study evaluates risk factors for LTF and associated mortality.
Methods: We retrospectively identified IEI patients ≥19 years old at a tertiary care center who were previously followed in pediatric immunology. Patients were categorized as "Transitioned" (documented immunology follow-up ≥1 year after pediatric care) or "Lost to Follow-Up." Variables included demographics, diagnosis, comorbidities, insurance type, and mortality. Associations with LTF and death were analyzed using univariate and multivariable logistic regression.
Results: Of 137 patients, 72.3% (n=99) transitioned successfully, while 27.7% (n=38) were LTF. Patients with ≥3 comorbidities were more likely to remain in care (OR 4.3, p<0.001). Cardiovascular and musculoskeletal comorbidities were each independently associated with successful transition in both univariate and multivariable models (p<0.05). Demographic variables, diagnosis, and insurance type were not significantly associated with LTF.

Eighteen patients (13.1%) died, with a mean age at death of 25.8 years (range 19–40), notably higher than expected for this age group. Mortality was significantly associated with ≥3 comorbidities (OR for death 3.45, p=0.038), cardiovascular (OR 3.7, p=0.011), and respiratory comorbidities (OR 3.0, p=0.047). In adjusted analysis, cardiovascular comorbidity remained a significant predictor of death (OR 4.5, p=0.012). Public insurance was associated with a trend toward increased mortality (OR 2.86, p=0.053).Conclusions: Patients with multi-organ involvement were more likely to remain in care but also faced higher odds of death, highlighting the complex intersection of disease severity and healthcare engagement. The elevated mortality rate and trend toward worse outcomes among those with public insurance underscore the need for proactive, structured transition planning and policies that support equitable, continuous care for young adults with IEI.

Oral Abstract

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Anti-Cytokine Autoantibodies in Inborn Errors of Immunity with Immune Dysregulation

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Introduction: Anti-cytokine autoantibodies can guide understanding of disease pathogenesis, diagnosis, and treatment. Examples include anti-interferon (IFN) gamma in disseminated nontuberculous mycobacterial infection; anti-GMCSF in pulmonary alveolar proteinosis, disseminated nocardiosis, and cryptococcal meningitis; and anti-IFN alpha autoantibodies exacerbating SARS-Cov-2 (COVID-19) infection. We sought anti-cytokine autoantibodies in inborn errors of immunity (IEI) patients with immune dysregulatory features.

Methods: We tested the serum of patients with STAT1 gain of function (GOF) (N = 53), DOCK8 deficiency (N = 57), CTLA4 haploinsufficiency (N = 16), and WAS (N = 16) for anti-cytokine autoantibodies using a 21-cytokine panel via a Luminex bead–based multiplex immunoassay. Those with high levels of autoantibodies were assessed for neutralizing activity by flow cytometry if available.

Results: Patients had more anti-cytokine antibodies of a wider variety than healthy controls (N = 62) despite being younger. Neutralizing anti-GMCSF autoantibodies were found in 1/62 healthy controls, while 2/62 had high non-neutralizing anti-IFNg antibodies. In contrast, high levels of neutralizing anti-IFNa and anti-IFNw antibodies were found in two patients (STAT1 GOF and CTLA4 haploinsufficiency), while neutralizing anti-IFN-lambda2 and anti-IFN-lambda3 antibodies were found in three patients (two WAS and one CTLA4 haploinsufficiency). High levels of different anti-cytokine autoantibodies were detected in 2/16 CTLA4 patients, 2/53 STAT1 GOF patients, 3/16 WAS patients, and 4/57 DOCK8 deficiency patients (see Table 1). Some patients had more than one type of anti-cytokine autoantibodies.

Table 1. **Prevalence of high anti-cytokine autoantibodies.**

Positive anti-cytokine autoantibody	All Healthy Controls (N = 62)	Young Healthy Controls (<40y) (subset, N = 21)	STAT1 GOF (N = 53)	DOCK8 (N = 57)	WAS (N = 16)	CTLA4 (N = 16)
Any high positive N (%)	3 (4.8%)	1 (5%)	2 (3.8%)	4 (7.0%)	3 (18.8%)	2 (12.5%)
Anti-GMCSF	1^ (1.6%)	1^x^ (5%)				
Anti-IFNg	2^x^ (3.2%)					
Anti-IL12				2 (3.5%)		
Anti-IL23						
Anti-IFNa			1^ (1.9%)			1^ (6.25%)
Anti-IFNw			1^ (1.9%)			1^ (6.25%)
Anti-IFNL2				1 (1.8%)	2^ (12.5%)	1^ (6.25%)
Anti-IFNL3				1 (1.8%)	1^ (6.25%)	1^ (6.25%)
Anti-TNFa			1 (1.9%)	2 (3.5%)	2 (12.5%)	
Anti-TNFb						
Anti-IL6					1 (6.25%)	
Anti-IL17A						
Anti-IL10				1 (1.8%)		
Anti-IL22				1 (1.8%)		

High levels of anti-cytokine autoantibodies (median fluorescence intensity >5,000) were detected in some patients with inborn errors of immunity. All values are expressed in number (%).
^Neutralizing antibodies. ^x^Non-neutralizing binding antibodies.

Conclusions: Patients with IEI and immune dysregulation had more anti-cytokine autoantibodies than healthy controls and of a wider variety. Different IEIs had different anti-cytokine autoantibodies, suggesting disease-specific patterns of anti-cytokine autoantibodies. The contributions of these and other autoantibodies to the clinical presentations and outcomes will be important to determine prospectively in future immune deficiency and other cohorts.

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Allelic Bias Contributes to Incomplete Penetrance of NK Cell Deficiency

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Natural killer cell deficiencies (NKDs) can be caused by partial loss-of-function variants in the CDC45-MCM-GINS (CMG) DNA replicative helicase complex. While these variants have been identified and attributed to be the monogenic causes of inborn errors of immunity (IEI), family members with the same variants often exhibit incomplete penetrance with NK cells detectable in the peripheral blood to varying degrees.

Here, we demonstrate the effects of NKD-causing compound heterozygous variants in GINS4, a critical member of the GINS tetramer that forms the CMG complex and is required for DNA replication and cell cycle progression. Two siblings with the same inherited biallelic GINS4 variants but differing severities of clinical disease were previously identified and characterized. To better understand the effect of these variants on NK cell maturation, induced pluripotent stem cell (iPSC) lines were generated from the siblings, their biological parents, and an unrelated healthy control. We profiled efficiency in NK cell differentiation, proliferative dynamics, and sensitivity to replication stress. Immunophenotyping and RNA-Seq were used to track the emergence of NK and non-NK cell populations over time from iPSCs.

The efficiency of NK cell differentiation correlated with clinical severity of NKD. iPSCs from the individual with more severe NKD failed to generate NK cells, and we identified impairment in cell proliferation after NK cell lineage specification as the cause of this failure. These phenotypes could be rescued by CRISPR correction of both variants, demonstrating the monogenic nature of this deficiency. In contrast, iPSCs from the less severely affected NKD individual were able to generate NK cells more efficiently, despite having the same GINS4 variants.

Further analysis of RNA species from iPSC-derived and primary NK cells revealed distinct allelic bias in GINS4 in the NK cells of the two individuals. NK cells from the more severely affected individual expressed more of the GINS4 allele shown to have greater destabilizing effect on protein. Conversely, the less severely affected individual's NK cells were biased toward a missense allele with less damaging effects. Therefore, this study identifies allelic bias as a nongenetic factor that contributes to the phenotypic variations of monogenic diseases.

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PPM1D-Mediated Regulation of the DNA Damage Repair Pathway in NK Cell Development and Migration

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PPM1D is a phosphatase that regulates the DNA damage response (DDR) by dephosphorylating some of its key players, including p53 and gH2AX. Inborn errors of immunity (IEI) with altered DDR have been associated with natural killer (NK) cell deficiency, including helicase deficiencies with increased p53 and gH2AX phosphorylation after activation.

We evaluated two patients with a syndromic IEI caused by biallelic loss of function of PPM1D with B and NK cell deficiency. Besides the reduction in peripheral blood NK cell number and frequency, the patients also showed increased immature NK cells (CD56+CD62L+) and decreased mature NK cells (CD56+CD57+), while degranulation function was preserved. To investigate the role of PPM1D in NK cell maturation, we evaluated NK cell development from induced pluripotent cells in the presence of a PPM1D inhibitor (PPM1Di). PPM1Di led to a significant decrease in viability during the first stages of development and premature NK cell differentiation, followed by a reduction in NK cell frequency at endpoint, particularly impacting terminally mature NK cells. NK cell evaluation in Ppm1d-KO mice revealed an accumulation of mature NK cells in the bone marrow relative to progenitor cells. This abnormal NK cell distribution also included conserved NK cell numbers in the spleen with decreased expression of maturation markers and a relative reduction of NK cells in the blood. Analysis of healthy control human tonsil and blood NK cell subset bulk transcriptomics (GSE169646) showed higher expression of PPM1D in peripheral blood NK cell subsets compared with equivalent tonsil maturation stages, altogether indicating the relevance of PPM1D for NK cell tissue distribution and homeostasis.

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BCMA Deficiency as a Novel Cause of Common Variable Immunodeficiency

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B cell maturation antigen (BCMA) is a TNF superfamily protein expressed predominantly on plasmablasts and plasma cells. BCMA, along with TACI and BAFF-R, has been implicated for proper B cell maturation, differentiation, and survival. Patients with variants in TACI and BAFF-R have common variable immunodeficiency (CVID), but the impact of BCMA variants on human disease has not yet been reported. Here, we describe three patients from two consanguineous families who presented with early onset recurrent upper and lower respiratory tract infections. Immunological assessments of the patients demonstrated hypogammaglobulinemia, poor vaccine responses, and/or reduced isohemagglutinin titers, which were consistent with CVID. Whole-exome sequencing identified the same homozygous missense variant in TNFRSF17 (encoding BCMA), in three patients from two unrelated families. All known related family members who were heterozygous for the variant were unaffected. Overexpression of the patients' BCMA variant in 293T cells revealed impaired protein stability and defective downstream signaling. Knockout of BCMA in naïve B cells from healthy controls resulted in impaired survival of in vitro–differentiated plasma cells. Together, our results indicate that BCMA is required for plasma cell survival in humans and that BCMA deficiency is a new genetic cause for CVID.

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EML4 Deficiency Causes Alveolar Macrophage Dysfunction and Interstitial Lung Disease

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We report a novel inborn error of immunity in two siblings born to consanguineous parents who presented with short stature, failure to thrive, eosinophilic esophagitis, severe eczema, and early onset, progressive interstitial lung disease with lipoid pneumonia or pulmonary alveolar proteinosis (PAP)-like features. Genetic testing revealed both affected siblings harbored a homozygous deletion of a region of the EML4 gene, which encodes for echinoderm microtubule-associated protein-like 4 (EML4). Further analysis confirmed a lack of EML4 RNA or protein expression. EML4 deficiency has not been reported in the literature and very little is known about its physiological function. Thus, we generated EML4-deficient mice by CRISPR/Cas9 gene editing of EmL4 to examine the role of EML4 in immune function and lung disease.

Consistent with the short stature of the patients, EML4-deficient mice were runted compared with wild-type (WT) mice. We also examined the lungs of EML4-deficient mice, particularly the alveolar macrophage (AMs) population, as defects in AM number or function are known to be associated with PAP. This revealed that EML4-deficient mice had significantly decreased alveolar macrophages (AMs) compared with WT mice, but no change in the frequencies of other immune cell populations. scRNA-seq demonstrated that among lung cells, EML4 deficiency had the greatest impact on the gene expression program of AMs. EML4-deficient AMs also showed increased lipid accumulation consistent with the foamy macrophages observed in the bronchioalveolar lavage of the patients. Under specific pathogen–free (SPF) conditions, EML4-deficient mice did not demonstrate lung pathology or fibrosis. However, colonization of EML4-deficient mice with more diverse microbiota by cohousing with "dirty" mice led to florid immune infiltration and fibrosis.

Together, our results reveal that EML4 deficiency results in defects in AM which combined with microbial exposure may trigger inappropriate inflammatory responses and subsequent lung fibrosis.

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Thymoma-Associated Autoimmunity Is Th1 Driven and Can Be Ameliorated with Baricitinib

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Background: Thymoma, a rare tumor arising from thymic epithelial cells, leads to autoimmunity in approximately half of the patients. Thymomas often lose their expression of AIRE, resulting in the escape of autoreactive T cells from the thymus mirroring inherited AIRE deficiency that causes the monogenic syndrome, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). While myasthenia gravis is the most common autoimmune manifestation in thymoma, the patients can share many similarities to APECED patients, including development of autoimmune manifestations such as pneumonitis, endocrinopathies, and production of anti-cytokine antibodies. Recently, we have shown that APECED is characterized by increased IFNγ-driven T-cell–mediated autoimmunity that can be ameliorated with JAK1/2 inhibition.

Results: We stained biopsies from four tissues (lung, liver, stomach, and duodenum) affected by autoimmunity in three patients with thymoma and found increased T cell infiltration and elevated expression of IFNγ-inducible chemokine CXCL9, indicating increased local type-1 immune responses. Moreover, a 45-year-old female thymoma patient who developed increasing autoimmune manifestations despite removal of thymoma >10 years ago was treated with the FDA-approved JAK1/2 inhibitor, baricitinib. The patient had long-standing myasthenia gravis, hypogammaglobulinemia, and immune thrombocytopenia and had developed recent-onset autoimmune lung disease and anemia prior to baricitinib initiation. Baricitinib lead to the clinical improvement of hematological autoimmune diseases and pulmonary symptoms, and at 3 months of treatment pulmonary infiltrates had diminished. At 6 months of treatment, the patient is still on immunoglobulin replacement.
Conclusions: Our results show that autoimmunity in thymoma, which is associated with an acquired AIRE defect, is characterized by increased type-1 immunity, and a blockade of IFNγ downstream signaling with JAK1/2 inhibition can ameliorate autoimmune manifestations.

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Autoantibodies in 22q11.2 Deletion Syndrome with and Without Schizophrenia

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Background: Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a common congenital primary immune deficiency that typically presents with conotruncal cardiac defects, hypocalcemia, palatal abnormalities, dysmorphic facial features, and diminished T cell numbers. In addition to increased risk of infection, increased rates of autoimmune disease have been associated with this condition. Disease progression can include neuropsychiatric symptoms. Autoimmunity has been linked to psychiatric disease in the general population and in the systemic lupus erythematosus (SLE) population. There is little known about patterns of autoantibodies in 22q11.2DS patients and whether they vary with age and neuropsychiatric symptoms.
Methods: The study population included children and adults with 22q11.2DS and healthy controls without 22q11.2DS or autoimmune disease. Plasma samples were sent to the University of Texas Southwestern Medical Center for panel IV and superpanel immunoglobulin G (IgG) and immunoglobulin M (IgM) autoantigen microarray. Normalized signal intensity was calculated for each antigen. Two-tailed Student's t test was used for statistical analysis with Bonferroni correction for multiple hypothesis tests. R and ggplot2 were used for data analysis and heatmap creation.
Results: Data are available for 50 autoantigens and 80 subjects: 57 patients (29 adults and 28 children) and 23 controls (15 adults and 8 children). 10 adult patients had a diagnosis of schizophrenia. Adults with 22q11.2DS and schizophrenia had significantly elevated IgM and IgG titers to 18 autoantigens compared with all adults (controls and 22q11.2DS patients without schizophrenia), including histone H3, Smith and ribonucleoprotein, centromere proteins A and B, single-stranded deoxyribonucleic acid, and myeloperoxidase. Anti-histone H1 and H2A IgG and IgM titers were significantly higher in child patients; anti-histone H2B and myosin IgM titers were also significantly higher in child patients. About half of autoantigens tested had significantly lower titers in child patients compared with child controls (26 for IgG and 23 for IgM). IgG and IgM titers to IL-6 were lower in patients than controls across all comparisons, though not all reached a level of statistical significance once adjusted.
Discussion: Differences in autoantibody production in patients with 22q11.2DS may contribute to the increased rate of autoimmune disease, loss of tolerance, and neuropsychiatric symptoms seen in this population.

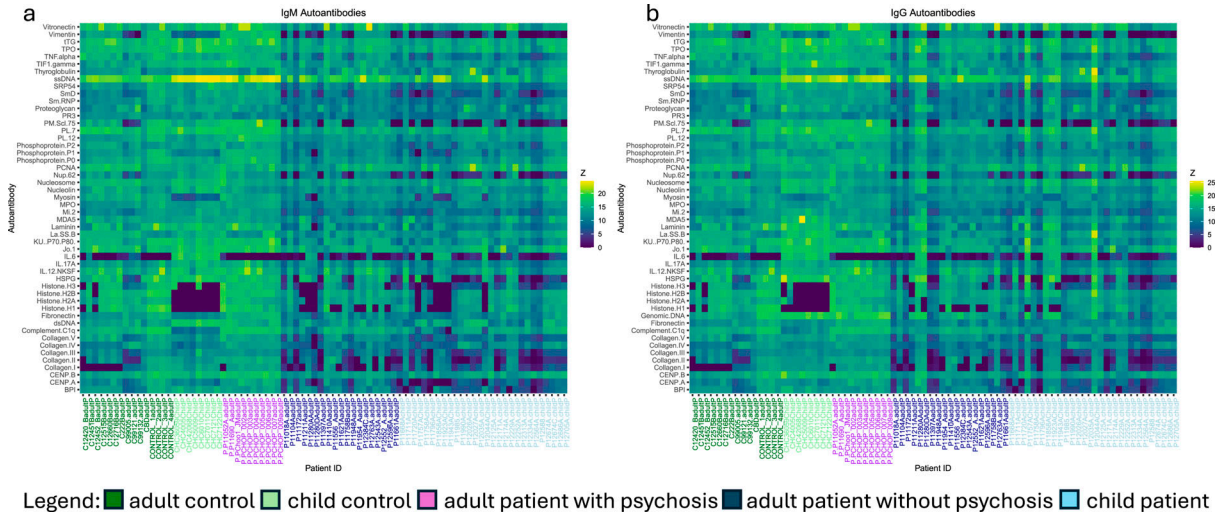

Figure 1. (a) Immunoglobulin M (IgM) autoantibodies normalized signal intensity for patients with 22q11.2 deletion syndrome and controls. (b) Immunoglobulin G (IgG) autoantibodies normalized signal intensity for patients with 22q11.2 deletion syndrome and controls.

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Massively Scalable Generation, Discovery, and Clinical (Re)Classification of Inborn Errors of Immunity Using Cutting-Edge Genome Engineering

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Clinical next-generation sequencing (NGS) is a pillar of diagnosis for inborn errors of immunity (IEI). However, for each pathogenic variant identified, these methods yield hundreds of variants of uncertain significance (VUS), creating ambiguity in clinical management. Here, we present a high-throughput framework to precisely generate genetic variants at endogenous loci and map them with the clinically established functional readout. Loss-of-function (LOF) variants in PIK3CD or PIK3R1 can lead to immune deficiency and/or the multisystem SHORT syndrome, while gain-of-function (GOF) variants lead to lymphoproliferation, autoimmunity, and infection—the activated PI3K-delta syndrome (APDS). In primary human T cells from multiple healthy donors, we performed saturation CRISPR base-editor screening of PIK3CD and PIK3R1 coupled with the clinical APDS-diagnostic flow cytometric assay to measure phosphorylated AKT and S6 after T cell receptor (TCR) stimulation. We successfully detected most known pathogenic variants and found >100 variants which were clearly novel GOF or LOF mutations. We individually validated 30 of these variants and show that many GOF, including those already associated with APDS, are sensitive to leniolisib, an FDA-approved PI3Kδ inhibitor for APDS. Next, we used structural modeling to map variant effects to defined regions in the PI3Kδ protein complex, identifying variant "hotspots" associated with pathogenic AKT/S6 signaling. Finally, we acquired peripheral blood samples from patients harboring germline mutations in PIK3CD or PIK3R1. We find that both exhibit pathogenic AKT/S6 signaling and leniolisib sensitivity at similar effect sizes as our screen-identified novel GOFs, emphasizing the clinical predictive value of our variant classification approach. We leveraged multiple precision genome editing approaches to correct the causative SNVs in these patient samples, improving signaling defects. Thousands of new functional annotations from our screens will be incorporated into public databases and used for variant reclassification, substantially broadening the population of previously undiagnosed patients who

can immediately benefit from this precision medicine approach. This proof-of-concept study is part of the Human Immune Variome Project, an effort to functionally classify variants across hundreds of genes implicated in IEIs, to remove ambiguity related to clinical management and treatment.

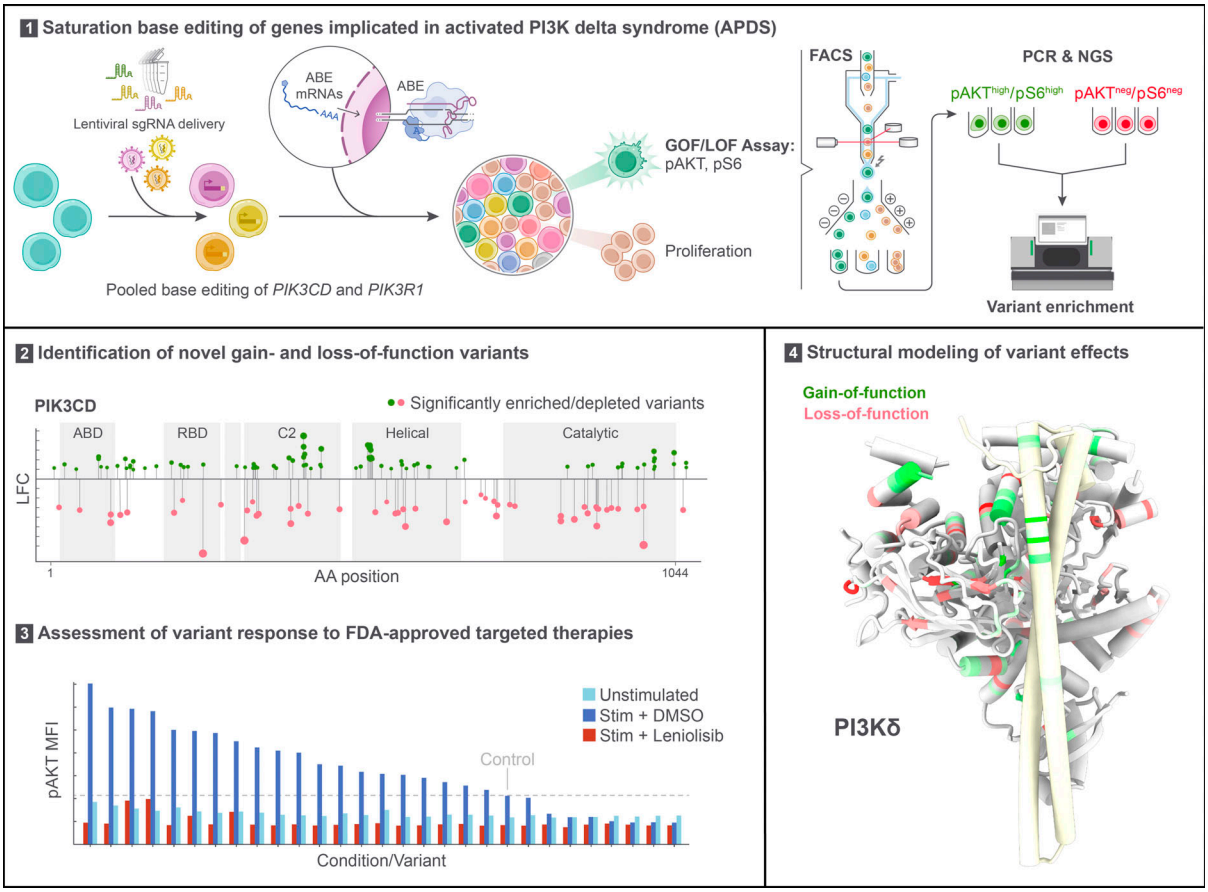

Figure 1.

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Defects in B Cell Differentiation and Antibody Production due to Biallelic TANK Mutation

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Exposure to bacterial respiratory pathogens is commonplace, but severe recurrent disease requiring hospitalization may suggest an underlying IEI. We studied a pair of siblings with decade-long histories of severe recurrent lower respiratory tract infections and positive cultures for *Streptococcus pnuemoniae*. These patients had normal total B cell counts but reduced generation of B cell memory and low antibody levels. CyTOF analysis showed all other immune cell subsets were present at normal frequencies. No mutations in known IEI-causal genes explained these patients' phenotypes. By whole-exome sequencing, we identified a novel mutation in TANK, which segregated in an autosomal recessive manner. This mutation caused a frameshift and early truncation of the TANK protein, and complete

TANK deficiency in the patients' cells. TANK is an adaptor protein with poorly characterized roles in both canonical and noncanonical NF-kB signaling. Using an in vitro B cell differentiation assay, we know that TANK-deficient patients' B cells seem "blocked" at the IgD-CD27-double-negative stage and proliferate poorly. Using scRNA-seq of patient and healthy control samples, we show an accumulation of intermediate B cells with a unique gene, including high SOX5 expression. Mechanistically, TANK suppresses the canonical NF-kB pathway and serves as a critical determinant of B cell proliferation and differentiation, antibody secretion, and protection from respiratory pathogens.

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Treatment of Autosomal Recessive Interleukin-7 Deficiency with NT-I7 (Efineptakin Alfa), Long-Acting Recombinant Human Interleukin-7: An Expanded Access Protocol

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Background: Interleukin-7 (IL-7) is a cytokine required for T cell development and homeostasis. IL-7 signal transduction is mediated by STAT5 phosphorylation and results in cell proliferation and anti-apoptotic effects. While genetic deficiencies in any of the components of IL-7 receptor (IL-7Rα or γ-chain) result in severe combined immunodeficiency, the recently discovered autosomal recessive IL-7 cytokine deficiency presents with a less severe phenotype characterized by T cell lymphopenia, recurrent HPV diseases complicated by cutaneous squamous cell carcinomas, and other opportunistic infections. NT-I7 is a long-acting human recombinant IL-7, and we hypothesize that treatment of patients with autosomal recessive IL-7 deficiency with NT-I7 will result in T cell expansion, regression of HPV-related diseases, and prevention of HPV-related cancers and opportunistic infections.
Methods: Peripheral blood mononuclear cells (PBMCs) from 2 patients with IL-7 deficiency were studied. Flow cytometric assays were used to evaluate the integrity of the IL-7 signaling axis and its downstream effect on T cell survival and proliferation by measuring the expression of CD127 (IL-7Rα), STAT5-phosphorylation, and BCL-2 and Ki-67 expression in response to IL-7 stimulation.
Results: Patients with IL-7 deficiency were found to have preserved expression of CD127 on CD4+ but not on CD8+ T cells. Accordingly, STAT5-phosphorylation in response to IL-7 stimulation was reduced in CD8+ T cells compared with healthy subjects. Nevertheless, prolonged ex vivo IL-7 stimulation increased BCL2 and Ki67 expression in both CD4+ and CD8+ T cells to a level comparable with that observed in healthy subjects. Furthermore, a preferential proliferation of CD31+ CD4+ naive T cells was noted. These ex vivo data supported the development of an investigational new drug expanded access clinical protocol using NT-I7, which was designed, approved, and launched. NT-I7 will be given up to 5 injections: 12 weeks apart for the first 3 doses, then every 24 weeks for the final 2 doses, allowing for dose escalation based on safety and clinical response.
Conclusions: The ex vivo anti-apoptotic and proliferative effect of IL-7 on T cells from patients with IL-7 deficiency raises the promising possibility that NT-I7 will have a similar effect in vivo in this as well as other inborn errors of immunity associated with impaired T cell homeostasis.

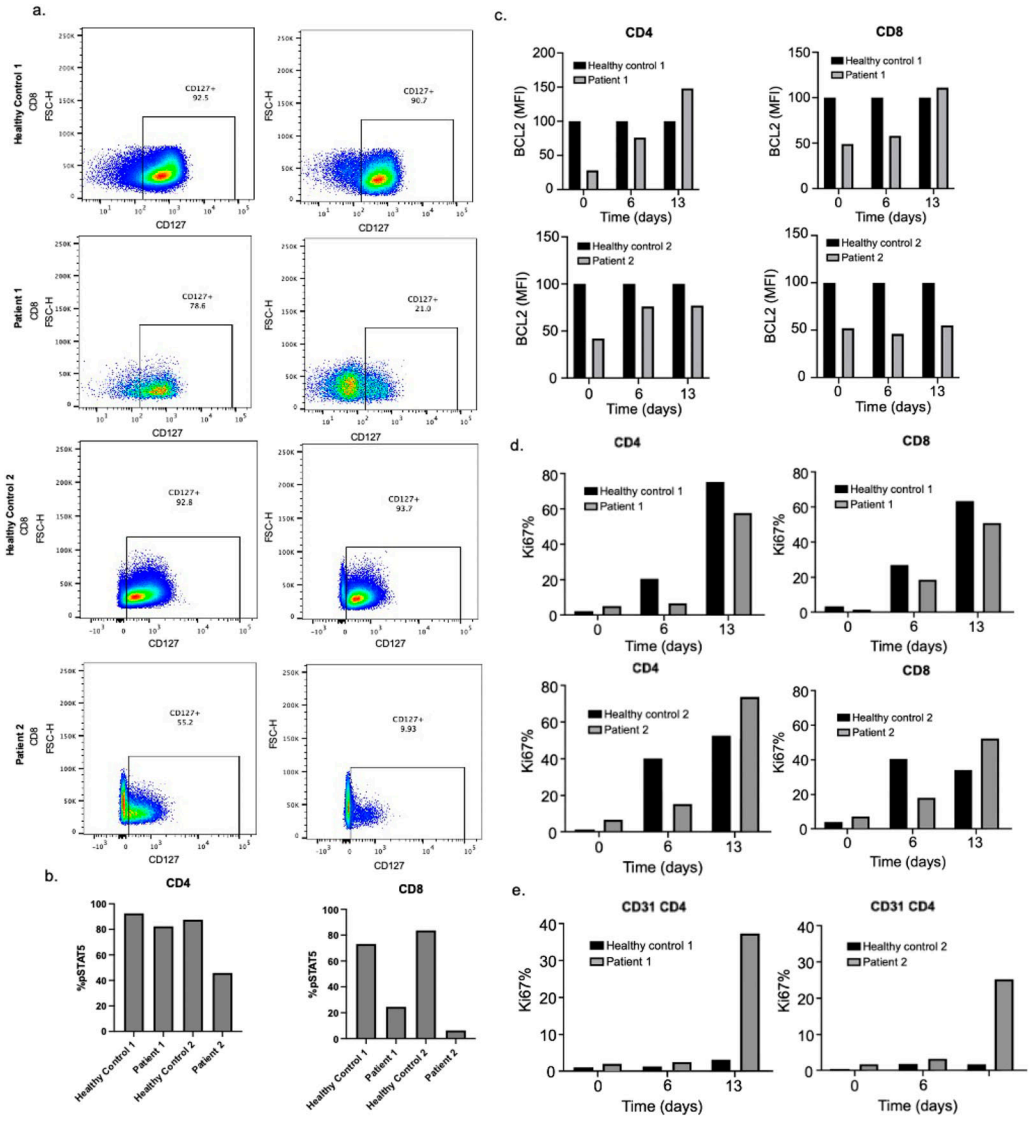

Figure 1. Baseline CD127 expression, phosphorylated STAT5 and BCL2 signal transduction with IL-7 stimulation, and T cell proliferation assays in IL-7–deficient patients as compared with healthy controls. (a) Expression of CD127 on CD4+ and CD8+ T cells. (b) Phosphorylated STAT5 percent in response to stimulation with IL-7 (1 ng/ml). (c) BCL2 expression after incubation of CD4+ and CD8+ T cells with IL-7. (d) CD4+ and CD8 + T cell proliferation in response to IL-7 incubation as measured by Ki67 expression. (e) Proliferation of naive CD4+ T cells in response to IL-7 incubation as measured by Ki67 expression.

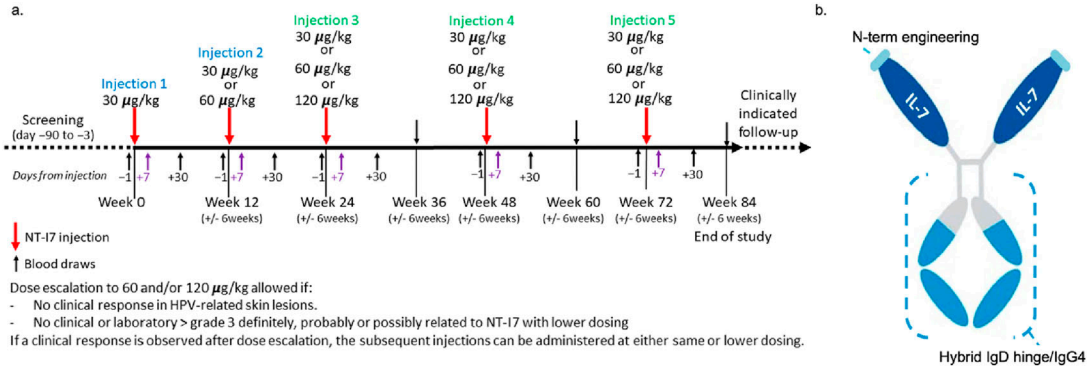

Figure 2. Timeline of expanded access protocol screening, NT-I7 dosing, and laboratory monitoring. (a) Timeline of expanded access protocol screening, NT-I7 dosing, and laboratory monitoring. (b) Structure of NT-I7 demonstrating N terminus human IL-7 fused to a hyFc long-acting platform that combines the hinge flexibility of IgD and recycling of IgG4 to minimize protein–protein interactions and increase serum half-life.

Table 1. **Baseline clinical features of two patients with IL-7 deficiency.**

	Patient 1	Patient 2
Age (years)	46	52
Sex	Female	Female
Clinical Manifestations		
Cutaneous warts	+	+
Squamous cell carcinoma	-	+
Cryptococcal meningitis	+	-
Laboratory Characteristics		
T cells (cells/μL)	107	93
CD4+ T cells (cells/μL)	31	50
CD8+ T cells (cells/μL)	94	43

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Elevated CD38 Expression and a Concomitant Reduction in NAD+ Levels Underlie CD8+ T Cell Dysfunction in STAT1 GOF

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Background and Aims: STAT1 gain-of-function (GOF) patients experience severe fungal and viral infections and autoimmunity. CD8+ T cells are key mediators of the adaptive immune response by combating infections. CD8+ T cell dysfunction, in turn, contributes to autoimmune pathogenesis and chronic viral infections. We therefore hypothesized that CD8+ T cell dysfunction contributes to STAT1 GOF pathophysiology and sought to identify the underlying mechanisms.
Methods: We collected high-dimensional immunophenotyping and cellular indexing of transcriptomes and epitopes sequencing (CITE-Seq) data on 24 STAT1 GOF patients and age-matched healthy control PBMCs. In addition, T cell function and metabolic data were collected on untreated and in vitro-treated patient and healthy control PBMCs.
Results: In patients with STAT1 GOF, CD8+ T cell dysfunction was best defined as reduced production of IFN-γ, TNF-α, and IL-2 upon αCD3/αCD28 stimulation. High-dimensional immunophenotyping identified CD38 as a significantly upregulated activation marker on CD8+ T cells and most immune cell populations, from patients with STAT1 GOF. CD38 expression could be further induced by αCD3/αCD28 stimulation and was correlated with the levels of total STAT1 protein. CD38 is an ectoenzyme that consumes nicotinamide

adenine dinucleotide (NAD+), and low NAD+ levels have been linked to immune dysregulation. Our CITE-Seq data confirmed that STAT1 GOF CD8+ T cells have transcriptional evidence of broadly altered NAD+ metabolism, with both NAD-consuming enzymes such as CD38 and PARP9 as well as NAD+ salvage pathway proteins such as NAMPT being increased. Using an NAD+ enzymatic assay, we confirmed that NAD+ levels were indeed reduced in STAT1 GOF CD8+ T cells while the NADH levels were comparable. By increasing NAD+ levels in patient PBMCs, it was possible to partially normalize CD8+ T cell function in CD8+ T cells from patients with STAT1 GOF. Finally, STAT1 GOF patients receiving JAK inhibitors show reduced CD38 RNA and protein expression and reduced PARP9 and NAMPT transcription. **Conclusion:** Elevated CD38 expression and reduced NAD+ levels contribute to CD8+ T cell dysfunction in CD8+ T cells from patients with STAT1 CD8+ T cells, which can be partially normalized by providing increased NAD+ levels.

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Enhancer Hijacking of the IGH Locus as a Novel Genetic Mechanism of an Inborn Error of Immunity Leading to Invasive *Streptococcus pneumoniae* Infection due to Antibody Deficiency

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We investigated the genetic cause of disease in five affected individuals from two unrelated families with an autosomal dominant pattern of invasive *Streptococcus pneumoniae* infection associated with a clinical phenotype of specific antibody deficiency. In Family A, two male siblings presented at <5 years with sepsis due to *S. pneumoniae*. The father had a history of meningitis and recurrent pneumonias, and a female sibling had less severe infections. In Family B, a male presented during infancy with *S. pneumoniae* meningitis with no family history of immunodeficiency. All patients had significantly decreased switched (CD27+IgD-) and unswitched (CD27+IgD+) memory B cells with normal serum immunoglobulin (Ig) levels, but poor responses to the polysaccharide pneumococcal vaccine or the serotype of *S. pneumoniae* causing infection. Primary B cells from patients had normal BCR spectratyping. Despite a hyperproliferative phenotype, plasmablast differentiation was diminished in vitro. Whole-genome sequencing identified similar ~650-kb tandem duplication events on Chr14q32.2 encompassing part of the IGH locus and upstream genes, with complete penetrance in all patients from both families. Bulk and scRNA-seq revealed B cell–specific massive overexpression (100-fold) of one gene within the duplication, JAG2, encoding the Notch ligand jagged-2. Primary B cells and patient-derived B-LCLs expressed high JAG2 protein. Long-read sequencing demonstrated the 3' regulatory region (3'RR) of the IGH locus in close proximity to JAG2 due to the duplication, and we hypothesize this leads to enhancer

hijacking and dysregulation of JAG2 in B cells. Enhancer hijacking is a well-described mechanism leading to cancer but has never been described in IEI and very rarely in Mendelian genetics. Consistently, Hi-C analysis of patient-derived B-LCLs demonstrated a new interaction of JAG2 with the IGH 3'RR. A bone marrow chimera model demonstrated that overexpression of human JAG2 leads to a defect in marginal zone B cell development. Together, these findings demonstrate the discovery of a novel genetic mechanism of IEI, a new role for JAG2 in B cell differentiation, and a genetic cause of specific antibody deficiency. Ongoing work is focused on the effects of JAG2 overexpression on B cell function in vitro and using an in vivo model of vaccination.

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Deep Sequencing Reveals Somatic Mosaicism in Genes Relevant to Genetic Errors of Immunity in a Cohort of Patients with Immune Dysregulation

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Somatic mosaicism is an important mechanism of immune dysregulation and explains a growing proportion of the 70% of patients with suspected IEI who lack a molecular diagnosis. Identifying disease-causing somatic mutations is challenging due to the presence of such variants in a small subset of cells, leading to a low variant allele fraction (VAF).

We developed a custom 71-gene capture-based panel for high-depth sequencing of genes known or hypothesized to be associated with dominant immune dysregulation. Sequencing was performed with samples from 223 patients with immune dysregulation phenotypes and 96 currently healthy individuals. Mean age was 24.5 years for patients and 17.8 years for healthy individuals. 52.5% of patients and 40.6% of healthy individuals were biologic males. Coverage across coding regions of targeted genes had an average depth of 5752×. Our custom analysis pipeline utilized the union of multiple variant callers to call somatic variants.

We identified 36 somatic variants in 21 genes from 28 patients (12.6% of patients) and 6 healthy controls (6.25% of healthy). To validate our assay, an independent library was sequenced for 60 patients and 18 healthy controls, including samples harboring 27 somatic variants. Droplet digital PCR (ddPCR) was used as an orthogonal method to validate 17 variants. All tested variants were confirmed as somatic. Genes with somatic mosaicism in >1 affected patient included FAS, STAT3, CARD11, NRAS, TNFAIP3, NLRP3, and PIK3CD. Three variants were previously described to cause somatic immune dysregulation. Immune cell populations from 7 patients with variants in FAS, NRAS, TNFAIP3, and UBA1 were purified and ddPCR performed, which identified enrichment of somatic variants in different cell types. This included somatic variants in FAS that had a VAF of 5-7% in whole blood but 21-28% in DNTs, all in individuals with a clinical phenotype consistent with ALPS.

Our studies demonstrate the utility of high-depth targeted sequencing of suspected IEI patients to identify pathogenic and potentially pathogenic somatic variants, including low VAF variants directly from whole blood. Ongoing studies include expanding our gene panel, in vitro functional validation of novel variants, and utilizing single-cell technologies to identify the functional impact of somatic variants.

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Identification of Serum Prognostic Biomarkers for 5-Year CVIDc Disease Progression

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Background: Noninfectious complications in CVID (CVIDc) are highly heterogeneous, characterized by variable end-organ involvement, immune phenotypes, and disease progression among patients. This complexity challenges the feasibility and efficiency of CVIDc clinical trial design and is further compounded by the absence of prognostic biomarkers and surrogate endpoints to predict disease trajectories and assess therapeutic responses.

Objectives: We sought to determine the relationship between baseline serum biomarkers and 5-year CVIDc disease progression.

Methods: Serum cytokine levels were measured by ELISA in 83 CVID participants at enrollment. Elevated cytokine levels were defined as values exceeding 2 standard deviations above the mean of healthy controls. Subsequent disease progression was defined as the onset of a CVIDc complication and/or worsening end-organ dysfunction. The association between baseline cytokine markers and CVIDc progression-free intervals was analyzed.

Results: Of the 83 CVID participants, 65% (n = 54) had CVIDc complications at enrollment. Elevated baseline IFN-ɣ was the strongest predictor of 5-year CVIDc progression (hazard ratio [HR] 6.9, 95% CI 3.9–12.4, P < 0.0001). Elevated baseline BAFF (HR 2.4, 95% CI 1.3–4.4, P < 0.04), TNF-α (HR 2.0, 95% CI 1.04–3.7, P < 0.04), and IL-6 (HR 2.1, 95% CI 1.1–3.9, P < 0.03) were also associated with disease progression, though less strongly. Among participants without baseline CVIDc phenotypes but elevated IFN-γ, 75% (6/8) subsequently developed a complication (lymphoproliferative disease, cancer, or autoimmunity, n = 2 each) within 5 years. CVID lung diseases were previously associated with increased mortality. When lung-specific disease progression was examined, elevated baseline IFN-γ (HR 11.4, 95% CI 3.8-33.7, P = 0.003) and BAFF (HR 8.5, 95% CI 2.9-24.8, P = 0.01) were the strongest predictors, whereas TNF-α showed no significant association despite elevation in many CVIDc participants.

Conclusion: Elevated baseline IFN-γ is a robust prognostic biomarker for overall CVIDc progression, while both high IFN-γ and BAFF are strongly associated with lung disease progression. These findings suggest their biological relevance in poor CVIDc trajectory and potential as candidate surrogate endpoints for CVIDc clinical trials.

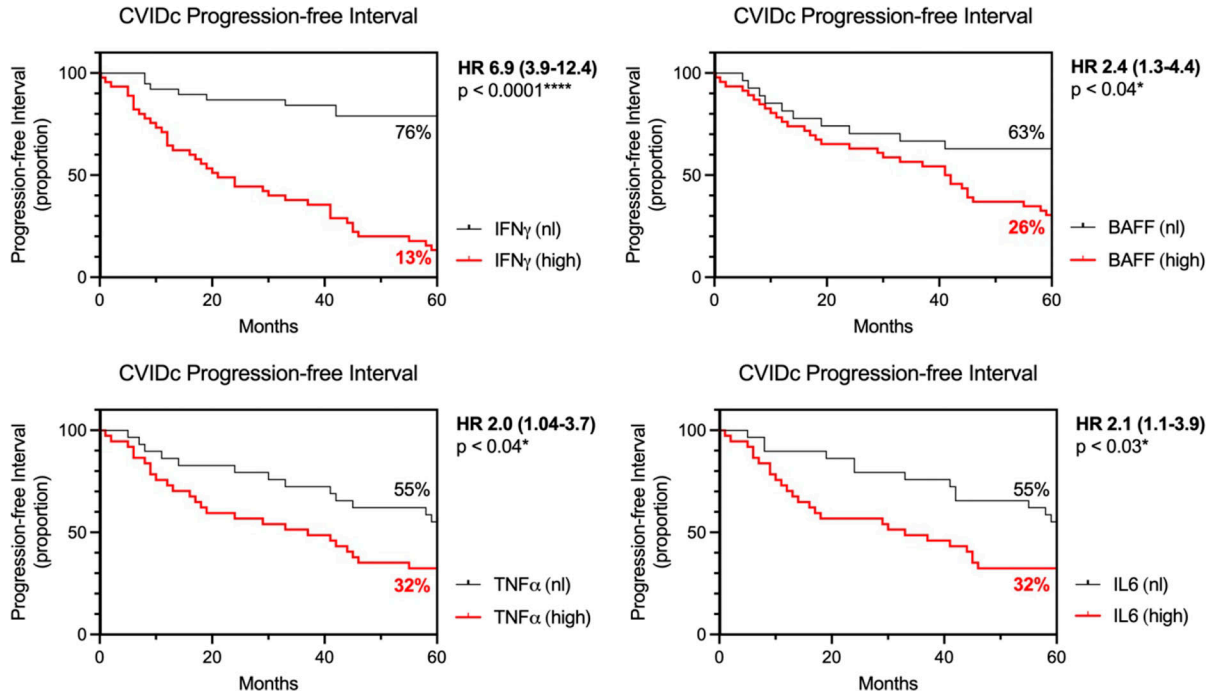

Figure 1.

Saturday Posters

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Relapsed and Difficult-to-Treat Histoplasmosis Infection Uncovers a Novel STAT1 Gain-of-Function Variant

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Introduction: Signal transducer and activator of transcription 1 (STAT1) plays a key role in gene expression for immune regulation. It receives signals from cytokines/interferons and growth factors and activates transcription of pathways involved in immune responses to viral, fungal, and mycobacterial infections. Pathogenic variants in STAT1 are associated with inborn errors of immunity. Loss-of-function variants have been linked to severe infections and increased susceptibility to mycobacterial disease, while gain-of-function (GOF) variants are associated with chronic mucocutaneous candidiasis and autoimmune diseases. In this presentation, we will discuss the finding of a novel STAT1 GOF variant associated with difficult-to-treat histoplasmosis.
Case Description: A 58-year-old female presented to adult immunology clinic for relapsed and difficult-to-treat histoplasmosis infection. Her medical history is significant for recurrent sinopulmonary infections, sarcoidosis, and cervical lymph node histoplasmosis. Her infectious history includes frequent diagnoses of pneumonia as a child and adolescent and frequent ear and sinus infections in adulthood that all resolved with oral antibiotics. She was initially diagnosed with cervical lymph node histoplasmosis while on a TNF-alpha inhibitor for sarcoidosis that was discontinued with the onset of her symptoms. She received treatment with itraconazole. However, she developed a relapse of her histoplasmosis. Initial immunologic testing revealed normal B and T cell panels with normal immunoglobulin levels. However, her relapsed and difficult-to-treat histoplasmosis infection with her history of granulomatous inflammation suggesting immune dysregulation raised concern for a primary immunodeficiency for which genetic testing was pursued. A next-generation sequencing primary immunodeficiency panel revealed a VUS in STAT1: c.736G>A (p.Ala246Thr). Commercially available studies assessing STAT1 GOF activity and Th17 levels were normal. However, a research functional assay of STAT1 performed at the National Institute of Health was consistent with GOF. This case highlights the importance of broad panel-based sequencing in unusual presentations of endemic fungal disease, as well as the limits of commercially available functional testing in assessing subtle missense variants.

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Pediatric Pyoderma Gangrenosum in Patients with a Novel Biallelic Mutation in OTULIN

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Pyoderma gangrenosum (PG) is an understudied inflammatory skin condition that causes significant morbidity and rarely mortality. Treatment options for PG are limited due to our relatively poor understanding of its molecular mechanisms. Prior studies have suggested a genetic basis for PG, but causal genes have remained elusive. Through the study of siblings with severe recurrent PG in childhood, we identified a novel mutation in OTULIN. OTULIN is a linear deubiquitylase that regulates several immune signaling pathways in ways that are cell type specific. Interestingly, this mutation affects the PIM domain, responsible for protein–protein interactions, but does not impair catalytic functions of the OTU domain, thus its mechanism of action is distinct from previously reported OTULIN mutations. Through a combination of in vitro mechanistic studies that isolate the functional impact of the variant, together with single cell analyses of patient and healthy control PBMC samples, we demonstrate this novel OTULIN mutation causes PG via i) hyperactivation of the NLRP3 inflammasome and elevated IL-1b secretion from patients' myeloid cells and ii) heightened keratinocyte sensitivity to TNF-driven cell death. The patients responded well to anti-TNF therapy and are now free of PG flares. This study establishes the first monogenic etiology of isolated PG of childhood, identifies the molecular mechanisms of disease, and suggests that TNF and/or IL-1b blockade may be effective therapeutic options.

