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Meeting Abstracts

JHI Journal of Human Immunity

Abstracts from the 2026 Clinical Immunology Society Annual Meeting: Immune Deficiency & Dysregulation

May 6–9, 2026

New Orleans, Louisiana

All abstracts were reviewed and approved by the Clinical Immunology Society Program Committee, which held full responsibility for the abstract selections

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CIS MEETING ABSTRACTS 2026

Oral Abstracts

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A First-in-Human Base Edit Gene Therapy for CD40L Deficiency X-Linked Hyper IgM (XHIGM) Syndrome

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CD40L-deficient X-linked hyper IgM (XHIGM) syndrome is characterized by defective B cell class switching, deficiency of immunoglobulins G, A, and E, plus other immune abnormalities due to disrupted CD40L–CD40 interaction. Allogeneic hematopoietic stem cell (HSC) transplant can cure XHIGM but requires myeloablative conditioning and risks graft versus host disease (GVHD), posing a high mortality risk. We developed ex vivo base editing (BE) of autologous HSC and T cells to treat a 37-year-old man (P1) diagnosed late in life with a CD40LG c.C>T p.Q220X mutation in a single-patient Investigational New Drug application targeting his mutation (IND32000; NIH protocol 002385). Preclinical studies achieved >90% gene correction of P1 HSC and T cells with base editor ABE8e SpWT/A5 guide, devoid of significant unintended off-target edits. BE-HSC was intended as a definitive transplant to achieve long-term hematopoietic and immune reconstitution, whereas the BE-T cells were designed to serve as a transient bridge therapy of functional T cells during the period preceding differentiation of T cells from the BE-HSC graft.

P1 presented pre-gene therapy with sclerosing cholangitis, cryptosporidium infection, nodular regenerative hyperplasia, portal hypertension, bronchiectasis, and lacked HLA-matched donors. Autologous BE-HSC transplant was given after low-dose busulfan conditioning together with prophylactic defibrotide to mitigate chemo-related veno-occlusive disease.

The original treatment schema was alemtuzumab (days −21, −20, −19), busulfan 6mg/kg total (days −3, −2) with prophylactic defibrotide, BE-HSC (day 0), and BE-T on day +14 and as indicated for lymphopenia and/or infection. Following alemtuzumab, P1's baseline abnormal liver function tests (LFTs) worsened (transaminases approximately doubled, bilirubin increased ∼18-fold) with persistent detection of previously undetectable cryptosporidium. We paused busulfan and BE-HSC and administered BE-T products, which corrected LFTs sufficiently to allow uneventful busulfan conditioning and BE-HSC product infusion. Post-treatment at months 1 and 2, blood studies confirmed robust engraftment with normal wild-type alleles in myeloid cells (>90%) and increasing levels in natural killer (>60%), B (>40%), and T (27%) cells and with first-time detection of class-switched IgG+ B cells.

This innovative, dual-product strategy provides immediate, on-demand immune protection through infusion of functional BE-T cells, effectively bridging patients through the critical pre-engraftment period and until BE-HSC achieves durable, multilineage reconstitution.

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A Novel Dominant-Negative IL-2Rβ Variant Underlies Immune Dysregulation Presenting with Lymphadenopathy and Evans Syndrome

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Background: IL-2Rβ (CD122) is essential for IL-2 and IL-15 signaling and for natural killer (NK) and T cell homeostasis. We and others have recently described biallelic loss-of-function IL2RB variants, primarily affecting the extracellular domain, cause immune dysregulation with defects in regulatory T cell (Treg) and NK cell function. These reports highlight growing allelic and functional heterogeneity in IL2RB-associated disease. Here, we describe the first monoallelic intracellular truncating IL-2Rβ variant that acts as a dominant negative, expanding the mechanistic and clinical spectrum of IL2RB deficiency.
Methods: To define the impact of this heterozygous variant IL2RB c.819-2_832del (p.W273Cfs*4), we performed flow cytometry–based immunophenotyping, phospho-flow analysis of IL-2/IL-15–induced STAT5 signaling, and ImageStream assessment of IL-2Rβ localization.
Results: A 4-year-old boy presented with lymphadenopathy and Evans syndrome with immune thrombocytopenia (ITP) and moderate autoimmune hemolytic anemia (AIHA) refractory to treatment—intravenous immunoglobulin (IVIG), steroids, eltrombopag, romiplostim, and sirolimus. Flow cytometric analyses of peripheral blood mononuclear cells (PBMC) revealed reduced $CD8^+$ T cell frequency but with normal CD4 T and mildly reduced Tregs. The B cell compartment showed signs of chronic activation/exhaustion (increased CD21low), while overall NK cell numbers were reduced yet enriched for immature cells. Whole exome sequencing (WES) identified a heterozygous IL2RB deletion, resulting in one allele producing a truncated protein predicted to eliminate endocytosis, JAK1 binding, and receptor signaling. STAT5 phosphorylation was intact in response to IL-7 (positive control) but drastically reduced in response to both IL-2 and IL-15. ImageStream analyses demonstrated increased surface expression of truncated IL-2Rβ over wild-type protein on NK and T cells.
Conclusions: The monoallelic IL2RB c.819-2_832del variant acts as a dominant negative, mechanistically resulting in both impaired IL-2Rβ signaling and endocytosis from the membrane and causing immune dysregulation. This work expands the spectrum of IL-2Rβ–associated disease and highlights distinctions among IL-2Rβ loss of function (LOF), hypomorphic, and dominant-negative states, as well as IL-2RA and IL-2Rγ deficiencies.