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Distinct Classes of Gain-of-Function KIT Mutations Distinguish Morphologic Phenotypes of Systemic Mastocytosis

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Mastocytosis encompasses a group of rare mast cell (MC) neoplasms classified as MC sarcoma, cutaneous mastocytosis (CM), or systemic mastocytosis (SM). Gain-of-function (GOF) variants in the KIT oncogene, encoding the receptor tyrosine kinase c-KIT (KIT), are linked to most cases of CM and SM. However, our understanding of if and how different KIT variants might distinguish morphologic SM phenotypes remains incomplete. We reviewed a large cohort of 454 patients diagnosed with SM based on bone marrow biopsy analysis and application of 2022 WHO diagnostic criteria. Established GOF KIT variants at codon 816 (D816V and D816Y) were detected in biopsy samples from >96% of SM cases (436/454), all of which showed spindled morphology in >25% of MCs. In 7 of the remaining 18 cases, all bone marrow MCs exhibited a uniformly round, slightly enlarged morphology consistent with SM with well-differentiated phenotype (SMWD). Next generation sequencing discovered germline missense KIT variants in 5/7 patients with SMWD, including two patients with p.Lys509Ile (K509I), two with p.Ala533Asp (A533D), and one with novel compound heterozygous variants p.Met541Leu (M541L) and p.Phe681Leu (F681L). We then developed a novel transfection assay to compare how each variant affected KIT expression, cellular localization, and autophosphorylation -/+ stimulation with the KIT ligand stem cell factor (SCF). Consistent with prior reports and in contrast to wild-type KIT, D816 KIT variants remained largely intracellular and displayed a strong, SCF-independent autophosphorylation of multiple tyrosine residues in the cytoplasmic tail. Conversely, SMWD-derived KIT variants displayed variable surface expression with distinct patterns of glycosylation and tyrosine phosphorylation relative to wild type. Baseline phospho-KIT levels were far lower than D816V/Y but higher than wild type, with additional enhancement observed after acute SCF stimulation. Immunohistochemical analysis further distinguished SMWD based on exclusive intracellular expression of CD25 on MCs in 6/7 cases. Overall, these results define unique molecular features of SMWD based on restricted intracellular CD25 expression and detection of milder, ligand-dependent hypomorphic KIT variants relative to strong D816 GOF mutations. Our findings provide new molecular insights into SMWD pathogenesis that should improve diagnostic accuracy and inform therapeutic application of (and response to) tyrosine kinase inhibitors targeting KIT.

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Molecular Circuits Driving Human iTfr Cell Development

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Recent work has identified and reported a distinct Tfr developmental pathway in which germinal-center resident Tfr cells are derived from Tfh cells [1,2]. These Tfh-induced regulatory cells are referred to as induced Tfr (iTfr) cells [2]. While the existence of a Tfh to iTfr developmental arc has been established in mice and humans, the cell-extrinsic stimuli and cell-intrinsic molecular machinery required for this transition are unclear. Our preliminary data suggest that when cultured alone, human tonsillar Tfh appear terminally differentiated, but when incorporated in a autologous tonsil organoid (TO), around half of these cells spontaneously divide and differentiate into iTfr cells [2]. TOs are an all-human model system containing a range of cell types and stimulatory molecules that recapitulates key features of

human follicular biology [2,3]. By intravitally labeling Tfh cells incorporated into TO systems, we have mapped the transcriptome of differentiating cells on a single cell, per-division bases. We have found that expression levels of key Tfh and Tfr transcription factors, including BCL6, BLIMP1, and FOXP3 change on a per-division basis as Tfh differentiate into iTfr cells. These data indicate that a key molecular event in the Tfh-to-iTfr transition is the downregulation of the transcription factor BCL6 and reciprocal upregulation of first BLIMP1 and then FOXP3. On this basis, we hypothesize that cellular and molecular components of TOs induce Tfh cells to adopt a BLIMP1-associated transcriptional program in Tfh cells, which licenses their transition into iTfr cells. Obstruction in this differentiation pathway contributes to autoantibody-production in CVID and potentially other immune conditions [4]. Thus, identifying the specific molecular levers controlling Tfh vs. iTfr cell fate will create translational opportunities to modulate humoral immunity.

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Clinical Implications of Cytopenias in the U.S. Immunodeficiency Network Registry

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Rationale: The correlation between cytopenias and infection, malignancy, and mortality has not been systematically characterized in patients with inborn errors of immunity (IEIs).
Methods: We evaluated the association between anemia, thrombocytopenia, lymphopenia, and neutropenia and infection, malignancy, and mortality rates in IEI patients enrolled in the United States Immunodeficiency Network (USIDNET) registry.
Results: Of the 4,005 IEI patients enrolled in the USIDNET cohort through April 2019, we excluded 438 patients due to prior solid organ or hematopoietic stem cell transplantation. In the final cohort (n = 3,657), the median age of participants was 27 (IQR 16-50) years. Approximately 47.9% of participants were female. The majority of patients (57.2%) were classified as predominantly antibody deficiencies per the International Union of Immunological Societies (IUIS) categorization with common variable immunodeficiency being the most common diagnosis (38.9%). A total of 1,093 (29.9%) patients had one or more cytopenias, including 656 (17.9%) with anemia, 481 (13.2%) with thrombocytopenia, 323 (8.8%) with lymphopenia, and 336 (9.2%) with neutropenia. Approximately 274 (7.5%) of patients had immune-mediated cytopenias. Patients with cytopenias exhibited higher odds of infection (OR = 4.00, 95% CI 3.07-5.28), malignancy (OR = 2.51, 95% CI 1.93-3.25), and mortality (OR = 2.81, 95% CI 2.01-3.92) as compared with patients without cytopenias. Neutropenic patients frequently developed bacterial infections (58.6%), followed by viral (51.5%), fungal (35.4%), and parasitic (5.1%). Our cohort also demonstrated a high rate of sinopulmonary infections (75.8%) and skin and soft tissue infections (31.9%).
Conclusions: Cytopenias are a common manifestation across various IEIs. Patients with cytopenias exhibited a heightened risk of infection, malignancy, and mortality, highlighting underlying immune dysregulation and calling for the need to address cytopenias in the management of IEIs.

Table 1. **Cytopenias in primary immunodeficiencies and IUIS categories**

Immunodeficiency	# Thrombocytopenia	# Anemia	# Neutropenia	# Lymphopenia	# Any cytopenia	Total count (N = 3511)
Agammaglobulinemia	10 (4%)	25 (10%)	23 (9%)	3 (1%)	45 (18%)	257
Ataxia telangiectasia	6 (23%)	6 (23%)	2 (8%)	7 (27%)	11 (42%)	26
Autoimmune lymphoproliferative syndrome (ALPS)	14 (22%)	29 (45%)	9 (14%)	7 (11%)	34 (53%)	64

Table 1. **Cytopenias in primary immunodeficiencies and IUIS categories (*Continued*)**

Immunodeficiency	# Thrombocytopenia	# Anemia	# Neutropenia	# Lymphopenia	# Any cytopenia	Total count (N = 3511)
Autoinflammatory disease	1 (8%)	0 (0%)	1 (8%)	0 (0%)	2 (17%)	12
CHARGE syndrome	0 (0%)	0 (0%)	0 (0%)	1 (33%)	1 (33%)	3
Chronic granulomatous disease	9 (6%)	45 (31%)	3 (2%)	0 (0%)	51 (35%)	145
Combined immune deficiency	9 (17%)	11 (21%)	10 (19%)	16 (31%)	22 (42%)	52
Common variable immune deficiency (CVID)	210 (15%)	259 (18%)	86 (6%)	79 (6%)	416 (29%)	1416
Complement deficiency	1 (4%)	2 (8%)	0 (0%)	0 (0%)	2 (8%)	26
DiGeorge syndrome	20 (4%)	16 (3%)	7 (1%)	41 (8%)	63 (13%)	496
Dyskeratosis congenita	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	1
Ectodermal dysplasia with immunodeficiency (nemo and others)	0 (0%)	5 (21%)	2 (8%)	3 (12%)	8 (33%)	24
HLH, including XLP and pigmentary disorders	5 (31%)	5 (31%)	4 (25%)	4 (25%)	8 (50%)	16
Hyper IgE syndrome	3 (3%)	14 (15%)	3 (3%)	0 (0%)	18 (19%)	96
Hyper IgM syndrome	1 (2%)	4 (9%)	18 (38%)	1 (2%)	19 (40%)	47
Hypogammaglobulinemia	11 (5%)	21 (10%)	10 (5%)	10 (5%)	35 (17%)	209
IgA deficiency	1 (1%)	2 (3%)	2 (3%)	7 (10%)	11 (16%)	68
IgG subclass deficiency	1 (4%)	3 (12%)	1 (4%)	0 (0%)	6 (23%)	26
Immune deficiency with syndromic features (not otherwise listed)	0 (0%)	1 (12%)	0 (0%)	0 (0%)	1 (12%)	8
Immune dysregulation	22 (29%)	25 (33%)	17 (23%)	18 (24%)	40 (53%)	75
Immunodeficiency unknown cause	3 (16%)	4 (21%)	2 (11%)	2 (11%)	5 (26%)	19
Immunodeficiency with myelodysplasia (GATA2 and others)	9 (33%)	11 (41%)	8 (30%)	9 (33%)	14 (52%)	27
Interferonopathy (Aicardi-Goutières and others)	0 (0%)	2 (29%)	0 (0%)	0 (0%)	4 (57%)	7
Leukocyte adhesion deficiency	0 (0%)	3 (33%)	0 (0%)	0 (0%)	3 (33%)	9
Mucocutaneous candidiasis	0 (0%)	5 (12%)	1 (2%)	1 (2%)	7 (16%)	43
Neutropenia	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	2
NK cell defect	1 (25%)	0 (0%)	1 (25%)	0 (0%)	2 (50%)	4
Omenn syndrome	0 (0%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1
Other immune deficiency - known cause	3 (6%)	7 (13%)	2 (4%)	0 (0%)	9 (17%)	54
Other T-cell problems	1 (14%)	1 (14%)	0 (0%)	1 (14%)	2 (29%)	7
Predisposition to severe viral infections	6 (20%)	12 (40%)	23 (77%)	1 (3%)	24 (80%)	30
Severe combined immune deficiency (SCID)	3 (5%)	11 (17%)	8 (12%)	16 (24%)	22 (33%)	66
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	4 (4%)	12 (12%)	2 (2%)	4 (4%)	18 (19%)	97
Susceptibility to mycobacteria (MSMD)	0 (0%)	1 (12%)	0 (0%)	0 (0%)	1 (12%)	8
TLR pathway abnormality	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2
Transient hypogammaglobulinemia of infancy with normal numbers of b cells	0 (0%)	0 (0%)	1 (7%)	0 (0%)	1 (7%)	14
Wiskott-Aldrich syndrome	35 (65%)	13 (24%)	3 (6%)	3 (6%)	38 (70%)	54

Table 2. **Sites of infection in IEI**

Immunodeficiency	Urogenital	SSTI	Sino-pulmonary	Cardiac	Odontogenic	Ophthalmic	MSK	CNS	GI	Bloodstream	Any site	Total count (N = 3511)
Agammaglobulinemia	18 (7%)	92 (36%)	221 (86%)	0 (0%)	1 (0%)	67 (26%)	25 (10%)	34 (13%)	66 (26%)	29 (11%)	235 (91%)	257
Ataxia telangiectasia	1 (4%)	3 (12%)	21 (81%)	0 (0%)	0 (0%)	2 (8%)	1 (4%)	1 (4%)	8 (31%)	3 (12%)	24 (92%)	26
Autoimmune lymphoproliferative syndrome (ALPS)	9 (14%)	32 (50%)	33 (52%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	2 (3%)	16 (25%)	9 (14%)	54 (84%)	64
Autoinflammatory disease	1 (8%)	3 (25%)	5 (42%)	0 (0%)	0 (0%)	2 (17%)	0 (0%)	1 (8%)	1 (8%)	0 (0%)	9 (75%)	12
CHARGE syndrome	1 (33%)	1 (33%)	2 (67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (67%)	3 (100%)	3
Chronic granulomatous disease	13 (9%)	115 (79%)	123 (85%)	0 (0%)	5 (3%)	8 (6%)	17 (12%)	14 (10%)	75 (52%)	15 (10%)	143 (99%)	145
Combined immune deficiency	5 (10%)	25 (48%)	40 (77%)	1 (2%)	0 (0%)	11 (21%)	3 (6%)	5 (10%)	12 (23%)	12 (23%)	43 (83%)	52
Common variable immune deficiency (CVID)	242 (17%)	381 (27%)	1211 (86%)	4 (0%)	18 (1%)	126 (9%)	32 (2%)	62 (4%)	248 (18%)	91 (6%)	1265 (89%)	1416
Complement deficiency	1 (4%)	9 (35%)	21 (81%)	0 (0%)	0 (0%)	1 (4%)	2 (8%)	7 (27%)	3 (12%)	6 (23%)	23 (88%)	26
DiGeorge syndrome	22 (4%)	34 (7%)	157 (32%)	7 (1%)	0 (0%)	11 (2%)	2 (0%)	1 (0%)	11 (2%)	19 (4%)	171 (34%)	496
Dyskeratosis congenita	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1
Ectodermal dysplasia with immunodeficiency (nemo and others)	2 (8%)	16 (67%)	18 (75%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	8 (33%)	8 (33%)	5 (21%)	24 (100%)	24
HLH, including XLP and pigmentary disorders	2 (12%)	5 (31%)	12 (75%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	1 (6%)	3 (19%)	2 (12%)	13 (81%)	16
Hyper IgE syndrome	18 (19%)	84 (88%)	88 (92%)	1 (1%)	3 (3%)	4 (4%)	7 (7%)	5 (5%)	19 (20%)	7 (7%)	91 (95%)	96
Hyper IgM syndrome	3 (6%)	12 (26%)	43 (91%)	0 (0%)	1 (2%)	4 (9%)	0 (0%)	3 (6%)	11 (23%)	5 (11%)	44 (94%)	47
Hypogammaglobulinemia	34 (16%)	56 (27%)	162 (78%)	0 (0%)	2 (1%)	10 (5%)	3 (1%)	1 (0%)	23 (11%)	6 (3%)	173 (83%)	209
IgA deficiency	8 (12%)	15 (22%)	63 (93%)	0 (0%)	0 (0%)	4 (6%)	1 (1%)	3 (4%)	16 (24%)	1 (1%)	66 (97%)	68
IgG subclass deficiency	7 (27%)	6 (23%)	25 (96%)	0 (0%)	2 (8%)	1 (4%)	1 (4%)	1 (4%)	2 (8%)	0 (0%)	25 (96%)	26
Immune deficiency with syndromic features (not otherwise listed)	4 (50%)	3 (38%)	6 (75%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (12%)	1 (12%)	8 (100%)	8
Immune dysregulation	15 (20%)	40 (53%)	66 (88%)	1 (1%)	5 (7%)	9 (12%)	1 (1%)	5 (7%)	20 (27%)	9 (12%)	69 (92%)	75
Immunodeficiency unknown cause	2 (11%)	5 (26%)	12 (63%)	2 (11%)	0 (0%)	0 (0%)	1 (5%)	2 (11%)	3 (16%)	1 (5%)	16 (84%)	19
Immunodeficiency with myelodysplasia (GATA2 and others)	7 (26%)	14 (52%)	16 (59%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (11%)	1 (4%)	22 (81%)	27
Interferonopathy (Aicardi-Goutières and others)	0 (0%)	2 (29%)	3 (43%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (14%)	4 (57%)	7
Leukocyte adhesion deficiency	3 (33%)	9 (100%)	8 (89%)	1 (11%)	2 (22%)	2 (22%)	1 (11%)	0 (0%)	4 (44%)	1 (11%)	9 (100%)	9
Mucocutaneous candidiasis	10 (23%)	37 (86%)	32 (74%)	1 (2%)	0 (0%)	3 (7%)	3 (7%)	3 (7%)	11 (26%)	4 (9%)	42 (98%)	43
Neutropenia	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	2
NK cell defect	1 (25%)	3 (75%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	4 (100%)	4
Omenn syndrome	0 (0%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	1 (100%)	1
Other immune deficiency - known cause	6 (11%)	13 (24%)	44 (81%)	0 (0%)	0 (0%)	4 (7%)	1 (2%)	1 (2%)	11 (20%)	3 (6%)	46 (85%)	54
Other T-cell problems	0 (0%)	3 (43%)	4 (57%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (14%)	0 (0%)	6 (86%)	7
Predisposition to severe viral infections	11 (37%)	21 (70%)	26 (87%)	0 (0%)	2 (7%)	4 (13%)	3 (10%)	3 (10%)	7 (23%)	3 (10%)	26 (87%)	30
Severe combined immune deficiency (SCID)	9 (14%)	23 (35%)	45 (68%)	0 (0%)	2 (3%)	4 (6%)	3 (5%)	2 (3%)	17 (26%)	8 (12%)	51 (77%)	66
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	19 (20%)	29 (30%)	96 (99%)	0 (0%)	1 (1%)	6 (6%)	0 (0%)	2 (2%)	16 (16%)	3 (3%)	96 (99%)	97
Susceptibility to mycobacteria (MSMD)	3 (38%)	5 (62%)	4 (50%)	0 (0%)	0 (0%)	0 (0%)	1 (12%)	2 (25%)	2 (25%)	1 (12%)	7 (88%)	8

Table 2. **Sites of infection in IEI (*Continued*)**

Immunodeficiency	Urogenital	SSTI	Sino-pulmonary	Cardiac	Odontogenic	Ophthalmic	MSK	CNS	GI	Bloodstream	Any site	Total count (N = 3511)
TLR pathway abnormality	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	2 (100%)	0 (0%)	2 (100%)	2
Transient hypogammaglobulinemia of infancy with normal numbers of b cells	3 (21%)	2 (14%)	13 (93%)	0 (0%)	0 (0%)	2 (14%)	0 (0%)	0 (0%)	0 (0%)	2 (14%)	14 (100%)	14
Wiskott-Aldrich syndrome	0 (0%)	20 (37%)	33 (61%)	0 (0%)	1 (2%)	6 (11%)	3 (6%)	2 (4%)	9 (17%)	5 (9%)	39 (72%)	54

Table 3. **Infection types in IEI**

Immunodeficiency	Bacterial	Viral	Fungal	Parasitic	Any Infection	Total count (N = 3511)
Agammaglobulinemia	129 (50%)	81 (32%)	23 (9%)	12 (5%)	235 (91%)	257
Ataxia telangiectasia	8 (31%)	7 (27%)	3 (12%)	0 (0%)	24 (92%)	26
Autoimmune lymphoproliferative syndrome (ALPS)	17 (27%)	22 (34%)	39 (61%)	3 (5%)	54 (84%)	64
Autoinflammatory disease	1 (8%)	2 (17%)	0 (0%)	0 (0%)	9 (75%)	12
CHARGE syndrome	1 (33%)	1 (33%)	0 (0%)	0 (0%)	3 (100%)	3
Chronic granulomatous disease	98 (68%)	33 (23%)	75 (52%)	2 (1%)	143 (99%)	145
Combined immune deficiency	25 (48%)	28 (54%)	12 (23%)	2 (4%)	43 (83%)	52
Common variable immune deficiency (CVID)	503 (36%)	332 (23%)	218 (15%)	35 (2%)	1265 (89%)	1416
Complement deficiency	14 (54%)	5 (19%)	3 (12%)	0 (0%)	23 (88%)	26
DiGeorge syndrome	51 (10%)	53 (11%)	29 (6%)	0 (0%)	171 (34%)	496
Dyskeratosis congenita	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1
Ectodermal dysplasia with immunodeficiency (nemo and others)	19 (79%)	10 (42%)	3 (12%)	0 (0%)	24 (100%)	24
HLH, including XLP and pigmentary disorders	5 (31%)	5 (31%)	2 (12%)	0 (0%)	13 (81%)	16
Hyper IgE syndrome	72 (75%)	29 (30%)	63 (66%)	4 (4%)	91 (95%)	96
Hyper IgM syndrome	14 (30%)	16 (34%)	19 (40%)	4 (9%)	44 (94%)	47
Hypogammaglobulinemia	70 (33%)	51 (24%)	26 (12%)	0 (0%)	173 (83%)	209
IgA deficiency	24 (35%)	13 (19%)	5 (7%)	0 (0%)	66 (97%)	68
IgG subclass deficiency	6 (23%)	5 (19%)	7 (27%)	0 (0%)	25 (96%)	26
Immune deficiency with syndromic features (not otherwise listed)	7 (88%)	4 (50%)	0 (0%)	0 (0%)	8 (100%)	8
Immune dysregulation	44 (59%)	39 (52%)	23 (31%)	3 (4%)	69 (92%)	75
Immunodeficiency unknown cause	11 (58%)	8 (42%)	4 (21%)	0 (0%)	16 (84%)	19
Immunodeficiency with myelodysplasia (GATA2 and others)	16 (59%)	10 (37%)	8 (30%)	0 (0%)	22 (81%)	27
Interferonopathy (Aicardi-Goutières and others)	2 (29%)	3 (43%)	1 (14%)	0 (0%)	4 (57%)	7
Leukocyte adhesion deficiency	9 (100%)	6 (67%)	4 (44%)	0 (0%)	9 (100%)	9
Mucocutaneous candidiasis	23 (53%)	20 (47%)	38 (88%)	1 (2%)	42 (98%)	43
Neutropenia	1 (50%)	0 (0%)	0 (0%)	1 (50%)	2 (100%)	2
NK cell defect	2 (50%)	3 (75%)	2 (50%)	0 (0%)	4 (100%)	4
Omenn syndrome	1 (100%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	1
Other immune deficiency - known cause	26 (48%)	23 (43%)	6 (11%)	1 (2%)	46 (85%)	54
Other T-cell problems	2 (29%)	3 (43%)	2 (29%)	0 (0%)	6 (86%)	7
Predisposition to severe viral infections	17 (57%)	21 (70%)	13 (43%)	3 (10%)	26 (87%)	30
Severe combined immune deficiency (SCID)	26 (39%)	29 (44%)	23 (35%)	1 (2%)	51 (77%)	66

Table 3. **Infection types in IEI (*Continued*)**

Immunodeficiency	Bacterial	Viral	Fungal	Parasitic	Any Infection	Total count (N = 3511)
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	49 (51%)	27 (28%)	18 (19%)	1 (1%)	96 (99%)	97
Susceptibility to mycobacteria (MSMD)	7 (88%)	2 (25%)	3 (38%)	1 (12%)	7 (88%)	8
TLR pathway abnormality	1 (50%)	1 (50%)	1 (50%)	0 (0%)	2 (100%)	2
Transient hypogammaglobulinemia of infancy with normal numbers of b cells	6 (43%)	3 (21%)	1 (7%)	0 (0%)	14 (100%)	14
Wiskott-Aldrich syndrome	18 (33%)	15 (28%)	6 (11%)	0 (0%)	39 (72%)	54

Table 4. **Malignancy in IEI**

Immunodeficiency	Hematologic	Solid / Lymphoma	Any Malignancy	Total count (N = 3511)
Agammaglobulinemia	2 (1%)	0 (0%)	2 (1%)	257
Ataxia telangiectasia	4 (15%)	2 (8%)	5 (19%)	26
Autoimmune lymphoproliferative syndrome (ALPS)	3 (5%)	1 (2%)	4 (6%)	64
Autoinflammatory disease	1 (8%)	0 (0%)	1 (8%)	12
CHARGE syndrome	0 (0%)	0 (0%)	0 (0%)	3
Chronic granulomatous disease	3 (2%)	0 (0%)	3 (2%)	145
Combined immune deficiency	4 (8%)	0 (0%)	4 (8%)	52
Common variable immune deficiency (CVID)	126 (9%)	14 (1%)	135 (10%)	1416
Complement deficiency	0 (0%)	0 (0%)	0 (0%)	26
DiGeorge syndrome	1 (0%)	0 (0%)	1 (0%)	496
Dyskeratosis congenita	0 (0%)	0 (0%)	0 (0%)	1
Ectodermal dysplasia with immunodeficiency (nemo and others)	0 (0%)	0 (0%)	0 (0%)	24
HLH, including XLP and pigmentary disorders	0 (0%)	0 (0%)	0 (0%)	16
Hyper IgE syndrome	7 (7%)	1 (1%)	8 (8%)	96
Hyper IgM syndrome	3 (6%)	0 (0%)	3 (6%)	47
Hypogammaglobulinemia	14 (7%)	2 (1%)	16 (8%)	209
IgA deficiency	2 (3%)	1 (1%)	2 (3%)	68
IgG subclass deficiency	2 (8%)	0 (0%)	2 (8%)	26
Immune deficiency with syndromic features (not otherwise listed)	0 (0%)	0 (0%)	0 (0%)	8
Immune dysregulation	6 (8%)	1 (1%)	6 (8%)	75
Immunodeficiency unknown cause	3 (16%)	1 (5%)	3 (16%)	19
Immunodeficiency with myelodysplasia (GATA2 and others)	9 (33%)	9 (33%)	15 (56%)	27
Interferonopathy (Aicardi-Goutières and others)	1 (14%)	0 (0%)	1 (14%)	7
Leukocyte adhesion deficiency	0 (0%)	0 (0%)	0 (0%)	9
Mucocutaneous candidiasis	3 (7%)	0 (0%)	3 (7%)	43
Neutropenia	0 (0%)	1 (50%)	1 (50%)	2
NK cell defect	1 (25%)	0 (0%)	1 (25%)	4
Omenn syndrome	0 (0%)	0 (0%)	0 (0%)	1
Other immune deficiency - known cause	3 (6%)	0 (0%)	3 (6%)	54
Other T-cell problems	0 (0%)	0 (0%)	0 (0%)	7
Predisposition to severe viral infections	4 (13%)	0 (0%)	4 (13%)	30

Table 4. **Malignancy in IEI (*Continued*)**

Immunodeficiency	Hematologic	Solid / Lymphoma	Any Malignancy	Total count (N = 3511)
Severe combined immune deficiency (SCID)	11 (17%)	0 (0%)	11 (17%)	66
Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	9 (9%)	0 (0%)	9 (9%)	97
Susceptibility to mycobacteria (MSMD)	0 (0%)	0 (0%)	0 (0%)	8
TLR pathway abnormality	0 (0%)	0 (0%)	0 (0%)	2
Transient hypogammaglobulinemia of infancy with normal numbers of b cells	0 (0%)	0 (0%)	0 (0%)	14
Wiskott-Aldrich syndrome	4 (7%)	2 (4%)	6 (11%)	54

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Monitoring of Immune Recovery After Hematopoietic Stem Cell Transplantation in Patients with Aplastic Anemia by Quantitative Determination of TREC and KREC

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Background and Aims: Analysis of T- and B-lymphocyte recovery after hematopoietic stem cell transplantation (HSCT) is important for assessing the positive dynamics of treatment. Flow cytometry is informative enough to monitor immune recovery in the post-transplant period. However, the determination of the number of TREC and KREC can be used to assess T and B cell neogenesis.

Methods: We describe 15 patients with aplastic anemia after allogeneic HSCT (HLA-matched-related [n = 8], transplantation from unrelated healthy donors [n = 7]). The age of patients was 15.0 (1.9-17.0) yrs. Monitoring points were 30, 45, 60, 100, 180, 245, 365 days after HSCT. Reconstitution of T and B lymphocytes was assessed based on the results of flow cytometry. Quantitative of TREC and KREC was performed using the multiplex RQ-PCR.

Results: KREC are detected by day 45 and reach the threshold of normal values by day 100. By day 245, the number of KREC begins to slowly decrease, which is not a sign of transplant rejection, but indicates an increase in the total number of CD19+ cells and the effect of dilution of KREC-positive lymphocytes. T-lymphocyte recovery begins later. TREC are determined by day 145 and by day 180 the median of TREC-positive lymphocytes is 800 copies per 1×10^6 lymphocytes without a dynamic decline up to a year after transplantation. In turn, according to immunophenotyping data, CD3+ begins to appear after day 30, which indicates that the number of activated T lymphocytes then decreases and the number of naive ones increases. This picture is due to the peripheral expansion of T lymphocytes, which predominate in the donor transplant, and the beginning of the production of the recipient's own cells. CD19+ lymphocytes appear by day 60 and reach the norm by day 100, which indicates that the newly formed pool of B lymphocytes mainly consists of naive cells.

No statistical differences were found between the groups with related and unrelated HSCT in the dynamics of TREC reconstitution. For KREC, significant differences in the increase in quantity are observed by day 100 ($p < 0.05$).

Conclusions: Quantitative determination of TREC and KREC allows assessment of T and B cell neogenesis without the use of additional research methods such as flow cytometry. This method can be used as a predictor of reconstitution of T and B cell function.

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Hypogammaglobulinemia, Infections, and Mortality in Patients Treated with Blinatumomab

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Introduction: Blinatumomab, a bispecific antibody targeting CD3 and CD19, utilizes a unique mechanism of action to selectively engage cytotoxic T cells and CD19-positive B cells, resulting in direct lysis of tumor cells and exerting antileukemia effect. Hypogammaglobulinemia and infectious complications post-blinatumomab are reported but not well characterized.
Methods: We performed a retrospective evaluation of 208 patients at a single center receiving blinatumomab therapy and evaluated demographics, hypogammaglobulinemia (IgG ≤ 600 mg/dL), and infections prior to and after blinatumomab therapy, and risk factors for hypogammaglobulinemia, infection, hospitalizations, and mortality. Incidence rates and risk for infections were calculated using Poisson regression. Risk factors for mortality were calculated using Cox proportional hazards regression.
Results: We identified 208 patients who had received blinatumomab (mean age 49.7 years [range 3-84], 54.3% male). Of the patients with IgG evaluated, 51/101 (50.5%) had hypogammaglobulinemia pre-blinatumomab therapy, which increased to 108/119 (90.8%) post-blinatumomab therapy. Mean IgG levels decreased from 640 mg/dL to 375 mg/dL pre- to post-blinatumomab ($p < 0.0001$). 50% of patients developed a serious infection post-blinatumomab therapy, with 15.6% of patients developing a serious infection within the first 30 days after blinatumomab initiation. Risk factors for hypogammaglobulinemia included younger age and hypogammaglobulinemia pre-blinatumomab therapy (hazard ratio [HR] 1.90; 95% CI 1.09-3.29; $p = 0.023$). When adjusted for age, sex, ANC/ALC, and prior stem cell transplant, risk factors for infection after blinatumomab included male sex and hypogammaglobulinemia pre-blinatumomab (adjusted IRR 1.57; 95% CI 1.15-2.15; $p = 0.005$). Risk factors for mortality after blinatumomab included age ≤ 18 years, hypogammaglobulinemia pre-blinatumomab (adjusted HR 2.35; 95% CI 1.15-4.82; $p = 0.02$), and severe infections (particularly in the first 30 days of therapy) (adjusted HR 5.44; 95% CI 2.41-12.25; $p ≤ 0.0001$).
Conclusion: Hypogammaglobulinemia and infection are common with blinatumomab therapy and may be higher than previously reported. Pre-blinatumomab hypogammaglobulinemia was associated with an increased risk of hypogammaglobulinemia, infection, and mortality post-therapy. Further research is needed to understand the role of immunoglobulin replacement given the frequency of hypogammaglobulinemia observed.

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Clinical Insight of Cytokine Panel Testing in Patients with Inborn Errors of Immunity

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Background: Cytokines play an important role in Th1 and Th2 inflammation. Both Th1 and Th2 cytokines can be utilized for evaluation and treatment response in many different disorders, including inborn errors of immunity. The role of broad cytokine panel testing in inborn errors of immunity is not well described.
Objective: To analyze broad cytokine panel testing in clinical practice.
Methods: A retrospective review of cytokine panel testing performed at Mayo Clinic was performed. Data were collected from patients at Mayo Clinic Rochester, Mayo Clinic Jacksonville, and Mayo Clinic Health System. Serum cytokine panel testing included the following cytokines: tumor necrosis factor (TNF), IL-6, IFN-β, IL-10, monocyte chemoattractant protein-1 (MCP-1), IL-1β, IFN-γ, macrophage inflammatory protein-1 alpha (MIP-1α), granulocyte-monocyte colony-stimulating factor (GM-CSF), IL-2 receptor α soluble, IFN-α, and IL-18. Data collection ranged from 03/2021 to 09/2024. The study was funded by Mayo CCaTS grant number UL1TR002377.

Results: A total of 88 cytokine panel tests were performed during the study period on 80 total patients. There was at least 1 elevated cytokine level in 70/88 (80%) tests performed. There was elevation in each individual cytokine level as follows: TNF (49), IL-2 receptor α soluble (40), IFN-α (0), IL-18 (26), IL-6 (33), IFN-β (4), IL-10 (13), MCP-1 (18), IL-1β, IFN-γ (11), MIP-1α (12), and GM-CSF (6). 18 patients that underwent cytokine panel testing had common variable immune deficiency (CVID), and 10 of those patients had granulomatous lymphocytic interstitial lung disease. 6 patients with early onset inflammatory bowel disease, 5 patients with autoimmune lymphoproliferative syndrome, 2 patients with Myhre syndrome, 2 patients with Hyper IgE syndrome, 1 patient with hypereosinophilic syndrome, 1 patient with autoimmune polyglandular syndrome type 1, 1 patient with XIAP deficiency, 1 patient with X-linked chronic granulomatous disease, and 1 patient with STAT 1 gain of function were tested. Other patients tested had other medical diagnoses or were undergoing immunodeficiency evaluation. There was no significant increase noted in any individual cytokine level when compared with the whole cohort.
Conclusion: Cytokine panel testing could be a potential diagnostic tool in evaluation of inborn errors of immunity. Further research is needed to better characterize the importance of cytokine panel testing in inborn errors of immunity.

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Clinical Features of Adults Aged 50 and Older with STAT3DN Hyper IgE Syndrome

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Backgrounds and Aims: Hyper IgE syndrome (HIES) resulting from dominant negative STAT3 (STAT3DN) mutations is a multisystem disease where pulmonary infections and complications are recognized as a cause of disability and mortality. Comorbidities for patients with STAT3 DN HIES include hypertension, chronic pain, and depression, which can lead to disruption of daily activities and contribute to decreased quality of life. The aim of this project is to describe the clinical features and disease burden of older patients with STAT3 DN HIES.
Methods: We retrospectively reviewed patients with STAT3 DN HIES, identifying 18 patients aged 50 years or older (9 male, 11 living, median age 56 years).

Fifteen patients (83%) had parenchymal lung abnormalities with 6 (33%) requiring oxygen.

Thirteen patients (72%) had decreased 6-minute walk distances, which was compounded by chronic pain, which was seen in 10 patients (55%). Three patients had joint replacement and seven had other orthopedic surgeries. 14 (78%) had osteoporosis/osteopenia.

Other comorbid conditions include significant gastrointestinal bleeding (5), reflux (12), history of cancer—lymphoma (2), lung (1), thyroid (1), and skin cancer (2). Hearing loss is documented in 9 patients. Eleven patients (61%) take medication for anxiety, depression, or sleep disturbance.

Causes of death include pneumonia, respiratory failure, sepsis, lung cancer, and suicide.
Conclusions: With earlier age of diagnosis, aggressive treatment for pulmonary infections, and availability of antifungal agents, people with STAT3 DN HIES may live longer with fewer complications of pulmonary disease. However, this population is medically complicated and has risk factors for cardiovascular disease, bleeding, fractures, and malignancy. There is significant musculoskeletal disease that often leads to chronic pain and decreased mobility. Further study of the vascular and musculoskeletal complications of this disease is needed to improve survival and quality of life.

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Immunomodulation in the Treatment of Disseminated Coccidioidomycosis

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Introduction: Coccidioidomycosis, commonly known as Valley fever, is an endemic fungal infection with a growing impact in the western United States. Patients with disseminated coccidioidomycosis (DCM) represent a rare and life-threatening subset of Valley fever who face years or a lifetime of antifungals to manage their disease. Immunocompromised patients with defective type 1 immunity or excessive type 2 immunity have an increased risk of dissemination. We previously published a single case employing the IL4/IL13 blocker dupilumab as an adjuvant to antifungal therapy. Here we present ten cases of patients in which adjuvant immunomodulation was provided for severe coccidioidomycosis.

Methods: This is not an interventional trial. Cases were identified at UCLA by infectious disease experts in conjunction with immunology, and all subjects were deemed to be maximally treated with multiple conventional antifungals. Informed consent was obtained. We performed intracellular cytokine staining on CD4+ T cells and measured proportions of interferon gamma (IFN-γ), IL-4, and IL-17A–producing T cells. Treatment with IFN-γ was offered to those subjects showing life-threatening progression of disease despite maximal conventional care. Treatment with dupilumab was offered to those with excessive type-2 skewing. Clinical outcomes were assessed by laboratory studies, imaging results, and mycosis score.

Results: Our data follow 10 subjects for a median of 6 months after treatment. Our subjects showed excessive type 2-to-1 ratios, mostly due to excessive type 2 immune skewing and less often in subjects with poor type 1 responses. We found reduction of polyclonal type 2 responses in response to treatment with dupilumab. Clinical outcomes in all ten subjects were improved above the baseline state.

Conclusions: Our work offers a new treatment employing immune modulation by cytokine blockade to treat a life-threatening infectious disease. Patients with poorly controlled disease may benefit from IFN-γ. Furthermore, subjects exhibiting a Th2-skewed response may benefit from dupilumab. Following the Casadevall damage–response framework, this tailored approach aligns immunomodulation with the underlying immunopathology. These observations provide evidence to support proper clinical trials of IFN-γ and dupilumab. Further research is needed to better characterize why cocci disseminates in certain subjects and which patients will benefit from immunomodulation.

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3-Year-Old Female with Specific Antibody Deficiency and 9p Duplication Treated with Replacement Immunoglobulin

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The patient is a 3-year-old female with a history of hypoxic-ischemic encephalopathy, cerebral palsy, global developmental delay, hypotonia, epilepsy, feeding intolerance with known aspirations, and chronic lung disease who presented to immunology for evaluation of recurrent, severe upper and lower respiratory tract infections. In the past year, she reported monthly upper respiratory infections, three of which progressed to pneumonia requiring antibiotic treatment, and two of which required hospitalization for severe respiratory failure. She denied lifetime otitis, sinusitis, cutaneous, or other invasive or serious infections.

Immunological evaluation demonstrated normal lymphocyte subsets, B cell phenotyping, naïve/memory T cell phenotyping, immunoglobulins, non-protective tetanus titer, protective diphtheria titer, and protective hepatitis B titer. The patient had 2/23 *Streptococcus pneumoniae* titers protective above 1.3 mcg/mL after initial Prevnar 13 administration and then only 4/14 *S. pneumoniae* titers protective above 1.3 mcg/mL after Pneumovax 23 booster. The patient had normal lymphocyte proliferative responses to PHA, PWM, soluble anti-CD3, and anti–CD3+IL-2 though decreased to soluble anti–CD+anti-CD28.

Genetic testing detected a heterozygous known pathogenic VARS2 variant (c.1546G>T and p.Glu516*) associated with autosomal recessive combined oxidative phosphorylation deficiency in addition to 9p24.2 duplication. VARS2 encodes a key enzyme for mitochondrial protein synthesis 1. 9p duplication is associated with global developmental delay similar to the patient's phenotype but has not been specifically linked to abnormalities in the immune system.

Despite initial treatment with prophylactic azithromycin and revaccination for *S. pneumoniae*, the patient developed COVID-19 pneumonia and rhino enterovirus with severe respiratory failure requiring two separate hospitalizations over three months and no significant improvement in strep pneumoniae titers. Subcutaneous immunoglobulin replacement therapy was initiated, and she has been on biweekly subcutaneous immunoglobulin replacement for four months with symptomatic improvement and no further infectious diagnosis.

This case highlights that patients with 9p duplication and other rare genetic disorders are at risk for immune dysfunction and can benefit from replacement immunoglobulin. Patients with rare genetic disorders that have not been previously linked to immune dysfunction should be evaluated by an immunologist if recurrent infections.

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Opportunities for Precision Medicine in Germline Genetic Testing for Inborn Errors of Immunity Inferred from Large-Scale, Real-World Diagnostic Genetic Testing Results

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A molecular diagnosis can be associated with medical actionability, informing clinical management of genetic disease, for example, by pointing to clinical guidelines for surveillance or to precision therapies. However, the rate of genetic test results that is medically actionable remains unknown in real-world clinical testing. Understanding the degree to which gene testing can inform medical care is important because it has broad relevance for clinical care, professional practice guidelines, patient advocacy, health economic research, and insurance reimbursement.

From May 2016 to May 2024, 86,767 unrelated probands had multigene panel testing (MGPT) for inborn errors of immunity (IEI) at a single commercial laboratory. Positive molecular diagnoses in this cohort were matched to expert-curated lists of genetic disorders with clinical management guidelines, which included ACMG secondary findings (PMID: 37347242), ClinGen actionability (PMID: 38757444), the rx-genes database (PMID: 33350578), and actionable disorders from newborn screening (PMID: 38585998). Actionable yield was calculated as the product of the diagnostic yield and the actionability rate. Results were stratified by clinician-reported race, ethnicity, or ancestry (REA) group. Additionally, the frequency of positive results was calculated for family members of probands diagnosed with actionable conditions who participated in cascade testing.

The diagnostic rate was 8.0% with 96.3% of those results being linked to medical actionability; thus, the overall actionable yield was 7.7%. Among patients with a molecular diagnosis, the rates of actionable results did not differ among REA groups overall. Finally, the rate of positive results in family members undergoing cascade testing for actionable disorders was 37.6%.

The majority of molecular diagnoses in MGPT for IEI conditions appeared to be associated with medical actionability, invoking opportunities for clinical care such as precision therapies, recommended surveillance, and other interventions. Our study suggests that in the setting of real-world clinical genetic testing, the gap between molecular diagnosis and medical actionability is surprisingly narrow. Our data highlight specific areas of medicine where research and professional practice guidelines are most needed to close the existing actionability gaps. Finally, these results underscore the potential high clinical utility of family cascade testing, which remains underutilized in clinical genetic testing.

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Haploinsufficiency of A20: Investigating Expanded Phenotypes, Immune Dysregulation, and Liver Injury in a Rare Autoinflammatory Syndrome

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Haploinsufficiency of A20 (HA20) is a rare genetic cause of complex immune dysregulation caused by pathogenic variants in TNFAIP3, encoding A20. A20 is a critical negative regulator of numerous inflammatory pathways. Although initially reported as a monogenic cause of Behcet's disease, it has become clear that heterozygous loss of A20 results in diverse clinical manifestations. We describe 4 individuals from 2 families with novel variants in TNFAIP3 (c.1069C>T, p.Gln357X and c.2093C>A, p.S698X) and significant variability in age of onset, phenotype, and severity. The 3 affected patients share common features, including oral ulcers, inflammatory skin lesions, leukocytosis, autoantibodies, and elevated interferon scores, but were diagnosed with antibody-negative neuromyelitis optica (NMO) at age 2, giant cell hepatitis with autoimmune cytopenias at age 12, and systemic lupus erythematosus without nephritis at age 35. One individual has not developed disease manifestations at the age of 40, despite an interferon score above healthy control levels. Transaminitis in the 3 patients supports a potential link between HA20 and immune-mediated hepatic injury. Although anti-TNF agents are most frequently used in treatment of HA20, the neuroinflammatory disease of the patient with NMO responded to rituximab as a corticosteroid-sparing agent. She has residual vision loss, spinal cord atrophy with lower extremity weakness, and neurogenic bladder, but she is now 22, and tofacitinib controls her oral ulcers, rashes, and arthritis. Her mother, age 61 and on hydroxychloroquine for her lupus, has a sister who also carries the family variant and has been diagnosed with adult-onset Still's disease. The patient with hepatitis and cytopenias, the daughter of the unaffected carrier, responded well to 6-mercaptopurine for her liver disease and rituximab for arthritis and rash. However, she subsequently developed fatal pulmonary hypertension age 16, in the absence of parenchymal lung disease. This case series provides important insights into HA20, highlighting its diverse clinical presentations and emphasizing the importance of liver injury as a potential phenotype. The breadth of phenotypes in HA20 combined with incomplete penetrance likely contributes to under recognition of this monogenic cause of complex immune dysregulation, and HA20 could be considered in any family with multiple members affected by inflammatory disease.

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A Family with a Novel Dominant Negative FOXN1 Heterozygous Variant of Uncertain Significance: A Case Report and Review of the Literature on the Clinical Course

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A 3-month-old male presented from Guatemala for a second opinion regarding an initial diagnosis of hyper IgE syndrome secondary to elevated IgE (50,000 IU/ml), eosinophilia (10 K/cu mm), and severe dermatitis complicated by staphylococcal abscesses. The patient had a history of early onset erythroderma, alopecia, and nail dystrophy. At our center, no thymic tissue was identified on ultrasound. He had a highly elevated CD4 T cell compartment (8,605 cells/μl), with a low fraction of naïve T cells (0.5%) with 98% Th2 skewing. His leading diagnosis was changed to Omenn syndrome. Subsequent genetic testing revealed a novel heterozygous variant of uncertain significance in FOXN1 (c.1444del and p.R482Gfs*68) that is predicted to have a dominant negative effect. The variant is also present in his father who has partial alopecia, nail dystrophy, and less than 5% T cells. Historically, heterozygous FOXN1 variants do not require definitive therapies such as thymic and/or bone marrow transplant due to reconstitution with age. Our patient has so far improved the naïve compartment of T cells to 9% now at 8 months of age. Nonetheless, recommendations for definitive therapies are less clear for our case, since dominant negative heterozygous variants can lower FOXN1 activity to less than 5% and immune reconstitution is delayed compared with other heterozygous variants. We reviewed the literature and through our collaborative network, we identified other dominant negative cases. Among these patients, one patient received a bone marrow transplant for severe T cell lymphopenia before the FOXN1 diagnosis was made.

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Immune and Genetic Insights into Kabuki Syndrome: A Case Series

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Introduction: Kabuki syndrome is a rare disorder primarily associated with mutations in the KMT2D (autosomal dominant) and KDM6A (X-linked) genes. While these mutations may be linked to immune dysregulation, including humoral immunodeficiencies resembling common variable immunodeficiency with recurrent infections and impaired B cell memory differentiation [1], these associations are not well established. This study aims to further characterize immune dysregulation, clinical manifestations, and genetic variability in Kabuki syndrome to address this gap.
Method: This case series involves patients diagnosed with Kabuki syndrome at the University of Miami, following Institutional Review Board approval (Study #20240903). Electronic medical records were reviewed to analyze demographics, history of infections, autoimmunity, and relevant laboratory data.
Findings: The study included seven patients (4 males and 3 females), aged 14 months to 26 years (mean: 11.7 years, median: 5 years). Hypogammaglobulinemia was observed in 6/7 patients (86%), with low IgG in 4/7 (57%), low IgA in 2/7 (29%), and low IgM in 3/7 (43%). Lymphopenia was identified in 3/7 patients (43%) for CD3, 3/7 (43%) for CD4, and in 2/7 (29%) for CD8. 1/7 patients (14%) showed significant B cell subset abnormalities.

Pathogenic or likely pathogenic KMT2D mutations were detected in 6/7 patients (86%), while 2/7 (29%) had variants of uncertain significance (CEP250, SALL1, and SRCAP). A duplication at 2q22.1 was noted in 1/7 patients (14%) without a clear clinical phenotype.

Recurrent infections occurred in 3/7 patients (43%), mainly involving upper respiratory infections, otitis media, and pneumonia. Autoimmunity was reported in 1/7 patients (14%) and lymphoproliferative disorders in 2/7 (29%).

Intravenous immunoglobulin therapy was administered to 3/7 patients (43%) and 1/7 (14%) received prophylactic vaccines for low pneumococcal antibody titers.
Discussion: This study finds that patients with Kabuki syndrome exhibit significant immune dysregulation, including hypogammaglobulinemia, lymphopenia, and recurrent infections, which are linked to genetic variability such as pathogenic KMT2D mutations and variants of uncertain significance. These findings support the need for routine immune evaluations, genetic testing, and targeted therapies, including immunoglobulin replacement and additional vaccinations, to guide personalized management and improve patient outcomes.

Reference

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Recurrent Sinopulmonary Infections in an 8-Year-Old Boy with Cornelia de Lange Syndrome

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Introduction: Cornelia de Lange syndrome (CdLS) is a rare genetic disorder with an estimated prevalence of 1 in 10,000 live births worldwide. It presents with a spectrum of severity, ranging from mild to severe marked by characteristic facial features, growth delay, intellectual disability, heart defects, gastrointestinal issues, hearing loss, myopia, and frequent upper and lower respiratory infections. The majority of genetic variants found in CdLS are associated with variants in the NIPBL gene, which encodes a regulatory protein crucial for the function of the cohesin complex.
Case Description: We present an 8-year-old male with a history of dysmorphic facial features, global developmental delay, aortic coarctation, lagophthalmos, hearing loss, and recurrent upper and lower sinopulmonary infections. There is no family history of immunodeficiencies or other genetic syndromes and patients born outside the United States. Commercial whole-exome sequencing performed at 7 years of age revealed a

heterozygous de novo pathogenic variant in NIPBL (c.8257 C>G, p.R2753G). Complete blood count with differential, basic lymphocyte subsets, and immunoglobulins were within normal limits. Patient was immune to varicella, hepatitis B, tetanus, and diphtheria post-vaccination but only had 1/23 strep pneumoniae titers above 1.3 ug/mL and only 4/23 above 0.5 ug/mL after primary Prevnar 13 series. Advanced phenotyping showed increased percentage of transitional B cells, increased proportion of CD8+ TEMRA cells, reverse CD4/CD8 ratio at 0.69, and normal mitogen-induced lymphocyte proliferation to PHA and ConA with PWM at 50% below the lower limit of normal. Patient given booster vaccination with Pneumovax and had improvement in strep pneumoniae titers to 16/23 protective above 1.3 ug/mL and decreased clinical infections.
Discussion: The cohesin protein complex plays a significant role in the immune system, and altered expression of immune-related genes in patients with CdLS may explain the varying degrees of immunodeficiency observed in these individuals. Although no specific immune defect has been universally identified in CdLS, and there are no established guidelines for managing immune issues or vaccination in this population, it is important to conduct clinical immunologic evaluations for CdLS patients who experience recurrent infections as booster vaccinations can significantly improve these patients' quality of life.

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Treatment Barriers for Pediatric and Adult Patients with Chronic Granulomatous Disease

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Introduction: The lifespan of patients with chronic granulomatous disease (CGD) has increased with the use of prophylactic medications. Despite a reduction in infections, however, patients rely on lifelong medications and remain at risk of severe infections and immune dysregulation. While hematopoietic stem cell transplantation (HSCT) and gene therapy now offer curative options with improved safety profiles, barriers to accessing these definitive therapies remain poorly characterized.
Objective: This study aimed to determine the rates of prophylactic and definitive treatment therapies in pediatric and adult patients with CGD and identify barriers to their implementation.
Methods: We conducted an IRB-approved cross-sectional survey study of 76 CGD patients (41 adults and 35 children). Participants were recruited through national patient advocacy organizations (Immune Deficiency Foundation and CGD Association of America) and an academic immunology center in Northern California. The survey, created with input from AAAAI PID committee, patients, and advocates, assessed treatment history, healthcare experiences, and perceived barriers to care. Descriptive statistics and chi-square analyses were performed.
Results: Mean ages were 12 years (pediatric) and 40 years (adult). Notably, 15.5% (n = 11) of patients lacked antimicrobial prophylaxis, and 32.9% (n = 25) had never received IFNg therapy, with 48% (n = 12) reporting no provider discussion. Only 17.3% (n = 13) of participants had undergone HSCT, predominantly children (69.2%, n = 9). Among the non-transplanted subjects, 68.3% (n = 43) had never received transplant specialist consultation. Despite the limited racial and ethnic diversity, 43% (7/16) of non-white participants considered HSCT unlikely for them. Primary barriers included physician expertise (32.0%), cost (28.0%), and equally distributed factors (12% each), including lack of information, geographic distance, physical limitations, and medication side effects.
Conclusion: Despite advances in HSCT safety and efficacy, significant disparities exist in accessing definitive therapy for CGD, particularly among adults and racial/ethnic minorities. Identified barriers suggest the need for improved provider education, healthcare navigation support, and targeted interventions to address demographic disparities. Future research should focus on developing systematic approaches to expand access to transplant evaluation and address socioeconomic barriers to definitive therapy.

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The Value of Pneumovax Testing in the Prevnar 20 Era

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Background: Humoral immune disorders, such as common variable immunodeficiency (CVID) and specific antibody deficiency (SAD), require functional testing for proper assessment and management. The most common testing involves the measurement of pre- and post-vaccination pneumococcal titers to assess polysaccharide antibody response to the 23-valent pneumococcal vaccine (PPSV23). Guidelines for this testing remain controversial and have become increasingly challenging with the widespread use of pneumococcal conjugate vaccines (PCV) such as PCV20, which have decreased the number of unique serotypes contained in PPSV23 that are available for assessing anti-polysaccharide antibody responses.

Objective: To determine the diagnostic utility in evaluating the polysaccharide antibody response to the four or eleven pneumococcal serotypes unique to PPSV23 in patients previously vaccinated with PCV20 or PCV13, respectively.

Methods: We performed a retrospective chart review using electronic medical records of patients aged 2-65 years old seen in University of Virginia Health Immunodeficiency Clinics who received PPSV23 and had pneumococcal titers measured within 8 weeks of vaccination (see table). Pneumococcal titers were measured using a 23-serotype bead-based multiplex immunoassay panel via Mayo Clinic Laboratories. A protective response was defined as ≥1.3 µg/mL, and a response to PPSV23 was classified as "positive" based on responding to ≥70% of the unique serotypes not contained in previously received PCV for each subject.

Table 1. **Pneumococcal Vaccine Serotypes**

Serotypes	PCV-7[a]	PCV-13[b]	PCV-15[c]	PCV-20[d]	PCV-21[e]	PPSV23
1	–	1	1	1	–	1
2	–	–	–	–	–	2
3	–	3	3	3	3	3
4	4	4	4	4	–	4
5	–	5	5	5	–	5
6A	–	6A	6A	6A	6A	–
6B	6B	6B	6B	6B	–	6B
7F	–	7F	7F	7F	7F	7F
8	–	–	–	8	8	8
9N	–	–	–	–	9N	9N
9V	9V	9V	9V	9V	–	9V
10A	–	–	–	10A	10A	10A
11A	–	–	–	11A	11A	11A
12F	–	–	–	12F	12F	12F
14	14	14	14	14	–	14
15A	–	–	–	–	15A	–
15B	–	–	–	15B	–	15B
15C	–	–	–	–	15C	–
16F	–	–	–	–	16F	–
17F	–	–	–	–	17F	17F
18C	18C	18C	18C	18C	–	18C
19A	–	19A	19A	19A	19A	19A
19F	19F	19F	19F	19F	–	19F
20	–	–	–	–	20	20
22F	–	–	22F	22F	22F	22F
23A	–	–	–	–	23A	–
23B	–	–	–	–	23B	–
23F	23F	23F	23F	23F	–	23F
24F	–	–	–	–	24F	–

Table 1. **Pneumococcal Vaccine Serotypes (*Continued*)**

Serotypes	PCV-7[a]	PCV-13[b]	PCV-15[c]	PCV-20[d]	PCV-21[e]	PPSV23
31	–	–	–	–	31	–
33F	–	–	33F	33F	33F	33F
35B	–	–	–	–	35B	–

[a]16 serotypes contained in PPSV23 that are not contained in PCV7: 1, 2, 3, 5, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, 33F
[b]11 serotypes contained in PPSV23 that are not contained in PCV13: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F
[c]9 serotypes contained in PPSV23 that are not contained in PCV15: 8, 10A, 11A, 12F, 15B, 2, 9N, 17F, 20
[d]4 serotypes contained in PPSV23 that are not contained in PCV20: 2, 9N, 17F, 20
[e]11 serotypes contained in PPSV23 that are not contained in PCV21: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B, 2

Table 2. **Diagnostic agreement summary between the pneumococcal antibody 4 and 11 serotype panel findings and the pneumococcal antibody 23 serotype panel findings when the pneumococcal antibody 23 serotype panel finding is considered the gold standard.**

	23 Serotype Response	
11 Serotype Response	**Responder (≥70% Positive)**	**Non-responder (<70% Positive)**
Responder (≥70% Positive)	23	0
Non-responder (<70% Positive)	4	12
Diagnostic Agreement Summary		
Diagnostic Parameter	Estimate [95% CI]	
Sensitivity	96.7 [82.8, 99.9]	
Specificity	66.7 [48.2, 82.0]	
PPV	72.5 [56.1, 85.4]	
NPV	95.7 [78.0, 99.9]	
FPER	33.3 [18.0, 51.8]	
FNER	3.3 [0.1, 17.2]	
Accuracy	81.0 [69.1, 89.8]	

	23 Serotype Response	
4 Serotype Response	**Responder (≥70% Positive)**	**Non-responder (<70% Positive)**
Responder (≥70% Positive)	22	2
Non-responder (<70% Positive)	5	10
Diagnostic Agreement Summary		
Diagnostic Parameter	Estimate [95% CI]	
Sensitivity	81.5 [61.9, 93.7]	
Specificity	83.3 [51.6, 97.9]	
PPV	91.7 [73.0, 99.0]	
NPV	66.7 [38.4, 88.2]	
FPER	16.7 [2.1, 48.4]	
FNER	18.5 [6.3, 38.1]	
Accuracy	82.1 [66.5, 92.5]	

	11 Serotype Response	
4 Serotype Response	**Responder (≥70% Positive)**	**Non-responder (<70% Positive)**
Responder (≥70% Positive)	33	7
Non-responder (<70% Positive)	3	20

Table 2. **Diagnostic agreement summary between the pneumococcal antibody 4 and 11 serotype panel findings and the pneumococcal antibody 23 serotype panel findings when the pneumococcal antibody 23 serotype panel finding is considered the gold standard. (*Continued*)**

	11 Serotype Response	
4 Serotype Response	**Responder (≥70% Positive)**	**Non-responder (<70% Positive)**
Diagnostic Agreement Summary		
Diagnostic Parameter	Estimate [95% CI]	
Sensitivity	91.7 [77.5, 98.2]	
Specificity	74.1 [53.7, 88.9]	
PPV	82.5 [67.2, 92.7]	
NPV	87.0 [66.4, 97.2]	
FPER	25.9 [11.1, 46.3]	
FNER	8.3 [1.8, 22.5]	
Accuracy	84.1 [72.7, 92.1]	

Results: We initially analyzed responses in 39 subjects who received PPSV23 but no prior PCV. We analyzed diagnostic agreement between the responsiveness as determined by evaluating all 23 serotypes compared with the 11 unique serotypes not found in PCV13 or those 4 unique serotypes not found in PCV20. When comparing 23 serotypes to 11 serotypes, we found the accuracy to be 81%. When comparing 23 serotypes to 4 serotypes, we found the accuracy to be 82%. For 63 subjects who previously received PCV13, we examined the diagnostic agreement between the 11 serotype and 4 serotype panels and found the accuracy to be 84%.
Conclusion: Even in subjects who have previously received PCV13 or PCV20, there is still diagnostic utility in administration of PPSV23 and evaluation of the response to the unique serotypes as a means of assessing anti-polysaccharide antibody responses.

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A Case of Very Early-Onset Inflammatory Bowel Disease due to a Novel RIPK1 Variant Confirmed by Western Blot

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Background: Very early-onset inflammatory bowel disease (VEO-IBD), diagnosed before the age of 6, is a severe IBD subtype often associated with monogenic causes. Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is a critical regulator of inflammation and cell death. Biallelic pathogenic variants in the RIPK1 gene lead to RIPK1 deficiency, which disrupts these processes, causing immunodeficiency and autoinflammation, such as recurrent infections, early-onset IBD, and polyarthritis. Here, we report a VEO-IBD case associated with a novel variant in the RIPK1 gene.
Case Presentation: A 3-month-old male with suspected milk protein allergy presented with a 3-week history of hematochezia, intermittent fevers, vomiting, poor feeding, irritability, and large oral ulcers. Initial evaluation revealed anemia, elevated fecal calprotectin (>3000 µg/g), and gastritis with erosions, lymphocytic infiltrates in the duodenum, crypt abscesses in the sigmoid colon, focal active colitis, and colon ulcers. Imaging demonstrated splenomegaly, and an infectious workup was negative. Initial management included nasogastric tube feeds, total parenteral nutrition, RBC transfusions, iron supplementation, metronidazole, and anti-inflammatory therapy with an IL-1 receptor antagonist. Despite treatment, the patient was readmitted 1 week later with worsening symptoms. Repeat

endoscopy revealed severe ulcerations and a cobblestone appearance in the stomach, along with ulcers and cobblestoning in the duodenum and the colon. In response, therapy was transitioned to infliximab, to which the patient thus far has shown a good response.
Diagnostic Workup: The patient underwent genome sequencing, which identified a homozygous c.460-5C>A variant in the RIPK1 gene, inherited from consanguineous unaffected parents. Reported as a variant of uncertain significance (VUS), it was predicted to disrupt the splice acceptor site of exon 5, likely resulting in aberrant splicing and loss of function. The pathogenicity of this previously unreported variant was validated through western blot analysis, which served as a crucial diagnostic tool in confirming the deficiency of RIPK1 in the patient.
Discussion: RIPK1 deficiency causes severe VEO-IBD. Western blot analysis confirmed a novel pathogenic variant. Anti-TNF therapy stabilized symptoms. Early diagnosis and personalized treatment are critical for management.
Conclusion: A novel RIPK1 variant highlights the importance of genetic testing and functional studies in VEO-IBD. Early recognition and targeted therapies improve outcomes in severe cases.

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A Gene Therapy Approach for the Treatment of Inborn Errors of Immunity Caused by Mutations in Large Genes

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Inborn errors of immunity (IEIs) are rare genetic disorders caused by mutations in genes critical for immune cell function, development, or signaling pathways. Gene therapy represents a potential curative treatment for these conditions, with lentiviral vectors (LVs) emerging as a promising tool in this field. However, one of the significant limitations related to the use of LVs is their cargo capacity of around 8 kilobases. This prevents their application for the treatment of conditions requiring the delivery of larger DNA sequences and the stable expression of the transgene in actively proliferating cells. Recent studies have shown that protein trans-splicing is a powerful tool for expanding the cargo capacity of AAV vectors upon co-infection of a host cell with different vectors, each expressing a split-intein–flanked portion of the full-length protein. The aim of our study is to translate the same technology to the platform of LVs. We developed dual-intein LVs, each expressing either the N- or the C-terminal half of the EGFP reporter protein fused to the N- and C-terminal halves of the DnaE split-inteins from *Nostoc punctiforme*, under the control of EF1A promoter. We co-infected HEK293 cells and observed the reconstitution of a functional full-length protein of the proper size. This demonstrates that trans-splicing applied to LVs is as efficient as for AAVs.

This system could be helpful to design a gene therapy approach for specific IEIs, including LRBA deficiency and ataxia-telangiectasia (A-T), caused by mutations in genes larger than 8 kb. We are currently developing dual-intein LVs expressing either the N- or the C-terminal half of the ATM protein, mutated in A-T patients, that will be tested in vitro for their ability to reconstitute a functional protein of the correct size and for the ability to correct the mutant phenotype.

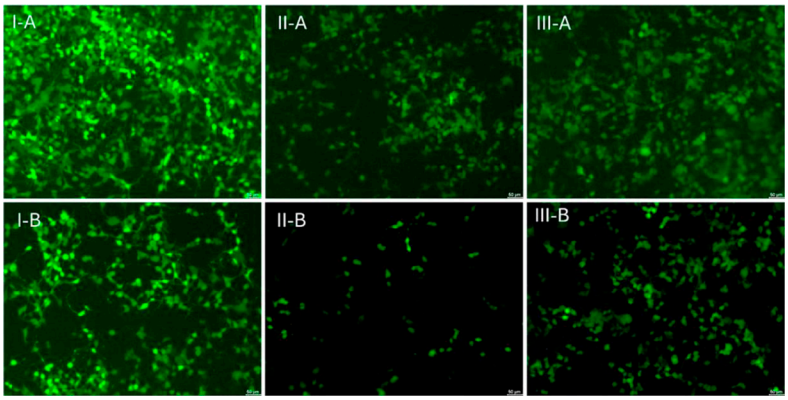

Figure 1. Dual-intein LVs reconstitute EGFP in vitro. Spontaneous fluorescence in HEK293 cells detected 72 hours post-infection. I: HEK293 cells infected with EGFP LV at (A) MOI 5 and (B) MOI 3; II: HEK293 cells co-infected with the dual-intein EGFP LVs at (A) MOI 2.5 each vector and (B) MOI 1.5 each vector; III: HEK293 cells co-infected with the dual-intein EGFP LVs at (A) MOI 5 each vector and (B) MOI 3 each vector. The image is representative of N = 3 independent experiments.

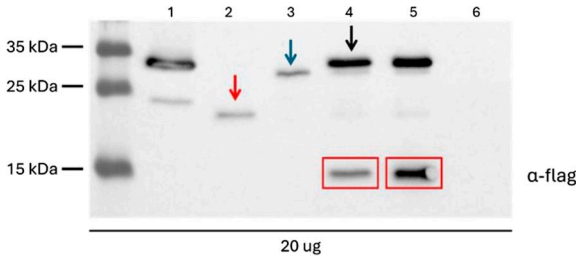

Figure 2. Western blot analysis performed on HEK293 cell lysates infected with dual-intein EGFP LVs. Cell lysates from cells transduced with: 1. EGFP full-length LVs at MOI = 5; 2. dual-intein N-term EGFP LV at MOI = 5; 3. dual-intein C-term EGFP LV at MOI = 5; 4. dual-intein N-term and C-term EGFP LVs at MOI = 2.5 each vector; 5. dual-intein N-term and C-term EGFP LVs at MOI = 5 each vector; 6. untreated cells. Black arrows indicate the correct spliced EGFP produced from co-infection; blue and red arrows indicate the single halves produced by LVs expressing for the N-term and C-term EGFP, respectively; red boxes indicate the spliced intein.

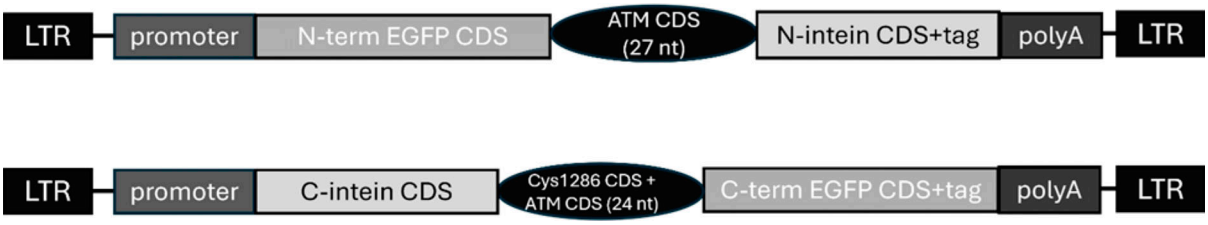

Figure 3. Schematic representation of dual-intein EGFP pLenti containing the nucleotides surrounding the ATM splitting point. In the pLenti encoding for the EGFP N-term half ATM CDS corresponds to nucleotides 3826...3852. In the pLenti encoding for the C-term EGFP, ATM CDS corresponds to nucleotides 3853...3879 and comprises the triplet encoding for Cys1286. nt: nucleotides.

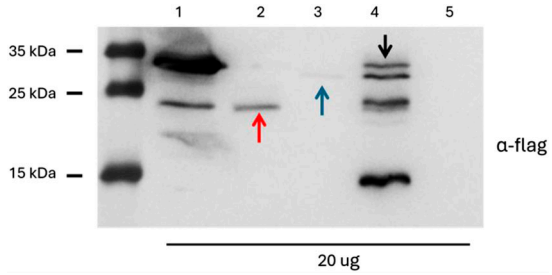

Figure 4. Western blot analysis performed on HEK293 cell lysates transfected with dual-intein pLenti EGFP plasmids with the additional ATM nucleotides surrounding the splitting point. Cell lysates from cells transfected with: 1. pLenti EGFP full-length; 2. dual-intein pLenti N-term; 3. dual-intein pLenti C-term EGFP; 4. dual-intein pLenti N-term + dual-intein pLenti C-term with additional nucleotides from ATM CDS; 5. untransfected cells. Black arrow indicates EGFP full length with additional amino acids from ATM CDS; red and blue arrows indicate the N- and the C-term products, respectively.

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VPS45 Deficiency with Features of Hemophagocytic Lymphohistiocytosis and Progressive Neurologic Involvement

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Background: Biallelic mutations in VPS45 disrupt endosomal protein trafficking, leading to a rare immunodeficiency syndrome characterized by neutrophil dysfunction, with fewer than 40 cases reported. Key features of the condition include neutropenia, recurrent infections, hepatosplenomegaly, nephromegaly, and myelofibrosis. Neurodevelopmental abnormalities, such as global developmental delay, hypotonia, nystagmus, and cortical blindness, have been associated with a specific variant c.712G>A; p.Glu238Lys. Here we present a case with presumed familial hemophagocytic lymphohistiocytosis (HLH) in infancy and progressive neurological symptoms.
Case Presentation: The patient is a 15-year-old female, who initially presented at 4 weeks of age with severe mastoiditis. She was found to have poor NK cell function, perforin deficiency, and neutropenia. Bone marrow biopsy showed toxic granulation and cytoplasmic vacuolation in some neutrophils. Few histiocytes and no hemophagocytes were seen. She underwent bone marrow transplant (BMT) at 4 months old due to presumed HLH and a history of a brother with HLH who died from an infection post-BMT. She has a history of global developmental delay, dysgraphia, ADHD, primary ovarian insufficiency, multiple fractures, atypical bony development in the feet, and hypercholesterolemia. On examination, she has short stature, facial dysmorphism, atypical dentition, nystagmus, choreiform movements, and gait ataxia. Brain imaging at 10 years of age showed basal ganglia and subcortical white matter calcifications in the frontal lobes.
Diagnostic Workup: Extensive genetic testing, including genome sequencing and mitochondrial DNA sequencing, was negative. Research-based reanalysis revealed novel biallelic VPS45 missense variants (c.652C>T; p.Arg218Cys and c.1157G>A; p.Arg386His), confirmed by Sanger sequencing. Parental testing demonstrated the variants were inherited in trans from unaffected carriers and were also found in the deceased brother's exome data.
Discussion: While a specific variant (p.Glu238Lys) has been linked to neurological symptoms in VPS45 deficiency, it was absent in our case. The patient's progressive neurological phenotype, including chorea, basal ganglia, and subcortical white matter calcifications, suggests further phenotype expansion. The overlap with HLH and post-BMT complications underscores the diagnostic and therapeutic complexities, emphasizing the need for further research into VPS45-related pathophysiology and its clinical implications.
Conclusion: This case expands the understanding of VPS45 deficiency by highlighting pronounced neurological involvement, which appears more striking in our proband.

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Therapeutic Use of Recombinant Interferon-Gamma in Patients with Refractory Disseminated Coccidioidomycosis

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Introduction: Disseminated coccidioidomycosis (DCM) is a serious illness with significant morbidity and mortality, especially in patients with impaired host defense mechanisms in interferon-gamma (IFN-gamma)/interleukin-12 and STAT3 axes. With standard treatments, these patients often require prolonged, sometimes lifelong, antifungal therapy, which are not curative. The therapeutic benefits of adjunctive IFN-gamma in DCM remain unclear.

Methods: We conducted a retrospective chart review of DCM patients treated with adjunctive IFN-gamma at our institutions and performed a literature review to identify additional cases. Treatment responses were assessed using modified EORTC/MSG criteria.
Results: We identified 17 cases (12 from our institutions, 5 from the literature; 7 females) who received 19 courses of IFN-gamma therapy. Genetically confirmed inborn errors of immunity included STAT1 gain of function (GOF) in 2 and autosomal dominant partial IFNGR1 deficiency in 1. The median age at first diagnosis was 19 years (range: 4-57), and the median interval from diagnosis to initiation of IFN-gamma therapy was 10 months (range: 0.5-120). All had extensive diseases prior to treatment, as evidenced by multiorgan involvement (median 4, including 5 with CNS involvement), despite various antifungal agents (median 4) and surgical interventions in 13 patients. Five patients required hospitalization in the intensive care unit, including 1 on VV-ECMO. The median maximum dose of IFN-gamma was 50 mcg/m^2 (subcutaneous, range: 25-200 mcg/m^2, 3×/week) with a median treatment duration of 8 months (range: 2-39). Adverse events were recorded in 8 patients. They were uncomfortable but manageable with supportive care in all, except for three who ultimately discontinued therapy because of cytopenia, headache, and fever, respectively. Of the 19 treatment courses, there were 11 responses, 5 partial responses, and 3 nonresponses, including both STAT1 GOF patients who eventually died from DCM. In those who achieved at least partial responses, significant improvements were observed in C-reactive protein levels (pre- vs. post-treatment, median 42.6 vs. 7.0 mg/L, p = 0.001), and anti-*Coccidioides* antibody titers (1:128 vs. 1:16, p = 0.002). No neutralizing anti–IFN-gamma autoantibodies were detected before, during, or after IFN-gamma therapy.
Conclusion: IFN-gamma therapy failed in 2 STAT1 GOF patients but may provide benefits for other patients with DCM despite standard treatments.

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Immunodeficiency in Mitochondrial DNA Depletion Syndrome 20: A New Phenotypic Insight into LIG3 Mutations

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Background: Mitochondrial DNA depletion syndrome 20 (MTDPS20) is a rare disorder caused by variants in the LIG3 gene, which encodes a DNA ligase essential for mitochondrial DNA repair and replication. Defects in LIG3 impair mitochondrial replication, leading to reduced mitochondrial DNA copy numbers and mitochondrial dysfunction. Since its description in 2021, fewer than 20 cases have been reported, with features including gastrointestinal dysmotility, leukoencephalopathy, muscle weakness, neurogenic bladder, and cognitive decline. A more severe phenotype, including progressive myopathy, fatal muscle degeneration, decreased cytochrome c oxidase (COX) activity, and lipid accumulation in muscle fibers, was also reported. Here, we report a case of MTDPS20 with biallelic LIG3 variants that presented with immunodeficiency as part of the clinical phenotype for the first time.
Case Description: The patient was a 23-month-old female with a history of developmental delay, infantile spasms, sensorineural hearing loss, bilateral cataracts, optic nerve hypoplasia, failure to thrive, gastroesophageal reflux, gastrointestinal dysmotility, anhidrosis, and progressive encephalopathy. On examination, she had severe hypotonia with no head control, microcephaly, and choreiform movements. Immune findings included hypogammaglobulinemia requiring subcutaneous immunoglobulin therapy, while endocrine features included central hypothyroidism and type 1 diabetes mellitus. Muscle biopsy demonstrated COX-negative muscle fibers with lipid accumulation. Neuroimaging demonstrated mildly delayed myelination and volume loss. The patient died at age 4 due to respiratory distress.
Diagnostic Workup: Comprehensive genetic testing, including exome sequencing, RNA sequencing, genome sequencing, and metabolomics, was uninformative. Reanalysis of genome sequencing data identified biallelic LIG3 variants: a missense mutation (c.1209-2A>G) and a 93-bp insertion, each inherited from unaffected parents. Functional validation via western blot and Sanger sequencing confirmed the pathogenic nature of these variants.
Discussion: This case includes the first report of immune dysfunction in MTDPS20, characterized by hypogammaglobulinemia and type 1 diabetes mellitus, suggesting involvement of immune dysregulation. These findings, alongside typical manifestations such as

gastrointestinal dysmotility, leukoencephalopathy, and COX-negative fibers, expand the recognized phenotype of MTDPS20 to include immunodeficiency.

Conclusion: Immunodeficiency is identified as a feature of MTDPS20 in this case, expanding the clinical spectrum of the disorder. Further research is needed to investigate the underlying mechanisms and implications for diagnosis and management.

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A Case of Post-COVID-19 Neuroinflammation and Demyelination: Highlighting the Role of Elevated IL-18

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Background: Long COVID frequently presents with neurological complications, including neuroinflammation and demyelination. Proinflammatory cytokines, particularly interleukin-18 (IL-18), play a pivotal role in immune dysregulation, contributing to neuroinflammation and white matter damage.

Case Presentation: A 29-year-old previously healthy man developed mild COVID-19 in October 2023, recovering within two weeks. In late December 2023, he experienced a generalized tonic-clonic seizure, followed by transient right arm rigidity and postictal aggression. Brain MRI revealed multifocal juxtacortical T2/FLAIR hyperintensities with faint gadolinium enhancement. CSF analysis showed no pleocytosis, a normal IgG index, and an absence of oligoclonal bands. MOG and AQP4 antibodies were negative, ruling out neuromyelitis optica and MOG-associated disorders. High-dose corticosteroids resolved the lesions, as observed on follow-up imaging in January 2024.

In May 2024, MRI revealed new subcortical enhancing lesions, despite the absence of symptoms. By November 2024, the patient developed intermittent paresthesia in the left leg and right-sided hyperreflexia. Imaging demonstrated progressive lesions in the brainstem and cervical spine. Neurological examination remained largely normal, apart from hyperreflexia and mild sensory disturbances. Despite extensive testing for infectious and autoimmune etiologies, no alternate causes were identified. Repeated corticosteroid therapy provided symptom relief. The relapsing-remitting radiological course was consistent with an ADEM/MOGAD spectrum diagnosis, and the patient was planned to receive rituximab.

In December 2024, despite being on high-dose steroids, analysis revealed markedly elevated serum IL-18 (759.55 pg/mL), indicating immune dysregulation. CSF analysis showed normal results, ruling out multiple sclerosis and direct infectious causes. These cytokine elevations correlated with imaging findings of progressive demyelination, supporting a diagnosis of post-viral neuroinflammation.

Discussion: IL-18 plays a central role in neuroinflammation through blood–brain barrier disruption, glial activation, and oxidative stress, all of which contribute to neuronal damage and demyelination. Elevated IL-18 has been observed in COVID-19–associated encephalopathy and encephalitis, correlating with white matter degeneration and sustained immune activation. In this case, IL-18's involvement highlights its utility as a biomarker and potential therapeutic target in post-viral demyelination. Early cytokine profiling and tailored immunomodulatory interventions may mitigate progressive neuroinflammatory damage and improve outcomes in similar patients.

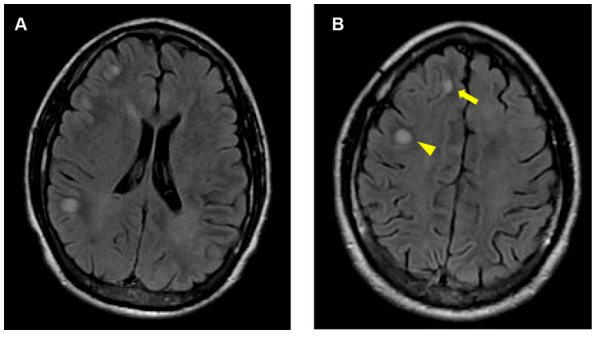

Figure 1. The patient's magnetic resonance imaging (MRI) of the brain at presentation. *A*, axial fluid-attenuated inversion recovery (FLAIR) imaging of the brain shows multifocal hyperintensities at the gray–white matter interface. *B*, axial FLAIR imaging of the brain shows a hyperintense lesion at the right frontal gray–white matter interface (*arrow*) and a hyperintense lesion in the right frontal white matter (*arrowhead*).

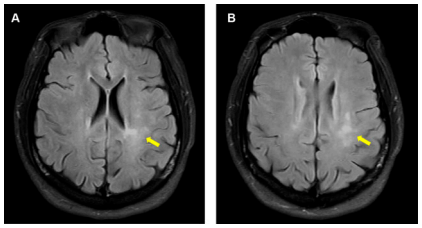

Figure 2. The patient's magnetic resonance imaging (MRI) of the brain at 5 months after the seizure onset. He had no symptoms. Axial fluid-attenuated inversion recovery (FLAIR) imaging of the brain shows new poorly demarcated hyperintense lesions in the left frontoparietal white matter (*arrows*).

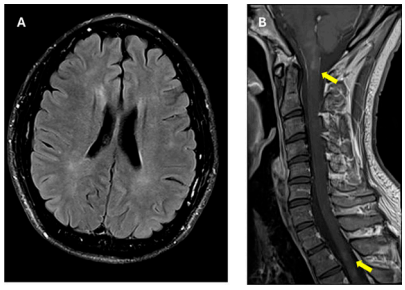

Figure 3. The patient's magnetic resonance imaging (MRI) at 10 months after the seizure onset. He had intermittent paresthesia in the left leg, and his reflexes were increased in his right arm and leg. *A*, Axial fluid-attenuated inversion recovery (FLAIR) imaging of the brain shows ill-defined hyperintense lesions in the periventricular regions. *B*, Sagittal T1-weighted image of the spinal cord shows new short hyperintense lesions affecting the brainstem, the cervical spinal cord, and upper thoracic spinal cord (*arrows*).

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X-MAID Disease Caused by a Novel Synonymous MSN Variant that Disrupts mRNA Splicing

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Introduction: Inborn errors of immunity (IEIs) are a group of genetic disorders in which parts of the human immune system are missing, dysfunctional, or poorly regulated. MSN encodes moesin, a cytoskeletal adaptor protein that plays a critical role in maintaining cell rigidity and is primarily expressed in lymphocytes and endothelial cells. Missense and premature stop variants in the MSN gene are known to cause X-linked moesin-associated immunodeficiency (X-MAID), a rare, sex-linked disease.
Methods: Clinical assessments and an IEI gene panel were performed. The identified MSN variant was segregated through the family. RNA was isolated from blood samples collected from the brothers, their mother, and healthy controls and then sequenced. RNA-sequencing results were validated using quantitative PCR.
Results: We identified two brothers with a hemizygous, synonymous variant in MSN (NM_002444.3: c.795G>A, p.Pro265=) that was predicted by in silico prediction tools to be damaging (CADD score of 25) and likely to alter mRNA splicing (SpliceAI delta score for donor loss was 0.82). The brothers inherited the variant from their healthy, carrier mother. The brothers presented with a very similar phenotype of severe lower leg dermatitis, chronic nonhealing ulcers (clinically diagnosed as pyoderma gangrenosum but with histology more consistent with reactive angiomatosis), clinical features of venous insufficiency, hypogammaglobulinemia, and mild lymphopenia. RNA sequencing revealed aberrant splicing of the MSN transcript in the brothers, consisting of either a complete skip of exon 7 or the retention of intronic sequences that result in a premature stop codon. These aberrant splicing events were observed at low levels in the carrier mother and were absent in the healthy controls. Quantitative PCR validated the splicing events, revealing minimal MSN transcript levels in the brothers, consistent with transcript degradation. Investigations into moesin expression in the brothers' lymphocytes are currently underway.
Conclusion: This study is the first to report X-MAID caused by an MSN splicing variant and further emphasizes the possibility that synonymous variants can be disease causing.

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Safe Off-Label Use of Icatibant as Treatment for Acute Hereditary Angioedema Attacks in a Pediatric Patient

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Introduction: Hereditary angioedema (HAE) is a rare, potentially life-threatening disease characterized by recurrent attacks of subcutaneous and submucosal swelling. Currently, only intravenous (IV) therapies are approved in the USA for treatment of HAE attacks in children younger than 12. IV therapy is difficult for caregivers to administer to young children, and these patients often require care in the emergency department (ED) for administration, delaying resolution. Subcutaneous injection allows earlier therapy, decreasing risk of more serious complications of acute attacks and reducing need for ED-level care. Icatibant is a selective antagonist of the bradykinin B2 receptor and administered subcutaneously. In the European Union (EU) and Canada, it is approved down to the age of 2. Here, we describe a single case of a 6-year-old female with HAE type 1 for whom icatibant was safely used off-label for an acute attack with resolution of her symptoms.

Case Description: Despite previous success with Berinert for abortion of peripheral attacks, this patient's family was frustrated with long wait times and care in the ED. Given a sibling's success with icatibant, review of preexisting literature, and the Canadian package insert, we opted to prescribe this off-label as a rescue using shared-decision making. She was initially given icatibant 0.4 mg/kg for abortive treatment in the ED. Eventually, the patient was approved through her insurance to use icatibant 15 mg SQ for attacks, and lanadelumab was also initiated for maintenance therapy given increasing attack frequency through manufacturer assistance and eventual insurance approval through assistance of a multidisciplinary team. The only adverse event was injection site pain, and her attack frequency decreased.

Discussion: This case illustrates the potential for safe off-label use of icatibant down to 2 years of age for acute attacks of HAE. Penn State Health has been prescribing and administering icatibant down to 2 years of age despite being off-label, and we hope this work encourages FDA approval and other institutions to make icatibant available as a weight-adjusted dose as an option for abortive treatment until oral rescue medications are available to reduce drug burden in pediatrics.

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Two Siblings with Possible Concurrent Atypical Papillon-Lefèvre Syndrome (PLS) and Activated Phosphoinositide 3-kinase Delta Syndrome 1 (APDS1)

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PLS is an autosomal recessive disorder with palmoplantar hyperkeratosis, early-onset destructive periodontitis, and premature tooth loss, caused by mutations in CTSC leading to deficiency of cathepsin C. APDS1 is an autosomal dominant disorder due to heterozygous gain-of-function mutations in PIK3CD causing increased PI3K/mTOR/AKT intracellular signaling.

We present 2 siblings with an atypical presentation in which both disorders may be coexisting.

P1 is an 18-year-old male with palmoplantar erythema and hyperkeratosis since early childhood without periodontitis or dentition issues. At 16, he presented in ARDS and a CT chest showing multifocal consolidation, early cavitation, and a pattern suspicious for chronic hypersensitivity pneumonitis from the retinoid dermatological treatment. All infectious investigations were negative. He had lymphopenia and low IgG and IgM. He improved after methylprednisolone pulses and remained asymptomatic for 7 months when he had hypoxemia and a repeat CT showing multifocal nodular opacities and splenomegaly. EBV viral load was high. Despite a course of high-dose steroids, his symptoms and CT worsened with multifocal round opacities and nodules. An open lung biopsy showed histiocytes, CD4+ T cells, and B cells obliterating the normal lung architecture with areas of necrosis and positive EBER staining. Genetic testing showed compound

heterozygosity for 2 CTSC variants (a pathogenic and a VUS), heterozygous pathogenic variant in FLG, and heterozygous VUS in PIK3CD. He was treated with rituximab clearing EBV and is on sirolimus. He is asymptomatic but with progressive T cell lymphopenia.

P2 is 19 years old and has palmoplantar erythema and hyperkeratosis but no history of severe infections or periodontic disease. He has normal IgGAME and normal T/B/NK cell subsets. Genetic testing revealed the same variants as P1. They are adopted and thus have no known family history and no possibility for variant segregation or verification of cis vs. trans for CTSC variants.

There are no reports of PLS without periodontitis. The skin manifestations in our patients are characteristic. The FLG variant may be contributing. Functional validation of the PIK3CD missense variant is pending. Tools predict a deleterious change in the protein; it is not in gnomAD and is located near the hotspot for mutations in APDS1.

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Clinical Manifestations of Phosphoglucomutase 3 (PGM3) Deficiency

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Background and Aims: Phosphoglucomutase 3 (PGM3) deficiency is a congenital disorder of glycosylation characterized by elevated IgE, atopy, recurrent infections, autoimmunity, cognitive impairment, and cytopenias. As more patients have been described, the variability in clinical presentation has become apparent. We aimed to further characterize the phenotype of PGM3 deficiency at our center.
Methods: Medical records were retrospectively reviewed for 10 patients from 4 families with PGM3 deficiency seen at the NIH Clinical Center.
Results: Ten patients (7 males and 3 females), aged 5 to 38 years, were evaluated at our center. Atopy was the most common manifestation, with eczema seen in all 10 patients and food and drug allergies in 9 and 8 patients, retrospectively. Sinopulmonary infections were noted in 8 patients, complicated by bronchiectasis in 5, and 5 had viral mucocutaneous infections. Seven patients had varying levels of neurocognitive impairment. Five patients had autoimmunity, including vasculitis in 4, glomerulonephritis in two, and psoriasis in one. Three affected siblings had malignancy: two with EBV-positive Hodgkin's lymphoma, two with EBV-positive diffuse large B cell lymphoma (including one with prior Hodgkin's), and one with squamous cell CA (SCC). Additional findings included bony abnormalities in 8 (6 with scoliosis, 2 with endplate abnormalities), single kidney (1), and heart failure (1). Nine patients had lymphopenia, 7 had severe chronic neutropenia (ANC < 500), and one had hemolytic anemia. Bone marrow biopsies were evaluated for 7 patients; three were normocellular despite neutropenia, one was hypocellular with no dysplastic features, and one had erythroid hypercellularity due to chronic hemolysis. One patient is alive and well after hematopoietic cell transplantation (HCT), with resolution of recurrent infections, severe neutropenia, and atopic dermatitis, and one patient had a lung transplant for severe bronchiectasis. There were 3 fatalities between ages 36 and 42 from malignancy (2 with lymphoma and one SCC) and one COVID-related fatality at age 18.
Conclusions: Although this is a multi-systemic disorder, the 30% mortality in early adulthood due to virally driven malignancies along with severe infection and chronic neutropenia suggests that HCT should be strongly considered.

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United States Immunodeficiency Network (USIDNET) Reimagined as a Semiautomated Data Extraction Method for Registry Building

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Studying rare immunodeficiency conditions or inborn errors of immunity (IEI) on a large scale is important to understand their natural history, associated morbidities, and long-term outcomes. Compiling such comprehensive data is necessary to gain a detailed understanding of these conditions and improve treatment and care for those affected. To support researchers in this effort, we created United States Immunodeficiency Network (USIDNET) registry V2, a secure, structured, standardized database with automated yearly updates for enrolled patients across the United States. This design offers access to current and consistent information. Standardized data fields ensure harmonization across sites, and the availability of longitudinal data will afford new insights into disease evolution and therapeutic responses.

USIDNET utilizes our Translational Data Warehouse (TDW) system, built with PostgreSQL, to store and manage data securely. To streamline this effort and minimize the burden on participating sites, we created an automated data extraction tool consisting of an extract, transform, and load (ETL) process to combine all the data. This process collects data from multiple sites that execute USIDNET registry V2 queries and stores the data in a consistent format. We implemented a dual de-identification method: receive all data in a de-identified format from participating sites (passive de-identification) and then perform a second layer of de-identification on all IDs (active de-identification) by assigning a new unique ID to each record. These newly assigned IDs are automatically included in subsequent tables. This technique ensures that there are no duplicate IDs in the combined dataset.

Since August 2024, we have successfully enrolled 1,145 patients into the registry, with multiple additional sites initiating their data extraction processes. The ages range from 1 to 58 years and are roughly equal in sexes. USIDNET represents a community-driven approach to understanding the evolution of disease, comorbidities, and response to intervention. Semiautomated data extraction enables a structured collection of longitudinal data, which is important for IEI because the phenotypes evolve over time. De-identified data collection with a waiver of consent enables more complete ascertainment. The current USIDNET registry V2 is a growing endeavor to support longitudinal research, while the original USIDNET registry V1 continues to support cross-sectional research on IEI.

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Common Variable Immunodeficiency Clinical Manifestations Are Shaped by Presence and Type of Heterozygous NFKB1 Variants

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Background: NFKB1 encodes p105, which is processed to p50 to mediate canonical NF-κB signaling. Though NF-κB is a central driver of inflammation and heterozygous NFKB1 variants are considered the most common monogenic etiologies of common variable immunodeficiency (CVID), few studies have explored how NFKB1 variants shape clinical course or inflammation in CVID.
Objective: We leveraged a regional cohort of CVID patients with and without heterozygous NFKB1 variants to assess how clinical and inflammatory features of CVID are shaped by the presence of these variants.
Methods: We compared clinical complications, immunological features, and plasma cytokine levels of 15 CVID patients with heterozygous NFKB1 variants with 77 genetically undefined CVID patients from the same referral base. We also assessed differences between CVID patients with frameshift or nonsense NFKB1 variants compared with those with missense NFKB1 variants.
Results: We found CVID patients with heterozygous NFKB1 variants to have increased autoimmune disease, bronchiectasis, gastrointestinal infections, inflammatory bowel disease (IBD), and plasma cytokines compared with genetically undefined CVID patients. These findings were more pronounced and included elevation of monocytes, in CVID patients with frameshift or nonsense NFKB1 variants relative to those with missense NFKB1 variants.
Conclusion: In a regional cohort, heterozygous NFKB1 variants were associated with worsened CVID clinical course and increased evidence of inflammation in the blood. CVID patients with frameshift or nonsense NFKB1 variants had more significant increases in

noninfectious complications and peripheral monocytes than those with missense NFKB1 variants. Presence of pathogenic NFKB1 variants in CVID patients may be associated with more severe disease course and warrant closer monitoring.

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Understanding the Burdens of Illness and Treatment in Severe Leukocyte Adhesion Deficiency Type I (LAD-I): Results from a Multi-Case Study with Caregivers

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Background: Leukocyte adhesion deficiency type I (LAD-I) is a rare inborn error of immunity affecting approximately 1 in 1 million individuals worldwide. Severe LAD-I is characterized by frequent life-threatening infections and significant pediatric mortality. Although this can have devastating effects on children and their families, there is little research about the lived experience of the disease. To fill this gap, we executed a multi-case study to describe the burden of severe LAD-I from the caregiver perspective.
Methods: Caregivers from 5 families with children with severe LAD-I participated in individual, in-depth interviews. Interviews followed a study-specific guide using concept and photo elicitation to obtain descriptions of caring for a child with severe LAD-I. Interview transcripts were analyzed using inductive and deductive approaches to describe the burdens of illness and treatment.
Results: Nine parents were interviewed. Among the 7 children, treatments included: allogeneic hematopoietic stem cell transplantation (alloHSCT; n = 2), investigational gene therapy (GT; n = 4), and antimicrobial prophylaxis (n = 1).

Findings were organized under themes of burden of illness and burden of treatment (Table 1). The burden of illness included challenging journeys to diagnosis and frequent, hard-to-treat infections, leading children and caregivers to isolate physically and socially to reduce infection risk. All caregivers rearranged their jobs or career trajectories substantially to accommodate caregiving. Most parents were frustrated by the absence of LAD-I–specific resources and information. The burden of treatment differed by therapy. AlloHSCT families described difficult recoveries and, for 1 child, only partial success in treating LAD-I. GT families experienced a significant reduction of burden of illness, yet some expressed concerns for their child's future given the novelty of the treatment. All participants agreed that antimicrobials were not a long-term treatment solution.

Table 1. **Main themes within burden of illness and treatment in severe LAD-I.**

Burden	Themes	Examples
Illness	Frequent and varied infections	Rashes, skin/mucosal lesions, and infections in the lungs, ears, gums; poorly healing umbilical cords
	Physical restrictions	Avoiding water parks, beaches, other outdoor activities; limiting sports; preventing contact with pets
	Social restrictions	Limiting visitors to the home; avoiding daycare; home schooling
	Journey to diagnosis marked by lack of information	Failure of frequent severe infections and slow healing wounds to drive investigation and diagnosis; lack of resources, guidance, and information pre- and post-diagnosis
Treatment	AlloHSCT	Searching for a bone marrow match; complexity of alloHSCT process; managing alloHSCT complications; side-effects from post-transplant treatments; waning efficacy
	Gene therapy	Generally positive outcomes, despite a long and complex process; required relocation for the duration of treatment; uncertainty about durability and longer-term effects given the novelty of GT
	Prophylactic antimicrobials	In 1 case, in the absence of a family donor match for alloHSCT, the clinician recommended this approach; parents indicated it is not a long-term nor complete solution

Conclusion: Together, the burdens of illness and treatment had profound impacts on these families. The parents' descriptions also demonstrated that while none of the current treatments for severe LAD-I is perfect, GT shows great potential for improving patients' health and minimizing disease burden. Moreover, this research provides critical insights for clinicians, whose care of children with severe LAD-I can be informed by understanding the struggles associated with the burdens of illness and treatment.

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Patient Insights Expand Understanding of APDS

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Rationale: Discovery of primary immunodeficiencies (PIDs) has rapidly increased, from 180 known PIDs in 2012 to more than 450 today. Patient perspectives are essential to deepen understanding of these conditions and, in turn, improve health outcomes. Patient advisory meetings provided insights into experiences with activated PI3K delta syndrome (APDS), a PID named in 2013.
Methods: A virtual advisory board meeting was conducted with 7 patients living with APDS in 2024. Participants also reviewed a patient journey illustration and handout. The meeting included polls and a chatroom.
Results: Participants reported symptoms not commonly reported in published literature, including fatigue, brain fog, joint and diffuse pain, temperature sensitivity, headaches, and dental issues. Apart from headache and dental issues, these symptoms were also reported in a 2023 patient advisory meeting by a separate cohort of 7 people living with APDS.

Participants' disease understanding was limited, with low awareness of common symptoms and signs of APDS, including autoimmune or autoinflammatory conditions, frequent and severe diarrhea, and developmental and cognitive delays. Participants were asked to confirm the year of their diagnosis twice, and several provided different years; more than half were unsure which APDS genetic variant they have.

Participants expressed challenges with physicians understanding APDS, believing their symptoms, and coordination of care. For example, 5 of 7 participants experienced diarrhea, which was misdiagnosed or overlooked in all but one. Participants have up to 10 physicians for their APDS-related conditions and take many medications.

Fatigue, brain fog, and pain impact quality of life. All participants experienced frequent fatigue, daily for more than half. Brain fog impacts most participants a few times each week, and many live with daily pain. Three participants are unable to work.
Conclusions: More patient-friendly APDS education resources are needed. Additional research is suggested to confirm the prevalence of newly identified symptoms in those living with APDS. Research is also suggested to explore challenges in disease understanding, specifically analyzing the impacts of brain fog, developmental delays, socioeconomic impacts, or potential variance in the expression of APDS based on genetic variants.

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Late Diagnosis of Primary Immunodeficiency Following Post-Vaccine Encephalitis: The Importance of Neonatal Screening

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Background: X-linked agammaglobulinemia (XLA) is a rare primary immunodeficiency caused by mutations in the Bruton tyrosine kinase (BTK) gene, resulting in absent B cells and agammaglobulinemia. Although early diagnosis significantly improves survival rates, a large proportion of cases are still diagnosed late, especially those with atypical clinical presentations. Neonatal screening using kappa-deleting recombination excision circles (KREC) is a promising method to detect B cell deficiencies early.
Objective: To describe the case of a pediatric patient from Brazil with XLA who presented with an atypical neurological manifestation and to emphasize the role of KREC in the early diagnosis of immunodeficiencies.
Methods: This is a case report based on medical record analysis. The case describes a 1-year-old male with a history of live-attenuated vaccination (yellow fever) and no prior significant infections, who presented with ataxia, encephalitis, and progressive neurological deficits. Diagnostic evaluation included immunoglobulin levels, immunophenotyping, genetic analysis, and imaging studies. The treatment consisted of administering intravenous immunoglobulin (IVIg). Informed consent was obtained prior to the preparation of this report.
Results: The patient exhibited agammaglobulinemia and a near-complete absence of B cells (CD19+ 0.1%). A mutation in the BTK gene confirmed the diagnosis. Neurological symptoms, initially suspected to result from infectious encephalitis, were secondary to

agammaglobulinemia-related immune dysregulation. The treatment with IVIg led to the resolution of neurological deficits. Retrospective analysis of the case revealed that KREC screening could have facilitated an earlier diagnosis and mitigated the neurological complications observed after receiving the yellow fever vaccine with live attenuated virus.

Conclusion: This case highlights the importance of recognizing atypical presentations of XLA and underscores the critical role of neonatal KREC screening in early diagnosis. The implementation of KREC in newborn screening represents a major advancement in the detection of primary immunodeficiencies in Brazil. Broader adoption of screening programs could transform the clinical course of XLA, allowing for timely interventions, prevention of complications, and improvement of patient outcomes.

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The Impact of Immune Dysregulation on Clinical Outcomes in Common Variable Immunodeficiency: A Systematic Literature Review

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Introduction: Common variable immunodeficiency (CVID) is the most common symptomatic inborn error of immunity. Complications of immune dysregulation in CVID are reported in cohort and consortia studies but have not been formally summarized. We performed a systematic literature review to generate a comprehensive reference focused on collating clinical manifestations of immune dysregulation and relevant outcomes.

Methods: Studies of humans with CVID were identified using predefined search terms to mine Embase, MEDLINE, and CENTRAL databases. The initial search resulted in 2,361 English-language articles. Filtering details are summarized in Figure 1. Studies that reported <10 patients, focused on immunoglobulin replacement, COVID-19, or lacked relevant data were excluded. Data were extracted from 92 articles.

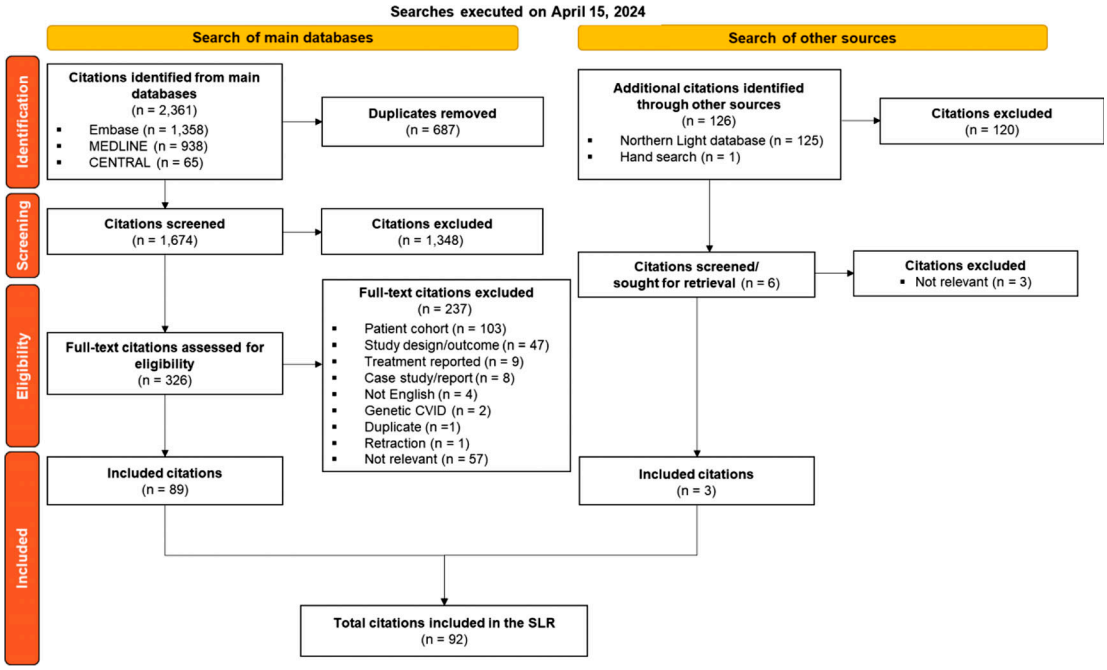

Figure 1.

Results: Out of patients with CVID who underwent genetic testing across 8 studies, the most frequently reported gene variants were LRBA (median, 10.1%), CTLA4 (median, 7.4%), and TACI (median, 6.5%). Manifestations of immune dysregulation were common and included gastrointestinal, lung, liver, rheumatologic, dermatologic, and others. Splenomegaly was reported in a median of 34.8% of patients (54 studies). Autoimmune cytopenias were reported in a median of 19.1% of patients (19 studies). Interstitial lung disease was reported in a median of 9.7% of patients (29 studies). Hepatomegaly and nodular regenerative hyperplasia were present in a median of 21.9% (17 studies) and 11.0% (13 studies) of patients, respectively. Frequent gastrointestinal manifestations reported in up to 38 publications included CVID enteropathy (median, 35.5%; 1 study), diarrhea (median, 26.9%; 21 studies), autoimmune enteropathy or villous atrophy (median, 8.5%; 17 studies), malabsorption (median, 6.4%; 10 studies), and inflammatory bowel disease (median, 5.3%; 23 studies). Treatment information and outcomes data were limited. Steroids and rituximab were used most frequently in a median of 35.4% and 14.0% of patients, respectively. A lack of robust or consistent complete responses was observed. Risk of death was adversely affected by lung, liver, and gastrointestinal disease, as indicated by median hazard ratios of 2.1-2.5.

Conclusion: These comprehensive summary data illustrate the pervasiveness and negative end-organ impact of unchecked immune dysregulation in CVID. Development of effective treatments to improve the morbidity and mortality associated with immune dysregulation in CVID is needed.

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Leniolisib, a PI3Kδ Inhibitor, Improves Lymphoproliferative Disease in a Murine Model of Autoimmune Lymphoproliferative Syndrome

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Introduction: Autoimmune lymphoproliferative syndrome (ALPS) is an inborn error of immunity characterized by lymphadenopathy, splenomegaly, autoimmune cytopenias, and an increased number of double-negative T cells (DNTs). ALPS is most often caused by pathogenic variants in FAS (ALPS-FAS). ALPS-FAS is linked to enhanced PI3Kδ/mTOR signaling. Leniolisib is a selective oral PI3Kδ inhibitor approved for treatment of activated PI3Kδ syndrome (APDS). We hypothesized that leniolisib could be effective in ALPS and tested this in a murine model.

Methods: Six-week-old female MRL/MpJ-Faslpr/J (MRL/lpr-/-) mice were daily dosed by oral gavage for 7 weeks at 40 or 80 mg/kg leniolisib or vehicle (8 mice per group). Body weight was monitored daily, and urine for protein analysis was collected pre-study and at weeks 3 and 7. After 7 weeks, mice were sacrificed to quantify spleen and lymph node weights; blood counts and lymphocyte subsets in blood, bone marrow, spleen, and lymph nodes.

Results: No changes in body weight were observed, but leniolisib caused a significant decrease in urinary protein at 3 weeks. A significant decrease in weights of spleen (40 and 80 mg/kg) and lymph nodes (80 mg/kg) was seen after leniolisib treatment. Leniolisib did not induce changes in any cell type in bone marrow. In blood, white blood cells, lymphocytes, and monocytes decreased in the 80 mg/kg leniolisib group. A slight increase in hemoglobin, hematocrit, and red blood cell distribution width was seen in both leniolisib groups. No effect was seen on cell count of neutrophils, eosinophils, basophils, red blood cells, or platelet numbers. At 80 mg/kg, leniolisib significantly decreased cell counts of CD4-/CD8- DNTs and CD3+ T cells in blood, spleen, and lymph nodes. In spleen, cell counts of CD19+ B cells and CD4+ T cells decreased.

Conclusion: It is concluded that leniolisib is an effective treatment in a murine ALPS model, which has potential as a treatment for ALPS patients with significant lymphoproliferation.

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22q11.2 Deletion Syndrome Causes a Sox-9–Mediated Expansion of Chondrocytes Limiting Embryonic Thymus Growth Correctable by Minoxidil

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Thymic hypoplasia, hypoparathyroidism, cardiac defects, and/or dysmorphic facial features are frequent congenital malformations resulting from chromosome 22q11.2 deletion syndrome (22q11.2DS; aka DiGeorge syndrome). Thymus hypoplasia results in reduced peripheral T cells, with patients suffering from more frequent and severe infections. Embryonic thymuses from mouse models of 22q11.2DS (Tbx1neo2/neo2) are smaller than controls. Such thymuses had a distinct mesenchymal cell subset representation, altered transcriptomes, and elevated levels of collagens and extracellular matrix (ECM) proteins. We report that the administration of minoxidil or PGE2 to pregnant mice restored thymic tissue growth in Tbx1neo2/neo2 embryos. The drugs normalized the embryonic thymic mesenchymal subcluster representation, their respective transcriptomes, and corrected the underdeveloped vasculature. Importantly, the restoration of thymic growth matched the reduced number of perivascular/chondrogenic-derived mesenchymal subsets. Comparative transcriptomic, gene expression, and immunofluorescence analyses revealed elevated expression levels of a trio of Sox family transcription factors (Sox5, 6, and 9) in the small thymuses. Sox9 positively regulates the expression type II, IX, and X cartilaginous collagens and other ECM proteins, which are elevated in the hypoplastic lobes. Notably, minoxidil or PGE2 treatments reduced Sox9 expression and the correspondingly regulated collagens. This treatment also corrected the location of the parathyroids, indicating that a therapeutic drug treatment can correct several congenital defects associated with 22q11.2DS.

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Calcium Leaking from the Endoplasmic Reticulum Caused by a Human ITPR3 R2524C Variant Causes Immunodeficiency, Ectodermal Dysplasia, and Charcot-Marie-Tooth Syndrome

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Patients with mutations in various inositol tris-phosphate receptor (ITPR) family members display diverse clinical phenotypes. We report on two unrelated individuals with the ITPR3 p.Arg2524Cys variant who have growth retardation, immunodeficiency, partial anhidrosis, and peripheral neuropathy. To delineate the mechanisms leading to these phenotypes, a mouse line was developed to genocopy human ITPR3 p.Arg2524Cys. Mice heterozygous for the homologous Itpr3 p.Arg2523Cys variant were small, had severe B cell lymphopenia, milder T cell loses, sweat defects, ectodermal dysplasia, and sciatic nerve transcript alterations. B cell development was blocked at the pre–B cell stage, leading to low peripheral B cells. T cell development was impacted at the single-positive stage. Structural modeling suggested the ITPR3 p.Arg2524Cys change may result in a "leaky calcium channel," although some reports suggested a dominant negative effect. Our ability to perform calcium analyses in immediately ex vivo cells revealed that endoplasmic reticulum calcium stores were depleted in the Itpr3 p.Arg2523Cys mice relative to littermate controls. This calcium depletion diminished extracellular calcium influx following T cell receptor and co-receptor stimulations, consistent with poor calcium uptake following ionomycin treatment (calcium ionophore). In addition to immune cells, the ITPR3 R2524C variant reduced water release by sweat glands. The leaky calcium pool from the ER mediated by the ITPR3 variant and the clinical phenotypes was consistent with selected cell types being more severely impacted by the single allelic p.Arg2524Cys substitution. Our findings suggest clinical strategies to improve immune functions in affected patients.

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Development and Implementation: The Registry for Autoimmunity and Infections in Female Carriers of Chronic Granulomatous Disease: Surveillance and Evaluation (RAISE) Study

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Background: X-linked chronic granulomatous disease (XLCGD) is a rare inborn error of immunity (IEI) associated with infections, inflammation, and autoimmunity. Female carriers of XLCGD experience similar symptoms due to skewed X-chromosome inactivation (lyonization). National registries for IEI currently do not capture XLCGD carriers, creating deficiencies in understanding prevalence, clinical manifestations, complications, management, and long-term outcomes. We developed a patient survey to collect clinical and laboratory data to address these current gaps.
Methods: Thirteen XLCGD carriers were recruited to complete a REDCap® survey. Data collected included demographics, clinical symptoms, infections, autoimmune conditions, laboratory details, family history, and treatment, including antimicrobial and immunomodulatory medications. Dihydrorhodamine (DHR), used to assess neutrophil function, was collected when available.
Results: Symptoms were reported in 11 of 13 (84%) participants. The median age was 54.0 (range: 22-78) years. In those symptomatic, the age of symptom onset was median 13.8 years (range: 0.4-52) and duration of symptoms averaged 39 (range: 24.9-52.3) years. The most common symptoms were infection in 11 of 13 (84%), including pneumonia (n = 5), skin abscess (n = 7), cellulitis (n = 3), organ abscess (n = 1), lymphadenitis (n = 2), and urinary tract infections (n = 7). *Serratia marcescens* (n = 1), *Staphylococcus aureus* (n = 1), and *Prevotella* species (n = 1) were isolated from skin abscesses. Five (41%) participants received infection prophylaxis, including trimethoprim-sulfamethoxazole (n = 5), itraconazole (n = 3), and interferon gamma-1b (n = 1). One subject declined interferon gamma-1b due to insurance concerns. Autoimmunity was noted in 9 of 13 (69%) participants, including inflammatory bowel disease and photosensitive rash (both present in 25% of patients), and less commonly oral ulcers, rheumatoid and psoriatic arthritis, uveitis, celiac disease, pyoderma gangrenosum, lupus, Raynaud phenomenon, and autoimmune thyroid disease. The median DHR, available in 4 patients, was 9% (range: 6-33.5%) in those with infections (n = 3) and 52% in the asymptomatic participant.
Conclusion: To our knowledge, this is the first national patient registry for XLCGD carriers. The majority of XLCGD carriers were symptomatic, had a long duration of symptoms, and had a high symptom burden including infections and autoimmunity. A lower DHR percentile was associated with increased infections. Management often included antimicrobial prophylaxis. Recruitment is ongoing, and a larger cohort size is needed to expand these findings.

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A Novel PEPD Mutation (Prolidase Deficiency) Presenting as Refractory HLH Treated with Bone Marrow Transplant

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Prolidase deficiency (PD) is a rare inborn error of immunity due to autosomal recessive pathogenic variants in the PEPD gene. Clinical presentation of this condition is highly variable, making diagnosis difficult. The most common presentations of PD are cutaneous (ulcers) followed by dysmorphism, developmental delay, and frequent infections. Genetic testing can be helpful in the diagnosis of PD and other inborn errors of immunity. The limitations of genetic testing lie in the interpretation of genomic results for rare or ultra-rare disorders, particularly variants of unknown significance (VUS). Clinical correlation is still vital in the era of genomic medicine.

We present a case of a two-year-old female who presented with recurrent episodes of hemophagocytic lymphohistiocytosis (HLH). HLH episodes were triggered by multiple organisms, including EBV. HLH was managed with systemic steroids and anakinra while stem cell transplant workup was being performed. While on therapy, type 1 and 2 IFN signaling were normal, but CXCL9 and IL-18 were elevated. Genetic testing identified a pathogenic variant in PEPD (deletion in exon 7) and a VUS c.79C>T p.(Arg27Trp). Other VUSs were found in NFAT5, POLD2, and POLE. HLH is reported in at least one patient with PD, making the diagnosis a consideration. Familial genetic study confirmed the pathogenic mutation was paternally inherited and VUS maternally inherited. The proband's sister carried only the paternal pathogenic mutation. Urine amino acid studies showed marked proline elevation in the proband (similar to another known affected individual) and was normal in all other family members. Confirmation of two PEPD variants in trans, markedly elevated urine proline, and a phenotype compatible with PD allowed for reclassification of the VUS to likely pathogenic variant. The patient underwent matched HSCT from her sister. The patient so far has not had recurrence of her HLH.

This case is the second known case of PD treated with HSCT. The first case resulted in fatality within the first 100 days of transplant due to invasive fungal infection. It is unclear if HSCT will correct the entirety of PD complications, but we are hopeful early intervention will reduce sequalae and improve quality of life.

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Humoral Immunodeficiency in an Adult with Dual 16q22.1 Deletion and 1q21.1 Duplication Syndrome

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Introduction: 16q22.1 deletion syndrome is associated with failure to thrive, recurrent infections, and developmental delays, while 1q21.1 duplication causes dysmorphia and neurodevelopmental delays. Neither has been linked to significant immune dysfunction.
Case Presentation: A 30-year-old male with recurrent sinusitis/otitis and a complex medical history (developmental delay, club feet, cerebral palsy, severe gastroparesis, CKD, VSD, and asthma) was evaluated for immunodeficiency. He exhibited depressed IgG1, IgA, and IgM with impaired response to pneumococcal vaccination despite normal T and B cell subsets, TCR Vbeta repertoire, and lymphocyte function. Subsequent cytogenomic analysis revealed a 1.8-Mbp 1q21.1 duplication and a 5.3-Mbp 16q22.1 deletion encompassing NFAT5, a gene critical for immune cell function and cellular response to hyperosmotic stress. He remains stable on prophylactic antibiotics and is monitored for progression to CVID and CVID-associated conditions, including enteropathy.
Discussion: This is the first report of immune dysfunction associated with either 16q22.1 deletion or 1q21.1 duplication. We propose NFAT5 haploinsufficiency as a potential mechanism for his humoral immune deficiency. Future biochemical evaluation is needed to characterize these novel findings.
Conclusion: This case foremost highlights the utility of genetic testing in patients with recurrent infections and complex phenotypes to uncover potential links between chromosomal abnormalities and immunodeficiency. It also illustrates the growing clinical heterogeneity of the two genetic syndromes (16q22.1 deletion or 1q21.1 duplication), which now includes humoral immune deficiency.

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OTULIN Haploinsufficiency Caused by a Novel Splice Acceptor Variant

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Inborn errors of immunity (IEIs) represent a diverse group of genetic disorders that compromise immune function, leading to susceptibility to infections and immune dysregulation. Biallelic and heterozygous loss-of-function variants in OTULIN have recently been found to cause IEIs. OTULIN is an important regulator of inflammatory signaling through its role as a deubiquitinating enzyme of linear ubiquitin

chains. While complete deficiency of OTULIN causes a severe and early-onset autoinflammatory syndrome, heterozygous loss-of-function has been associated with a variably penetrant phenotype of environmental and infection-triggered inflammation. We report a 43-year-old male with recurrent soft tissue inflammation, osteomyelitis, and inflammatory bowel disease. His childhood was characterized by frequent episodes of severe soft tissue inflammation since 2 months of age, triggered by minor trauma, immunizations, and infections, followed by a diagnosis of inflammatory bowel disease in adolescence. The episodes of soft tissue inflammation have persisted into adulthood, though they have lessened in frequency and respond to corticosteroids. Whole-exome sequencing revealed a heterozygous OTULIN variant (NM_138348.6: c.788G>A, p.(R263Q)). Surprisingly, in silico analysis using the splice site prediction tool SpliceAI indicated that the variant would create a novel splice acceptor site 2 base pairs from the variant (delta score 0.91). This was validated by RT-PCR amplification of cDNA derived from patient whole blood RNA. While control mRNA demonstrated a single band at the expected molecular size, the patient mRNA showed one band at the expected size with additional amplified bands, in keeping with alternative splicing. Sanger sequencing demonstrated that the full-length band contained wild-type cDNA, and the second largest band contained cDNA with a partial deletion of exon 6. This study further expands on the phenotypic characterization of OTULIN haploinsufficiency and highlights the importance of considering monogenic immune disorders in both pediatric and adult patients with unexplained severe inflammation.

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STAT5B Haploinsufficiency Presenting with Severe Atopic Dermatitis Without Immune Dysregulation

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Signal transducer and activator transcription 5B (STAT5B) is a critical mediator of multiple cytokines (e.g., IL-2 and IL-7) and growth hormone signaling and plays a key role in hematopoiesis, particularly in lymphocyte development, proliferation, and survival. Loss-of-function and dominant-negative mutations in STAT5B have been associated with growth failure and immune dysregulation, including atopy. While short stature has been reported in individuals with heterozygous loss-of-function mutations (haploinsufficiency), allergic manifestations have not been reported in depth.

The proband is an adult female who presented with neonatal-onset atopic dermatitis, which progressively worsened to severe, diffuse involvement of her face and extremities by adulthood (SCORAD of 59) and was refractory to topical corticosteroids. She was ultimately started on dupilumab with significant improvement. Initial evaluation revealed markedly elevated IgE (20,756 IU/mL) and mild eosinophilia (660 cells/μL). Her medical history was notable for slightly reduced height, moderate asthma, seasonal allergies managed with immunotherapy, and peanut allergy. Her family history was notable for moderate-severe atopic dermatitis affecting her father, sister, and niece. There was no history of recurrent infections, enteropathy, endocrine abnormalities, autoimmune disease, or malignancy. Detailed immunophenotyping revealed reduced central memory CD4+ and CD8+ T lymphocytes, increased effector memory CD4+ T lymphocytes, and a high proportion of TEMRA CD4+ and CD8+ cells. Immunoglobulin levels and vaccine titers were within normal limits. Genetic sequencing identified a heterozygous nonsense variant in the STAT5B gene (c.361C>T, p.R121*) that has not previously been reported in publicly available datasets. This variant segregated with atopic dermatitis in the proband's sister and niece. Consistent with impairment in STAT5B signaling in vivo, IGF1 levels were low, while GH and IGFBP3 levels were within normal limits. Western blot analysis confirmed reduced total p-STAT5 and STAT5B expression in primary dermal fibroblasts.

This study identifies a novel heterozygous nonsense variant in the STAT5B gene that results in haploinsufficiency associated with severe atopic dermatitis and mild growth impairment with notably absent autoimmune endocrinopathy or other immune dysregulation. These findings expand the phenotypic spectrum of STAT5B-associated disorders and highlight the importance of targeted therapeutic interventions.

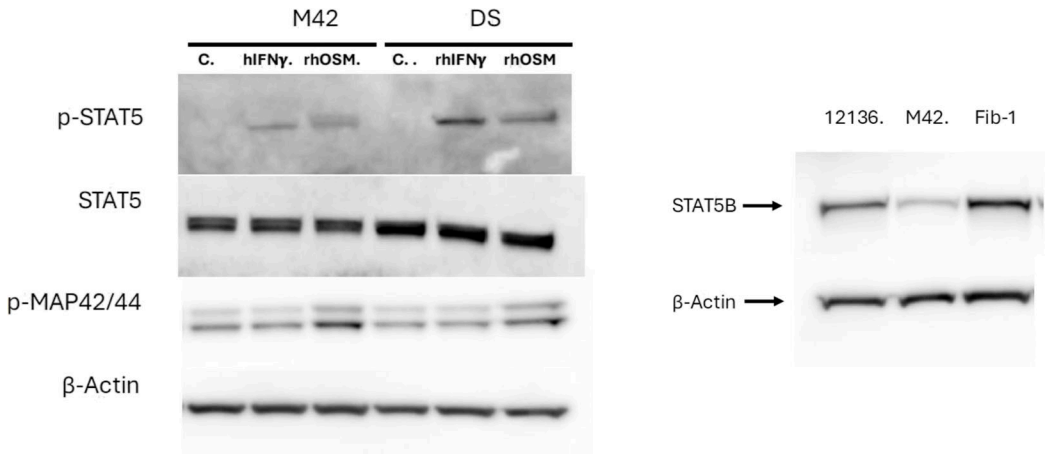

Figure 1. Reduced p-STAT5 and STAT5B expression in dermal fibroblasts (M42).

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Clinical and Genetic Characteristics of Global Cohort of 132 Individuals with Janus Kinase-3 Deficiency

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Background and Aims: Janus kinase-3 (JAK3) deficiency, first described in 1995, is an autosomal recessive inborn error of immunity that mostly results in variants of severe combined immunodeficiency (SCID). The frequency is estimated to account for 7-14% of heritable SCID, with sporadic cases in the Western world. Neither preferential "hot spots" nor founder effects have yet been documented. Hereby, we aim to describe the global experience of JAK3-related diseases regarding clinical spectrum, genetic landscape, including founder variants and treatment strategies.

Methods: We extracted clinical, genetic, and immunological data from published cases on patients with CID/SCID phenotype caused by defects in the JAK3 gene. The literature search included unpublished cases from collaborators, reports from meetings of the European Society for Immunodeficiencies (ESID), of the Clinical Immunology Society (CIS), and published data in the biomedical research search engine (PubMed) from 1995 to 2024.

Results: Our cohort includes 132 patients with 47 unique genetic defects, including 35 novel variants (18 homozygous, 17 heterozygous). The patients were from 5 continents with majority of Asian ancestry. Country of diagnosis included North America (USA [n = 42]); South America (Brazil [n = 3]); Europe (Turkey [n = 8], Hungary [n = 1], Poland [n = 6], UK [n = 5], Italy [n = 5], Israel [n = 4], Belarus [n = 4], Russian Federation [n = 3], Georgia [n = 3], Spain [n = 1], Germany [n = 1]); Asia (India [n = 16], Iran [n = 6],China [n = 4], Pakistan [n = 1], Japan [n = 1]); and Africa (Egypt [n = 16], Saudi Arabia [n = 1], Sudan [n = 1]). Forty-five (35%) of patients from the cohort were born to consanguineous parents in 31 families from Georgia (n = 3, 1-family), Russian Federation (n = 3/2-family), Sudan (n = 1), Turkey (n = 8, 5-family), Israel (n = 4, 2-family), India (n = 3, 2-family), Egypt(n = 13, 8-family), UK (n = 5, 4-family), China (n = 1), Brazil (n = 1), Spain (n = 1), Italy (n = 1), Pakistan (n = 1), and Saudi (n = 1). 13 novel founder variants are identified. The same founder variant was seen in several countries. The majority of genetic defects were homozygous (68%); 40/132 compound were heterozygous, and 2 patients had germline heterozygous gain-of-function. The variants occurred across the entire JAK3 gene with no hotspots. Only 6 (5%) of 132 cases developed Omenn syndrome. 61 patients were transplanted, 17 died at the age of 9 months (mean age 9-18 months), and 44 are alive.

Conclusions: We describe for the first time a global cohort of JAK3 with 132 patients with founder effects in a subgroup. Patients were identified in four continents but are most common in countries with a high rate of consanguinity. Founder effect was identified in 14 regions.

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Congenital Athymia Patient Registry: Patients Treated with Allogeneic Processed Thymus Tissue-agdc Post-FDA Approval

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Allogeneic processed thymus tissue-agdc is approved in the US for use as a cultured thymic tissue (CTT) implantation for immune reconstitution in pediatric patients with congenital athymia, a rare form of severe T cell immunodeficiency. An observational cohort study (Congenital Athymia Patient Registry) was initiated in May 2022, to better understand immune reconstitution, long-term survival, and adverse events after administration of allogeneic processed thymus tissue-agdc in patients with congenital athymia.

Enrollment criteria include a confirmed congenital athymia diagnosis, treatment with allogeneic processed thymus tissue-agdc, and written informed consent. Primary endpoints are survival at 12 months post-treatment and extent of T cell immune reconstitution. Secondary endpoints are incidence of serious adverse events (SAE) and AEs of special interest (AESI), such as acute kidney injury (AKI) and autoimmunity. Survival beyond 24 months post-treatment is evaluated as an exploratory objective. Results are from medical record data abstraction at baseline (pre-implantation), every 3 months during the first year after implantation, every 6 months during year 2, and annually thereafter.

As of December 1, 2024, 38 patients have been enrolled. All patients received treatment at Duke University. Of the 37 patients with data available, 11 (30%) are female and 26 (70%) are male. The median (range) age was 10 (4–97) days at diagnosis and 854 (235–2328) days at implantation. The median time from diagnosis to implantation in days (range) was 813 (230-2,231). Genetic etiologies included 22q11del (15 patients, 41%), and CHD7 mutations (10 patients, 27%), with TBX1, PAX1, FOXi3, TP6, EXTL3 mutations, and 2p11.2 microdeletion under 5% prevalence. 26 patients (70%) were diagnosed with an atypical phenotype (autologous graft-versus-host disease) prior to implantation, based on rash, cytopenia, adenopathy, and other symptoms. To date, 2 patients have died; both deaths were unrelated to allogeneic processed thymus tissue-agdc and occurred within 12 months of implantation. 22 (58%) patients have reached 12 months post-treatment. Preliminary lymphocyte enumeration results indicate that 10 patients have recorded naive CD4+ cell counts ≥50 cells/mm^3 since implantation, 3 patients (30%) by 6 months and 9 (90%) by 12 months.

The high percentage of pretreatment autoimmunity supports the need for CTT treatment as early as possible.

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Primary Immunodeficiency Initially Identified as Sarcoidosis

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Introduction: Sarcoidosis is a granulomatous disease with an incidence of up to 18 in 100,000 in some populations. Symptoms range from asymptomatic benign lesions to organ failure, with up to 90% of patients presenting with lung involvement. Sarcoidosis is often a diagnosis of exclusion: inflammation, lymphadenopathy, and sterile granulomata without an identifiable cause. Granuloma formation occurs in primary immunodeficiencies, but the full landscape of these deficiencies and their association with sarcoid is not fully understood.

Results: We looked retrospectively at patients initially diagnosed with sarcoidosis referred to the National Institutes of Health (NIH). Many people had refractory inflammation or had a diagnosis of sarcoidosis in the setting of other immune dysfunction such as common variable immunodeficiency (CVID). Within this group of 37 patients with completed whole-genome or whole-exome sequencing, 22 had pathogenic variants, likely pathogenic variants, or variants of unknown significance in relevant candidate genes including SP110, GATA2, NFKBIA, NFKB1, IRF8, CTLA-4, NCF1, SLC26A9, RFX5, MEFV, GFI1, PLCG2, STAT1, BACH2, IKZF3, JAK1, ADCY10, and STXBP2.

Conclusion: This study highlights the diseases often gathered under the diagnosis "sarcoid". Prior studies have highlighted immune dysregulation within multiple pathways, including the interferon-gamma (IFN-γ) response pathway (GATA2, STAT1, NFKBIA, and IRF8), Th17.1 signaling (STAT1 and IRF8), and inflammasome response (IRF8, MEFV, and PLCG2), as being important in granuloma formation. Numerous mutations within this cohort have previously been associated with common immunodeficiencies (RFX5, NFKBIA, SP110, and IKZF3) or predominant antibody deficiencies (NFKB1). This cohort also showed defects of phagocyte number or function (GFI1, NCF1, and GATA2). Within this study, two variants were identified that are not associated with immunodeficiencies, including SLC26A9, an ion transporter for chloride previously identified in atypical cystic fibrosis, and ADCY10, a catalyst for the formation of cAMP. Though it is possible that some of these variants may not be causal or even relevant to the formation of granulomas, this cohort shows how some patients presenting with lymphadenopathy and sterile granulomata in various organs were identified to have Mendelian traits underlying their diagnoses of sarcoidosis.

Table 1.

Subject ID	Genetic Defect Identified	Allele Frequency gnomAD v4.1.0	Classification (ClinVar)	Zygosity	CADD Score	Inheritance Pattern	Organ Involvement	Infection History
1	NFKBIA (IkBa) (c.691G>T, p.Asp231Tyr)	4.7e-5	VUS	Het	27.3	AD	CNS, Exocrine, Cutaneous	NTM, EBV
2	CTLA4 (c.567+5G>C)	0	Pathogenic	Het	26	AD	Ocular, LN, Cutaneous, Pulmonary	
3	No defect identified						Ocular, Cutaneous, Pulmonary	EBV
4	NCF1 (p47phox Deficient CGD) (c.75_76del, p.Tyr26fs)	8.5e-4	Pathologic	Homo	35	AR	Pulmonary, Exocrine, LN	*S. capitis*
5	No defect identified						Cutaneous	*Sphingomonas paucimobilis*
6	No defect identified						Pulmonary	*M. avium*

Table 1. **(*Continued*)**

Subject ID	Genetic Defect Identified	Allele Frequency gnomAD v4.1.0	Classification (ClinVar)	Zygosity	CADD Score	Inheritance Pattern	Organ Involvement	Infection History
8	No defect identified						Pulmonary, Neuro, LN	JCV
9	No defect identified						Pulmonary	disseminated *M. tilbergii*
11	NCF1 (p47phox Deficient CGD) (c.75_76del, p.Tyr26fs)	8.5e-4	Pathologic	Homo	38	AR	Pulmonary	
12	NCF1 (p47phox Deficient CGD) (c.75_76del, p.Tyr26fs)	8.5e-4	Pathologic	Homo	38	AR	MSK, Ocular, Splenic	*A. fumigatus*
14	1q41 222762100-224070013 1.308 Mb-1.636 Mb Loss IFIH1 NOD2 LRBA FAT4 KMT2D			Het			Hepatic, Pulmonary	*S. pneumo*
15	SP110 (c.1428_1429del, p.Tyr476Ter)	1.8e-6	Not Reported	Het	34	AR	Cutaneous	*M. chelonae*
16	SLC26A9 (c.1459G>A, p.Ala487Thr)	6.9e-5	Not Reported	Het	20.8		Pulmonary	MAC
17	GATA2 (c.1021_1024dup, p.Ala342GlyfsTer43)	0	Pathologic	Het	NA	AD	Pulmonary	
18	No defect identified						Pulmonary, Cutaneous	
19	IRF8 (c. 536C>T, p.Ala179Val)	6.5e-6	VUS	Het	17.54	AR/AD	Neuro	MAC
20	No defect identified						Pulmonary, GI	MAC
23	GATA2 (c.1021_1024dup, p.Ala342GlyTer43)	0	Pathogenic	Het	NA	AD	BM	
25	STXBP2 (c.1001 C>T, p.Pro334Leu)	4e-5	Likely pathogenic	Homo	29.9	AR	Hepatic	
26	No defect identified						Pulmonary	
27	No defect identified						Pulmonary	
28	NFKB1 (c.1513A>C, p.Lys505Gln)	6.85e-7	VUS	Het	26.2	AD	Pulmonary, Cardiac	
29	RFX5 (c.353+2T>G)	1.8e-4	Likely pathogenic	Het	33	AR	Pulmonary, Cutaneous	
30	IKZF3 (c.244G>A, p.Glu82Lys)	1.4e-4	VUS	Het	23.6	AD	Hepatic, Ocular	Recurrent Pneumonia
31	No defect identified						Pulmonary	EBV
32	No defect identified						Cardiac	
33	No defect identified						Neuro	VZV
34	MEFV (c.289C>A, p.Gln97Lys)	9.43e-5	VUS	Het	9.8	AD/AR	Pulmonary, Hepatic	
35	GFI1 (c.200G>A, p.Arg67Lys)	3.4e-5	VUS	Het	21.2	AR	Pulmonary	Aspergillus, pneumocystis
36	PLCG2 (c.2931C>G, p.Tyr977Ter)	6.19e-7	VUS	Het	38	AD	Pulmonary, Splenic, Cutaneous	Recurrent sinusitis

Table 1. **(*Continued*)**

Subject ID	Genetic Defect Identified	Allele Frequency gnomAD v4.1.0	Classification (ClinVar)	Zygosity	CADD Score	Inheritance Pattern	Organ Involvement	Infection History
37	STAT1 (c.736G>A, p.Ala246Thr)	0	VUS	Het	24	AD	Pulmonary	Histoplasmosis
38	BACH2 (c.2327 C>T, p.Pro776Leu)	1.8e-5	VUS	Het	16.9	AD	Pulmonary	
39	No defect identified						Pulmonary	
40	ADCY10 (c.4477del, p.Leu1493SerfsTer24)	3e-4	Pathogenic	Het	33	AD	Pulmonary	
41	No defect identified						Pulmonary	
42	No defect identified						Cardiac	
43	JAK1 (c.1078C>T, p.Arg360Trp)	5.9e-5	VUS	Het	25.1	AD/AR	T1DM, Pulmonary, Ocular	Histoplasmosis

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Evaluation of Presenting Symptoms in Pediatric Patients with Hemophagocytic Lymphohistiocytosis (HLH) Versus HLH Mimics

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Background and Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome characterized by a hyperactive but ineffective immune response, resulting in excessive cellular proliferation and cytokine secretion. This causes end-organ damage that is typically fatal without immunosuppressive therapy. Multiple disease processes share clinical and laboratory features with HLH, which contributes to diagnostic uncertainty and treatment delays. We sought to determine whether HLH and these disease mimics demonstrate differences in presenting symptomatology that can aid in tailoring a differential diagnosis.

Methods: We queried the UCSF Electronic Medical Record Search Engine using the terms "hemophagocytic lymphohistiocytosis" and the related disease process "macrophage activation syndrome" and filtered results to include 635 previously healthy pediatric patients. Patients were subdivided into 68 patients with a diagnosis of HLH (HLH-diagnosed), defined by the presence of the ICD-10 code, and 567 patients in whom HLH was considered on the differential diagnosis prior to assignment of an alternate diagnosis (HLH-considered). Presenting symptoms were ascertained through review of the admission note. Fischer's exact test was used to compare frequencies of presenting symptoms between groups. False discovery rate (FDR) correction was used to account for multiple hypothesis testing.

Results: The most common primary discharge diagnoses in the HLH-considered group included rheumatologic diseases (31%), infections (29%), malignancies (12%), and fever of unknown origin (11%). We identified 64 distinct presenting symptoms across the cohort. The five most common symptoms in each group were identical between the two groups and included fever (63% and 63%, respectively), rash (31% and 24%), emesis (25% and 21%), fatigue (25% and 27%), and anorexia (18% and 22%). Of the 64 presenting symptoms identified in this cohort, none demonstrated statistically significant differences in frequency between the two groups.

Conclusion: HLH and its disease mimics, including rheumatologic diseases, infections, and malignancies, share overlapping symptom profiles that preclude prioritization of a differential diagnosis in the absence of additional diagnostic testing. Clinicians should therefore maintain a low threshold for including HLH on the differential diagnosis in patients presenting with these common symptoms.

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HLH-like Hypersensitivity Reaction Secondary to Prolonged Piperacillin/Tazobactam: A Case Series

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Background: Prolonged (>10 days) use of intravenous (IV) piperacillin/tazobactam has been associated with a risk of developing hemophagocytic lymphohistiocytosis (HLH) syndrome. However, clinical and biological descriptions of this rare complication are lacking in the literature, such as management guidelines.
Objectives and Methods: We describe a series of five children who presented with an HLH-like hypersensitivity reaction after prolonged use of IV piperacillin/tazobactam therapy between February 2024 and October 2024 in a single pediatric tertiary center.
Results: Five patients aged between 6 and 15 years received IV piperacillin/tazobactam for various bacterial infections. The reaction occurred between 7 and 19 days after the start of therapy. While initial infections were well controlled, all patients presented with a reoccurrence of high fever, malaise, and a maculopapular rash in 4 of them. All developed biological abnormalities with elevated ferritin (range: 913-124895 µg/L), LDH (range: 565-3130 U/L), liver enzymes (ALT range: 113-363 U/L), and severe neutropenia (range: 0.1-0.4 x 10^9/L). Eosinophils were normal in 4/5 and mildly elevated (0.8 x 10^9/L) in 1/5. Increased HLADR+ CD8+ T cell frequency was observed in 3/3 patients tested (range: 25-30%). Investigations for classical secondary HLH triggers were negative.

Piperacillin/tazobactam discontinuation led to resolution of fever and associated symptoms within 24 hours in all patients. All biological features resolved within a few days. Only one child received a short course of steroids for severe pruritus and myalgia. One patient reported a similar reaction after a previous course of 14 days of piperacillin/tazobactam therapy, 1.5 years earlier.

Four patients were evaluated in allergology: 1/4 reacted to intradermal testing for piperacillin/tazobactam. Patch tests and one dose provocation challenge were negative (tested in 4 and 2 patients, respectively).
Conclusion: We provide further evidence that prolonged use of IV piperacillin/tazobactam may be associated with hypersensitivity reactions reminiscent of HLH (although only 1/5 formally fulfilled HLH-2004 criteria). We propose the term of HLH-like hypersensitivity reactions. Usual allergy testing is not useful to the diagnosis. Spontaneous resolution of symptoms can be expected after discontinuation of piperacillin/tazobactam. Clinicians should be aware of this rare disorder to avoid overtreatment or unnecessary investigations.

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Dual Heterozygous LRBA Variants in an Adult with Combined Immunodeficiency: A Diagnostic Challenge

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Autosomal recessive forms of CVID are rare in the Western world, with LRBA deficiency being a key example. Caused by biallelic mutations in the LRBA gene, it leads to a spectrum of immune dysfunctions, including combined immunodeficiency (CID). We present the case of a 34-year-old female whose late-onset symptoms and dual heterozygous LRBA gene variants at distinct loci challenge the conventional understanding of this condition.

The patient experienced recurrent respiratory infections over two years, chronic sinusitis, arthralgia, and severe diarrhea, later diagnosed as microscopic colitis. Initial immune evaluation revealed hypogammaglobulinemia, low specific antibody titers, and significantly reduced T and B cell subsets. Family history includes a sister with severe refractory Evans syndrome, requiring hematopoietic stem cell transplantation. Treatment with weekly subcutaneous immunoglobulin replacement therapy (IgRT) resulted in decreased infection frequency. Though meeting CVID criteria, her lymphopenia and strong family history prompted consideration of a monogenic CID.

Genetic testing identified pathogenic heterozygous LRBA variants—c.2836_2839del (p.Glu946*) and c.7480C>T (p.Gln2494*)—without determination of compound heterozygosity. Flow cytometry findings include low naïve CD4+ T cells (10% of CD4+ T cells), immune dysregulation evident by expansion of T follicular helper (Tfh) cells (32% of CD4+ T cells) and increased CD19 high CD21lo B cells (26% of naïve B cell compartment), and absence of transitional B cells.

LRBA deficiency is strongly suspected due to immunophenotypic and clinical features consistent with previously reported cases, along with the presence of two heterozygous pathogenic LRBA variants. Interestingly, her late-onset presentation raises the possibility that heterozygous LRBA variants may delay disease onset compared with the early presentation (preschool years) typically seen in biallelic LRBA deficiency.

Ongoing studies aim to elucidate shared genetic factors and CTLA4 expression. Despite current IgRT, the patient's immune dysregulation, arthralgias, mild cytopenias, and thyroid antibodies suggest immunomodulation with CTLA4-Ig may benefit her management.

This case emphasizes the diagnostic challenges of primary immunodeficiencies with atypical, late-onset presentations and highlights the role of heterozygous LRBA variants in influencing disease progression. Identifying monogenic causes in adult "CVID" cases can expedite targeted therapies, improve outcomes, and aid early management of at-risk family members.

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Novel Variants in Biallelic Complement Factor I Deficiency

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Complement factor I (CFI) deficiency is a rare autosomal recessive disorder resulting from homozygous or compound heterozygous variants in CFI, which encodes a crucial regulatory protein in the alternative complement pathway. We report two families with novel genetic variants in CFI.

Patient A, a 3-year-old girl, presented with recurrent infections, including three hospitalizations for pneumonia and giardiasis starting at 19 months. Immune testing revealed low C3 (28; 82.0-173 mg/dL), CH50 (30; 31-60 U/mL), and Factor I levels (<16; 29-59 mcg/mL). Genetic testing identified two in trans variants: a likely pathogenic variant (p.E434Kfs*2) inherited from her father and a variant of uncertain significance (p.V152M) inherited from her mother. The maternal history was notable for autoimmune and inflammatory conditions.

Patients B and C, 2.5-month-old identical female twins, also presented with severe infections. Patient B developed meningitis, pneumonia, and bacteremia due to *Streptococcus pneumoniae* and died from complications. Patient C experienced recurrent fevers and infections, including enteroviral meningitis and multidrug-resistant *Escherichia coli* urinary tract infection. Immune testing revealed low C3 (151; 11249-42887 units/mL), CH50 (<10; 31-60 U/mL), and Factor I levels (<11.3; 29.3-58.5 mcg/mL). Genetic testing identified biallelic pathogenic variants in CFI: p.N103Kfs11 and p.W393Yfs5. Their older sister, with recurrent otitis media and bronchitis, and their younger asymptomatic brother were found to carry the same genetic variants, exhibiting low or absent AH50 levels and low CH50 and Factor I levels. The sister's CH50 was <10 (31-60 U/mL), AH50 < 10 (≥46%), and CFI levels < 12.7 (29.3-58.5 mcg/mL). The brother's CH50 was 44 (176-382 U/mL), AH50 0 (77-159 U/mL), and CFI levels < 16 (29-59 mcg/mL).

Complete CFI deficiency is rare, with only a limited number of cases documented. Our report introduces three new pathogenic variant associations and highlights the variability in clinical presentation. Physicians should consider CFI deficiency in children with invasive or recurrent bacterial infections, even when pathogens are nonencapsulated. Of note, unlike many alternative complement

protein deficiencies that typically present with isolated low AH50 and normal CH50, regulatory component deficiencies like Factor I deficiency led to uncontrolled complement activation and C3 consumption, affecting both pathways, leading to low CH50 and AH50 levels.

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Beyond the Norm: Managing Reactions to Immunoglobulin Replacement

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Immunoglobulin replacement is frequently associated with adverse reactions which are commonly managed by changing the route or rate of administration, premedication, or changing products. Some patients with life-threatening reactions to replacement do not respond to these interventions. We present two cases where alternative methods are used to prevent life-threatening reactions to immunoglobulin replacement.

Patient 1 is a 36-year-old female with a humoral immunodeficiency and a history of chronic spontaneous urticaria but no history of anaphylaxis. She was started on IVIG 600 mg/kg every 4 weeks, which she initially tolerated for multiple months. She then developed urticaria, dyspnea, and chest tightness within 60 minutes of starting an infusion. Pretreatment with IV corticosteroids, antihistamines, infusion rate reduction, IVIG brand changes, and switching to subcutaneous replacement did not prevent anaphylaxis. Based on her history of chronic urticaria and now immunoglobulin replacement induced anaphylaxis, she was initiated on omalizumab 300 mg monthly. After three months of therapy, IVIG was restarted which has been tolerated without further reactions.

Patient 2 is a 49-year-old male with a humoral immunodeficiency. IVIG 600 mg/kg every 4 weeks was initiated and initially tolerated but multiple months into therapy he developed urticaria, chest pain, dyspnea, and mental status changes near the end of his infusions with one reaction requiring mechanical ventilation. He had no benefit with the management changes previously noted or with increasing the frequency of IVIG administration to decrease the amount of IVIG administered per infusion. Because the reactions appeared to be dose-dependent as he did not react until the end of infusions, he was switched to daily dosing of SCIG with 1/28 of the monthly dose administered daily and has tolerated this with no reactions.

Our findings showcase that adverse reactions to immunoglobulin replacement therapy that are not responsive to conventional management may be effectively treated by considering specific patient features and possible pathophysiologic mechanisms; reactions that are consistent with mast cell–mediated processes may respond best to anti-IgE therapy, while those with dose-dependent mechanisms may benefit from low-dose daily dosing to avoid dose thresholds triggering a reaction.

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A Novel Dominant Negative Variant in IL2RG Gene that Failed to Be Corrected by Lentiviral Gene Therapy

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X-linked severe combined immunodeficiency (SCID-X1) is caused by mutations of interleukin-2 receptor γ chain (IL2RG), resulting in a lack of response to common γ-chain (γc, IL-2Rγ, or CD132)–dependent cytokines and T- B+ NK- SCID. For patients who lack matched related donors, autologous gene therapy transducing CD34+ hematopoietic progenitors with a viral vector expressing the IL2RG cDNA is a

promising intervention that avoids graft-versus-host disease. Whether all IL2RG variants, particularly those that express a mutant protein, can be corrected through gene therapy is not clear.

Here, we report a novel variant in exon 8 of IL2RG (c.961_962insC, p.Leu321fsX327), an insertion at position 961-962, that causes a frameshift and premature stop codon in the cytoplasmic tail of IL2RG. This mutation disrupts the Box 2 JAK3–binding motif essential for cytokine-induced signaling. The patient (XSCID05) presented with typical SCID and underwent two infusions autologous CD34+ stem cells transduced with a self-inactivating gammaretroviral vector without chemotherapy conditioning, resulting in poor T cell reconstitution despite sustained gene marking in CD3+ T cells (Figure 1A, 1B).

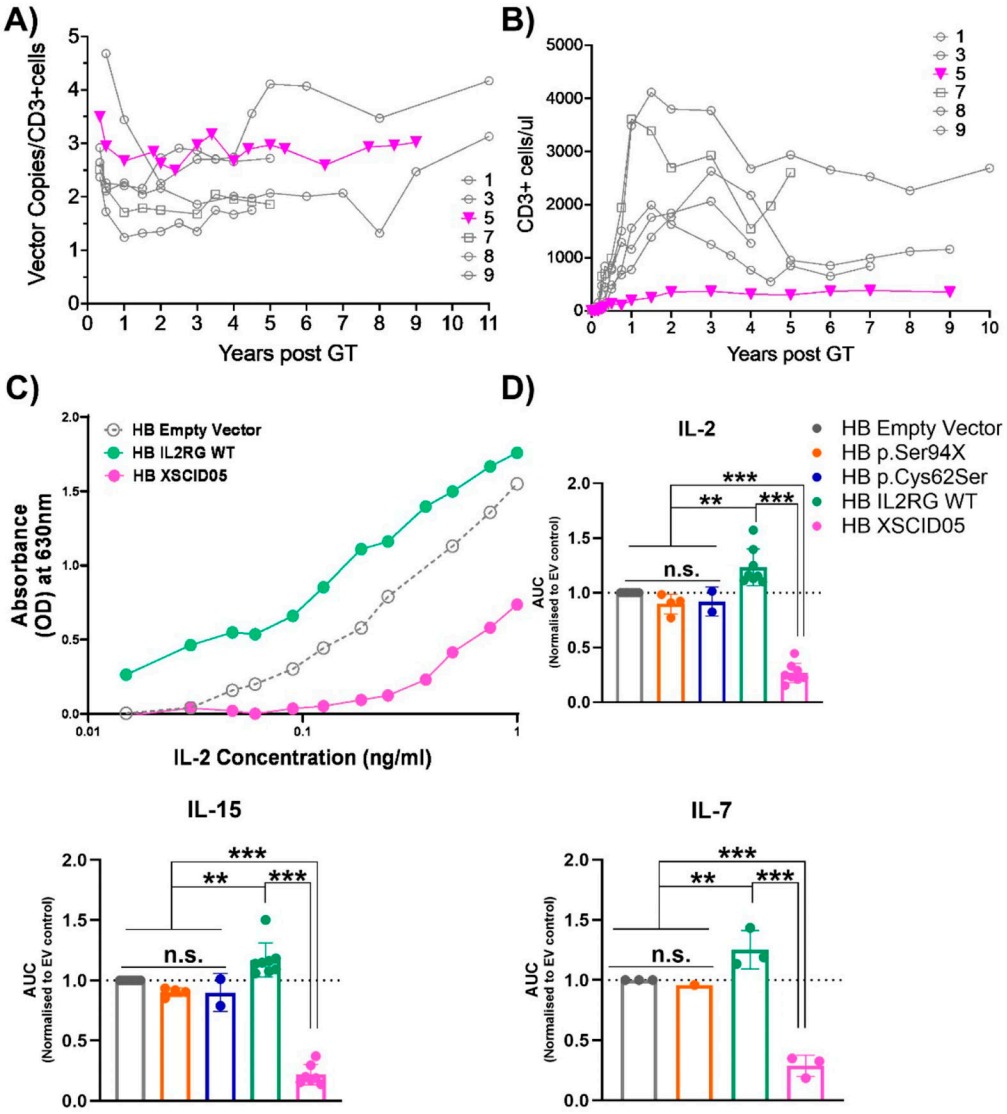

Figure 1. Summary of abstract. A) The vector copy number (VCN) for the patient (#5) compared with other patients in the trial. B) The CD3 T cell count in patient (#5) after two rounds of gene therapy is shown compared with other patients in the trial. C) HEK-Blue *(HB)* reporter assay cell lines *that express IL2RG, IL-2/-15, or IL-7 receptors, and a STAT5-sensitive reporter gene were transduced with lentiviral vectors expressing* the patient's IL2RG mutation *(XSCID05)*, WT IL2RG, or empty vector control, then treated with *increasing* concentrations of IL-2, IL-15, or IL-7. pSTAT5-*sensitive reporter gene activity* was quantified using spectrophotometry. Representative *data showing* that overexpression of the patient mutation interfered with signaling of the endogenous *IL2RG*. D) Results of multiple experiments plotted as area under the curve (AUC) *normalized to the empty vector control of that experiment*. *IL2RG* mutants lacking surface expression (p.Ser94X, p.Cys62Ser) were used as additional controls. *n.s. = not significant, **p = 0.01-0.001, ***p ≤ 0.001.*

We utilized HEK-Blue reporter assay cell lines to study the function of this mutant. HEK-Blue cells stably overexpress components of the relevant cytokine receptor and signaling pathway, including IL2RG, and a STAT5-sensitive reporter protein. We hypothesized that overexpression of WT IL2RG would render cells more sensitive to lower amounts of cytokine, shifting the curve to the left, and transduction with empty vector or mutants lacking surface expression (p.Ser94X, p.Cys62Ser) would have no effect, while the putative XSCID05 dominant negative mutant would interfere with endogenous IL2RG signaling, shifting the curve to the right. Lentiviral

transduction of these constructs followed by treatment with increasing concentrations of IL-2, IL-15, or IL-7 revealed interference of mutant IL2RG with endogenous IL2RG signaling (Figure 1C, 1D). These findings suggest this mutant exerts a dominant negative effect on transgene function, providing an explanation for the poor T cell reconstitution observed in the patient and demonstrating that some IL2RG variants may not be correctable by lentiviral gene therapy. Our data highlight the need for further investigation into IL2RG variants that may mitigate otherwise successful curative use of gene therapy.

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The Many Faces of A20

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Introduction: Genetic testing is often pursued when evaluating patients with suspected inborn errors of immunity but interpreting variants of uncertain significance (VUS) remains challenging. Functional assays are an important avenue to characterize variant pathogenicity but are infrequently commercially available. We report a single case in which research-based functional testing was critical in determining variant pathogenicity.
Case Report: A 12-year-old male with a history of recurrent childhood infections presented with recurrent episodes of bone pain in the upper arms, elbows, thoracic spine, femurs, and ankles. Medical history included oral ulcers, eczema, asthma, elevated IgE, and eosinophilia. Following an extensive work-up, he was diagnosed with chronic noninfectious osteomyelitis (CNO). Immunologic evaluation, including lymphocyte flow cytometry, immunoglobulin levels, antibody vaccine responses, and neutrophil respiratory burst, was reassuring. Exome sequencing revealed tumor necrosis factor, alpha-induced protein 3 (TNFAIP3): c.1033T>C (p.Tyr345His), suggesting possible haploinsufficiency of A20 (HA20). Other family members had milder symptoms of immune dysregulation that segregated with TNFAIP3: c.1033T>C.

To test the effect of TNFAIP3: c.1033T>C on protein function, A20-deficient HEK293T cells were transfected with wild-type versus mutant TNFAIP3, and tumor necrosis factor–induced Nuclear Factor Kappa B (NF-κB) activation (luciferase) was measured. TNFAIP3: c.1033T>C failed to suppress NF-κB activation. Hence, this variant was determined to be pathogenic. This information helped guide treatment with anakinra after bisphosphonates and tumor necrosis factor alpha inhibitors failed to control disease.
Discussion/Conclusion: A20 is a potent inhibitor of multiple pro-inflammatory pathways. HA20, caused by loss-of-function mutations in TNFAIP3, is an early-onset immune dysregulation disease. Clinical phenotypes are heterogenous and may resemble Behcet's disease, juvenile idiopathic arthritis, inflammatory bowel disease, lupus, periodic fever syndromes, or other syndromes.

The absence of easily accessible testing for several immune pathways may result in a delay of accurately diagnosing inborn errors of immunity. This case emphasizes the importance of genetic testing when seeing patients with complex immune phenotypes. After genetic variants are identified, functional assays are often needed to accurately interpret genetic findings. Furthermore, identifying aberrant immune pathways in inborn errors of immunity is critical to the process of selecting targeted therapeutics.

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Immunoglobulin Replacement Therapy in a Child with EIF2AK2-Related LEUDEN Syndrome and Antibody Deficiency

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Introduction: Variants in EIF2AK2 are associated with leukoencephalopathy, developmental delay, and episodic neurologic regression (LEUDEN) syndrome. EIF2AK2 regulates stress response and lymphocyte transcription factors. Presentations of LEUDEN syndrome vary and include developmental delay, abnormal myelination, tone differences, neurologic regression, seizures, and movement disorders. Neurologic regression classically follows systemic stressors such as febrile illness.

Case Presentation: A 30-month-old boy with LEUDEN syndrome experiencing episodic neurologic regression after viruses presented to Immunology. His parents, informed through community groups, sought evaluation due to reported benefits from immunoglobulin replacement therapy (IgRT).

Around 4-5 months old, the patient experienced viral infections, requiring hospitalizations for feeding difficulty, weakness, and head lag. Despite meeting early developmental milestones, developmental delay was diagnosed at 1 year, and he began therapies. Delays improved until 22 months when he presented to the ED for parainfluenza and acute otitis media, where he was prescribed antibiotics and discharged. A few days later, he re-presented for head lag and lethargy. He received empiric antibiotics for possible meningitis. EEG showed diffuse slowing. Brain MRI showed extensive white matter abnormalities. Broad infectious and metabolic workup was unrevealing besides low IgG (478 mg/dL). Post-discharge with intensive therapy, the patient gradually improved starting 2-3 weeks after his initial illness, regaining milestones. Whole-genome sequencing identified a likely pathogenic variant in EIF2AK2 (c.1382C>G, p.Ser461Cys), confirming LEUDEN syndrome.

Immune evaluation at 30 months showed reassuring T/B/NK cell counts, IgG/IgA/IgM/IgE, and vaccine titers. The patient continued to have intermittent viruses with variable neurologic impacts. Immune re-evaluation one year later showed protective but waning titers to tetanus (0.65 IU/mL) and diphtheria (0.11 IU/mL) and poor pneumococcal protection with <50% of serotypes with titers >1.0 ug/mL. This antibody pattern with normal IgG (666 mg/dL) suggested specific antibody deficiency, and IgRT was offered.

After starting monthly IVIG (~450 g/kg) at 4 years old, his infections decreased in frequency and severity. He showed neurological improvements without regression during viral illnesses.

Conclusion: This single case report highlights subtle antibody deficiencies in a patient with LEUDEN syndrome and his improvement following IgRT. Further studies are needed to characterize the immune profiles and the potential utility of IgRT in LEUDEN syndrome.

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The Importance of Chest Imaging in Newly Diagnosed Common Variable Immunodeficiency

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Introduction: Common variable immunodeficiency (CVID) is an immune disorder characterized by a defect in immunoglobulin production secondary to compromised B cell differentiation. It is often diagnosed between the second and fourth decades of life with initial presentations varying widely from recurrent infections to autoimmunity. Those diagnosed with CVID have a higher incidence of malignancy including non-Hodgkin lymphoma.

Case presentation: A 36-year-old male presented to the hospital after labs for an outpatient workup of fatigue and bruising revealed a platelet count of 7 K/µL (150-350 K/µL). Significant past medical history includes asthma, eczema, and psoriasis. He was admitted to the hospital and treated for presumed immune thrombocytopenia with 1 g/kg IVIG and 4-day course of 40 mg dexamethasone. Platelets improved to 23 K/µL and IVIG was discontinued after one dose. During hospitalization, he was noted to have a serum IgG of 495 mg/dL (660-1690 mg/dL) before initiation of IVIG and IgA level of 24 mg/dL (57-543 mg/dL). After discharge, labs showed initial improvement of IgG to 1,850 mg/dL but decreased to 605 mg/dL on repeat testing; the patient was subsequently referred to an Immunologist for suspected CVID. He reported a 2-year history of recurrent cellulitis and upper respiratory infections and noted generalized fatigue. CT chest during workup showed multiple prominent mediastinal lymph nodes and left axillary lymphadenopathy. Repeat imaging 6 weeks later showed persistence of lymphadenopathy and the patient underwent lymph node biopsy with findings consistent with diffuse large B cell lymphoma. He completed 6 cycles of chemotherapy and achieved remission.

Discussion: Due to the vast clinical presentations of CVID, initial screenings are often initiated based on presenting symptoms. This case highlights the necessity of radiographic chest imaging in newly diagnosed CVID. Although this patient did not present with pulmonary symptoms, fever, or night sweats, early imaging allowed for the detection and diagnosis of underlying lymphoma.

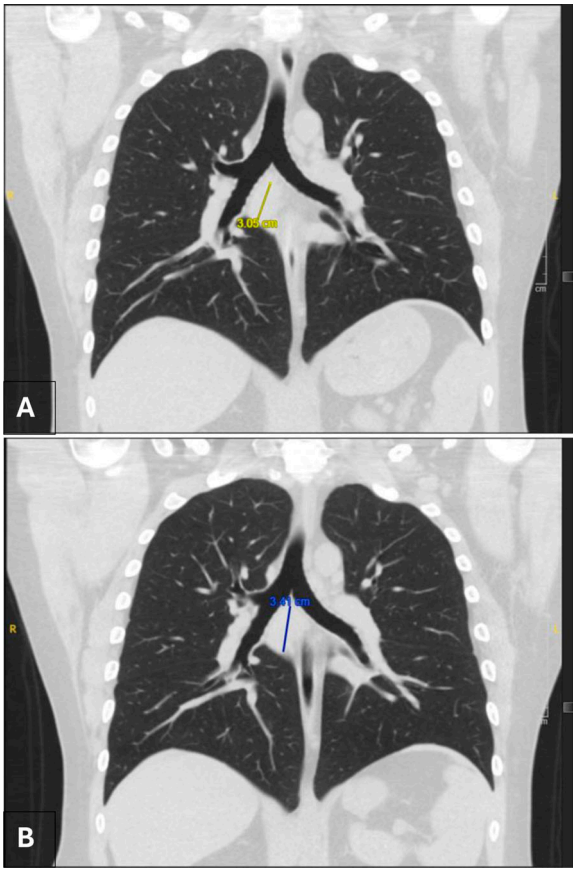

Figure 1. (A) Initial CT chest with mediastinal lymphadenopathy. (B) Repeat CT chest 6 weeks later with persistent lymphadenopathy.

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An Early Presentation: Familial Mediterranean Fever Diagnosed in a 3-Year-Old Child

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Familial Mediterranean fever is one of the most common hereditary autoinflammatory diseases with episodic serositis resulting in secondary amyloidosis, small bowel obstruction, and infertility if untreated.

A 3-year-old boy of Syrian and Egyptian descent, with 3 healthy older siblings, presented at 28 months old, with abdominal pain. His examination was unremarkable, X-ray of the chest/abdomen normal, and an ultrasound negative for intussusception. He improved on non-steroidal analgesics and constipation was thought probable. At 29 months old, he awoke screaming with umbilical pain. He was afebrile with an abdominal X-ray revealing a loaded colon and improved on non-steroidal analgesics. At 30 months old, he presented febrile at 38 degrees Celsius, with a painful right knee following minor trauma during play. A joint effusion was seen on X-ray, and 3cc of serosanguinous cloudy fluid was drained revealing 22,000 white blood cells (WBCs)/μL, few WBCs on gram stain and a negative culture. Laboratory investigations revealed a WBC count of 12,500 cells/μL, sedimentation rate of 28 mm/hour, and

C-reactive protein of 32 mg/L, with an MRI suggesting septic arthritis. He improved on doxycycline for 28 days; however, Lyme serology which resulted after discharge was negative. At 31 months old, he presented with 4 days of fever, diarrhea, vomiting, and abdominal pain. A CT scan suggested an inverted Meckel's diverticulum and laparoscopy revealed serous-free fluid, mild thickening of the small bowel with no Meckel's and mildly prominent lymph nodes. An appendectomy was completed. His investigations revealed elevated WBCs of 15,200 cells/µL, sedimentation rate 60 mm/hour, and C-reactive protein 128 mg/L, with stool PCR revealing rotavirus and astrovirus.

In view of recurrent and worsening symptoms, he was investigated for chronic/recurrent infection and other inflammatory syndromes. A primary immunodeficiency panel revealed two heterozygous pathogenic variants of the MEFV gene, c.2040G>A and c.2040G>C, associated with familial Mediterranean fever. Five other variants of undetermined significance (ATM, DSG1, FANCB, TNFRSF4, and TP63) were also detected. With a working diagnosis of familial Mediterranean fever, treatment with colchicine was initiated, and further testing of his parents and other siblings is being undertaken to complete genetic evaluation.

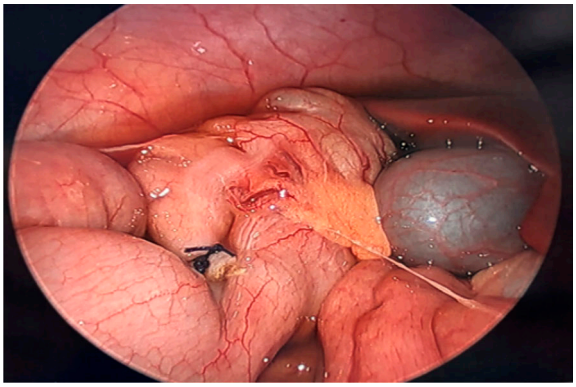

Figure 1. Image depicting a moderate amount of serous fluid lateral to the right colon and above the liver as well as a ligated appendix base and stump.

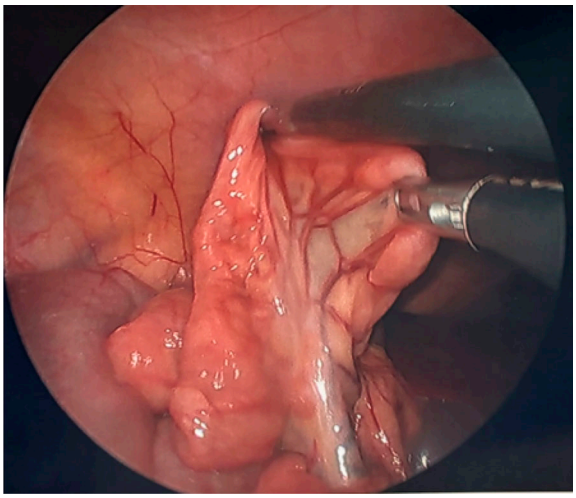

Figure 2. Image depicting the small bowel and its mesentery with mildly prominent lymph nodes.

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Immunodeficiency and Autoimmunity as a Result of CD40LG Copy Number Gains

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X-linked CD40LG encodes CD40L (CD154), a transmembrane protein transiently expressed primarily on activated CD4+ T cells. By binding CD40 on B cells and antigen-presenting cells (APCs), CD40L delivers a co-stimulatory signal that enhances antigen presentation, T cell priming, and activation, as well as class-switch recombination (CSR) in B cells. Inherited deficiency of CD40L in males leads to X-linked hyper-IgM syndrome (XHIGM), a combined immunodeficiency (CID) marked by CSR defects, recurrent infections, and significant morbidity and mortality. However, CD40LG copy number gains (CNGs) are much less recognized: only two male patients with either duplications or triplications have been previously described. Here, we expand the clinical and immunological understanding of this entity by presenting a case series of five male patients, including the two previously reported. We describe the clinical progression, immunological characteristics, and treatment responses of five patients with CD40LG CNGs, comprising three duplications and two triplications. The clinical phenotypes ranged from recurrent infections to early-onset, treatment-refractory autoimmunity. Thus, X-linked CD40LG CNG represents a variable spectrum of immunological phenotypes, including recurrent infections and autoimmunity, underscoring the importance of considering these genetic alterations in patients with immune dysregulation.

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Correlation of IgG Levels and Frequency of Infections in Antibody-Deficiency Patients

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Introduction/Background: Patients with antibody deficiency commonly receive immunoglobulin replacement therapy (IgRT), but markers for disease control vary. The normal range for IgG ranges from 600 to 1700 mg/dL, with providers commonly aiming for a lower threshold of at least 550 mg/dL in these patients. A case series of two patients suggested that levels >800 mg/dL could provide significantly increased protection against infection and advocated tailoring IgRT doses based on specific patient outcomes (1).
Methods: Data collection was completed for 75 antibody-deficiency patients receiving subcutaneous immunoglobulin (SCIG) or intravenous immunoglobulin (IVIG). Of 75 patients, 13 were adults and all had CVID. Among pediatric patients, 55 had primary immunodeficiencies (PID): 9 CVID, 29 hypogammaglobulinemia, 7 Bruton's agammaglobulinemia, 3 STAT-1 gain-of-function (GOF) mutation, 3 autoimmune lymphoproliferative syndrome (ALPS), and 4 specific antibody deficiency (SAD) with normal immunoglobulins and B cells. Seven remaining pediatric patients had secondary immunodeficiencies (SID) caused by end-stage renal disease or lymphoma. Data were annualized and patients were divided into "well-controlled" and "uncontrolled" disease. Lack of disease control was defined as greater than three courses of oral antibiotics or steroids yearly and >1 ED/ICU admission annually.
Data/Results: On average, well-controlled patients had three to four infections per year, while uncontrolled patients had six despite consistent IgRT treatment. The upper limit of IgG levels for any patient in this study did not exceed 1,394 mg/dL.

The calculated average steady state IgG levels across the key subgroups are as follows:
Well-controlled CVID: 844 mg/dL
Well-controlled hypogammaglobulinemia: 899 mg/dL
Suboptimally-controlled CVID: 635 mg/dL
Suboptimally-controlled hypogammaglobulinemia: 606 mg/dL

Bruton's patients had no fewer than 4 infections annually, and an average IgG level of 637 mg/dL. Patients with SAD and ALPS had better disease control with an average steady-state IgG of 1,012 mg/dL. Patients with STAT-1 GOF had the highest steady-state IgG levels (988 mg/dL).

In SID, IgG levels were difficult to capture due to inconsistent therapy use. There was no statistically significant difference between the adult and pediatric cohorts.
Conclusion: These results indicate the optimal IgG level for treatment should change based on diagnosis, but likely begins at least 800 mg/dL.

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Unconditioned Hematopoietic Stem Cell Transplant in Hypomorphic RAG1-Associated Severe Combined Immunodeficiency Complicated by Cytomegalovirus Viremia and Inflammatory Bowel Disease

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Introduction: Managing hypomorphic RAG1-associated severe combined immunodeficiency (SCID) prior to hematopoietic stem cell transplant (HSCT) represents a unique therapeutic challenge as clinicians are charged with preventing and treating opportunistic infections while often simultaneously controlling the consequences of immune dysregulation. We describe a particularly challenging case of treatment-resistant cytomegalovirus (CMV) viremia and significant inflammatory bowel disease in a Mennonite infant with hypomorphic RAG1-associated SCID, ultimately treated with unconditioned HSCT.

Case: A Mennonite breastfed female with SCID secondary to homozygous RAG1 c.527G>T variants (older brother shared genotype) presented at 10 months old with an acute diarrheal illness, found to have cryptosporidium gastroenteritis and CMV viremia. She had rising CMV viral load despite treatment with ganciclovir, valganciclovir, foscarnet, and cidofovir sequentially, as well as 5 maternally derived CMV-specific cytotoxic T lymphocyte infusions. She had poor weight gain, chronic diarrhea, feed intolerance requiring parenteral nutrition, peri-rectal ulcers, and colonoscopy consistent with IBD. IBD was treated with triple antibiotic therapy alone given significant risk with further immunosuppression. B cell depletion with rituximab was pursued to eliminate potential anti–type I interferon antibody–producing B cells and augment CMV clearance. CMV-directed therapies were ultimately discontinued given continued treatment resistance and adverse side effects. She received an unconditioned haploidentical peripheral stem cell transplant with TCRαβ+/CD19+ cell depletion at 18 months old. Engraftment studies showed 34% donor chimerism in the T cell lineage at 3 months post-HSCT, which gradually increased to 80% at 1 year post-HSCT. At 1 year post-HSCT, immune phenotyping showed modestly increased naive T cells, normalized lymphocyte proliferative response to mitogen stimulation, and predominantly polyclonal TCR Vb repertoire. She remained with minimal B cell and myeloid donor engraftment and is maintained on immunoglobulin replacement therapy. Clinically, her GI disease improved with tolerance of complete enteral feeds since 10 months post-HSCT. At 1 year post-HSCT, her CMV viral load was undetectable.

Conclusions: We report a remarkably positive and unexpected outcome of rising T cell engraftment, clearance of previously treatment-resistant CMV viremia, and marked improvement in IBD symptoms after unconditioned HSCT for hypomorphic RAG1-associated SCID, adding to the field's important and ever-growing experience in managing this challenging condition.

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Diversity in the United States Immunodeficiency Network (USIDNET) Patient Registry

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Introduction: The United States Immunodeficiency Network (USIDNET) is an NIH-funded research consortium that advances scientific investigation in the field of inborn errors of immunity (IEI). Capturing demographic diversity within the patient registry is important for improving research on IEI and supporting health equity in clinical immunology. Formerly, registry data were collected via an opt-in system with patient informed consent. Now, the registry uses semi-automated de-identified data extraction from EPIC with a consent waiver. This study was performed to assess whether the new ascertainment method improved diversity using data from one site.

Methods: De-identified data contributed from CHOP was reviewed from both the old and the new USIDNET registries. Race, ethnicity, sex, and age within the new (n = 1,145) and old (n = 551) registries were defined. Patients without data for a given demographic (i.e. race) were excluded from the analysis for that demographic. Chi-squared and Fisher's exact test were completed using GraphPad Prism to determine statistical significance.

Results: The racial breakdown of the new registry was: 0.18% American Indian or Alaska Native, 2.55% Asian, 6.94% Black, 72.93% White, and 17.40% other or more than one race. This was a significant ($p < 0.0001$) difference in racial distribution compared to the old registry: 0.78% Asian or Pacific Islander, 10.85% Black, 86.05% White, and 2.33% other or more than one race. Relative to the old registry, the new registry had a significantly higher proportion of patients from racial minority backgrounds for the diagnosis of agammaglobulinemia ($p = 0.0194$), but not for severe combined immunodeficiency ($p = 0.3937$) or chronic granulomatous disease ($p = 0.7305$). The new registry trended toward a younger median age: 17 years old (0-54) versus 28 years old (9-72).

Conclusions: The design of the new USIDNET registry may better capture a greater representation of patients from racial minority backgrounds compared to the old registry. However, the proportion of patients from racial minority backgrounds within the registry continues to be lower than the populations seen in either total or immunology department CHOP patient visits. While there are many contributing factors, our data may indicate disparities in accessing tertiary care or receiving an IEI diagnosis.

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CGD Female Carriers Can Be Highly Symptomatic due to Lyonization: A de novo CYBB Variant

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Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder caused by mutations in NADPH oxidase subunits, leading to an inability to produce reactive oxygen species, recurrent infections, and autoimmune phenomena. The most common form, X-linked CGD, predominantly affects males. We describe a de novo mutation in the CYBB gene with skewed X-inactivation (lyonization) resulting in a symptomatic CGD carrier female.

Presented at age 4 with fever and rash, diagnosed with incomplete Kawasaki disease, treated with IVIG. Later, the patient had a Burkholderia cepacia thigh abscess. Additionally, she had perianal streptococcal dermatitis, multiple ear infections, upper respiratory infections, intermittent oral ulcers, and pustular cutaneous infections.

Dihydrorhodamine (DHR) assay had only 17.7% activation, in line with a CGD phenotype. Genetic testing identified a likely pathogenic CYBB variant, c.45 + 2dup (intronic), heterozygous. Additional labs further showed absent expression of gp91phox. This was a de novo variant, not present in parents' genetics and both with normal DHR and gp91phox expression. Subsequent three-month DHR trends showed 13.1% and 12.1% activation, respectively. The patient was recommended triple therapy (TMP-SMX, itraconazole, and IFN-gamma) prophylaxis; however, parents opted for TMP-SMX only. The patient has been well controlled on that therapy. Skin biopsy also showed cutaneous lupus, well controlled after starting daily hydroxychloroquine.

The lack of awareness of highly symptomatic CGD carriers can lead to significant delay in diagnosis and management of their CGD phenotype with recurrent infections and multiple autoimmunity phenomena.

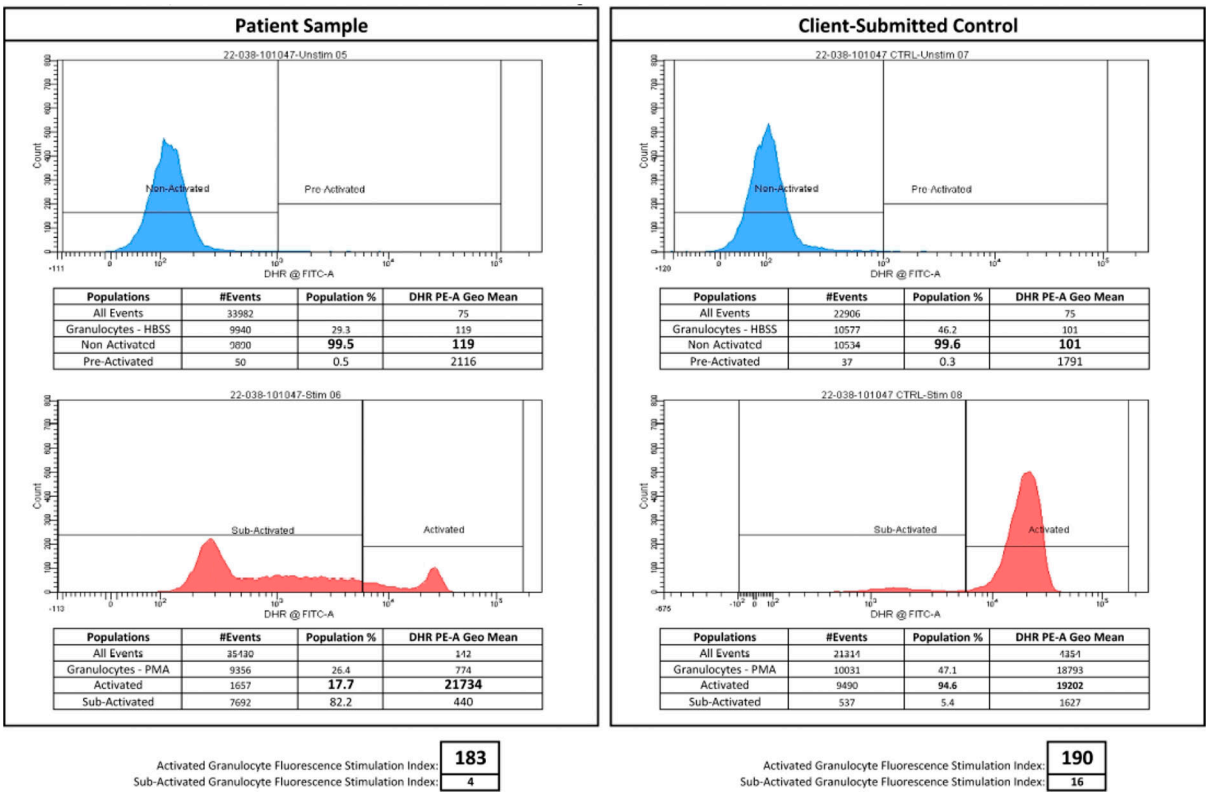

Figure 1.

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Dysregulated T Cell Cytokine Responses Characterize a High-Risk Pediatric Sepsis Subphenotype

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Background: Sepsis is the leading cause of pediatric in-hospital mortality worldwide, driven in part by immune dysregulation. As sepsis biology is marked by immune heterogeneity, precision medicine approaches to identify actionable phenotypes are crucial to improving patient outcomes. Among three molecular subphenotypes we previously identified in children with sepsis, Group C patients have poor clinical outcomes and a unique immune profile involving dysregulated STAT3 signaling. In this analysis, we sought to evaluate cytokine production in CD8+ T cells from pediatric sepsis patients across molecular subphenotypes.

Methods: We measured T cell cytokine production by flow cytometry in pediatric sepsis samples (n = 17) after 24-hour stimulation with αCD3/αCD28. We calculated absolute and relative change in geometric mean fluorescent intensity from baseline for both conditions for six cytokines: IL-2, IL-13, IL-17, IL-21, TNF-α, and IFN-γ. Samples were acquired via a Cytek Aurora spectral flow cytometer and analyzed in FlowJo and Rstudio. We compared cytokine expression across sepsis subphenotypes by ANOVA.

Results: Baseline, unstimulated cytokine production was minimal in all groups. In response to αCD3/αCD28 stimulation, CD8+ T cells from Group C patients demonstrated significantly increased IL-2 production ($p = 0.012$) compared with Groups A and B, and a trend toward sustained TNF-α production ($p = 0.11$). Conversely, Group C showed an exaggerated reduction in IL-17 production in response to stimulation ($p = 0.03$). CD4+ T cells from Group C patients similarly demonstrated significantly increased IL-2 production ($p = 0.003$) after

stimulation compared with Groups A and B, and a similar trend toward sustained TNF-α production (p = 0.11). IFN-γ, IL-13, and IL-21 expression increased with stimulation in all groups but did not vary by subphenotype.

Conclusions: Group C patients demonstrate increased pro-inflammatory cytokine production in CD8+ T cells following αCD3/αCD28 stimulation compared with Groups A and B. This dysregulated response to T cell stimulation in the most severe molecular sepsis subphenotype is a potentially reversible cause of organ dysfunction in pediatric patients with sepsis.

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Development of Varicella Zoster Encephalitis Following Live Vaccination in a Patient with Ataxia Telangiectasia

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This case describes a 4-year-old female with a history of ataxia telangiectasia (AT) with compound heterozygous variants (ATM; c.1339C>T (p.Arg447*) and c.829G>T (p.Glu277*)) who received measles, mumps, rubella (MMR) live vaccine and varicella zoster virus (VZV) vaccination in error in the setting of moving and change of pediatrician. After receiving live vaccines, she was referred to the immunology clinic. She had no concerning symptoms and was started on IgG replacement for low IgG level (474 mg/dL). One month later, the patient developed an itchy rash and fever, diagnosed as a coxsackie infection. Four months following vaccination, the patient presented to her hematologist for scheduled evaluation and was noted to have facial palsy and sent to the emergency room for evaluation. Over the preceding few weeks, her parents had started to notice some slurring of words and her walking had become unstable with frequent falls and increasingly difficult time ambulating.

Emergency room evaluation was significant for tachycardia without fever, right-sided facial droop with conjunctival injection, diffuse weakness, and healing skin lesions. Lab findings at the time showed stable lymphopenia. A lumbar puncture was performed with positive VZV PCR. Peripheral blood was also positive for VZV PCR. MRI brain was performed which showed nonspecific global inflammation which was consistent with VZV encephalitis given infectious studies. While inpatient, she was treated with intravenous acyclovir, and intravenous immunoglobulin (IVIG) replacement was started under the direction of neurology, infectious diseases, and immunology services. Her neurologic condition improved with antiviral treatment. With infectious workup, Epstein Barr virus (EBV) PCR was also positive in the blood. She was discharged and received 6 months of high-dose acyclovir therapy. 6 months following her admission for VZV encephalitis, the patient was diagnosed with EBV-associated lymphoma and is currently undergoing treatment.

This case prompted reflection in terms of the prevention of accidental/contraindicated vaccinations and a discussion on the management of live vaccination administration to a patient with ataxia telangiectasia. The recommendation following vaccination is to monitor clinically for the development of infectious sequelae. For this particular patient, the lesions diagnosed as coxsackie viral infection were more likely acute disseminated VZV infection.

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Successful Use of Anifrolumab and Baricitinib Combination Therapy in an Infant with Spondyloenchondrodysplasia with Immune Dysregulation (SPENCD-I)

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Our patient is a 21-month-old male, born in Texas to consanguineous parents from Afghanistan. He presented as a newborn with petechiae, severe thrombocytopenia, and hepatitis. Family history was notable for two female siblings who had died in infancy and early childhood, one with neonatal thrombocytopenia and hemorrhage, the other with pulmonary hemorrhage and renal failure due to large vessel vasculitis.

Our patient had an extensive workup which ruled out neonatal alloimmune/autoimmune thrombocytopenia, infection, and hemophagocytic lymphohistiocytosis. Bone marrow biopsy was unrevealing. Liver biopsy showed diffuse, spotty hepatocyte necrosis, rare foci

of lobular neutrophilic, and periportal lymphocytic infiltration. He met clinical and histologic criteria for autoimmune hepatitis. He was given IVIG and started on dexamethasone. The thrombocytopenia responded partially and the hepatitis worsened.

Whole-exome sequencing identified a homozygous mutation in ACP5 (p.H205Y) which was predicted to be deleterious and was not found in population databases. ACP5 deficiency causes spondyloenchodrodysplasia with immune dysregulation (SPENCD-I), a type 1 interferonopathy. This has been associated with neonatal thrombocytopenia and other autoimmune manifestations.

The serum interferon alpha level and type 1 interferon response signature were found to be elevated. We therefore initiated baricitinib at 1 mg every 12 hours and continued steroids. Thrombocytopenia normalized. The hepatitis responded only partially, and we were unable to wean steroid (Figure 1). Furthermore, the type 1 interferon signature continued to be very elevated.

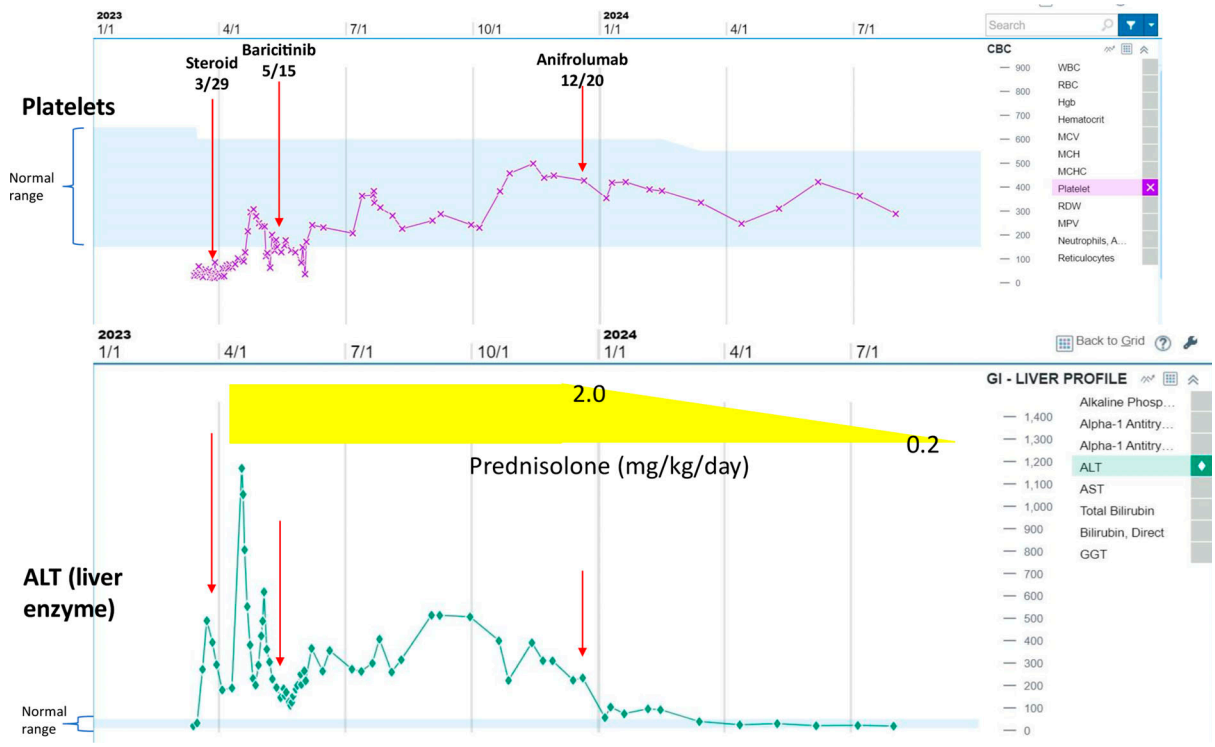

Figure 1.

We then initiated anifrolumab at 5.5 mg/kg/month intravenously and overlapped with baricitinib and systemic steroid. Two months after initiation of anifrolumab, the patient's interferon signature normalized, liver function normalized, platelet count has remained normal, and we have been able to wean systemic glucocorticoid by over 10-fold. We are in the process of weaning baricitinib. The patient has thus far had no adverse effects from this medication regimen. He is on acyclovir and pentamidine for infectious prophylaxis, along with regular PCR monitoring for EBV, CMV, and BK virus.

There is a paucity of published experience with baricitinib and anifrolumab in this age-range. This case demonstrates the safe and effective use of these medications in this young child with SPENCD-I, a severe type 1 interferonopathy.

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Clinical Characteristics and Outcomes of Leukemia in Patients with Germline IKZF1 Mutations

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Background: Germline mutations in IKZF1 are associated with immunodeficiency and predisposition to hematologic malignancies, including acute lymphoblastic leukemia (ALL). The penetrance of leukemia and associated clinical spectrum in affected individuals remain incompletely defined due to the rarity of these mutations.
Objective: To describe the clinical features, leukemia subtypes, therapeutic responses, and outcomes of four individuals with germline IKZF1 mutations.
Methods: Four unrelated patients with germline IKZF1 mutations were identified through clinical genetic testing. Clinical data, including leukemia diagnosis, treatment regimens, remission status, and long-term outcomes, were retrospectively reviewed. Genetic findings, including somatic alterations, were also evaluated to identify cooperative events driving leukemogenesis.
Results: The cohort included four patients (age 3–25 years) diagnosed with B-ALL (n = 3) or T-ALL (n = 1). All patients harbored pathogenic or likely pathogenic germline IKZF1 variants, missense variants (n = 3) in DNA-binding domain, and an entire gene deletion (n = 1), causing haploinsufficiency. Two patients were diagnosed with germline IKZF1 mutation during therapy due to identification of IKZF1 alterations from tumor profiling (confirmed with skin biopsy), while the other two were diagnosed after therapy was completed. Three patients were classified as NCI high risk at diagnosis, with one patient harboring very high-risk molecular features, including Philadelphia chromosome, additional somatic IKZF1 mutation, and CDKN2A deletion. Treatment protocols varied, with three patients receiving standard ALL chemotherapy and one undergoing hematopoietic stem cell transplantation (HSCT) due to very high-risk disease. At follow-up, three patients were alive and remained in complete remission, while one relapsed during therapy and succumbed to his leukemia. Those who survived developed prolonged hypogammaglobulinemia, requiring immunoglobulin replacement therapy due to recurrent infections. One patient who received HSCT developed chronic lung GVHD. None of these patients had history of recurrent infections or autoimmunity prior to leukemia diagnosis.
Conclusion: Germline IKZF1 mutations confer a predisposition to leukemia, with a spectrum of phenotypes and variable outcomes. The presence of somatic IKZF1 alterations is uncommon but if present may accelerate acquisition of high-risk molecular features which warrant more intensive therapy. Early identification of germline IKZF1 mutations (through routine tumor profiling) and tailored management strategies, including consideration of HSCT, may improve outcomes in this high-risk population.

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Diverse Clinical Presentations of Primary Hemophagocytic Lymphohistiocytosis in Adulthood

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Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by pathologic T cell activation. Primary (pHLH) is caused by defects in cytotoxicity with 90% of cases presenting before two years of age. Rare cases in adolescents have been described; however, the prevalence and phenotypic spectrum of pHLH in adults is unknown.

We report on eight patients with pHLH evaluated between 2006 and 2024. The median age was 33 years (range: 17-50). Five (62.5%) were women and seven (87.5%) were White. Three patients had homozygous or compound heterozygous variants in PRF1, while one each had protein-altering variants in RAB27A, UNC13D, and STXBP2. One woman had a heterozygous XIAP variant with skewed lyonization (XIAP expression ~10%) and one man had SAP deficiency with a somatic reversion in CD8 T cells (SAP expression ~15% on CD8 T cells). Flow cytometry showed decreased perforin in patients with PRF1 variants and impaired CD107 degranulation in those with vesicle-trafficking defects. All individuals demonstrated classic HLH laboratory changes (cytopenias, liver injury, and increased sCD25). Ferritin was not markedly elevated (median: 538 ng/mL [IQR: 405-4856]), but CXCL9 (a surrogate for IFNγ) showed dramatic elevations (median: 69,720 pg/mL [IQR: 23,596-112,904]). Increases in activated T cells (CD38hiHLADR+) closely associated with disease activity. Four patients (x3-PRF1, x1-RAB27A) developed progressive, fulminant HLH. Two received successful hematopoietic stem cell transplant (HSCT) and two died prior to HSCT. The other four demonstrated a partial phenotype with chronic, smoldering HLH-like inflammation associated with acute flares triggered by infections. These flares responded to corticosteroids and a variety of steroid-sparing agents were trialed

with variable success. These patients had a shared phenotype which included cytopenias (4/4), splenomegaly (4/4), migraines (3/4), and GI symptoms (3/4). Since their inflammatory syndromes have been controllable with immunomodulation, HSCT has not yet been pursued.

This series emphasizes the striking diversity of adults presenting with pHLH and highlights the substantial unknowns in terms of prevalence, pathogenesis, and long-term outcomes. Due to the atypical and sometimes subtle HLH phenotype, the current literature based on genetic testing of retrospective cohorts may substantially underestimate the burden of pHLH in adults. Our findings underscore the importance of recruiting prospective, longitudinal cohorts of adults with HLH and maintaining a low threshold to pursue genetic testing.

Table 1.

ID	Age at evaluation (years)	Sex	Gene	Clinical Presentation	Age at first HLH onset (yrs)	Prior Therapy	Current Treatment	Outcome
Patient-1	49	male	*PRF1-/-* (F-HLH Type 2)	Acute HLH	49	Dexamethasone, Anakinra, Ruxolitinib	N/A	Deceased
Patient-2	52	female	*STXBP2-/-* (F-HLH Type 5)	Granulomatous inflammatory syndrome	50	Dexamethasone, Azathioprine, Ruxolitinib	Mycophenolate mofetil	Alive
Patient-3	21	female	*XIAP+/-* (XLP-2)	Acute HLH	18	Dexamethasone, Anakinra, Infliximab, Ustekinumab	Clinical Trial: MAS825	Alive
Patient-4	18	female	*PRF1-/-* (F-HLH Type 2)	EBV triggered DLBCL with HLH	17	EPOCH-R	Allo-SCT	Alive
Patient-5	43	female	*UNC13D-/-* (F-HLH Type 3)	Subacute HLH-like syndrome	42	Prednisone	Ruxolitinib	Alive
Patient-6	24	female	*RAB27A-/-* (Griscelli syndrome)	Acute HLH/Treated as PTCL-NOS at OSH	23	CHOEP, BV, ICE, Pralatrexate, HDAC	Emapalumab bridge to Allo-SCT	Alive
Patient-7	22	male	*PRF1-/-* (F-HLH Type 2)	Acute HLH	22	Dexamethasone, Etoposide	N/A	Deceased
Patient-8	42	male	*SH2D1A-* (XLP-1)	Recurrent infections, pancytopenia	N/A	Prednisone, IVIG	Prednisone	Alive

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Actinomycotic Hepatic Abscess in a Teenage Boy with Probable DNASE1 Deficiency

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Actinomyces species are ubiquitous, commensal, facultatively anaerobic, filamentous Gram-positive bacteria that live in our mouth and intestine but may translocate and invade brain, liver, or pelvis, usually through wounds or in immunosuppressed individuals. *Actinomyces'* main virulence/evasion factors are biofilms and (fungus-like) filament branching formation. The genetic etiology for actinomycosis susceptibility is not yet known.

A 15-year-old male from rural Veracruz, born of a non-consanguineous family with five asymptomatic siblings and a personal history of cleft lip and palate. At age 10, he developed a fever, malaise, chronic cough, and abdominal pain. On physical examination, an abdominal mass was found, as well as jaundice, multiple dental cavities, absent teeth, bifid uvula, neck lymphadenopathies, and hepatomegaly palpable 5 cm below the costal margin. Further investigation revealed a 12.5 x 15.5-cm liver tumor, undernutrition with Tanner stage 1, a lung cyst, hepato-cutaneous fistula, empyema, atelectasis, and kidney ectasis.

Laboratory workup reported a normal DHR oxidation, microcytic/hypochromic anemia (10.6 g/dl), leukocytosis (14,500-19,300/mm3 WBC), thrombocytosis (627-413k), and pan-hypergammaglobulinemia (IgG 2230, IgA 674, and IgM 237 mg/dl), with normal serum complement, liver function tests, coagulation assays, C-reactive protein, erythrocyte sedimentation rate, and lymphocyte subsets. Serum autoantibodies were negative, except for slight positivity of anti-phospholipid. The hepatic ultrasound found a vascularized mass of 62 x 45 x 45 mm; a liver biopsy identified fibrosis and chronic inflammation; and the Splendore-Hoeppli reaction, highly suggestive of *Actinomyces*, also observable in secretion from the fistula.

The patient was treated with penicillin, hydroxychloroquine, and ambulatory antimicrobial prophylaxis. Whole-exome sequencing analysis identified a compound heterozygous genotype: a nonsense variant in exon 8/9 of DNASE1 (c.730C>T, p.Arg244Ter), exceedingly rare (MAF gnomAD 3.58e-5), likely deleterious (CADD Phred 37), and highly conserved across species (GERP++RS 4.5), classified as a VUS; a (trans) heterozygous missense variant affecting the same codon (p.Arg244Gln); and a third heterozygous variant of interest in UNC93B1 (c.439G>A, p.Ala147Thr). Familial segregation analysis and functional validation assays are underway.

Immunity against *Actinomyces* is not understood. DNASEs are endonucleases that remove extracellular self-DNA. Studies have shown a role for DNASE1 in digesting neutrophil external traps and in limiting the damage caused by staphylococcal infection in mice, by facilitating removal of biofilms.

Gene	exo	cDNA	Protein	MAB zygo	MAF gnomAD	CADD Phred	GERP ++RS	DP	Comment
DNASE1	8/9	c.730C>T	p.Arg244Ter	0.52	3.58e-5	37	4.5	200x	Monogenic Lupus
DNASE1	8	c.731G>A	p.Arg244Gln	0.47	0.36	11.44	4.5	205x	
UNC93B1	4	c.439G>A	p.Ala147Thr	0.44	1.23e-5	26.1	5.37	321x	Monogenic Lupus, AR HSE
ERAP1	12	c.1712C>A	p.Thr571Asn	0.29	0	25.3	5.33	14x	Behcet's. MHC peptide trimmer

Figure 1.

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Vitamin D Deficiency Is Prevalent and Resistant to Correction in Patients with Hemophagocytic Lymphohistiocytosis

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Background: Vitamin D plays a key role in immunoregulatory functions, and many patients are deficient prior to hematopoietic cell transplant (HCT), which is associated with poor outcome. Worsening nutrient deficiencies can occur during HCT secondary to increased nutritional requirements, inflammation, and mucosal barrier breakdown affecting absorption, potentially leading to endothelial injury and post-HCT complications. Standard repletion often does not sufficiently replete vitamin D levels in patients undergoing HCT which has led to the implementation of high-dose replacement regimens, such as Stoss dosing (one-time dose of ~7,000 U/kg).
Objective: We sought to characterize the incidence and impact of vitamin D insufficiency in patients with HLH undergoing HCT. Additionally, we investigated the use of standard repletion versus Stoss therapy on the ability to achieve sufficient levels pre-HCT.
Methods: A retrospective chart review was performed on 135 patients with a diagnosis of HLH undergoing their first HCT at Cincinnati Children's Hospital Medical Center from 2010 to 2023. Demographic data, vitamin D levels at predetermined time points, vitamin D supplementation received (Stoss and/or standard therapy), length of supplementation, and post-transplant outcomes were recorded.
Results: Eighty-four patients met inclusion criteria and had documented vitamin D levels pre-HSCT. Of these, 76 (90%) were identified as vitamin D deficient (<30 ng/mL). At the time of transplant, 34 patients (45%) were corrected to sufficient levels (>30 ng/mL; 24 with standard therapy, 9 with Stoss therapy). Three patients who failed to correct with standard supplementation subsequently corrected with Stoss dosing and 1 patient corrected after receiving both standard and Stoss supplementation. The other 42 patients (55%) remained vitamin D deficient at HCT (22 were not on any supplementation, 19 received standard therapy, and 1 received Stoss therapy).
Conclusion: We show that there is a very high incidence of vitamin D deficiency in HLH patients, which may worsen outcomes. Many patients do not correct with standard therapy and often require aggressive repletion to achieve sufficient levels. Future analyses will include examining the impact of steroid exposure on vitamin D levels, describing optimal timing and degree of vitamin D supplementation needed to achieve and maintain sufficiency, and correlation with outcomes post-HCT.

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A Rare Case of MHC Class II Deficiency Diagnosed In Utero

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Introduction: MHC Class II deficiency, also known as Bare Lymphocyte Syndrome type II (BLS II) is a combined immunodeficiency syndrome that results from loss of HLA class II on antigen-presenting cells. There are four distinct groups of BLS II, each resulting from disease causing variants in either class II transactivator (CIITA) or 3 subunits of regulatory factor X. There are less than 100 reported cases of BLS II worldwide. Here we present a case of a newborn who was diagnosed with BLS II prenatally.
Case Discussion: The mother of an ex–full-term male was referred for an immunology evaluation after diagnostic fetal chorionic villous sampling (CVS) was positive for a homozygous likely pathogenic c.3317+1G>A CIITA variant. Earlier in her pregnancy, a routine prenatal ultrasound found increased nuchal translucency in the fetus, for which she was referred for evaluation by reproductive genetics. Screening for consanguinity was positive. Expanded genetic screening was performed and both parents were found to be carriers of a pathogenic variant c.3317+1G>A in CIITA. Diagnostic CVS confirmed homozygosity for this variant in the fetus.

At 39 weeks and 2 days gestational age, the mother delivered a male baby transferred to NICU for further isolation and immunological testing. Confirmatory immune studies including MHC II expression level testing are pending. He is to remain admitted for early-life evaluation for hematopoietic stem cell transplant (HSCT).

Discussion: The median age of diagnosis of BLS II is at 16 months of age. TREC levels are usually detected with this disease, so it is often missed with newborn screening and usually only diagnosed once the patient starts developing multiple recurrent bacterial infections. The identification of a pathogenic variant in CIITA while in utero resulted in early-life identification of BLS II, improving the chances of survival and prognosis for this patient with early HSCT. This case highlights the advancements in fetal medicine, genetics, and immunologic study techniques that have improved early diagnosis of MHC class deficiencies.

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Impact of Emapalumab on Patients with Hemophagocytic Lymphohistiocytosis

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Rationale: In 2018, emapalumab was introduced for treatment of hemophagocytic lymphohistiocytosis (HLH). Emapalumab targets cytosolic and receptor-bound interferon-gamma to attenuate hyperinflammation.
Methods: A large limited de-identified dataset from Epic Cosmos was used to examine treatment rates with emapalumab. Demographics, length of stay, and overall death rates were analyzed.
Results: Since emapalumab was introduced, 41,750 patients have been diagnosed with primary or secondary HLH. Treatment with emapalumab steadily increased from 0.73% in 2019 to 1.9% in 2024. Death rate of HLH in 2018 prior to introduction of emapalumab was 4%. The death rate in 2024 was 1.1%.

Prevalence of HLH was not affected by race or age. Overall prevalence across all ethnicities was 0.01%. Prevalence of HLH in patients under 10 years and between 10 to 19 years of age was 0.01%, but after age 19 years the prevalence decreased to between 0.002 and 0.006%. 39% of patients diagnosed with HLH not treated with emapalumab had a length of stay greater than 14 days compared with 13% of treated patients. Conversely, 69% of treated patients had a length of stay between 4 to 6 days, compared with 18% of untreated patients.
Discussion: Treatment rates of emapalumab have slowly increased since introduction but remain low despite benefits of treatment. Prevalence of HLH remains consistent among races but is lower in patients aged >20 years. Length of hospital stay was significantly reduced in patients treated with emapalumab. Death rates from HLH decreased from 4% to 1.1% in the time period since emapalumab became available.

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Every Third Baby with Lymphoma Under 3 Years of Age Has Inborn Error of Immunity

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Background and Aims: In children under 3 years of age, lymphoma is extremely rare and may be a manifestation of inborn errors of immunity (IEIs). The aim of this study was to determine TREC/KREC copy numbers and search for Slavic founder mutations (RAG1 p.Lys86ValfsTer33, IL7R p.Ser44Arg, NBN1 p.Lys219AsnfsTer16, ATM p.Glu1978Ter, UNC13D p.Arg782SerfsTer12) in patients with lymphoma up to 3 years of age from the Belarusian Cancer Registry (No.: 0170100025) over a 26-year period.
Methods: From 1998 to 2024, 39 patients younger than 3 years (29 males and 10 females) were diagnosed with lymphoma. The median age was 2.1 years (from 50 days to 2.8 years). 4 patients had Hodgkin's lymphoma (HL), 5—diffuse large B cell lymphoma (DLBCL), 13—lymphoblastic lymphoma (LL), 10—Burkitt lymphoma (BL), 2—peripheral T cell lymphoma (PTCL), 4—anaplastic large cell lymphoma (ALCL), 1—non-Hodgkin's lymphoma (NHL) of unspecified type. DNA was isolated from archival samples from 36 patients: bone marrow smears (n = 12), frozen bone marrow cells (n = 11), and peripheral blood cells (n = 13).
Results: Lymphoma in children aged 0-3 years accounted 3% (39/1237) of all pediatric lymphoma cases up to 18 years of age, including 7% (35/481) of NHL and 0.5% (4/756) of HL patients. 15/39 (38%) patients died and 3 were lost to follow-up. TREC/KREC copy numbers was reduced in 12/36 (33%) patients, 7 of whom were dead. Low TRECs/KRECs were present in all patients with DLBCL, 2 with ALCL, 2 with LL, and single cases with HL, BL, and PTCL. Homozygosity for the underlying Slavic variant of RAG1 [p.Lys86ValfsTer33] was found in a patient with DLBCL at the age of 14 months. One 12-month-old patient with PTCL was homozygous for the founder Slavic UNC13D variant [p.Arg782SerfsTer12].
Conclusions: Low TREC/KREC was detected in one-third of children aged 0-3 years with lymphoma and may be used as a step 1 method to suspect the IEIs.

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Clinical Scoring of Immune Deficiency and Dysregulation Correlated with Immune Biomarkers in Mennonite Patients with Hypomorphic RAG1 Variant Clinical Scoring of Immune Deficiency in Hypomorphic RAG

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Introduction: Monogenetic inborn errors of immunity disorders are often characterized by both immune dysregulation and infections. One such disorder is caused by hypomorphic mutations in the recombinase-activating genes 1 and 2 (RAG1/RAG2) known as partial Rag deficiency (pRD). Patients with pRD present with variable clinical phenotypes ranging from clinically well to severe infections and/or immune dysregulation and need of a combination of immunoglobulin replacement, immune modulation, and hematopoietic stem cell transplant. This clinical variability in pRD is well represented by the tight-knit U.S. Mennonite community with an inherited founder variant RAG1 p.C176F (25.6% recombinase activity).
Methods: In the current study, we applied assessment of clinical features of immune dysregulation and immune markers to understand disease progression and timing for intervention in this unique cohort. Specifically, we applied the Immune Deficiency and Dysregulation Activity (IDDA2.1 "Kaleidoscope") clinical scoring system to our Mennonite pRD cohort of 10 patients with 32 separate timepoints. We correlated IDDA2.1 scoring of these timepoints with plasma cytokine levels and immune subsets representing dysregulation (CD21loCD11c++ B cells, follicular helper T cells) throughout their clinical journey.
Results: IDDA2.1 point scoring at the most severe clinical stage timepoint segregated these monogenic patients into three distinct groups of mild (0-12 points), moderate (12-36), and severe (36-180). Of note, all severe patients required hematopoietic stem cell transplant, as well as the most highly scored moderate patient. When IDDA2.1 score severity was correlated with several immune

subsets, expansion of circulating T follicular helper cells (cTfh) positively correlated with IDDA2.1 disease score (R squared = 0.53, p = 0.017). Cd21loCD11c+ B cells also held a positive correlation with IDDA2.1 scores for mild and moderate patient groups only.
Conclusions: The combined method of using a clinical scoring system longitudinally and relating it to characteristic immune biomarkers within pRD may be important for the decision to proceed with definitive treatment, particularly if early biomarkers prove to be predictive of clinical state.

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T Cell Tropic Epstein Barr Virus in a Patient with Hemophagocytic Lymphohistiocytosis

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Hemophagocytic lymphohistiocytosis (HLH) is a severe inflammatory disorder affecting macrophages and cytotoxic lymphocytes. Primary HLH is typically caused by genetic mutations, whereas secondary HLH is typically triggered by infections or malignancy. Due to high mortality despite the current proposed diagnostic and treatment guidelines, a high index of suspicion is vital to expedite testing and determine the underlying trigger.

We present the case of a 13-month-old Native American female who was transferred to our facility with recurrent fever, cough, rash, oral sores, and seizure-like activity. Her clinical symptoms were complicated by multilineage cytopenias, transaminitis, and elevated inflammatory markers. A bone marrow biopsy was obtained with mildly hypercellular marrow with trilineage hematopoiesis, no hemophagocytosis, and no evidence of malignancy. Her ferritin was >10,000 mcg/L, which raised suspicion for HLH. Further testing demonstrated coagulopathy, hypofibrinogenemia, and elevated sIL2R and CXCL9levels. EBV quantitative PCR was extremely elevated at >300,000 IU/mL, raising suspicion that EBV triggered HLH. Immune evaluation was unremarkable. Rapid whole-exome sequence was obtained and did not reveal a candidate gene. Though the patient was well-appearing and afebrile after the bone marrow biopsy, she did meet the criteria for HLH. HLH-specific therapy was initiated with partial response to dexamethasone and emapalumab and minimal improvement in EBV viremia. EBV PCR was repeated on sorted lymphocytes which demonstrated T cell tropism, so nivolumab was added with gradual resolution of EBV viremia. Further genetic testing including an HLH gene panel did not demonstrate an underlying defect. The patient's ethnicity remained her only potential risk factor for the development of HLH.

HLH is a rare disorder that can be precipitated by inborn errors of immunity, infection, malignancy, and rheumatic disease. Identification of the underlying trigger is necessary to prevent recurrence by controlling the underlying disease. This case demonstrates the importance of considering other risk factors, such as our patient's T cell tropism and potentially her Native American ethnicity, when no other etiology can be identified.

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Characterization of Pathologic Inflammation in Patients with Pediatric Lymphoproliferative and Immune Dysregulation Disorders and Clinical Responses to Ruxolitinib

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Introduction: Pediatric lymphoproliferative and immune dysregulation disorders (PLPID) represent potentially lethal conditions with varied clinical presentation, frequently associated with IFNγ pathologic inflammation. The goal of this study is to describe immune activation in a PLPID cohort and safety and efficacy of JAK-STAT pathway inhibition with ruxolitinib.

Methods: Medical charts review identified PLPID patients treated with ruxolitnib at Texas Children's Hospital from 2015-2023. PLPID was defined as persistent lymphadenopathy, lymph organ involvement, or organ lymphocytic infiltration >3 months. Response to therapy (complete, partial, or no) was determined by a generated PLPID score, which evaluates clinical and laboratory features across ruxolitinib treatment (Table 1). Toxicity was graded with CTCAE.

Table 1. **PLPID scoring system.**

Clinical criteria	**0**	**1**	**2**
Recurrent fever	No fever = body temperature < 37.5°C		Recurrent fever >38.5
Fatigue	No		Yes
Recurrent infections:	No infections	≤3 infections in 6 months	>3 infections in 6 months
Infections treated at:	Home	Hospital	ICU
Lymphadenopathy	Normal size	≤2 lymph nodes enlarged (physical examination or imaging)	>2 lymph nodes enlarged (physical examination or imaging)
Liver involvement	Normal ALT, AST, bilirubin	ALT, AST increased <5 times bilirubin increased <3 times	ALT, AST increased >5 times bilirubin increased >3 times
Splenomegaly	Normal size		Enlarged
Respiratory failure	No	Nasal canula	O_2 supplement, mechanic ventilation
Enteropathy	No	<5 loose stools per day, no blood in stool, wounds in perianal area require local treatment	Bloody diarrhea, >5 loose stools per day, wounds in perianal area. Require surgical treatment
Arthralgia/Arthritis	No	Mild intermittent pain, NSAIDs as needed (1-2 times a week)	Persistent pain, requiring frequent use of NSAIDs
Dermatitis	No		Yes
CNS findings	No		Yes
Laboratory values			
Cytopenia*	No	In one cell line	Bicytopenia/pancytopenia
CRP	<10 mg/l	10-50 mg/l	>50 mg/l
Ferritin	<500 ng/ml	500-2,000 ng/ml	>2,000 ng/ml
CXCL9	≤647 pg/ml	648 – 5,000 pg/ml	>5,000 pg/ml
IL-18	89-540 pg/ml	541 – 3,000 pg/ml	>3,000 pg/ml
sIL2R	Level within the reference values	Level > reference values <3,000 U/ml	>3,000 U/ml
CD-163	Level within the reference values	Level > reference values <3,000 U/ml	>3,000 U/ml
Neopterin	<16.5 nmol/l	16.5 – 45 nmol/l	>45 nmol/l
CSF WBC	0-5/CU mm		>5/CU mm

Results: A previous study highlighted the difficulty in both diagnosing pathological inflammation and determining effective treatment approaches in PLPID. The 10-year survival rate of this cohort was 72.4%.

In this study, 26 patients (median age 8.1 years [1.9-21.7]) with PLPID were treated with ruxolitinib for immune dysregulation and pathologic inflammation. Underlying diseases included HLH, macrophage activation syndrome, STAT GOF, Kikuchi disease, T cell large granular lymphocytic leukemia, and inflammatory bowel disease.

Patients demonstrated activation of IFN-γ pathway, reflected by CXCL9 (median 16108 pg/mL), T cell activation (sIL2r: median 222 5U/ml), macrophage activation (ferritin: median 239 5ng/ml, CD163: median 2886 ng/ml), inflammasome activity (IL-18: median 17058 pg/ml). Twenty patients required ruxolitinib in combination with other immune modulators; 6 received only ruxolitinib, 4 of whom as a frontline therapy.

Based on PLPID score, overall response to ruxolitinib in a 2-year period was 69.2% (3.8% complete response; 65.4% partial response—Figure 1). Most patients exhibited a partial response with improvements in temperature, energy levels, splenomegaly, enteropathy, lymphadenopathy, malnutrition, infection frequency, and severity. Interestingly, most partial responders with initially elevated CXCL9 saw decreased levels with normalization in two of them within 6 months. Most adverse events were grade 3-4 cytopenias, transaminitis, and infections. Overall survival was 88.5% at a median follow-up of 1.1 years (range: 2 weeks to 7.1 years), with six patients undergoing BMT.

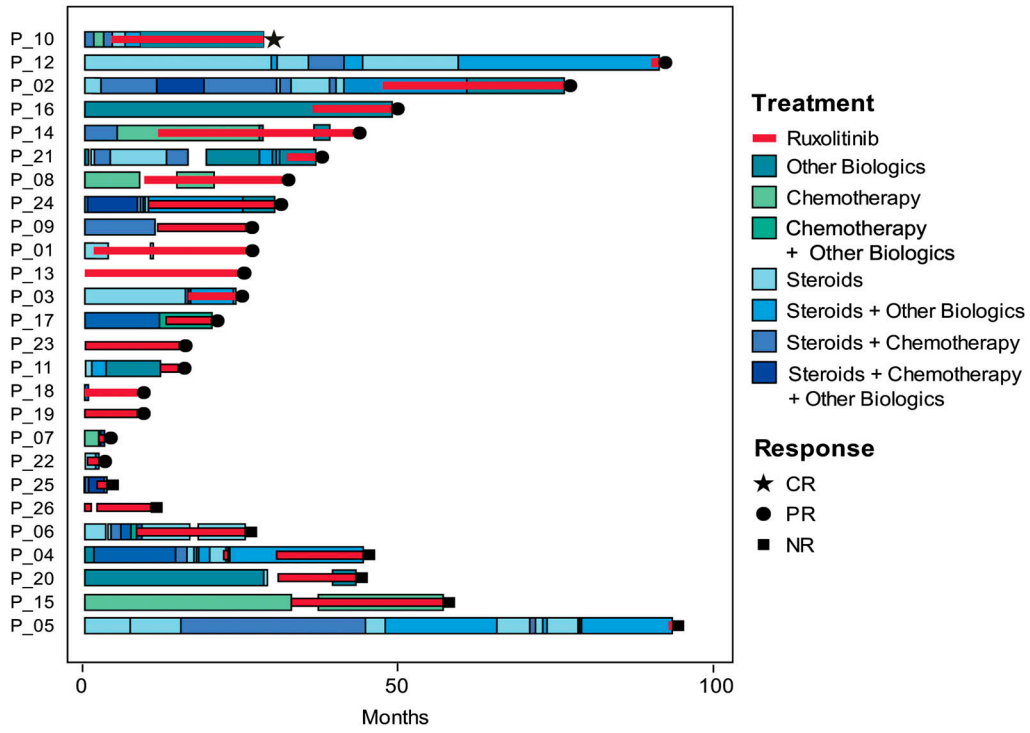

Figure 1. Response status in individual patients over 2-year period of ruxolitinib treatment.

Conclusion: PLPID represents a clinically challenging population at risk for poor outcomes with few biomarkers and no guidelines for treatment. Ruxolitinib demonstrated efficacy and safety and represents a potential "precision" therapy for PLPID patients with a pathologic IFNy signature.

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The Difference in Presentation of Cases of X-Linked Lymphoproliferative Disease Type 1 in a Family of Three Boys

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Introduction: X-linked lymphoproliferative disease type 1 (XLP-1) is a rare syndrome caused by an inactivating mutation in SH2D1A, which encodes for SLAM-Associated protein (SAP) on T and natural killer (NK) cells. The three classic manifestations of XLP-1 include Epstein–Barr virus (EBV)–induced hemophagocytic lymphohistiocytosis (HLH), B cell lymphoma, and dys-gammaglobulinemia. Genotype–phenotype correlation between patients with SH2D1A mutations is unknown. It is unclear how SAP protein levels are related to disease development. We describe a case of a family of 3 boys who had a pathogenic mutation in SH2D1A with different clinical phenotypes.

Case: Brother 1 is a 2-year-old fully vaccinated male who initially presented to our immunology clinic for evaluation of recurrent ear infections. He was found to have low IgG (179 mg/dL), low IgM (<10 mg/dL), and failure to respond to multiple pediatric vaccines. Genetic testing showed a variant of unknown significance (VUS) in SH2D1A (hemizygous, c.95G>A p.Arg32Lys). Flow cytometry for SAP showed decreased expression of SAP in CD4 (28%), CD8 (23%), and NK cells (46%), suggesting a pathogenic VUS.

Brother 2 is a 4-year-old boy who was initially referred to the hospital for hypoxia in the setting of a multifocal pneumonia of unclear etiology. He quickly decompensated and required ECMO for respiratory support. Genetic testing showed the same mutation in SH2D1A as brother 1. Flow cytometry showed decreased expression of SAP in CD4 (8%), CD8 (4%), and NK cells (47%). He met 5 of 8 criteria for HLH. He passed away despite treatment with gamifant and anakinra.

Brother 3 is an 8-year-old fully vaccinated boy who also has the same pathogenic mutation in SH2D1A as both brothers. His immune workup was essentially normal except for a non-protective titer to tetanus toxoid. Flow cytometry for SAP showed slightly higher but low expression in CD4 (68%), CD8 (40%), and NK cells (86%).

Conclusion: Our case highlights the clinical variability of XLP-1 presentation in a family with the same pathogenic variant in SH2D1A. We conclude that the SH2D1A VUS is pathogenic and that SAP levels can correlate with severity of disease.

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The Complexity of Patients with STAT Pathway Immunodeficiency

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Background: Patients with STAT pathway immunodeficiency have a diverse phenotype, presenting a challenge in establishing treatment guidelines. HSCT is often reserved for complicated and young patients. JAK inhibitors provide an important therapeutic option, yet data on the benefits and optimal patient selection are lacking.

Objective: To evaluate the spectrum of patients with STAT pathway immunodeficiency and immune dysregulation and the therapeutic experience with Jakinhibs and other therapeutic options.

Methods: We included patients followed by the immunology service at Schneider's Children Medical Center of Israel. Clinical, laboratory, genetic, and therapeutic data were gathered.

Results: 9 patients, all of which had different STAT pathway mutations, were followed during the study period 2012-2024. 5 had STAT1 GOF mutations, 1 had partial STAT1 LOF, 2 had STAT3 GOF mutations, and 1 had STAT3 LOF HIGES. The clinical presentation of patients with STAT1 GOF mutations was varied, from a severe neonatal course to a more typical course of mucocutaneous candidiasis. 3/5 of the patients with STAT1 mutations suffered from CMV viremia, 4/5 had significant bowel disease, and 3/5 had NTM infection. One patient underwent a successful HSCT. 2 patients were successfully treated with Ruxolitinb. 2 patients had severe esophagitis due to *Candida albicans* infections. Both had evolved to *Candida* strains resistant to azoles. One patient received oral amphotericin and the other is currently on IV Caspofungin. He is now starting Ruxolitinib treatment and underwent balloon dilatation of the esophagus. 2 patients had severe neurological manifestations of chronic meningitis and peripheral neuropathy. Increased ICP occurred in 2 patients.

Both patients with STAT3 GOF presented with immune cytopenias. Both were treated with Ruxolitinib. One stopped treatment due to significant weight gain.

Conclusion: STAT mutations causing immunodeficiency and immune dysregulation cause significant morbidity. Resistant *C. albicans* esophagitis, CMV and NTM infections, and enteropathy were the major symptoms of STAT1 mutations in our cohort, whereas immune cytopenias and lymphoproliferation were the common presenting picture in patients with STAT3 GOF. 3 patients suffered from severe neurological complications. Ruxolitinib therapy is effective but not without side effects. One patient presenting and diagnosed before one year of age underwent successful bone marrow transplantation

Table 1.

	Pt.1	Pt.2	Pt.3	Pt.4	Pt.5	Pt.6	Pt.7	Pt.8	Pt.9
Genetic disorder	STAT1 partial LOF	STAT1 GOF severe disease causing mutation	STAT1 GOF	STAT1 GOF	STAT1 GOF	STAT1 GOF	STAT3 LOF	STAT3 GOF	STAT3 GOF
Age of onset and Clinical phenotype	1 month CMV meningitis Salmonella OM Mycobacterial meningitis	1 month FTT genital and perianal ulcers CMV viremia	1y Diarrhea FTT	3y CMCC- azole resistant	10 y Disseminated abdominal mycobacteria	2m CMCC-azole resistant Severe esophagitis Blepharitis Severe Aphthous stomatitis.	5y IgE-20000 Skin infections Poor wound healing CMCC	3y Cytopenia IDDM Lymphadenopathy	3Y Cytopenia Celiac Short stature PTC
Mycobacterial infection	meningitis OM	Pulmonary disease	No	No	Yes	No	No	No	No
Autoimmunity	IgG4RD White matter lesions	IBD	IBD	IBD	caspr2 antibody-associated peripheral neuropathy	Positive anti histone antibodies	IBD? ASCA+ resolved	Immune cytopenia IDDM1 Lymphoproliferation	Cytopenia Celiac Lymphoproliferation
Treatment	Anti-Mycobacterial med-4 Valcyte Steroids antiepileptic	JAKAVI steroids HSCT	unknown	JAKAVI Fluconazole	Antimycobacterial Steroids IVIG	Caspofungin Esmoprazole JAKAVI	SMX\TMP Fluconazole	Steroids IVIG JAKAVI D/C-due to weight gain	Steroids IVIG Gluten FD JAKAVI
Outcome	Rec seizures Refused HSCT 19Y	Post transplant GVHD resolved alive and well of medication 8Y	Loss of follow up alive FTT 8y	Alive and well CMCC controlled IBD resolved 19y	Responded well to treatment and Rehab 21y	Alive and waiting esophageal balloon dilatation 14y	Alive and well 15y	Alive and well 15Y	Alive and well 6y

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Calculated Globulin: Early Detection of Immunodeficiency

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Serum calculated globulin (cGlob) (total protein – albumin) reflects immunoglobulins. We sought to validate cGlob as an aid to diagnosis of CVID using a large sample of patients with connected diagnostic testing from a national reference laboratory.

Simultaneous total protein and albumin tests from 2023 determined cGlob. Results for quantitative immunoglobulins, IgG and IgA subclasses, serum protein electrophoresis (SPEP), and immunofixation from one year before or after cGlob were obtained. For repeat testing, the first instance of low cGlob in 2023 was the index date; if no low cGlob was observed in 2023, the patient's first 2023 cGlob was used as the index. All group results were reported with median and first and third quartiles (Q1 and Q3). A sub-analysis was performed to identify a patient's time to first diagnosis of CVID using ICD-10 codes on test orders.

28,041,809 patients had both albumin and total protein results in 2023. When observed in combination, 86.9% of patients with cGlob ≥1.8 g/dL had IgG, IgM, and IgA all within normal ranges compared with only 35.4% of patients with low cGlob. Only 0.12% of the full cohort were tested for IgG subclasses (n = 32,529 patients) and 0.01% for IgA subclasses (n = 2,580); only 0.7% (n = 195,768 patients) also had serum protein electrophoresis, and a smaller proportion had immunofixation performed within a year of cGlob (n = 128,923 (0.5%)), where 3.3% (n = 4,308) had a low cGlob.

In the longitudinal sub-analysis, only 1.33% of the full cohort (n = 373,870 patients) had all three IgG, IgM, and IgA tested within one year of their index cGlob, 5.84% of which had a low cGlob (n = 21,817). 3,426 patients were identified who had a CVID ICD-10 code on a

test order after an instance of a low cGlob. Median number of days between first low cGlob and first CVID ICD-10 was 1,089.0 days [466.0, 1,827.0], a 3-year delay.

In conclusion, low cGlob was associated with low immunoglobulins. Only a very small minority of low cGlob patients had further laboratory evaluation within 1 year. Median time to CVID diagnosis following a low cGlob was 3 years. Laboratory investigation of low cGlob could accelerate diagnosis of CVID.

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Homozygous STAT-1 Loss of Function Presenting with Recurrent Respiratory Infections and *Pneumocystis jirovecii* Pneumonia

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Background: Autosomal recessive complete STAT-1 deficiency is a rare primary immunodeficiency characterized by predisposition to life-threatening viral and mycobacterial infections due to loss of STAT-1–dependent responses to type I/II interferons. We present a case of complete STAT-1 deficiency presenting with severe respiratory infections.
Case: A 5-week-old, ex–full-term female infant was admitted for RSV bronchiolitis with superimposed MRSA pneumonia and bacteremia requiring intubation. At 2 months, she required noninvasive ventilatory support for rhinovirus infection and treatment for aspiration pneumonia. At 4 months, she was treated for COVID-19 pneumonia. Her history prompted workup for immunodeficiency; she had normal T and B cells, immunoglobulins, and adequate titers to killed vaccines. Genetic testing revealed homozygous deletion in STAT1 (exons 7-9). Functional studies demonstrated absence of STAT-1 phosphorylation to interferon-gamma, supportive of complete STAT-1 deficiency. She was started on prophylactic IVIG and acyclovir and regularly screened for EBV, CMV, and HHV-6. At 5 months, she presented with fever, respiratory distress, and recurrent emesis with leukocytosis and elevated inflammatory markers without a clear source. Ultimately, *Pneumocystis jirovecii* pneumonia was diagnosed by PCR from bronchoalveolar lavage; she improved with trimethoprim-sulfamethoxazole. During infectious workup, Karius testing returned positive for *Mycobacterium abscessus*. Given high risk for mycobacterial infection, empiric treatment with azithromycin, amikacin, and linezolid was initiated.

At 10 months, she underwent an alpha-beta T cell–depleted haploidentical peripheral blood SCT from her father. Planned conditioning regimen was rituximab, targeted dosing rATG, targeted busulfan, targeted fludarabine, and thiotepa. She had an anaphylactic reaction to Rituximab on Day -1; no further doses of rituximab were given. Graft-versus-host prophylaxis was tocilizumab and abatacept. Engraftment occurred on Day +13. Immediate post-transplant course was initially complicated by persistent host T cells, concerning for a high risk of immunological rejection, but she has since continued to have improvement of donor CD3 chimerism. She is currently Day +50 without signs of GVHD or viral reactivation and continues abatacept monthly.
Discussion: Complete STAT1 deficiency is a severe immunodeficiency that is historically fatal in early life without curative HSCT. Our case supports the need for early transplant before the acquisition of and complications due to severe infections.

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JAK3 Gain-of-Function in a Young Adult with Chronic Epstein–Barr Virus Infection and Liver NK Cell Lymphoma

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Introduction: Rare monogenic germline variants in genes coding for immune system proteins often result in extreme and deadly phenotypes. JAK3 is a tyrosine kinase involved in cell growth, development, and differentiation, which mediates essential signaling in

hematopoiesis and immunity. Autosomal recessive JAK3 deficiency causes severe combined immunodeficiency that manifests early after birth and usually results in death from infection within the first two years of life. Gain-of-function (GOF) variants in immune system genes may present at a later age with hyperinflammation, autoimmunity, and lymphoproliferation.

Case Report: A 19-year-old male was hospitalized for a history of fever of unknown origin. On physical examination, he had a disseminated rash with ulcers and hepatosplenomegaly. He also developed severe ulcerative colitis. Two years later, he died of intestinal perforation, with final diagnoses of T/NK cell liver lymphoma, inflammatory bowel disease (IBD), and ulcerative-necrotizing vasculitis.

Epstein–Barr virus (EBV) serology was IgG positive to EA and EBNA, with a viral count of 1,000,000 copies. A liver biopsy found acute inflammation with necrosis and eosinophilia. The routine immunological workup was essentially normal, except for NK cell predominance: 75% of lymphocytes were CD56+.

Whole-exome sequencing analysis identified a heterozygous germline missense variant (MAB 0.52, DP 71x) in exon 17 of JAK3 (c.2395C>T, p.Arg799Cys), located in a linker between the pseudokinase and kinase domains; exceedingly rare (gnomADe MAF 0.00005), possibly deleterious (CADD 24.9), and highly conserved across species (GERP++RS 5.11).

Discussion: In 2020, Lesmana and colleagues reported a mother and son with NK cell lymphoproliferation, lymphadenopathy, splenomegaly, and autoimmunity, including common-variable immunodeficiency, psoriasis, vasculitis, and autoimmune cytopenia. The immunological workup in the son revealed hypogammaglobulinemia, expanded NK cells between 40 and 60% of total lymphocytes, and decreased FOXP3 expression with low B cells. A novel germline heterozygous variant in JAK3 (Q507P) was identified at another linker domain and characterized as GOF with constitutive phosphorylation. Several other GOF somatic variants have been found in hematologic malignancies and chronic lymphoproliferative disorder of NK cells (CLDNK).

This case highlights EBV susceptibility and IBD as previously unrecognized features of JAK3-GOF. Next, we want to perform directed mutagenesis and functional validation assay to characterize this variant.

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Enterovirus Meningitis and Myocarditis in a Neonate with Absent B Cells in the Setting of Intrauterine Rituximab Exposure

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Introduction: Intact humoral immunity is essential for enterovirus immune defense. Severe enteroviral infections can occur in patients with humoral immunodeficiencies. We report a case of a neonate who presented with enterovirus meningitis and myocarditis in the setting of intrauterine Rituximab and maternal enterovirus meningitis exposure, found to have absent B cells.

Case Presentation: A two-week-old full-term male presented with hypothermia, hypoglycemia, seizures, respiratory failure, and myocarditis. Family history was significant for mother with granulomatosis with polyangiitis and rheumatoid arthritis, who received Rituximab at seven months gestational age. On the infant's fourth day of life, his mother was hospitalized for seizures due to enteroviral meningitis.

The patient's initial workup was notable for elevated troponin, rhinovirus/enterovirus on Respiratory Pathogen Panel, and enterovirus on Meningitis/Encephalitis CSF PCR Panel. Transthoracic echocardiogram showed reduced biventricular function with left ventricular ejection fraction (LVEF) 30%. He was intubated and required pressor support. He was treated with antibiotics, intravenous immunoglobulin (IVIG), steroids, and pocapavir. His hospital course was also notable for necrotizing enterocolitis and MSSA bacteremia. He improved after seven weeks and was discharged on room air with improved LVEF.

His inpatient immune workup after initiation of IVIG and steroids was notable for decreased T cells, absent B cells, and low NK cells. Immunoglobulin G (IgG) levels remained normal throughout his hospitalization. Repeat labs at 39 weeks old demonstrated near normal T cell, B cell, and NK cell counts with normal IgG level. Genetic testing is currently pending.

Discussion: Here we report a disseminated enteroviral infection in a newborn and his mother following third trimester exposure to Rituximab. Absent B cells at birth with subsequent improvement is consistent with Rituximab effect on B cells. However, primary immune defects, such as leaky X-linked hypogammaglobulinemia and NK cell defects, are currently being investigated with further genetic testing.

Conclusion: Both primary and secondary immune defects should be considered in patients with severe enteroviral infections.

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Functional Characterization of a Hypomorphic IL-17A Variant Associated with Recurrent Pneumonias

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IL-17 cytokines, particularly IL-17A and IL-17F, play a pivotal role in eliciting neutrophils for protection against fungal and bacterial infections. Hypomorphic IL-17F deficiency was reported in 2011 in a child with chronic mucocutaneous candidiasis (CMC), but IL-17A deficiency has not yet been reported. We consulted on a 14-year-old patient, with no history of CMC or autoimmunity, who was hospitalized for a third serious pneumonia. She carried a novel missense variant in IL-17A, resulting in a Y66C mutation. This variant is structurally homologous to a pathogenic S65L variant identified in IL-17F, which is known to impair cytokine function. Functional assays using IL-17–responsive reporter cells demonstrate that the Y66C mutant has significantly impaired signaling compared with wild-type IL-17A. Ongoing studies aim to delineate the molecular and structural consequences of this variant and its impact on host defenses. These findings underscore the importance of IL-17A in lung infections, and the lack of CMC in this patient suggests that IL-17F plays a more important role than IL-17A in the mucosa. We offer here the first report of IL-17A deficiency, expanding our understanding of IL-17–associated immunodeficiencies.

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Early Detection of Immune-Dysregulation Predicts a Better Response to Immunosuppressive Treatment in Chronic Immune Thrombocytopenia

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Introduction: Chronic immune thrombocytopenia (ITP) may represent the epiphenomenon of a complex immune-dysregulation process. Not all patients respond with equal effectiveness to different therapies as immunosuppressant (MMF and Sirolimus) or TPO-agonists, and no specific indicators at diagnosis are available to predict response.
Aims: To identify a group of clinical and immunological variables predictive of response to a specific second-line therapy.
Methods: Lymphocytes subsets including ALPS panel (double-negative T-lymphocytes—DNTs-, B220+DNTs, CD27+B cells, and CD3+CD25+/HLADR+ ratio), ALPS biomarkers (IL10, IL18, and sFAS), Ig serum levels, autoantibody screening, and Coombs test were analyzed at diagnosis, after at least 6 months, and after response to a second-line therapy.
Results: 72 consecutive patients with persistent/chronic ITP have been retrospectively studied. 17/72 (24%) responded to first-line therapy consisting of steroids and/or IVIG. Thirty-three of the remaining 55 responded to immunosuppressants (28) or TPO-agonists (5) given as second-line treatment. The remaining 22 patients underwent treatment with TPO-agonist after immunosuppressant failure (20) or immunosuppressant after TPO-agonist failure (2). Overall, 17 (24%) patients responded to first-line therapy, 31 (43%) and 16 (22%) patients responded to immunosuppressant and TPO-agonists, respectively, and 8 (11%) patients did not respond to any treatment. Table 1 shows patients' demographic/clinical characteristics according to the response. Signs of immune-dysregulation in the acute phase such as DNT>1.5%, reduced in CD4 ($p = 0.05$) and NK cells ($p = 0.05$), and the simultaneous presence of ¾ positive parameters of the ALPS panel ($p < 0.05$) predicted a better response to immunosuppressant than to TPO-agonists. Furthermore, 51 patients were studied after the response to the treatment: in addition to platelets count, patients responding to immunosuppressants showed a statistically significant reduction of lymphoproliferation (p 0.025) and normalization of CD4+ (p 0.01), NK cells (p 0.08), (p 0.016), B220+DNTs (p 0.001), CD25/HLADR+ ratio (p 0.035), IL-18 (p 0.02), and ANA positivity compared with the others.

Table 1. **Demographic and clinical characteristics of the 72 patients according to the response**

	Total n=72	First-line th response n=17	IS response n=31	TPO-A response n=16	Non responder n=8	Overall response (P-value)	IS vs tpo-A (P-value)
Female, n (%)	39 (54)	11 (65)	16 (52)	9 (52)	3 (37)	0.666	0.763
Age at onset, yrs, median (IQR)	9.1 (5.2-12.4)	9.9 (6.8-13.5)	9 (5.5-12.3)	10 (6.5-14.3)	4.2 (3.1-6)	**0.017**	0.296
Age at onset >9.1 yrs, n (%)	36 (50)	10 (59)	15 (48)	11 (69)	0	**0.009**	0.183
Cutaneous/mucosal diathesis, yes, n (%)	65[1] (90)	14 (82)	28 (90)	15 (94)	8 (100.0)	0.670	1.000
Family history,[2] yes, n(%)	17 (24)	6 (35)	9 (29)	2 (12)	0	0.149	0.287
Splenomegaly[3]/ Lymphofoproliferation[4], n (%)	9 (12.5)	0	9 (29)	0	0	**0.004**	**0.019**
Low IgA, n (%)	13 (18.1)	1 (5.9)	9 (29)	2 (12.5)	1 (12.5)	0.220	0.287
Low IgG n (%)	7/66 (11)	0/16	4/31 (13)	3/16 (19)	0/3	0.347	0.676
Low IgM n (%)	3/70 (4.3)	0/17	3/30 (10)	0/16	0/7	0.514	0.542
IgG subclasses abnormalities, n (%)	8/60 (13)	4/16 (25)	3/29 (10)	1/12 (8)	0/3	0.515	1.000
Reduced response to vaccines	6/32 (19)	0/9	6/19 (32)	0/2	0/2	0.231	1.000
Antinuclear antibodies, yes, n (%)	17/70 (24)	4/16 (25)	10/31 (32)	2/16 (12)	1/7 (14)	0.519	0.176
Antithyroid antibodies, yes, n (%)	5/70 (7)	1/16 (6)	2/31 (6)	2/15 (13)	0/8	0.768	0.587
Anti-red blood cells antibodies, yes, n (%)	8/70 (11)	0/16	8/31 (26)	0/16	0/7	**0.013**	**0.038**
Anti-transglutaminase antibodies, yes, n (%)	1/71 (1)	1/16 (6)	0	0	0	0.563	

[1]Exclusively cutaneous involvement, n=33;
[2]family history of autoimmune diseases in first-degree relatives;
[3]defined based on age-specific values of longitudinal spleen diameter, measured by abdominal ultrasound;
[4]defined based on the presence of persistent lateral cervical and/or axillary and/or inguinal and/or intra-abdominal adenopathies identified by clinical examination or targeted ultrasound, lasting for more than 6 months and without an alternative diagnosis.

Conclusions: An early immunophenotypic characterization at diagnosis represents a useful tool in the choice of second-line therapy and an indicator to perform early genetic studies for a potential target therapy.

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Early-Onset Persistent Secondary Hypogammaglobulinaemia from In Utero Rituximab Exposure

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We present a case of persistent hypogammaglobulinaemia secondary to antenatal rituximab exposure.

The mother of our patient was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for non-Hodgkin lymphoma from 17 to 34 weeks of pregnancy. The patient presented with recurrent infections, including cervical lymphadenitis (16 months), two right upper lobe pneumonias (28 and 31 months), multiple episodes of otitis media, frequent wet coughs, and growth below 3rd centile. At 31 months, he was found to have profound hypogammaglobulinaemia (IgG < 0.3 g/L, IgA < 0.05 g/L, and IgM 1.6 g/L). Lymphocyte subsets were within normal range; however, switched memory B cells were low. A primary immune deficiency gene panel was negative (Blueprint Genetics 14/01/2022–Primary Immunodeficiency Panel Plus).

The patient commenced immunoglobulin replacement and had marked reduction in acute infections, with no further invasive bacterial infections. At 5.5 years, his IgA and switched memory B cells are undetectable. This suggests a persistent effect on B cell class switching despite B cell compartment reconstitution.

Rituximab causes transient depletion of CD20-expressing B cells and is placentally transferred by the FcRn receptor, detectable for months after delivery. Early-life exposure to rituximab may profoundly affect infant B cell compartment development, likely dependent on dose and timing. There are limited descriptions of immunological outcomes following in utero rituximab exposure; however, case series report transient B cell lymphopenia in some infants, which resolves within six months [1-3]. In a recent case series, four of eleven patients antenatally exposed to R-CHOP required immunoglobulin replacement, one of whom had persistent hypogammaglobulinaemia at four years of age [1].

Our case describes early-onset persistent secondary hypogammaglobulinaemia from in utero rituximab exposure and highlights the importance of immune monitoring following maternal immunosuppression during pregnancy.

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Bone Marrow Failure in Deficiency of Adenosine Deaminase 2: A Case Report

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The deficiency of adenosine deaminase 2 (DADA2) is an inborn immunity error caused by loss-of-function mutations in the ADA2 gene. Manifestations include vasculopathy and immunological and hematological abnormalities. It is unknown how ADA2 loss causes bone marrow (BM) failure, and understanding these mechanisms is essential for developing new targeted therapies.

A 31-year-old man was admitted to our hospital with suspicion of myelofibrosis and myelodysplastic syndrome, with unclear etiology.

His records include the product of a twin pregnancy; since his early infancy, he has presented with recurrent oral ulcers and denies any other symptoms.

At 29, in a routine assessment for an orthopedic surgery, tricytopenia was found.

At 30, his clinical condition got worse, and he started to need blood transfusions weekly. Myelofibrosis was suspected but did not fulfill the criteria. His hematological assessment included CBC and differentials: Hb 10.7 mg/dl, GBC 2,830/mm^3 (neutrophils 70%, lymphocytes 17%, monocytes 13%, eosinophils 0%, and B 0%), Plat 92.000/mm^3, BM biopsy that showed altered CD4/CD8, with development arrest, and infiltration of CD8+ T cells. Molecular evaluation: Jak2 V617f, Gata1, Gata2, Tet2, and CALR were negative. Immunological workup: he presented with mild hypogammaglobulinemia; vaccine responses: good response to the tetanus vaccine but no response to the polysaccharide pneumococcal vaccine. Flow cytometry assays showed that T cells were normal, NK decreased, and B cells and memory B cells were low.

At physical examination, he presented warts on both hands and a geographic tongue with leukoplakia and peripheral edema.

An inborn error of immunity was highly suspected. WES: A missense pathogenic variant in ADA2 (missense, variant ID: 22-17207107-C-T) was found. Measurement of plasma ADA2 enzymatic activity was deficient. DADA2 was diagnosed.

The patient is under anti-TNF treatment and Ig replacement therapy and is being evaluated for a BM transplant.

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Impaired Development of Memory B Cells and Antibody Responses in Humans Deficient in PD-1 Signaling

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T follicular helper (Tfh) cells abundantly express the immunoreceptor programmed cell death protein 1 (PD-1), and the impact of PD-1 deficiency on antibody (Ab)-mediated immunity in mice is associated with compromised Tfh cell functions. Here, we revisited the role of the PD-1-PD-L1 axis on Ab-mediated immunity. Individuals with inherited PD-1 or PD-L1 deficiency had fewer memory B cells and impaired Ab responses, similar to Pdcd1-/- and Cd274-/-Pdcd1lg2-/- mice. PD-1, PD-L1, or both could be detected on the surface of human naive B cells following in vitro activation. PD-1– or PD-L1–deficient B cells had reduced expression of the transcriptional regulator c-Myc and c-Myc–target genes in vivo, and PD-1 deficiency or neutralization of PD-1 or PD-L1–impeded c-Myc expression and Ab production in human B cells isolated in vitro. Furthermore, B cell–specific deletion of Pdcd1 prevented the physiological accumulation of memory B cells in mice. Thus, PD-1 shapes optimal B cell memory and Ab-mediated immunity through B cell–intrinsic and B cell–extrinsic mechanisms, suggesting that B cell dysregulation contributes to infectious and autoimmune complications following anti–PD-1-PD-L1 immunotherapy.

Virtual Posters

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Pharmacokinetics of a New Intravenous Immunoglobulin (IVIg) 10% (KIg10) in Primary Immunodeficiency (PI) Patients

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Introduction: Intravenous immunoglobulin (IVIg) therapy is commonly used in the treatment of primary immunodeficiency (PI) disorders.

This open-label, prospective, single-arm, multicenter phase III study in adult PI patients (KIG10_US3_PID01; NCT01581593) investigated efficacy, safety, and pharmacokinetics (PK) of a new 10% IVIg product (KIg10), given 200 to 800 mg/kg every 21 or 28 days for 48 weeks.

Objective: Primary PK endpoints included total IgG levels, IgG subclasses levels, selected specific antibody levels, and PK parameters of total and baseline-corrected IgG.

Methods: PK assessments were performed in 23 adult patients, and blood samples from them were taken for PK parameters' analysis before and after the 5th infusion for the 28-day infusion schedule or the 7th infusion for the 21-day infusion schedule and at protocol prespecified time points.

Results: The estimated mean serum half-life (T1/2) for uncorrected total IgG was 24.5 days (587 h) and 37.3 days (896 h) for patients on 21- and 28-day schedule, respectively. The total serum IgG PK profiles were comparable between the two dosing schedules, with a numerically higher exposure for the 21-day schedule. All the mean values of IgG subclasses were maintained within the reference ranges following IV infusion of KIg10. All anti-tetanus toxoid antibody levels, mean values of anti-pneumococcal capsular polysaccharide antibodies, and mean levels of anti-*Haemophilus influenzae* type b antibodies were maintained above protective levels.

Conclusion: In study KIG10_US3_PID01, measured PK parameters for KIg10 in adult patients with PID were considered comparable with previously published data for other IVIg treatments.

Table 1.

Baseline-corrected PK Parameter	KIg10 Dosing Schedule	
	21-day (N = 5)	28-day (N = 18)
C_{max} (mg/dL), mean (SD)	1510 (12.1)	1210 (33.8)
$T_{1/2}$ (hours), mean (SD)	107 (45.5)	158 (48.4)
AUC_{0-t} (day*mg/dL), mean (SD)	8250 (20.0)	8870 (34.7)

C_{max} = maximum observed concentration; $T_{1/2}$ = terminal half-life; AUC_{0-t} = area under the concentration-time curve from time 0 to time t of the last quantifiable concentration.

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Safety and Tolerability of a New Intravenous Immunoglobulin (IVIg) 10% (KIg10) in Primary Immunodeficiency (PI) Adult Patients

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Objective: Safety and tolerability endpoints from this study are reported here and included treatment-emergent adverse events (TEAEs) from Day 1 to Week 51/52.

Methods: Forty-seven patients received study treatment and were analyzed for safety and efficacy.

As per protocol, the 1st infusion was administered at an initial rate of 1 mg/kg/min for 30 minutes. If well tolerated, the rate was progressively increased to a maximum of 8 mg/kg/min. The rate of administration of subsequent infusions progressively increased to a maximum of 8 mg/kg/min at 15-min intervals.

Results: Among both dosing schedules, 22 (46.8%) subjects reported 75 TEAEs. Most frequently reported (≥5%) were headache (25.5%), infusion-related reaction (10.6%), nausea, fatigue, and positive Coombs direct test (8.5% each).

The most frequently reported (≥5%) infusional adverse event (AE) (defined as occurring during or within 72 hours after an infusion) were headache (25.5%), fatigue (14.9%), infusion-related reaction (10.6%), nausea (10.6%), positive Coombs direct test (10.6%), diarrhea (6.4%), dizziness (6.4%), and sinusitis (6.4%).

No hemolysis events were reported, and no laboratory findings were suggestive of hemolysis associated with positive Coombs tests. No safety signal or trend was observed. None of the reported TEAEs were serious; no significant or life-threatening TEAEs were reported. No AEs led to study discontinuation, and no subjects died during the study due to an AE.

Conclusion: In study KIG10_US3_PID01, KIg10 showed a favorable safety profile and was well tolerated in adult patients with PI at the dosing schedules and infusion rates used.

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Two Cases of B Cell Lymphopenia Associated with IGLL1 Variants Identified Through Newborn Screening in Ukraine

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The kappa-deleting recombination excision circles (KREC) assay in newborn screening (NBS) facilitates the identification of conditions associated with B cell lymphopenia. The use of the KREC assay has been controversial and less commonly implemented compared with the TREC assay. We present two cases of children with positive KREC screening results to highlight the importance of early detection and support the consideration of this assay for global indication.

Case presentation: Case 1: A full-term, healthy female newborn had a positive NBS result with undetectable KREC but normal TREC levels at birth. Follow-up revealed low B cell counts (70 cells/μL) but preserved T and NK cell subsets at 3 months. Immunoglobulin levels (IgA, IgM, and IgG) remained within normal ranges at 3, 6, and 11 months of age. No severe infections occurred until 1 year. Vaccine

responses were notable for normal tetanus antibody titers but borderline diphtheria titers. Genetic testing identified variants of uncertain significance (VUS) in the IGLL1 gene: the one allele with c.425C>T (p.Pro142Leu) and the other with c.368C>G (p.Ser123Cys) and c.377T>C (p.Leu126Pro).

Case 2: A full-term healthy male newborn also presented with undetectable KREC but normal TREC. B cell counts were low at one month (97 cells/μL) and decreased at seven months (68 cells/μL), with normal T and NK cell subsets. A transient IgG decline was noted at 3.5 months and increased to low normal by 7 months. Genetic testing revealed two IGLL1 variants on separate alleles: a missense VUS c.425C>T (p.Pro142Leu) and a likely pathogenic nonsense variant c.258del (p. Gln88Asnfs*7). Immunoglobulin replacement therapy (IRT) was recommended but not administered due to low compliance. Over one year, the child experienced mild respiratory symptoms and transient fever episodes.

Conclusions: Both patients carried the c.425C>T variant, and one also had the c.258del variant in the IGLL1 gene, which have been recently reported with high allele frequency in the general population but also linked to cases of B cell lymphopenia and low KRECs. These cases highlight the potential underdiagnosis of B cell deficiencies secondary to IGLL1. Early detection via KREC screening enabled close monitoring and consideration of IRT. The broader impact of KREC assay for IGLL1-related disorders remains to be determined.

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Clinical and immunological Characteristics of 10 X-linked Chronic Granulomatous Disease Female Carriers

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Background and Aims: Chronic granulomatous disease (CGD) is a rare inherited disorder with affected neutrophil "respiratory burst" due to defective NADPH-oxidase function. The most common form, X-linked CGD, is associated with disease manifestations also in female carriers. Increased susceptibility to infections is observed in females with skewed X-chromosome inactivation. Additionally, carriers have increased risk of autoimmunity.

Methods: We analyzed clinical manifestations, evaluated respiratory burst on neutrophils (%burst), and performed lymphocytes immunophenotyping in a cohort of 10 CGD carriers (aged 26-46 years, median = 41 years).

Results: Autoimmune disorders and infections observed in 3/10 and 2/10 females, correspondently. Discoid lupus, rheumatoid arthritis, systemic lupus erythematosus, and antiphospholipid syndrome were described. 6/10 were asymptomatic; 1 female has both infections and autoimmune complications. %Burst varies from 16% to 90% (median = 38.5%): 18-72% in females with autoimmunity, 18-22 with infections, and 16-90% asymptomatic. Thus, all carriers with infections have decreased %burst, but %burst decrease does not necessarily lead to infectious manifestations. %Burst correlates with the number of switched (CD19+CD27+IgD-) and non-switched (CD19+CD27+IgD+) memory B cells ($r = 0.75$ and 0.68, $p = 0.0001$ and 0.0009), DN B cells (CD19+CD27-IgD-), and CD21 low CD38 low B cells ($r = -0.76$, $p = 0.0001$). Carriers with autoimmunity have decreased NKT cells ($p = 0.04$) and have a tendency to increase naïve CD4 (CD4+CD45RA+CCR7+) and CD8 (CD8+CD45RA+CCR7+) T cells and RTE (CD4+CD45RA+CD31+) (statistical significance was not reached due to small sample size). However, lymphocyte subsets usually associated with autoimmune disorders in PID (Tregs, activated/memory T cells, and CD21 low B cells) did not differ in carriers with autoimmunity from those in asymptomatic careers.

Conclusions: Increased susceptibility to infections and B-memory cells differentiation in X-CGD female carriers are concerned with a % of neutrophils with normal NADPH-oxidase function.

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CEBPE Variant as a Cause of Inflammasomopathy

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Background: The CEBPE gene encodes CCAAT enhancer–binding protein epsilon (C/EBPε), which is an important transcription factor in the differentiation of granulocytes. Mutations in the CEBPE gene primarily result in autosomal recessive neutrophil-specific granule deficiency (SGD). SGD is characterized by poor neutrophil chemotaxis and impaired bactericidal activity, resulting in recurrent bacterial infections. Additional sequelae of CEBPE pathogenic variants are not widely reported in the literature. Currently, there is only one published case study that has reported concomitant inflammasomopathy. Herein we report a patient with interferonopathy in the setting of a CEBPE variant.

Case Study: A 6-year-old female presented for evaluation of chronic anemia of unknown cause not responsive to iron supplementation and with persistently elevated inflammatory markers. She was born at 35 weeks to non-consanguineous parents and was cyanotic at birth, but the remainder of her birth history is unclear. Early life was characterized by poor feeding, poor growth, and global developmental delay. Infection history was remarkable for recurrent acute otitis media that improved after tympanostomy tubes and one episode of pneumonia. Initial immunologic workup at age 6 revealed iron deficiency anemia intermixed with anemia of chronic disease, normal bone marrow, and markedly elevated ESR and CRP. Cytokine panel revealed elevated IL-6, IL-8, and IL-10. Lymphocyte subsets were unremarkable. Genetic testing showed a heterozygous VUS in CEBPE (c.437C>T, p.Ala146Val, CADD phred: 27.5, polyphen-2: probably damaging). She was lost to follow-up prior to treatment initiation but resumed care at age 10. During this period, she began to develop seizures with identification of intracranial calcifications on MRI. Immunologic workup resumed and showed persistent elevated IL-6, IL-8, and IL-10; interferon signature consistent with type 1 interferonopathy; and serum titers positive for MOG antibodies. She does not currently have clinical evidence of MOG-antibody–mediated disease but is undergoing evaluation to assess optic neuritis. She was initiated on tofacitinib. Inflammatory markers have remained elevated but are downtrending.

Conclusion: While CEBPE pathogenic variants are primarily associated with neutrophil dysfunction, features of autoinflammation can be attributed to CEBPE gain-of-function variants. Further investigation is needed to better characterize phenotypes of CEBPE mutations and their response to treatment.

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Insights into EBV Infection in an Adult with X-Linked Lymphoproliferative Syndrome

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Introduction: X-linked lymphoproliferative disease (XLP) is a rare inborn error of immunity (IEI) characterized by increased susceptibility to Epstein–Barr Virus (EBV) and other features of immune dysregulation. We present a case of XLP1, diagnosed in a 37-year-old male with EBV viremia treated with nivolumab.

Case: The proband was diagnosed with common variable immunodeficiency (CVID) and started on IVIG at age 8. Infections were recurrent pneumonias and an episode of septic hip arthritis. He remained infection free over the next 3 decades until presenting with Evans syndrome at age 37, which was initially treated with prednisone. Shortly after, his course was complicated with hepatic and brain abscesses and liver decompensation. Thus, he was referred to our service for workup. Genetic testing revealed the diagnosis of XLP1 (SH2D1A c.138-2A>G).

He was found to have EBV viremia, and a liver biopsy suggested EBV hepatitis. He was not a liver transplant candidate due to concern of sepsis given his immunosuppression and IEI. Hematopoietic stem cell transplant (HSCT) was not offered due to high risk of mortality.

Despite treatment with rituximab, his repeat EBV titers continued to rise. Virus-specific T cell therapy was pursued; however, the patient was clinically too unstable to be transferred for treatment to the United States from Canada. He was given one nivolumab dose, significantly reducing his viremia. He ultimately succumbed to sepsis and respiratory failure.

EBV is the leading cause of mortality in patients with XLP who forego HSCT. Rituximab has been well-documented in the treatment of EBV. We present a patient with an EBV susceptibility syndrome and progressive viremia, who responded well to one dose of nivolumab which significantly reduced his EBV viral load. Despite limited literature, nivolumab may play a significant role in the treatment of certain EBV-associated conditions, particularly in patients with IEIs.

In conclusion, nivolumab should be considered for any patient with an overwhelming EBV infection. Severe EBV-induced disease is an unexpected finding in an individual with CVID and warrants genetic testing to exclude other primary immunodeficiencies. Treatment options for EBV susceptibility syndromes need further exploration and accessibility.

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Idiopathic T Cell Lymphopenia Described in First Cousins

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Introduction: Newborn TREC screening for SCID has identified infants with idiopathic T cell lymphopenia (TCL) with no identifiable genetic causes. We describe 2 first cousins who both presented with low TRECs and T cell lymphopenia without a common genetic cause.
Case description: Subject A, a 2-year-old male, was referred for low TRECs: 24 (0, 73, and 0). Flow cytometry at 2 weeks of age revealed decreased absolute CD3+ T cells: 1148 cells/μL (nl 2500-5500 cells/μL), CD4+ T cells: 977 cells/μL (nl 1600-4000 cells/μL), and CD8+ T cells: 216 cells/μL (nl 560-1700 cells/μL). At 6 months of age, Subject A developed hypogammaglobulinemia: IgG = 140 mg/dL (nl 217-904 mg/dL), IgM = 17 mg/dL (nl 19-192 mg/dL), and IgA = 6 mg/dL (nl 2-83 mg/dl).

Subject B, a 3-month-old female cousin (mother is the sister of Subject A's father), was referred for absent TRECs of 0. Initial lymphocyte subsets at 2 weeks of age were CD3+ T cells: 771 cells/μL, absolute CD4+ T cells: 642 cells/μL, and CD8+ T cells: 138 cells/μL. She had normal IgG and IgM levels.

Both children had normal numbers of CD19+ B cells and CD16, 56+ NK cells, nl CBCs, and mitogen responses. Variants of unknown significance (VUS) identified on Invitae IEI panels included ANKZF1, POLD1, and TNFAIP3 in Subject A and TFRC in Subject B. There were no common VUSs, confirmed on whole-genome testing. Neither child had an NICU stay or birth trauma. They remain asymptomatic with no severe viral or bacterial infections.
Discussion: Extensive genetic testing did not identify any underlying genetic cause for their lymphopenia. Presently, both infants are being studied at NIH for possible thymic-derived IEIs. Artificial thymic organoids (ATO) generating CD34+ cells with stromal cells expressing the Notch ligands DLL1 or DLL4 allow the generation of mature TCRαβ+ CD3+ T cells in culture, which could reliably discriminate hematopoietic versus thymic defects of lymphopoiesis in these children.
Conclusions: Idiopathic TCL in infants is often difficult to characterize. Thymus-derived IEIs and epigenetic mechanism may be responsible for some of these cases.

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Clinical Profile of Pediatric Primary Immune Deficiency (PID) Disorders in a Highly Consanguineous Population from South India

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Primary immune deficiency disorders (PIDs) are a heterogeneous group of disorders with symptoms overlapping with common diseases leading to delay in diagnosis. Many have autosomal recessive inheritance and present in early childhood. We report the phenotypic and molecular profile of PIDs from a tertiary care center in south India that caters to a population with high (~35%) rate of consanguinity. The clinical data of a total of 101 unrelated patients diagnosed to have PIDs were collected and analyzed. Among our patients, hyper IgE syndrome (15.8%) followed by CVID (12.9%) were the two most common diagnoses of PIDs. Predominant antibody defects (28.7%) and well-defined syndromes (27.7%) were the two most common categories of PIDs, according to the 2017 IUIS phenotypic classification. Male gender was (1.4:1) slightly predominant. One-fourth had family history of undiagnosed early deaths and 17.8% had family history of PIDs. Parental consanguinity was present in 52.4%, significantly more than the population figure of 35%. Most common age at time of onset of symptoms was 1-3 months. Median time lapse between symptom onset and diagnosis was 18 months. Mortality rate in those admitted to ICU was significantly higher ($p < 0.027$) than general ICU mortality rate over the same period. Molecular analysis could be done in 26 patients, many of whom carried very rare or novel variants and some had >1 concurrent PIDs. Three patients with disseminated tuberculosis were found to have Immunodeficiency type 30 and 28. "Well-defined syndromes" and "Predominantly antibody deficiency" were the two most common classes according to the IUIS classification (2017). We conclude that PIDs are more commonly encountered than expected in the setting of high consanguinity, likely due to an excess of autosomal recessive inheritance. Very rare mutations were common when parents were consanguineous. Majority presented during early infancy. Mortality was higher than in general patients among those admitted to ICU.

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Genetic Basis of NK Cell Deficiency in 16 Patients with Inborn Errors of Immunity: Belarusian Single-Center Experience

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Background and Aims: Decreased NK cell numbers or impaired NK cell function are associated with increased susceptibility to viral infections, including HSV, CMV, EBV, and VZV. In children with inborn errors of immunity (IEI), viral infections are a frequent cause of severe complications and death.
Methods: This is a retrospective study of NK cell deficiency (%/absolute) in patients from Belarusian IEI registry over the past 10 years.
Results: We have found 16 patients (10 male and 6 female) with low (<5%, <100 cells/μl) NK cells. 13 are alive, one of them after HSCT; three patients died in early childhood from primary hemophagocytic lymphohistiocytosis (HLH). Most patients (58%) had mutations in genes associated with diseases of immune dysregulation PRF1, UNC13D (n = 2), SH2D1A (n = 2), XIAP, STAT3 GOF, FAS, AIRE, and NFAT5; predominantly antibody deficiency NFkB1, AICIDA, and also MYSM1, STAT3, PTPN6, and RUNX3. 6/16 had herpes viral infections, including CMV and EBV. Also, patients with low NK cell counts had clinical manifestations, such as anemia (n = 7), splenomegaly (n = 8), and lymphadenopathy (n = 3); infectious episodes in the form of bilateral pneumonia (n = 2), recurrent otitis (n = 1), and herpetic stomatitis (n = 1). Four patients had HLH. One of the patients developed Burkitt lymphoma; the other had juvenile arthritis since childhood.
Conclusions: In our cohorts, NK cell deficiency is more common in children with diseases of immune dysregulation.

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New-Onset IBD in 19-Year-Old Female with Colon Perforation, Multi-Organ Thrombi, and Possible Catastrophic Antiphospholipid Syndrome, Concerning for Genetically Driven Immune Dysregulation

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Background: IBD may be a manifestation of a genetically driven immune disorder (GID). We present a case of previously healthy 19-year-old female with new onset IBD acutely complicated by colon perforation and hemorrhagic shock, renal failure, and acute liver injury secondary to multi-organ thrombi, likely due to catastrophic antiphospholipid syndrome.

Case Presentation: The patient presented with constipation, abdominal pain, and rectal bleeding for 6 months; symptomatic treatments were given pending diagnostic evaluation. Over the next 1-2 months, her symptoms worsened; she developed low-grade fevers and was admitted for expedited evaluation and management. Initial workup consistent with IBD without certainty regarding type. She appeared to respond to treatment with IV steroid and infliximab but then experienced acute deterioration notable for hemorrhagic shock secondary to severe GI bleed and colon perforation; evidence of thrombi in liver and kidney leading to acute liver and renal failure briefly requiring dialysis; viral, bacterial, and fungal infections, including bacteremia.

Diagnostic Workup:

-CT: pancolitis, filling defect in hepatic veins, small renal infarcts.

-Colonoscopy: diffuse severe/moderate inflammation on descending colon with atypical purple discoloration.

-Pathology: glandular architectural distortion of colonic mucosa, lymphoplasmacytosis, cryptitis, and crypt abscesses; no granulomas.

-Incidental NET of appendix.

-Serology: +Cardiolipin IgM antibody (-IgG); +anti-PR3.

-Immunoglobulin, lymphocyte subset WNL (after discharge, off medication); noted to have protective titers for 3/14 pneumococcal serotypes.

-Evidence of complement activation acutely, normalized after discharge.

-Genetic IBD panel: two missense variants in LRBA, missense variant in TNFAIP3, all VUS.

Management and Outcomes: Underwent abdominal surgeries, including subtotal colectomy with ileostomy, and recovered well. Currently with no GI symptoms off steroids, biologicals, and anticoagulation therapies. However, still with persistent inflammation on recent MRE and cytokine panel (elevated IL-6, IL-8, IL-10, and IL-13).

Discussion: Unusual presentation of IBD with extraintestinal manifestation—notably multi-organ thrombi with autoantibody and complement activation—initial immunological and genetic workup concerning for genetically driven immune dysregulation. This case highlights the importance of interdisciplinary multimodal diagnostic efforts to guide care for patients with acute hyperinflammatory diatheses, even after resolution of the acute state. Ongoing studies include trio-WGS, functional studies to validate LRBA and TNFAIP3 variants, and additional immune studies, including IFN and inflammasome activations screens.

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Investigation into the Viscosity of Commercial IVIG Preparations

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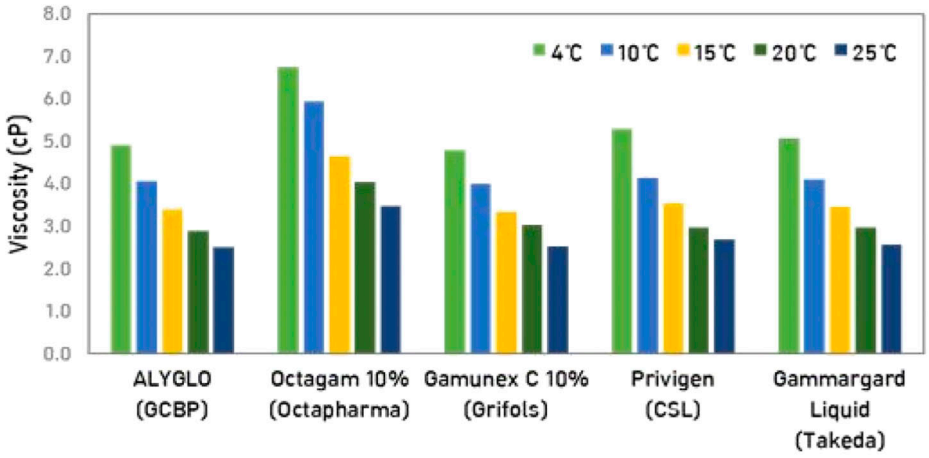
All intravenous immunoglobulin (IVIG) products carry a boxed warning for the risks of renal dysfunction and thromboembolic events (TEEs). Patient-related thrombotic risk factors include hyperviscosity, a condition in which increased blood "thickness" heightens the risk of TEEs. Studies have shown that IVIG infusions increase plasma viscosity. To assess whether the viscosity of IVIG products themselves might be a parameter of interest in product selection, particularly for at-risk patients, we undertook an initial investigation into the viscosities of 5 commercially available 10% IVIG products.

Experiments were performed using ALYGLO® [immune globulin intravenous, human-stwk 10% liquid], GC Biopharma; OCTAGAM® 10% [immune globulin intravenous (human) 10% liquid], Octapharma; GAMUNEX®-C [immune globulin injection (human), 10% caprylate/chromatography purified], Grifols Therapeutics LLC; PRIVIGEN® [immune globulin intravenous (human), 10% liquid], CSL Behring LLC; and GAMMAGARD LIQUID® [immune globulin infusion (human) 10%], Takeda Pharmaceuticals. IgG content was determined using the Lunatic system (Unchained Labs, USA). Samples were diluted with deionized water as necessary to normalize their concentrations for

accurate viscosity comparison. Sample viscosities were determined using a Honeybun microvolume viscometer (Unchained Labs, USA) at 4, 10, 15, 20, and 25° C. Results were reported in centipoise (cP), a unit of measurement for a fluid's resistance to flow, with a higher cP indicative of greater viscosity.

The results at 25° C were as follows: ALYGLO: 2.506 cP; OCTAGAM: 3.484 cP; GAMUNEX-C: 2.535 cP; PRIVIGEN: 2.698 cP; and GAMMAGARD LIQUID: 2.575 cP. For reference, the viscosity of human plasma at 25° C generally ranges from 1.5-1.72 cP. All products showed consistent, sequential decreases in viscosity as temperatures increased, suggesting that IVIG infusions at room temperature (25°C) may be a safety consideration for the prevention of TEEs. These preliminary results warrant further investigation to identify potential differences in the viscosities of commercially available IVIG products, which may have implications for product selection in at-risk patients.



Product	Viscosity (cP)				
	4℃	10℃	15℃	20℃	25℃
ALYGLO (GCBP)	4.910	4.058	3.391	2.893	2.506
Octagam 10% (Octapharma)	6.750	5.947	4.658	4.034	3.484
Gamunex C 10% (Grifols)	4.800	3.997	3.341	3.043	2.535
Privigen (CSL)	5.290	4.146	3.537	2.970	2.698
Gammargard Liquid (Takeda)	5.080	4.103	3.450	2.964	2.575

Figure 1.

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Autoimmune Lymphoproliferative Syndrome (ALPS): A Brazilian Single-Center Pediatric Series

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Background: Autoimmune lymphoproliferative syndrome (ALPS) is a primary immune regulatory disorder typically manifesting in childhood and characterized by chronic nonmalignant lymphadenopathy, hepatosplenomegaly, and autoimmune cytopenias. This study examines 6 Brazilian pediatric patients treated at our immunology and hematology divisions.
Methods and Results: This retrospective review analyzed the medical records of 6 pediatric patients with heterozygous germline pathogenic or likely pathogenic variants in the gene FAS (c.676+1G>C, c.748C>T:p.Arg250*, c.778G>C:p.Asp260His). Regarding family history, all parents were asymptomatic. However, the mother of P1 and P2 (sisters) and the father of P4 carried the same variants as their children, while other parents were untested. Median age at probable clinical diagnosis, based on ESID 2019 criteria, was 8.4 years (range: 1.16–16.83 years), while genetic confirmation occurred at a median age of 12 years (range: 1.75–20.75 years). Symptoms onset occurred at a median age of 1 year (range: 0.58–3.75 years), with autoimmune cytopenia (n = 4) (ITP: n = 2; AIHA: n = 1; Evans' syndrome: n = 2) and benign chronic lymphadenopathy (n = 2). During follow-up, all patients developed chronic lymphoproliferation (lymphadenopathy: n = 5; splenomegaly: n = 4) and autoimmune cytopenias (AIHA: n = 5; ITP: n = 3; neutropenia: n = 2). Patients P1 and P2 presented with AIHA; three patients had cytopenias affecting two cell lineages. P3 exhibited cytopenia across all three hematopoietic lineages. At the time of ALPS suspicion, all patients exhibited elevated vitamin B12 levels and increased TCRαβ+ DNT cells. Four patients had hypergammaglobulinemia, while two had normal IgG levels for their age. Two patients reported allergic manifestations: P3 with recurrent urticaria and P6 with both recurrent urticaria and allergic rhinitis. Prior diagnoses included Castleman syndrome (P2), leishmaniasis, and acute lymphocytic leukemia (P3). Two patients underwent splenectomy before receiving an ALPS diagnosis. One patient initially treated with MMF transitioned to Sirolimus due to uncontrolled cytopenia, and another developed oral ulcers while on Sirolimus, which improved with laser treatment. All patients were stable and alive by study's end.
Conclusion: Recognition of clinical and laboratory features of ALPS is essential for early diagnosis and can significantly impact management and improve survival outcomes.

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Genotype–Phenotype Correlations in Patients with STAT1 Gain-of-Function Mutations: A Case Series

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Introduction: STAT1 gain-of-function (GOF) mutations result in a broad clinical spectrum characterized by complex phenotypic manifestations. In addition to the hallmark chronic mucocutaneous candidiasis (CMC), patients are predisposed to bacterial and viral infections, autoimmunity, endocrinopathies, lymphoproliferative disorders, and malignancies. Severe complications, including invasive infections, cerebral aneurysms, and malignancies, are significant predictors of poor outcomes. Understanding genotype–phenotype correlations is critical for optimizing management in this challenging patient population.
Methods: We conducted a retrospective review of electronic medical records for five patients diagnosed with STAT1 GOF mutations at Mayo Clinic, Rochester, MN. This case series included data on demographics, clinical history, immunologic evaluations, genetic testing results, disease manifestations, treatments, and outcomes.
Results: The cohort included five patients (1 male, 4 females; mean age at diagnosis: 21.7 years) with heterozygous STAT1 GOF mutations. Three patients had c.1154C>T (p.Thr385Met), one had c.1310C>T (p.Thr437Ile) in the DNA-binding domain (DBD), and one had c.856A>G (p.Lys286Glu) in the coiled-coil domain (CCD). Universal features included CMC and recurrent sinopulmonary infections. Patients with c.1154C>T presented with early-onset infections, severe autoimmunity (e.g., pancytopenia and enteropathy), and bronchiectasis, requiring ruxolitinib in all three cases. The patient with c.1310C>T had a late childhood onset of symptoms, later complicated by persistent histoplasmosis. The c.856A>G case experienced severe multidrug-resistant infections, splenomegaly, coagulopathy, neurological complications, poor response to ruxolitinib, and died from complications of MSSA pneumonia and monkeypox.
Conclusion: Genotype–phenotype correlations in STAT1 GOF mutations highlight a diverse clinical spectrum driven by mutation-specific mechanisms. DBD mutations are associated with more severe outcomes, including early-onset immunodeficiency, invasive infections, and autoimmunity, due to faster nuclear accumulation and impaired dephosphorylation of STAT1. CCD mutations present with multisystem involvement, further emphasizing the heterogeneity of clinical manifestations. These variations underscore the importance of genetic

insights for prognostication and tailored management. Early interventions, including hematopoietic stem cell transplantation for severe cases, and emerging therapies like JAK inhibitors show promise; however, ruxolitinib's need for individualized dosing, vigilant monitoring, continuous treatment to maintain benefits, and lack of epigenetic correction warrant further evaluation.

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Activated PI3K Delta Syndrome in a Pediatric Patient: A Case Report on Diagnosis and Management

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Background: Activated PI3K delta syndrome (APDS) is a rare inborn error of immunity caused by pathogenic variants in the PIK3CD or PIK3R1 genes. It presents with recurrent infections, lymphoproliferation, autoimmunity, and an increased risk of malignancy. Without prompt diagnosis and treatment, APDS can result in severe complications and high mortality.
Aim: To diagnose and manage a 5-year-old girl with chronic diarrhea and failure to thrive, using a multidisciplinary approach to uncover the underlying cause and initiate therapy.
Results: The patient exhibited chronic diarrhea, significant growth retardation, and generalized weakness. On physical examination, hepatomegaly and splenomegaly were noted. Laboratory analysis revealed anemia and thrombocytopenia, as well as T CD4 lymphopenia with normal serum immunoglobulin G, A, and M levels. Imaging studies, including ultrasound and CT, revealed hepatomegaly, splenomegaly, and an abdominal tumor of unknown etiology. MRI findings were pending at the time of this report. Biopsy of the ileum and colon demonstrated malakoplakia, an unusual histopathological finding that may suggest underlying immune dysregulation. Whole-exome sequencing revealed a heterozygous pathogenic variant, c.3061G>A (p.Glu1021Lys), in the PIK3CD gene, confirming the diagnosis of APDS.

Based on the clinical and genetic findings, treatment included monthly intravenous immunoglobulin (IVIG), everolimus to control lymphoproliferation, and antibiotic prophylaxis. The patient is under evaluation for hematopoietic stem cell transplantation (HSCT), a potentially curative option.
Conclusions: APDS is a challenging condition to diagnose due to its variable presentation. This case highlights the importance of genetic testing in patients with unexplained immune dysfunction and lymphoproliferative features. The finding of malakoplakia in this patient is notable and underscores the spectrum of immune dysregulation associated with APDS. The use of everolimus reflects an evidence-based approach to managing lymphoproliferation, as supported by emerging literature. HSCT remains the only curative therapy for APDS, but it is associated with significant risks. Early initiation of supportive treatments, such as IVIG and prophylactic antibiotics, is crucial while evaluating candidates for transplantation.

Our team at Hospital Nacional Edgardo Rebagliati Martins remains committed to advancing the diagnosis and management of inborn errors of immunity.

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Identifying Knowledge Gaps in Primary Immunodeficiency (PID) Awareness Among Pediatric Residents: A Cross-Sectional Study

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Background: Inborn errors of immunity (IEIs), formerly primary immune deficiencies (PIDs), are a group of rare yet profoundly impactful conditions that compromise immune function, leading to recurrent infections, autoimmunity, and malignancies. While early diagnosis is critical to improving outcomes, awareness of the Jeffrey Modell Foundation's "10 Warning Signs of PID" remains insufficient among healthcare professionals. This study explores the knowledge and preparedness of pediatric residents at SUNY Downstate Health Sciences University to identify and manage IEIs.

Objective: To evaluate the baseline knowledge of IEIs among pediatric residents, highlight areas of strength and gaps, and assess the impact of training exposure on diagnostic confidence and accuracy.
Methods: An anonymous questionnaire assessing recognition of IEI warning signs, diagnostic protocols, and management strategies was distributed among pediatric residents. Out of the total 81 residents in the program, 43 completed the survey. Responses were analyzed by postgraduate year (PGY) and prior rotations in Allergy and Immunology (AI).
Results: Progressive knowledge growth: The overall percentage of correct answers improved with training level: PGY-1 residents answered 67.5% of questions correctly, PGY-2 residents 71%, and PGY-3 residents 79%. Specialized training matters: Residents with prior AI rotations had an accuracy rate of 79.5% compared with 69% among those without, emphasizing the value of targeted exposure. Key strengths: Most participants were able to recognize patterns of severe IEI presentations, such as persistent oral thrush (93%) and recurrent sepsis (97%). Critical gaps: Participants rate of recognizing cases with subtle signs such as frequent ear infections (27%) and recurrent sinusitis (54%) was lower, potentially delaying diagnoses.
Misconceptions in management: Misunderstandings about vaccine safety (70%) and universal immunoglobulin therapy (18%) further highlight the need for comprehensive education.
Conclusions: While residents show proficiency in identifying severe IEI manifestations, gaps remain in recognizing subtle presentations and understanding management protocols. These findings emphasize the need for targeted educational interventions, including case-based learning and diagnostic frameworks, to improve early detection, appropriate management, and patient outcomes.

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An Uncommon Case of a Patient with CVID and PANDAS

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Introduction: Pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus* infections (PANDAS), a subset of pediatric acute-onset neuropsychiatric syndrome (PANS), is characterized by new-onset neuropsychiatric symptoms temporally associated with *Streptococcus* infection. Some patients with PANS/PANDAS have also been found to have antibody deficiency (IgG, IgA, and vaccine antibody to *Streptococcus pneumoniae*). However, PANDAS in patients with common variable immunodeficiency (CVID) has not been previously reported.
Case Presentation: A 16-year-old male with CVID and psoriasis was diagnosed with PANDAS at 9 years old after a febrile illness with group A *Streptococcus* infection. Given his ongoing severe neuropsychiatric symptoms, including obsessive compulsive disorder, he transitioned from intravenous immunoglobulin (IVIG) dosing for CVID to a higher dose (2 gram/kg/month) for the treatment of PANDAS. He did not have additional major infections, and after approximately a year of higher dose IVIG treatment, his neuropsychiatric symptoms of PANDAS improved.
Discussion: The prevalence of PANDAS in children with CVID is unclear. The mechanism of IVIG in the treatment of PANDAS has not been elucidated. Mechanisms may involve the binding and neutralization of autoantibodies by anti-idiotypic antibodies and also the eradication and prevention of streptococcal infection. PANDAS should be considered on the differential for patients with CVID and antibody deficiency who develop new onset or suddenly worsening neuropsychiatric symptoms in the setting of an acute upper respiratory tract infection. Prompt diagnosis, timely treatment of an underlying streptococcal infection, and appropriate doses of IVIG, especially in patients with immunodeficiency, may prevent the development of severe PANDAS and improve the quality of life of patients.

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A Unique Pathogenic Heterozygous Hyou1 Mutation Presenting with Recurrent Osteomyelitis

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Several genetic mutations have been linked to recurrent infections that vary in severity from mild to life threatening. A mutation of the hyou1 gene has been associated with a defective protein resulting in poor cellular homeostasis from stress related to lack of necessary substrates for energy production, which is known to lead to a unique pattern of recurrent infections and hypoglycemia. We present a case of a 32-year-old female with chronic shortness of breath, a history of recurrent osteomyelitis, chronic sinusitis, and medically treated hypoglycemia. The patient's family history was notable for hypoglycemia in other family members. Investigative results indicated a fixed airway obstruction and a heterozygous pathogenic mutation in the hyou1 gene (exon 23, c.2638G>A), with normal immunoglobulins, lymphocyte subpopulations, and neutrophil oxidative burst assay within normal ranges. The airway obstruction was attributed to an infectious subglottic stenosis. We propose that her recurrent osteomyelitis, the infectious subglottic stenosis, and medically treated hypoglycemia are linked to her pathogenic heterozygous hyou1 mutation. Previous reports of other hyou1 homozygous mutation variants have similarly documented recurrent infections, an undefined immunodeficiency and hypoglycemic episodes. This is the first reported case of a unique pathogenic heterozygous hyou1 mutation presenting with recurrent osteomyelitis, chronic subglottal infections, and medically treated hypoglycemia.

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From Agammaglobulinemia to Neutropenia: The TCF-3 Has Different Clinical Presentations

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Agammaglobulinemia is caused by genetic disorders affecting B cell development and is assumed to be autosomal recessive in up to 15%. Autosomal recessive agammaglobulinemia (ARA) is a condition that causes immunodeficiency, and it can lead to severe complications such as otitis, sinusitis, and pneumonia. Genetic mutations include μ heavy chain, λ5, Igα, Igβ, BLNK, PIK3R1, and TCF3. There are several genes, including μ heavy chain, λ5, Igα, Igβ, BLNK, PIK3R1, and TCF3, that have been associated with ARA. TCF-3 is responsible for the development of T and B cells. This report describes four cases, one of which was agammaglobulinemia, followed by two cases of Immunoglobulin (Ig) subgroup deficiency, one of neutropenia, and one of hypogammaglobulinemia.

This report expands the spectrum of TCF3 deficiency types and highlights the crucial role of this transcription factor in B-lymphocyte differentiation.

Table 1. **The clinical and immunologic parameters of the patients.**

	Patient1	**Patient2**	**Patient3**	**Patient4**
Age/ gender	**8/M**	**3/M**	**5/M**	**26/M**
Clinical findings	Recurrent bronchiolitis	Enterovirus encephalitis	Recurrent upper respiratory tract infections, peritonsillar abscess	Recurrent otitis media and pneumonia, hearing loss
	Failure to thrive	Facial dsymorfism		
Diagnosis at admission	**THI**	**Agammaglobulinemia**	**Neutropenia**	**Ig subgroup deficiency**
Current diagnosis	**Ig subgroup deficiency**	**Agammaglobulinemia**	**Hypogammaglobulinemia**	**Ig subgroup deficiency**
Mutation	**TCF- 3 p.Pro177Leu (c.530C>T) heterozygous**	**TCF-3 p.Ala161Val (c.482C>T) heterozygous**	**TCF-3 C.1939C>A p.(pro647Thr) heterozygous**	**TCF-3 c.1813+8C>T (rs993094051) heterozygous**
Immunologic parameters				
ANS × 10^9 cells/L	3240	5660	**62**	3290
ALS× 10^9 cells/L	3780	2010	2850	2730
IgG(mg/dl)	**304**	**145<**	924	690
IgA(mg/dl)	81	**6.7<**	**33**	110

Table 1. **The clinical and immunologic parameters of the patients. (*Continued*)**

	Patient1	**Patient2**	**Patient3**	**Patient4**
Age/ gender	**8/M**	**3/M**	**5/M**	**26/M**
IgM(mg/dl)	105	**18<**	113	113
Ig Subgroups (mg/dl)	**IgG1:238⬇**	**N/A**	**N/A**	IgG1 483
	IgG2:255			**IgG2 166⬇**
	IgG3:16.7⬇			**IgG3 36.7⬇**
CD3 × 10^9 cells/L	2683	1440	1995	1701
CD4 × 10^9 cells/L	1738	**274**	769	1107
CD8 × 10^9 cells/L	793	1080	1254	**459**
CD19 × 10^9 cells/L	756	**44**	**133**	351
CD3-CD16CD56+NK cells × 10^9 cells/L	185	**880**	**684**	459
Switched memory BCD19-IGgM-IgD+CD27 × 10^9 cells/L	**18.9**	**0**	**28**	**21.6**
Vaccine response	**positive**	**positive**	**positive**	**positive**

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Elapegademase in Patients with ADA-SCID Previously Treated with Pegademase: A Case Series

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Introduction: Elapegademase (Revcovi®), a PEGylated recombinant bovine adenosine deaminase (ADA), is the only FDA-approved enzyme replacement therapy (ERT) for ADA-severe combined immunodeficiency (SCID), replacing pegademase (Adagen®) since 2018. Elapegademase is typically used from diagnosis until hematopoietic stem cell transplant (HSCT) or gene therapy (GT) can be performed, or as a bridge therapy if failed HSCT/GT or continued long term if neither option is feasible. In a phase 3 trial (NCT01420627), patients maintained metabolic detoxification, improved/stabilized lymphocyte counts, and tolerated elapegademase. Given the rarity of ADA-SCID, real-world data are crucial for evaluating its long-term effectiveness and safety.

Methods: This analysis included 4 patients from 4 U.S. sites who started elapegademase in the phase 3 trial (January 2014–May 2019) and continued treatment in the U.S. registry (NCT03878069; September 2019–January 2023). All 4 patients received pegademase for 13–24 years before starting elapegademase. Assessments included plasma ADA activity, erythrocyte deoxyadenosine nucleotide (dAXP) levels, and safety outcomes.

Results: Four patients with ADA-SCID, diagnosed in infancy (2 males) or early childhood (2 females), began ERT (pegademase) within a year of diagnosis (Table 1). Patient 1 with unsuccessful GT continued ERT. For the other 3, HSCT was not an option. Mean (range) age at elapegademase initiation was 21 years (16–31 years). Mean (standard deviation) total duration of elapegademase, including in the phase 3 trial, was 69.5 (22.6) months (range, 40.1–95.1 months). At registry end, ADA activity levels were numerically higher than at elapegademase baseline and also exceeded levels at phase 3 trial end. Additionally, all 4 patients were considered metabolically detoxified as satisfactory dAXP levels were maintained (≤ 0.02 mmol/L). Two patients required dose adjustments based on clinical assessments. Three patients experienced eight infections that resolved without sequelae and required no treatment interruption. No patients had any elapegademase-related adverse events.

TABLE 1. **Patient demographics, baseline characteristics, and primary effectiveness outcomes.**

Patient (ID)	Sex / Race / Ethnicity	Age at diagnosis	Pegademase treatment, duration	Age at first elapegademase initiation	Dosing,mg/kg/week	Last data collection	ADA activity levels (mmol/h/L)[a] before and during elapegademase treatment			dAXP levels (mmol/L)[b] before and during elapegademase treatment		
							Baseline	At end of phase 3	At last visit	Baseline	At end of phase 3	At last visit
1	M / White / Hispanic or Latino	4 months	Pegademase, 18 years	19 years	0.08–0.18	Jan 12, 2023	10.9	33.74	103.76	<0.002	0.010	0.007
2	F / White / Other	~2 year	Pegademase, 13 years	16 years	0.3	Jan 17, 2023	14.26	46.17	97.66	<0.002	0.008	0.004
3	M / White / Other	~2 months	Pegademase, 17 years	18 years	0.17	Mar 23, 2021	12.35	36.25	65.39	<0.002	<0.002	0
4	F / White / Hispanic or Latino	~5 years	Pegademase, 24 years	31 years	0.26–0.3	Jan 18, 2023	11.33	34.55	57.6	<0.002	<0.002	0.003

[a]Optimal trough plasma ADA activity was considered to be 30 mmol/h/L or higher.
[b]Detoxified erythrocyte dAXP concentration was defined as 0.02 mmol/L or lower.

Conclusions: Long-term elapegademase was well tolerated with patients achieving stable plasma ADA and dAXP levels and maintaining metabolic detoxification for up to 8 years. This cohort received long duration of ERT for ADA-SCID to date, with up to 30 years of continuous treatment, remaining clinically stable without any new safety concerns.

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Breaking Barriers in Eosinophilic Cellulitis: Dupilumab's Game-Changing Role in Refractory Treatment

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Eosinophilic cellulitis (EC), also known as Wells' syndrome, is a rare and challenging skin disorder marked by diverse clinical manifestations and a lack of standardized diagnostic and treatment guidelines. This case report focuses on a 48-year-old woman with persistent dermatitis resistant to traditional therapies, highlighting the potential for dupilumab, a monoclonal antibody targeting interleukin-4 (IL-4) and interleukin-13 (IL-13), as an innovative treatment option for refractory EC.

The patient presented with annular, erythematous skin lesions and had undergone multiple treatment attempts, including griseofulvin, doxycycline, topical steroids, cyclosporine, methotrexate, and antihistamines, with limited or no success. Skin biopsies revealed interstitial eosinophilic infiltration, confirming a diagnosis of EC. Despite initial improvement with corticosteroids, the dermatitis recurred after treatment was discontinued. Given the ineffectiveness of conventional therapies, dupilumab was introduced based on its ability to modulate immune responses by inhibiting IL-4/IL-13 signaling, reducing inflammation.

Remarkably, the patient experienced a significant resolution of symptoms following a single dose of dupilumab, and long-term management with this biologic led to sustained control of her condition. While attempts to transition to mepolizumab, an anti-IL-5 agent, resulted in flare-ups, dupilumab continued to offer superior results, suggesting it may be more effective for this condition.

This case demonstrates dupilumab's transformative potential in treating EC, particularly in patients resistant to standard therapies. By targeting the underlying immune dysregulation and inhibiting key inflammatory pathways, dupilumab provided durable relief where other treatments failed. This report also highlights the need for further research into dupilumab's role in managing EC and other rare inflammatory skin conditions. Its success underscores the importance of exploring innovative therapies for complex dermatologic disorders, offering new hope for patients with challenging conditions like EC.

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Autoinflammation due to RIPK1 Defects

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Introduction: RIPK1 plays a role in mediating apoptosis, necroptosis, and inflammatory pathways downstream of death receptors and pattern recognition receptors. Loss-of-function mutations of RIPK1 have been shown to lead to immune deficiencies and/or autoinflammation. Cleavage resistant RIPK1-induced autoinflammatory (CRIA) syndrome has shown to be caused by heterozygous mutations in different areas of RIPK1. Normally, cleavage of RIPK1 by caspase 8 prevents abnormal cell death; however, mutations may lead to overactivation and increased RIPK1-dependent apoptosis and necroptosis, leading to autoinflammation.
Case: 16-year-old female with recurrent fevers, rashes, arthralgias, and oral ulcers. Healthy until age 12, when she developed abnormal gait, joint hypermobility, headaches, musculoskeletal pain, at the time diagnosed with Lyme disease, long COVID syndrome, and myalgic encephalomyelitis/chronic fatigue syndrome. Three years later she started to develop further symptoms consisting of periodic daily fevers that would last for weeks at a time without an infectious source, as well as oral ulcers and joint pain during these episodes with new-onset rectal bleeding. She saw rheumatology and was subsequently started on colchicine, with some symptomatic improvement. She then saw Immunology, with workup showing normal serum immunoglobulins and lymphocyte subsets, as well as normal and switched memory B cells. A targeted gene panel was sent and identified a heterozygous RIPK1 variant, c.1934C>T (p.Thr645Met), previously described in a CRIA cohort. Family history is notable for her mother having a similar autoinflammatory phenotype without fulminant symptoms and with the same RIPK1 variant.
Discussion: Cleavage-resistant RIPK1 variants have been shown in a small subset of individuals to be associated with autoinflammation. This case reinforces the importance of genetic testing to identify potential molecular diagnoses in autoimmune/autoinflammatory presentations, as it may shape management. Despite partial response to colchicine, this patient is undergoing discussion to potentially start an IL6-R antagonist or IL-1 inhibitor, given their previous success in some patients with CRIA.

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Extremely Delayed Diagnosis of Cystic Fibrosis in an Elderly Female Presenting with IgG Subclass Deficiency

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Cystic fibrosis (CF), caused by mutations in the CFTR gene, leads to defective ion transport and multisystem complications. While typically diagnosed in childhood, atypical or late-onset presentations can delay recognition. CF often mimics immunodeficiency with recurrent infections and bronchiectasis, and early diagnosis remains critical for optimizing outcomes.

A 65-year-old female, being seen by multiple subspecialists, ultimately referred for suspected immunodeficiency after decades of multisystem health issues. Her childhood was marked by recurrent sinopulmonary infections, progressing to pneumonia at 13. By her mid-20s, she experienced weight loss and malabsorption, initially diagnosed as celiac disease. Pancreatic insufficiency, identified through low fecal elastase, improved with enzyme replacement.

In her 50s, she was diagnosed with Hansen's disease and experienced complicated pneumonia with parapneumonic effusions. CT imaging (Figure 1) revealed bronchiectasis and pulmonary nodules. Diagnosed with non-tuberculous mycobacteria (NTM), she initially

underwent triple therapy, later switched to inhaled amikacin due to medication intolerance. Despite treatment, sputum cultures persistently grew *Mycobacterium abscessus*, *Mycobacterium avium* complex, *Pseudomonas*, and *Aspergillus*, the latter treated with voriconazole and steroids for suspected allergic bronchopulmonary aspergillosis.

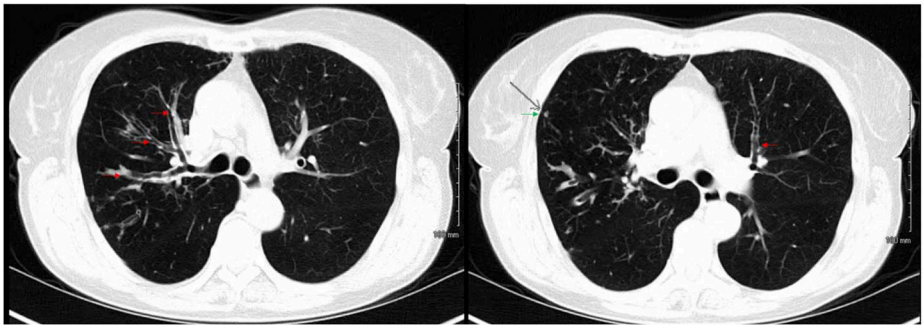

Figure 1. Red arrows showing bilateral bronchiectatic changes. Green arrow showing pulmonary nodule.

An immunodeficiency workup showed mildly low IgG1 subclass and poor pneumococcal vaccine response. However, a detailed history revealed infertility and Ashkenazi Jewish ancestry, raising suspicion for CF. Genetic testing confirmed two pathogenic CFTR variants, including delta F508. Sweat chloride testing revealed intermediate results, and she was started on elexacaftor/tezacaftor/ivacaftor, leading to marked improvement in sputum clearance and overall health.

This case highlights the diagnostic challenge of potential bias in atypical CF in adults, where recurrent infections, bronchiectasis, and pancreatic insufficiency may mimic immunodeficiency. Misattributed symptoms delayed appropriate treatment for decades. CFTR modulators significantly improved outcomes in this patient, emphasizing the need for a high index of suspicion in adults with similar clinical features, particularly those with infertility or high-risk ancestry.

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A Practical Approach to the Management of Anaphylaxis Induced by the Infusion of Intravenous Immunoglobulins: A Case Report

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Introduction: Allergic reactions, including anaphylaxis, are a well-known complication in some patients who receive blood/plasma transfusions and have an immunoglobulin A (IgA) deficiency. Even patients with panhypogammaglobulinemia and deficient vaccine response may experience anaphylactic episodes probably because the infused immunoglobulins may induce antibody-mediated reactions when these patients receive the treatment (IgIV).

Case: We present a 26-year-old woman with a history of Burkitt's lymphoma treated in 2014 with chemotherapy. A profound hypogammaglobulinemia was generated over the next few years with a progressive decrease in immunoglobulins from 2015 until the total absence of IgA and IgM (2018) and IgG (2020). During that period, she had to be assisted in the emergency room frequently for many respiratory infections, including pneumonia. In 2020, after symptomatic and progressive bronchiectasis with severe hemoptysis, immunoglobulins were recommended. The first infusion of intravenous immunoglobulins was administered. Close to the end of infusion, she suffered a facial edema and acute bronchospasm that was resolved after suspending the infusion and administering treatment. A new slow infusion with a classical pretreatment was attempted in November 2020 with a recurrence of symptoms a few minutes after the start; the patient was ruled out for new infusions. Later she was referred to the Primary Immunodeficiency Unit in December 2021.

Immune Function Studies: Lymphocytes 2300 cells/dl (CD69+ < 10 and CD3+2200); IgG < 3 mg/dL; IgA < 6 mg/dL; and IgM < 3 mg/dl. Antibodies post-vaccine: anti-diphtheria toxoid < 0.01 IU/ml, anti-pneumococcus < 3.33 mg/L, anti-salmonella < 7.40 U/ml, anti-tetanus toxoid < 0.01 IU/ml, anti-COVID IgA antibodies 0.30 (OD), and anti-COVID IgG antibodies 0.10. The COVID vaccine response study was positive for DTH (delayed type hypersensitivity). Anti-IgA antibodies were absent.

Practical Approach: A desensitization program was designed using a variant of Castells' 12-step desensitization protocol (Castells M., Brigham and Women's Hospital, Harvard Medical School, Boston, MA) at the Hematology Day Hospital with full pretreatment and culminated with 20 g of intravenous immunoglobulin. The protocol was developed and successfully completed with only a slight subsequent headache. Since then, the same regimen was scheduled every 4 weeks with an improvement in her symptoms and quality of life.

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Late-Onset Blau Syndrome: A Case of Misdiagnosis, Delayed Diagnosis, and the Impact of Social Challenges

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Blau syndrome is a rare, autosomal dominant, autoinflammatory disease caused by mutations in the NOD2 gene, characterized by arthritis, dermatitis, and uveitis. Symptoms typically appear in early childhood, before age 4, and later presentation is uncommon. We present a patient with late-onset Blau syndrome, with symptom onset at age 10 and diagnosis at age 18.

At age 10, our patient developed a severe, refractory generalized rash initially diagnosed as eczema, along with eye redness and irritation initially diagnosed as allergic conjunctivitis. These diagnoses were not challenged due to inconsistent follow-up. The rash was complicated by multiple superimposed skin infections leading to scarring.

Our patient was an excellent athlete, but at age 14, he developed thoracic back pain, hip and wrist arthritis, and malformations, including prominent bending of the fifth fingers and toes, which hindered physical activity.

The family suspected undiagnosed food allergies, leading to food withholding and resulting in protein deficiency over three years.

A skin biopsy, planned several times, was delayed due to family hesitancy but was finally performed at age 16, revealing granulomatous dermatitis.

At the same time, he was experiencing chronic diarrhea and bloating, but colonoscopy was never completed due to intolerance of the preparation. Although his symptoms were concerning for inflammatory bowel disease, diagnostic pathology was never obtained for this reason.

However, an upper endoscopy revealed *H. Pylori* gastritis and changes suggestive of celiac disease, including blunted villi. Pathology demonstrated chronic duodenopathy.

At age 18, he was referred to allergy and immunology, where genetic testing confirmed a pathogenic NOD2 mutation, diagnosing Blau syndrome. Other laboratory findings included low IgM (33), elevated IgE, but normal IgG and IgA, and fluctuating CRP. QuantiFERON was negative.

A unique aspect of this patient's case is the delayed onset and the significant impact of social determinants of health on the patient's care. Since diagnosis, consistent in-person follow-up has been difficult to arrange due to frequently missed appointments for unknown reasons.

This case highlights the challenges of diagnosing late-onset Blau syndrome in the setting of inconclusive laboratory evaluation and underscores the role of social factors in medical management.

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WHIM Syndrome Diagnosis in a Parent and Child

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Warts, hypogammaglobulinemia, immunodeficiency/infections, and myelokathexis (WHIM) syndrome is a rare autosomal dominant primary immunodeficiency (PID) caused by defects in the C-X-C motif chemokine receptor 4 (CXCR4) gene. Here we present the presentation, evaluation, and management of a father and son diagnosed with WHIM syndrome.

Case 1 was a 39-year-old male with WHIM syndrome diagnosed 6 years prior via bone marrow biopsy with FoundationOne genetic testing positive for CXCR4 mutation (T322fs*26 and C1012dup with protein sequence change pser338Phefs*6). History was significant for frequent warts, rashes, and recurrent pneumonia since his early 20s, occurring 5-6 times a year. CT chest from the previous year showed tree-in-bud opacities in the right middle and posterior left lower lobes with mediastinal lymphadenopathy. He was treated with peg-filgrastim for the 6 months prior to representation. Initial workup showed reduced CD4, CD8, CD19, and pneumococcal antibody titers. Tetanus antibody titers, CBC, CMP, and total immunoglobulins were normal. Response to pneumococcal polysaccharide vaccine (PPSV23) revealed mild improvement in protective pneumococcal titers at 8 weeks. Mavorixafor was started and pegfilgrastim discontinued with no sinopulmonary infections or hospitalizations since initiation. However, skin rashes worsened, and he developed an axillary abscess requiring trimethoprim-sulfamethoxazole and cephalexin therapy.

Case 2 was an 8-year-old male presenting for evaluation of WHIM syndrome given his father's (Case 1) diagnosis. History was significant for warts and recurrent acute otitis media, requiring 2 bilateral myringotomy and tubes procedures. Initial workup showed absent absolute neutrophil count (ANC) with reduced white blood cells (WBCs), absolute lymphocyte count (ALC), CD4, CD8, IgG, and pneumococcal antibody tiers. Tetanus antibody titers and CMP were normal. Invitae IEI panel showed CXCR4 c.952dup (p.Thr318Asnfs*26) heterozygous variant, RNU4ATAC n.48G>A (RNA change) heterozygous variant, and AP3D1 c.3400A>C (p.Ile1134Leu) heterozygous variant of uncertain significance. Response to PPSV23 revealed adequate response in protective pneumococcal titers at 8 weeks. He was started on filgrastim. Eight weeks following initiation, WBCs, ALC and ANC normalized. Patient has had no infections, hospitalizations, or need for antibiotics since initiation.

PIDs with milder phenotypes are often not considered in adult patients until severe manifestations occur, as seen in Case 1. Diagnosis of PIDs should prompt early immune evaluation with consideration of genetic testing in family members.

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Roles of Common Gamma Chain on Intestinal Lymphoid Organogenesis using an Animal Model and Patients' Samples of X-SCID

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Background: Organ-level research for intestinal lymphoid organogenesis regulated by IL2RG, the gene responsible for X-linked severe combined immunodeficiency (X-SCID), is clinically unavailable in humans. The establishment of in vivo animal model lacking IL2RG could be a powerful tool for gaining deeper insights into the roles of common gamma chain on intestinal immunity in patients with X-SCID.

Methods: We established an X-SCID animal model, which was first reported by our group, by deleting the IL2RG in pigs, to understand the clinical significance of IL2RG in intestinal lymphoid organogenesis and microenvironment. Pigs with X-SCID underwent bone marrow transplantation (BMT) to mimic the current therapeutic treatment for patients with X-SCID. We investigated the effect of BMT on organ-level immune reconstitution. Moreover, the results were confirmed using serum and fecal samples collected from patients with X-SCID treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1].

Results: We demonstrated that pigs with X-SCID completely lacked Peyer's patches (PPs) and IgA production in the small intestine but possessed some dysfunctional intestinal T and B cells. Moreover, pigs with X-SCID developed a heterogeneous intestinal microflora, indicating that X-SCID could be an immune disorder that affects normal intestinal lymphoid organogenesis and microenvironment. Importantly, PP organogenesis in pigs with X-SCID was not completely reconstituted by BMT. Although a few isolated lymphoid follicles developed in the small intestines of BMT-treated pigs with X-SCID, there was no evidence that they contributed to IgA production and normal microflora formation. Consistently, most patients with X-SCID who underwent allo-HSCT showed insufficient IgA production and dysbiosis, especially those with incomplete immune reconstitution and low serum IgG levels after allo-HSCT.

Conclusion: Our results indicate that common gamma chain has indispensable roles in intestinal lymphoid organogenesis and microenvironment, suggesting that loss of function of IL2RG product is associated with an increased risk of intestinal infections, malnutrition, and dysbiosis in untreated patients with X-SCID. Our animal model indicated that current allo-HSCT for patients with X-SCID may be insufficient to induce complete reconstitution of intestinal lymphoid organogenesis in vivo.

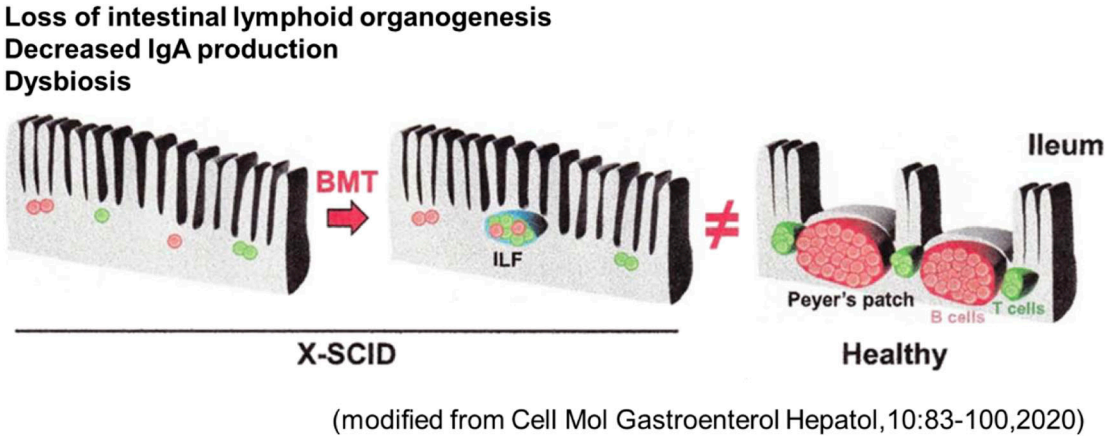

Figure 1.

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Experience of Germline Genetic Testing for Inborn Errors of Immunity: Using Multigene Panel Testing Compared with Exome Sequencing at a Diagnostic Laboratory

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Next-generation sequencing is a valuable tool to help diagnose inborn errors of immunity (IEIs) because it can interrogate many genes concurrently and has enabled a quick expansion of IEI-related genes. While exome sequencing (ES) can analyze novel and established IEI genes, fixed multigene panel tests (MGPTs) are still broadly used. The aim of this study was to examine the molecular diagnosis (MolDx) rate from both MGPT and ES and the phenotypic pattern of patients referred for ES.

Patients were referred for MGPT and/or ES between March 2017 and May 2024 at a diagnostic laboratory. MGPT contained up to 574 genes and were curated based on the International Union of Immunological Societies phenotypic classification list of IEI-related genes and expert opinion. Patients in the ES cohort were selected based on clinician-provided ICD-10 and Human Phenotype Ontology (HPO) terms. We required patients in the ES cohort to have at least one HPO term under "abnormality of the immune system." Odds ratios (OR) and p-values were calculated using G-tests; p-values < 0.05 were considered statistically significant.

The overall MolDx was higher in the ES cohort (378/2,167; 17.4%) versus MGPT (3,754/40,994; 9.2%) (OR 2.1, $p < 2.2 \times 10^{-16}$). Of the 121 patients in the cohort tested by both ES and MGPT, 11 had discordant results due to a non-IEI–related finding on ES (n = 8) or MGPT (n = 1), technical differences (n = 1), and novel gene not available on MGPT (n = 1). There were 42 unique genes that were reported from ES; 16 (38.1%) were also available on MGPT at the time of testing. Out of the 26 (61.9%) genes that were not available on MGPT, 2 were related to IEI conditions, while the remainders were not primary IEI conditions (e.g., neurological conditions causing epilepsy and/or neurodevelopmental disorders or skeletal/dermatological/dental conditions).

Despite the growing number of genes associated with IEIs, the increase in MolDx rate from ES cannot be exclusively attributed to novel IEI-related genes. This difference may be explained by the indication for testing, which suggests patients who present with an IEI phenotype and involvement with another organ system may benefit from ES. Granular characterization of the phenotypic spectrum of patients who receive a MolDx from ES is warranted.

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Expanding the Landscape of Inborn Errors of Immunity in Hematological Disorders: A Prospective Study on Hidden IEI and IEI Phenocopies

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Background: Inborn errors of immunity (IEI) are increasingly associated not only with recurrent infections but also with hematological complications. The discovery of somatic mutations leading to "IEI phenocopies" has expanded the genetic understanding of these disorders. However, the clinical and genetic scope of IEI in hematological disorders remains underexplored in large-scale studies.
Methods: This study recruits patients under 25 years old with hematological abnormalities, categorized into four subgroups: autoimmune cytopenias (AICs), polyclonal lymphoproliferation (PL), monoclonal lymphoproliferation (ML), and bone marrow failure/myelodysplasia (BMF/MDS). Participants undergo immunological evaluations, including immunophenotyping, cytokine profiling, and autoantibody assays. Next-generation sequencing (NGS) is used to identify germline and somatic variants, with bulk RNA sequencing applied to validate variants and explore pathways in inconclusive cases. Additionally, this study aims to establish a dedicated consortium for the comprehensive study of IEI-related hematological disorders, bringing together multiple centers to collaborate on data collection and analysis. Patient advocacy organizations (PAOs) are involved to raise awareness and support participants.
Results: Retrospective data from Meyer Children's Hospital IRCCS in Florence (2020–2024) showed feasibility, identifying 71 eligible patients: 38 with AICs, 15 with PL, 20 with lymphoma, and 12 with BMF/MDS. A similar number of patients are expected to enroll at this site over three years, with collaborating referral centers projected to recruit approximately 680 participants in total. Preliminary results from the initial 71 participants show a 35% detection rate of hidden IEI, supporting the study's premise.
Conclusions: This research is poised to enhance the understanding of IEI and IEI phenocopies in hematological disorders, revealing novel genetic contributors and biomarkers. The findings could lead to earlier diagnoses, personalized therapies, and more timely hematopoietic stem cell transplantation. Collaboration with PAOs will improve patient education, treatment adherence, and overall outcomes, while reducing healthcare burdens. This study represents a significant advancement in addressing the unmet needs of patients with hematological complications of IEI.

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Genetic Characterization of a Cohort of Patients with Suspected Inborn Error of Immunity in Follow-Up at a Single Center

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Next-generation sequencing (NGS) is a powerful tool for the diagnosis of inborn errors of immunity (IEIs). However, one of the main limitations is the risk of identifying inconclusive results. In this context, we estimated the overall diagnostic rate of different NGS techniques, comparing the rate of targeted panels (TP), mendeliome trio, and whole-exome sequencing (WES). Moreover, we evaluated the ability of the recently developed PIDCAP score to predict the diagnosis of IEIs by comparing the diagnostic rate of NGS among different categories of risk.

198 patients with suspected IEIs were genetically investigated using either TP (73%), mendeliome trio (10%), or WES (17%). The genetic variants were classified according to 2015 ACMG standard guidelines and filtered based on frequency and category. The analysis was limited to coding and splicing variants with a minor allele frequency (MAF) or equal to 1% in internal and public databases. The PIDCAP scoring system was used to stratify the cohort in risk categories: >75 high, 35-75 moderate, and <35 low risk.

192 variants in 136 genes were identified, including 67 (52%) VUS, 28 (22%) likely pathogenic, 26 (20%) pathogenic, 4 (3%) reclassified as benign or likely benign, and 4 (3%) with conflicting interpretation. The remaining 63 have not been previously reported in the databases. The number of reported VUS was significantly lower for mendeliome trio compared with TP (p 0.03) and WES (p 0.00004). The diagnostic rate considering all techniques is 17%, and it was significantly higher for WES (34%) and mendeliome (38%) compared with TP (12.5%). In cases with high suspicion, the diagnostic rate rose to 34% in the high-risk group and to 21% in the medium-risk group vs 1.3% in the low-risk group, whereas when the clinical picture met ESID diagnostic criteria up to 78%. Interestingly, the analysis of the patients with medium risk revealed alterations in non-immune genes in 5/7 cases.

The analysis of many genes leads to the identification of a large number of variants, and the trio analysis facilitates the attribution of pathogenicity. The diagnostic rate is higher when the analysis is limited to patients with high suspicion.

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Quantitative Analysis of TREC and KREC Molecules in Patients with Acute Lymphoblastic Leukemia at the Stage of Maintenance Therapy

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Background and Aims: Maintenance therapy (MT), which aims to destroy the remaining tumor cells after hematopoietic stem cell transplantation (HSCT), is the final stage of treatment for acute lymphoblastic leukemia (ALL). The restoration of naive T lymphocytes is extremely important after HSCT because it provides a wide variety of T cell receptor repertoire, which is necessary to avoid recurrence of the leukemic clone. The recovery of both naive T and B lymphocytes can be demonstrated by measuring TREC/KREC-positive cells
Methods: The group of patients receiving maintenance therapy after going into remission included 18 patients (male, 11; female, 7) with ALL. According to the immunophenotype ALL: common B (n = 14), cortical T cell ALL (n = 2), pre-B cell (n = 2). According to the FAB classification, 6/18 (33%) had stage L1; the remaining 12/18 (67%) had stage L2. Peripheral blood for analysis was collected from patients at the time of MT, regardless of the date of initiation of treatment; thus, the median time when the material was collected was 9 (1.2 to 15.8) months. Quantitative analysis of TREC and KREC molecules was performed by RQ-PCR.
Results: During 1.5 years of maintenance therapy in patients with ALL, the TREC count increases but does not reach normal values. B lymphocytes, in turn, recover extremely slowly and have extremely low values in all patients studied. In 5/18 patients, B cells were not detected at all. Reliable differences were found between the KREC content in patients receiving PT and healthy donors ($p < 0.0001$), as well as between the KREC and TREC counts in these patients. It was found that at the stage of remission induction on day 22, there is a reliable decrease and redistribution of the subpopulation composition of T and B lymphocytes, which continues until the end of consolidation. After the cancellation of high-dose chemotherapy, lymphocytes begin to gradually recover, but the rate of T lymphocytes significantly exceeds that of B lymphocytes.
Conclusions: Quantitative analysis of TREC and KREC molecules allows us to judge the renewal of the pool of naive T and B lymphocytes without the use of additional immunological research methods. This method can be used at the stage of maintenance therapy to monitor immune reconstitution.

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Evaluation of Immune Reconstitution using TREC/KREC in Patients with Acute Lymphoblastic Leukemia after Hematopoietic Stem Cell Transplantation

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Background and Aims: One of the important criteria after hematopoietic stem cell transplantation (HSCT) is the reconstitution of naive lymphocytes, since they form the cellular repertoire. The number of newly formed lymphocytes after HSCT is determined by flow cytometry, but in some cases this is not always possible. As an alternative to assessing T and B cell neogenesis, determination of the number of TREC and KREC can be used.
Methods: The study included 9 patients diagnosed with acute lymphoblastic leukemia aged 10.1 (4.0 to 16.1) yrs after allogeneic HSCT [HLA-matched-related (n = 4), unrelated healthy donors (n = 5)]. Monitoring points were: 30, 45, 60, 100, 180, 245, and 365 days after HSCT. Reconstitution of T and B lymphocytes was assessed based on the results of flow cytometry. Quantitative of TREC and KREC was performed using the multiplex RQ-PCR.
Results: According to the results, T-lymphocyte recovery begins 3.5 months after HSCT. TREC are detected by day 145 and by day 180 TREC is 1.8×10^3 ($1.22\text{-}2.0 \times 10^3$)/$10^6$ leukocytes) without a dynamic decline up to a year after transplantation. CD3+ lymphocytes begin to appear after day 30, this picture is due to the fact that in the early post-transplant period the thymus-independent pathway of immune recovery prevails, which is mediated by donor T lymphocytes. KREC are detected from day 60 and by day 100 cross the threshold of normal values (1.8×10^3($1.7\text{-}3.1 \times 10^3$)/$10^6$ leukocytes). By day 245, KREC begins to slowly decrease, which is not a sign of transplant rejection, but indicates an increase in the total number of CD19+ lymphocytes and the effect of dilution of KREC. CD19+ lymphocytes appear by day 60 and reach the norm by day 100, this indicates that the newly formed pool of B lymphocytes mainly consists of naive cells. The recovery of naive T lymphocytes was characterized by slow dynamics up to day 100 (median 26.4%) after HSCT. Then the number of naive cells gradually increased and the recovery dynamics were similar to the recovery of TREC. By day 180 after HSCT, the median quantitative of naive T lymphocytes was 35.0%. There were no statistically significant differences in the dynamics of TREC/KREC recovery between the groups with related and unrelated transplantation.
Conclusions: Quantitative determination of TREC/KREC allows assessment of T and B lymphocyte neogenesis after HSCT without the use of additional research methods such as flow cytometry.

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Secondary Immunodeficiency in Marginal Zone Lymphoma and Impact of Bruton Tyrosine Kinase Inhibitor

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Secondary immunodeficiencies are clinically challenging and emphasize the need for a multidisciplinary approach. Our case underscores the importance of understanding the potential impact of B cell–targeting therapies, such as Bruton tyrosine kinase (BTK) inhibitors, on immune function, opportunistic infection prophylaxis, and clinical management.

A 55-year-old male with a history of systemic lupus erythematosus (SLE) on hydroxychloroquine, antiphospholipid antibody syndrome on warfarin, anal cancer s/p resection, long-standing splenomegaly, and lymphadenopathy with unremarkable core needle biopsy in 2018 was diagnosed with marginal zone lymphoma via excisional lymph node biopsy in 2023. His clinical course was complicated by a

hospitalization for septic shock secondary to *Streptococcus agalactiae* bacteremia and during this admission he was found to have significant immunodeficiency characterized by low T-lymphocyte counts (in cells/μL): CD3+ 141, CD4+ 65, and CD8+ 65, as well as low IgG levels 510 mg/dL (CD19 counts not obtained). Of note, he had persistent lymphopenia (0.06 to 0.49 cells/μL) and intermittent neutropenia (1.26-1.72 cells/μL) since 2009. After starting rituximab for lymphoma, he developed severe neutropenia (0.47 cells/μL), *Candida esophagitis* (requiring transient PEG tube placement), and a left ethmoid and sphenoid sinus abscess and orbital cellulitis due to *Aspergillus fumigatus*.

Given the severe side effects and disease progression after rituximab, he was transitioned to a selective BTK inhibitor, zanubrutinib. For *Pneumocystis jiroveci* (PCP), antiviral and antifungal prophylaxis, he receives dapsone, acyclovir, and voriconazole, respectively. He has remained infection free since initiating zanubrutinib despite persistent lymphopenia (in cells/μL: CD3+ 147-183, CD4+ 74-108, CD8+ 48-62, CD19+ 8). His IgG levels improved to 700-800 mg/dL. His most recent PET scan showed stable disease. Notably, genetic testing was nondiagnostic.

Our patient's secondary immunodeficiency is multifactorial from SLE, lymphoma, and rituximab. The impact of selective BTK inhibitors on immune function is not well studied. Ibrutinib, a first-generation BTK inhibitor, improves T cell exhaustion with treatment of B cell lymphomas; similar findings were not observed for zanubrutinib, although studies are limited. Furthermore, recommendations on opportunistic infection prophylaxis often rely on data from HIV patients, yet it is unclear if the immune dysfunction is similar in individuals with non-HIV immunodeficiencies.

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Chronic Urticaria in the Setting of Atypical Familial Mediterranean Fever with MEFV Gene Variant

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Introduction: Chronic urticaria (CU) has been previously associated with a variety of underlying conditions, including autoimmune disorders, infections, and atopic disease. The prevalence of the population with CU with a known underlying condition varies by study. The mainstay treatment for CU includes second-generation H1 antihistamines. This case demonstrates the importance of further investigation of underlying diseases in determination of treatment for chronic urticaria.
Case: 22-year-old female who presented with eight years of urticarial rash. Hives were located on the face, trunk, and limbs. Rash is exacerbated during illness, mechanical pressure, or stress, but frequency of symptoms progressed with no identifiable trigger. Hives were intermittently associated with fever, polyarthralgia, and angioedema of lips and eyes.
Investigations: Laboratory evaluation was notable for elevated IL-10 and TNF-alpha, reduced IgG subclass 2, with elevated IgE and IgD. Genetic testing of Periodic Fever 6 Gene NGS panel with DDC company revealed a heterozygous variant for MEFV gene coding for Familial Mediterranean fever (FMF). Secondary genetic testing within Invitae Primary Immunodeficiency Panel at Invitae genetic testing company showed variants of uncertain significance for AP3D1 and TONSL genes. Biopsy of skin lesion showed mild edema within the dermis with a very sparse mixed inflammatory cell infiltrate consistent with vasculitis.
Treatment: Patient initially trialed cetirizine and famotidine with some improvement, but no resolution of symptoms. After diagnosis of atypical FMF, the patient was started on colchicine, then a trial of hydroxychloroquine, with limited improvement. Follow-up discussions include initiation of omalizumab or IL-1 blockade as an escalation of therapy.
Discussion: There are established associations between several autoimmune disorders and CU. Gene mutation MEFV has been associated with chronic urticaria and FMF, which ultimately helped better symptomatically treat with medications that are not used for chronic urticaria. This case demonstrates the importance of recognizing underlying autoinflammatory disease in the setting of CU and the utility of genetic testing in identifying treatment options.

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A Novel Variant in STAT3 in a Patient with Immune Dysregulation

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Signal transducer and activator of transcription 3 (STAT3) plays a crucial role in immune system differentiation and regulation. Gain-of-function mutations in STAT3 have been linked to early-onset autoimmunity and lymphoproliferation, leading to dysregulated and hyperactive immune responses [1]. Here, we describe a previously unreported variant in the STAT3 gene in a pediatric patient with Evans syndrome.

The patient, a 13-year-old male, was diagnosed with Evans syndrome at age 3 after experiencing recurrent episodes of autoimmune anemia, neutropenia, and thrombocytopenia, which were poorly responsive to intravenous immunoglobulin (IVIG), frequently requiring corticosteroids, and he was transitioned to sirolimus. Evaluation for autoimmune lymphoproliferative syndrome at the time of initial diagnosis was significant for normal B and T cells, no mention of double-negative T cells, and hypocellular bone marrow. A variant of uncertain significance in FADD, (c.66G>A (p.Glu22=)) was reported, which has since been reclassified as likely benign. The patient continued to have thrombocytopenia and developed intermittent splenomegaly, and lymphadenopathy, and diffuse eczematous dermatitis. He has had multiple hospital admissions for refractory thrombocytopenia and viral and bacterial pneumonias. He also has extensive pansinusitis, mastoiditis, and recurrent otitis with hearing impairment. The family history is significant for liver failure of unknown etiology, necessitating a liver transplant, and a sister with inflammatory bowel disease. Genetic testing for inborn errors of immunity and cytopenias revealed a variant of uncertain significance: a missense mutation in exon 21 of the STAT3 gene, STAT3 (c.1987_1988delinsCT (p.Thr663Leu)).

The patient's clinical presentation is consistent with STAT3 gain-of-function syndrome, characterized by autoimmune cytopenias, lymphoproliferation, dermatitis, and frequent infections. Although this exact variant has not been previously documented, a similar missense mutation, p.Thr663Ile, has been implicated in STAT3 gain-of-function syndrome. Functional studies are ongoing to further assess the pathogenicity of this variant and familial variant testing is pending. We propose that this novel STAT3 variant may contribute to a phenotype consistent with STAT3 gain-of-function syndrome, leading to immune dysregulation in our patient.

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Paraneoplastic Hypereosinophilia Associated with Lung Squamous-Cell Carcinoma

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Introduction: Eosinophilia poses a unique diagnostic challenge due to association with a wide range of clinical presentations and underlying pathophysiology. Paraneoplastic syndromes represent an exceptionally rare cause for hypereosinophilia, though should be considered in association with solid tumors where infectious, inflammatory, and neoplastic evaluations are otherwise unrevealing.

Case Description: A 69-year-old man with a history of cardiovascular disease, type 2 diabetes, tobacco use, and recently diagnosed lung squamous cell carcinoma with extensive liver metastases was admitted to the hospital for altered mental status. The exam was unremarkable, and MRI brain noted interval small area of restricted diffusion in bilateral cerebral hemispheres which was ultimately felt to be artifactual; however, during admission, he developed intermittent fever and rigors with leukocytosis (WBC 44.8 K/μL) and progressive eosinophilia (peak 5.9 K/μL from ~2 K/μL) as well as elevated absolute neutrophil, monocyte, and granulocyte counts without blasts. Quantitative lymphocyte subsets reflected normal absolute counts with elevated CD4:CD8 ratio (3.08). Additional infectious evaluation included negative blood cultures, respiratory viral panel, HSV qPCR, *Cryptococcal/Histoplasma/Blastomyces* antigen, and *Coxiella/Echinococcus/Strongyloides/Toxicara* antibodies with no culture growth from IR-guided aspiration of liver lesions. Further targeted evaluation of eosinophilia reflected negative ANCA and MPO/PR3, stable troponin, normal tryptase level, negative KIT D816V mutational and clonal TRG rearrangement analyses, and eosinophilia FISH panel without evidence of FIP1LI::PDGFRA gene fusion or PDGFRA/PDGFRB/FGFR1/JAK2 rearrangements.

Discussion: Given the negative laboratory evaluation, lack of rash or defining features of EGPA, and inconsistent temporal association with any specific medications, the persistently rising eosinophil count was felt most likely secondary to underlying squamous cell carcinoma. Multidisciplinary discussion surrounding corticosteroid treatment was initiated in light of concurrent malignancy and septic

presentation, though while infectious evaluation remained pending, the focus of care was ultimately transitioned to comfort, so this has thus far been deferred. This case represents a rare but recognized phenomenon in the literature, particularly with carcinomas arising from mucin-secreting epithelium such as that found in the bronchus and gastrointestinal tract, which should be considered among the differential for eosinophilia and may portend more aggressive disease with poor prognosis.

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A Late Diagnosis of Chronic Granulomatous Disease

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A 49-year-old man presented for immunologic evaluation due to recurrent infections since childhood. He had frequent staphylococcal skin infections related to minor skin trauma, including forceps used during delivery, but no abscesses requiring drainage. He was first hospitalized as a teenager with lymphadenitis and pneumonia. At 21 years, he had spontaneous splenic rupture requiring splenectomy. At age 25, he was hospitalized with pulmonary nocardiosis. At age 30, he was hospitalized with pulmonary aspergillosis for the first time. By the time of presentation, he had five episodes of pulmonary aspergillosis and one episode of cutaneous aspergillosis, each treated with prolonged courses of antifungals. He had not received antimicrobial prophylaxis outside these treatment courses. He continued to have bacterial pneumonias, cellulitis, and onychomycosis throughout adulthood. In his early 40s, he developed a chronic cough and dyspnea. A lung biopsy demonstrated noncaseating granulomas, favored to be hypersensitivity pneumonitis. His symptoms were controlled with mycophenolate monotherapy for two years until he stopped taking it and subsequently required chronic corticosteroids. Given the recurrent *Aspergillus* infections, a neutrophil oxidative burst was sent and found to be 7%, raising concern for chronic granulomatous disease (CGD). He had no family history of immunodeficiency. Further immunologic evaluation revealed normal quantitative immunoglobulins with protective levels of tetanus, diphtheria, and pneumococcal titers, and normal lymphocyte subsets. Repeat neutrophil oxidative burst was 1.3% with a normal control. Genetic testing for inborn errors of immunity was negative, including CGD-associated genes CYBB, CYBA, NCF2, and NCF4. Daily antifungal and antistaphylococcal prophylaxis were started.

This case highlights a late diagnosis of CGD in the 5th decade of life. His infectious pattern was relatively mild until his 20s, when he began to have recurrent pulmonary infections with catalase-positive organisms, possibly due to some residual NADPH oxidase function. The mean age of diagnosis for X-linked CGD is 3 years, while the autosomal recessive form is diagnosed at a mean age of 7.8 years. Interestingly, initial genetic testing for this patient was negative, despite his phenotype being consistent with CGD and repeatedly abnormal oxidative burst. Additional testing, including NCF1, is being sent to further evaluate for a monogenic cause.

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Catatonia and Autoimmune Encephalitis Triggered by *Mycoplasma pneumoniae* Infection with GAD-65 Antibodies: A Case Report

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Background: Autoimmune encephalitis (AE) is a rare but significant neurological condition characterized by immune-mediated inflammation of the central nervous system. This report highlights a case of AE associated with GAD-65 antibodies following a *Mycoplasma pneumoniae* infection, emphasizing the immunological underpinnings and diagnostic challenges.
Case Presentation: An 18-year-old male with a history of ADHD and tics presented with altered mental status, disorientation, and catatonia. Initial symptoms included sore throat and fever treated with dextromethorphan-containing over-the-counter medications. In the emergency department, a positive rapid strep test raised concern for PANDAS, while suspicion of dextromethorphan toxicity prompted supportive care. Persistent symptoms, including autonomic instability, catatonia, and cognitive decline, led to further investigations for infectious and autoimmune etiologies. Diagnostic workup revealed positive *Mycoplasma pneumoniae* respiratory panel and

elevated inflammatory markers. Empirical treatments including ceftriaxone, vancomycin, and azithromycin were initiated. Neuroimaging was normal, and CSF analysis was unremarkable for infectious agents. Persistent encephalopathy and episodes of catatonia necessitated intravenous immunoglobulin (IVIG) for suspected autoimmune encephalitis, leading to significant clinical improvement. GAD-65 antibodies were later identified on the CSF encephalitis panel.

Discussion: The presence of GAD-65 antibodies, typically associated with neurological syndromes such as stiff-person syndrome and limbic encephalitis, underscores the autoimmune mechanism of this case. *Mycoplasma pneumoniae* is recognized as a trigger for post-infectious immune responses, further complicating the clinical presentation. This case highlights the interplay between infection and autoimmunity in precipitating encephalitis, necessitating a multidisciplinary approach involving neurology, psychiatry, infectious disease, and immunology. IVIG therapy demonstrated efficacy in reducing inflammatory markers and resolving catatonia.

Conclusion: This case emphasizes the importance of considering autoimmune mechanisms in encephalitis, particularly in the context of recent infections. The identification of GAD-65 antibodies and the role of *Mycoplasma pneumoniae* as a potential trigger provide critical insights into the immunopathogenesis of AE and its management.

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KMT2A Haploinsufficiency in a Patient with Multiple Congenital Anomalies, Recurrent Sinopulmonary Infections, and Relapsed Hodgkin Lymphoma

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Wiedemann-Steiner syndrome (WSS) is characterized by developmental delays, short stature, characteristic facial features, multisystem congenital anomalies, and hypertrichosis (especially hypertrichosis cubiti, or hairy elbows) [1]. Approximately 250 cases have been reported, and at least 89 likely pathogenic monoallelic variants identified in its causative gene, KMT2A. Though autosomal dominant, over 55% of KMT2A mutations are de novo [1-3]. Recent identification of novel KMT2A variants has illuminated significant heterogeneity in genotype–phenotype correlation with WSS and its increasing association with immunodeficiency [1-7].

We present a 10-year-old male with developmental delays, congenital cardiac defects, horseshoe kidney with VUR and recurrent UTIs, pyloric stenosis, constipation, and poor dentition, diagnosed with Hodgkin lymphoma at age 8. He achieved remission after six cycles of therapy but relapsed within 18 months. During treatment, he was hospitalized multiple times for pneumonia. BAL on separate occasions revealed EBV and *Haemophilus influenzae*. Before lymphoma, he had recurrent skin and respiratory infections. Immunologic evaluation with lymphocyte subsets at initial diagnosis showed lymphopenia with proportionally decreased T and B cell subsets. IgG and IgM were low-normal with elevated IgA. Four months off therapy, CD4 lymphopenia persisted with normal CD8 and B cell numbers with an inverted CD4/CD8 ratio. Evaluation is limited given the influence of immunochemotherapy. Respiratory infections persisted despite scheduled IVIG. Whole exome found a likely pathogenic, de novo nonsense mutation in KMT2A (c.9487 C>T p.(Arg3283Ter).

This fits the WSS phenotype, including hypertrichosis, downslanted palpebral fissures, and CVID-like phenotype [1-7]. KMT2A encodes a lysine methyltransferase with an integral role in transcriptional regulation of hematopoiesis [8, 9]. This case is first to report a KMT2A-associated Hodgkin lymphoma and additionally novel, its consistency with WSS [8-12]. ClinVar and GnoMad queries suggest his variant to be distinct in the clinical literature.

Currently, our patient is undergoing salvage immunotherapy, pending high-dose chemotherapy with BEAM/rituximab and autologous HSCT [13]. High-risk features of his lymphoma and immunodeficiency justify the plan for subsequent reduced intensity allogeneic HSCT [12, 14, 15]. This case emphasizes the need to improve understanding of the increased risk of lymphoma in CVID, its associated molecular pathways, and how these may impact treatment decisions.

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A Copy Number Gain in NFKB2 in a Patient with Immune Dysregulation

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Pathogenic variants in the NFKB2 gene are strongly associated with B cell dysregulation. Here, we present a copy number gain of the entire NFKB2 gene in a patient with immune dysregulation.

An 18-year-old young man previously diagnosed with immune thrombocytopenic purpura (ITP) at the age of 4 was admitted for pneumococcal meningitis. Regarding his prior history, he had been on eltrombopag, although required oral corticosteroids several times annually for ITP crises. The patient reported intermittent lymphadenopathy; a cervical lymph node biopsied at age 10 showed reactive lymphocytes. Two previous bone marrow biopsies revealed hypocellular marrow but no other significant abnormalities. Prior immune evaluation demonstrated poor vaccine responses despite boosters, although there were no previous serious infections. His mother reported she had autoimmune pancreatitis and the patient's brother having vitiligo. Imaging during admission demonstrated extensive sinus disease, enhancement concerning for bacterial meningitis, an incidental Chiari type 1 malformation, and a sinus venous thrombosis in the superior sagittal sinus. He was treated with a prolonged course of antibiotics and a bivalirudin drip and transitioned to apixaban upon discharge.

Given the history of long-standing ITP and a serious invasive infection, further evaluation for immune dysregulation was performed. Laboratory evaluation was remarkable for hypogammaglobulinemia, absent tetanus, diphtheria, pneumococcal, measles, mumps, and varicella titers, and low class-switched memory B cells. Abdominal ultrasound showed a spleen size at the upper limit of normal. Genetic testing via an inborn errors of immunity (IEI) and cytopenias panel revealed an NFKB2 gain (entire coding sequence), copy number = 3 of uncertain significance.

Currently, a monogenic cause is found in less than 30% of patients with IEIs, specifically in those with immune dysregulation. Including copy number variants (CNVs) will improve diagnostic yields for IEIs as CNVs may modify disease expression. In our patient, the copy number gain may lead to overactivation of NFKB2, causing immune dysregulation and inflammation. Parental testing is pending, and functional validation is being pursued. As genetic testing becomes standard of care, integrating CNV analysis into routine sequencing will aid in diagnosis and improve treatment options for patients.

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A Case of NEMO Deficiency Syndrome in a 2-Month-Old Male from Belarus

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Introduction: Nuclear factor kappa B essential modulator (NEMO) deficiency syndrome is a rare X-linked recessive genetic disorder characterized by a wide range of clinical features, including increased susceptibility to bacterial and mycobacterial infections, as

well as skin manifestations such as ectodermal dysplasia, dental abnormalities, hypospadias, and alopecia. The syndrome is caused by mutations in the IKBKG gene. Hypomorphic mutations in the IKBKG are associated with two clinically distinct conditions: hypohidrotic or anhidrotic ectodermal dysplasia with immunodeficiency and incontinentia pigmenti. These differences may result from the specific types and locations of the mutations, as well as the mosaic expression of IKBKG due to random X-chromosome inactivation in heterozygous females.

Materials and Methods: This case report describes a 2-month-old male who presented with a history of *Enterobacter aerogenes* and *Klebsiella pneumonia* infections, osteogenesis imperfecta, and erythematous skin lesions. The patient's mother and sister exhibited symptoms consistent with incontinentia pigmenti. Genetic analysis was carried out by whole-exome sequencing (WES) using Exome Capture V5 Probe Set (MGI). WES was performed using a DNBSEQ-G50 genetic analyzer (MGI). Clinically significant observations were confirmed by Sanger sequencing.

Results: Genetic analysis of the gDNA sample identified a heterozygous pathogenic variant in exon 10 of the IKBKG gene (NM_003639.4: c.1167dupC, p.Glu390ArgfsTer5). The presence of heterozygous variants in IKBKG gene, located on the X-chromosome in males, may be due to the presence of pseudogenes IKBKGP1. Long-range PCR (LR-PCR) was performed to confirm the presence of pathogenic mutation in the IKBKG gene. As expected, Sanger sequencing of the LR-PCR amplicon confirmed the pathogenic variant c.1167dupC in a hemizygous state.

Conclusion: We report the first genetically confirmed case of NEMO deficiency syndrome in Belarus. Our results demonstrate that heterozygous genetic variations in the IKBKG gene observed in boys may be caused by the presence of the IKBKGP1 pseudogene, and the approach to genetic diagnosis employed enables us to detect potential pathogenic variants and differentiate between them derived from IKBKG or its pseudogene.

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Acute Liver Failure Unmasking XIAP Deficiency in Very Early-Onset Inflammatory Bowel Disease

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Introduction: X-linked inhibitor of apoptosis (XIAP) deficiency is a rare inborn error of immunity with particularly pleiomorphic spectrum of manifestations. These include hemophagocytic lymphohistiocytosis (HLH) with and without primary EBV infection, inflammatory bowel disease (IBD), uveitis, and episodic fevers. Liver manifestations have been rarely reported. Herein we describe severe acute liver failure (ALF) in a patient with very early-onset IBD found to have XIAP deficiency.

Case Presentation: The patient presented at 5 years of age with intermittent bloody stools, a perianal skin tag, and a history of intermittent fevers since infancy. Endoscopic evaluation at 6 years of age showed ulcerations and histologic colitis and granulomas. He was initiated on infliximab with good clinical response. Concurrent with his IBD evaluation, he was noted to have elevated liver enzymes. Twenty-one months after diagnosis, he developed fever, right upper quadrant pain, nausea, scleral icterus, liver enzymes to the 2000s, and cholestasis without synthetic dysfunction. EBV serologies were IgM positive. Transaminases improved spontaneously, but five days later, he re-presented with marked transaminitis, worsened cholestasis, and new synthetic dysfunction. He was transferred to a tertiary academic referral center ICU with high fevers and encephalopathy for management of ALF. HLH biomarkers were only modestly elevated: ferritin 290, Hgb 9.2, Plts 177, ANC 1620, fibrinogen 103, sIL-2Ra 1500, IFNg 128, and CXCL9 2959. EBV serologies and serial PCRs were negative. IL-18 was 12079. He was treated with IV glucocorticoids and emapalumab with stabilization. Flow cytometry showed XIAP deficiency, and anakinra was added with gradual resolution of liver dysfunction. Whole-genome sequencing revealed an XIAP frameshift variant (c.1021_1022del, p.(N341Yfs*8)). Emapalumab was replaced with ruxolitinib as the patient was preparing for hematopoietic stem cell transplant.

Discussion: XIAP-deficiency is remarkable for its range and severity of inflammatory phenotypes, including HLH and refractory IBD. Here we present a rare case of ALF in XIAP-deficiency. Antecedent, transient EBV infection was a likely trigger. His ALF improved with steroids, emapalumab, and IL-1 blockade. A high index of suspicion for immune dysregulation should be employed in all cases of VEO-IBD and/or liver failure.

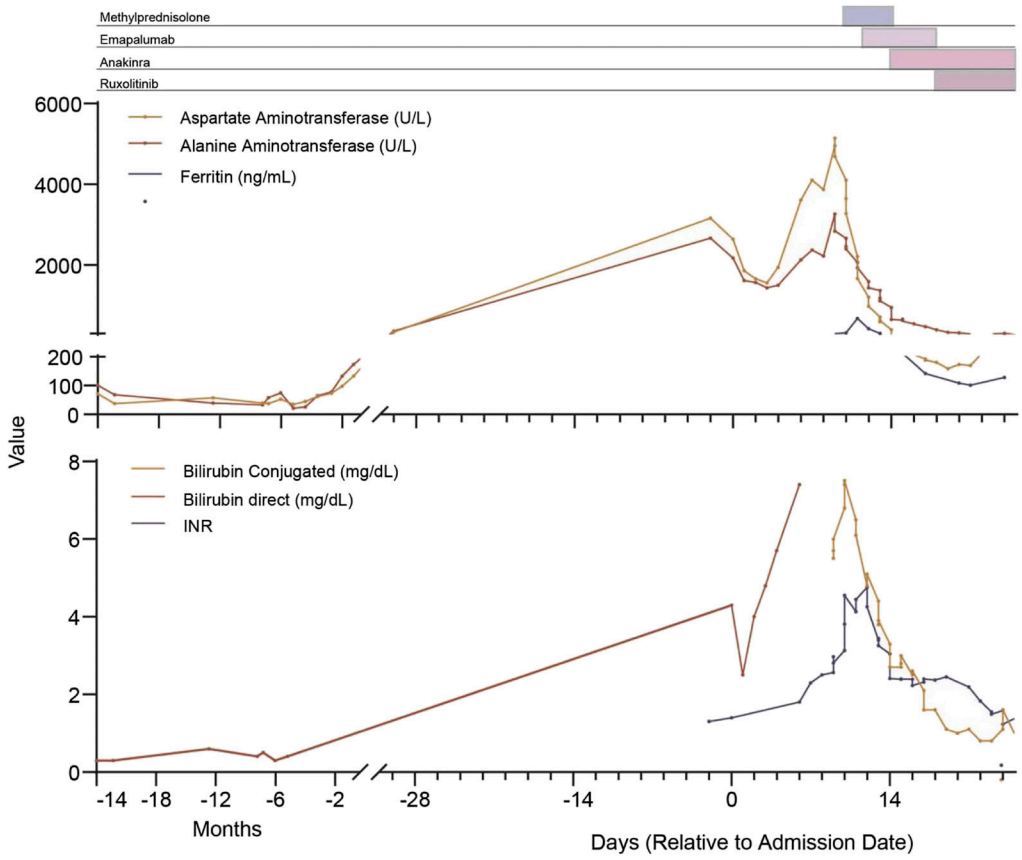

Figure 1. Laboratory trends and therapeutics. Day 0 represents initial hospitalization for acute liver failure.

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Immune Cells and Key Biomarkers in COVID-19 Patients

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Higher level of IP-10, MCP-1, IL-6, and functional exhaustion of cytotoxic lymphocytes, NK cells, and inflammatory monocytes causing excessive noneffective host immune responses which results in lung functional disability and quick mortality in COVID-19 patients.

The aim of this study is to observe the associations of IP-10, MCP-1, IL-6, and lymphocytes and monocytes in peripheral blood with disease severity in COVID-19 patients.

The study period was from March 2021 to January 2022. A total of 84 COVID-19 patients confirmed by positive RT-PCR and 28 healthy subjects were enrolled in this study. The peripheral venous blood sample was collected to detect the serum level of IP-10 and MCP-1 and IL-6 by ELISA method, immunophenotyping of lymphocytes, and monocyte was done by flow cytometry.

The serum IP-10 level (pg/ml) was significantly higher among critical patients (1525 ± 1523.1) compared with severe (610.7 ± 879.2) and moderate patients (92.0 ± 100.4) and healthy controls (46.7 ± 77.3). Serum MCP-1 level was also higher among critical patients (1132.3 ± 1510.8) compared with severe (485 ± 968.3) and moderate patients (246.7 ± 367.8) and healthy controls (79.7 ± 64.0). Serum IL-6 level (pg/ml) was considerably higher among critical patients (102.02 ± 149.7) compared with severe (67.20 ± 129.5) and moderate patients (47.04 ± 106.5) and healthy controls (3.5 ± 1.8). Correlation among IP-10, MCP-1, IL-6, and monocyte showed statistically significant with disease severity (IL-6 = severe group, $p < .001$, and .867*** and critical group $p < .001$ and .887***; IP-10 = severe group, $p < .001$, and .809*** and critical group $p < .001$ and .827***; MCP-1 = severe group, $p < .001$, and .839*** and critical group $p < .001$ and .856***).

T cells, B cells, NK cells, CD4+ T cells, CD8+ T cells and monocytes were significantly decreased in critical group compared with healthy, moderate, and severe group ($p < .001$), suggesting that count of lymphocytes and monocytes might be used as an indicator of disease severity.

Increased expression of exhaustion marker CD94/NKG2A on NK cells and CD8+ T cells in severe and critical group might contribute to the disease pathogenesis.

Serum level of MCP-1, IP-10, and IL-6 might be used as a diagnostic as well as prognostic marker for the assessment of COVID-19 outcome as it correlates with COVID-19 disease severity and mortality.