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A Whole-Blood Transcriptomic Assay, PrimDx, Reflects Cellular and Humoral Abnormalities in Primary Immunodeficiency

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Early diagnosis of primary immunodeficiency (PID) remains a significant clinical challenge, often delaying treatment and increasing the risk of severe infections. Accurate identification of antibody (Ab) deficiencies typically requires multiple diagnostic modalities, including flow cytometry (FACS), serum immunoglobulin measurements, and clinical criteria, each providing only partial insight into immune function. In this study, we evaluated whether PrimDx, a single whole-blood assay combining RNA sequencing with machine-learning algorithms, could provide a more integrated and reliable assessment of Ab deficiency and immune dysregulation.

Across 54 patients with clinically confirmed PID, including common variable immunodeficiency (CVID), specific antibody deficiency (SAD), X-linked agammaglobulinemia (XLA), activated PI3K δ syndrome, and others, and 16 non-PID controls (non-cystic fibrosis bronchiectasis without clinical immune deficiency), PrimDx showed strong concordance with established clinical tests. Individuals with higher PrimDx scores, reflecting greater immune dysfunction, demonstrated immune profiles consistent with Ab deficiency: reduced total, memory, and switched-memory B cells; lower natural killer (NK) and CD4 T cell counts; and a shift toward naïve-skewed B cell architecture. Transcriptomic patterns of immunoglobulin genes and B cell markers aligned closely with these cellular findings. Serum IgA, IgG, and IgM levels similarly tracked with PrimDx scores, reinforcing this multidimensional coherence.

A multivariate model integrating cellular parameters explained substantial variance in PrimDx scores ($R^2 \approx 0.78$), with naïve B cells, NK cells, and IgM contributing most strongly. Several patients also showed NK cell abnormalities, supporting PrimDx's capacity to detect broader innate-adaptive dysregulation. Vaccine-response testing had been performed clinically, but formal results were available for only

14 PID (11 CVID; 2 SAD; 1 APDS) participants due to interpretability limitations. Among these, three demonstrated normal responses, ten had inadequate responses, and one result was uninterpretable due to high baseline antibody titers. PrimDx classified all 14 as PID positive, aligning with their clinical diagnoses and suggesting that it captures global immune impairment more comprehensively than vaccine-response results alone.

Together, these findings demonstrate that PrimDx integrates cellular, transcriptomic, and immunoglobulin information into a coherent assessment of immune dysfunction. As a single, minimally invasive assay reflecting B cell impairment, Ig reduction, and broader immune imbalance, PrimDx has the potential to streamline and enhance PID diagnostic workflows.

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Autologous Ex Vivo Lentiviral Gene Therapy for Pediatric Patients with Severe Leukocyte Adhesion Deficiency-I Provides Sustained Efficacy with a Favorable Safety Profile

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Background: Severe leukocyte adhesion deficiency-I (LAD-I) results from biallelic deleterious ITGB2 variants leading to deficient/defective CD18 leukocyte expression and impaired endothelial adhesion and extravasation.

Children with <2% of normal CD18 neutrophil expression experience recurrent, life-threatening bacterial and fungal infections, and extensive mortality. Allogeneic hematopoietic stem cell transplantation (alloHSCT) is potentially curative but limited by donor availability, graft-versus-host disease (GvHD), and graft failure (GF).

Aims: To evaluate the long-term safety and efficacy of RP-L201 (marnetegragene autotemcel), an autologous CD34+ hematopoietic stem cell gene therapy utilizing the Chim-CD18-WPRE lentiviral vector carrying ITGB2, including restoration of peripheral blood (PB) polymorphonuclear cell (PMN) CD18 and CD11 expression.

Methods: Patients ≥3 months old with severe LAD-I enrolled in the pivotal phase I/II study (NCT03812263), underwent G-CSF/plerixafor mobilization, apheresis, ex vivo transduction of CD34+ cells with RP-L201, and myeloablative busulfan (cAUC 71.6mg/L*h) conditioning, including therapeutic drug monitoring prior to infusion. Assessments included alloHSCT-free survival, PB PMN CD18 expression, PB vector copy number (VCN) and integration site analysis (ISA), leukocytosis normalization, and infection-related hospitalization annualized events. All patients subsequently entered the long-term follow-up (LTFU) study (NCT06282432).

Results: As of June 18, 2025, nine patients (age at infusion 9.8–117.4 months) were treated and followed for a median (range) of 50.92 (42.6–67.9) months. AlloHSCT-free survival is 100% with no GF. VCN was 0.42–2.4 at 3 months post-infusion and remained durable thereafter with a mean VCN of 1.73 at M12, sustained through M24 and beyond with concomitant sustained PMN CD18 expression. There were no new skin or oral lesions from the end of the parent study to the data-cut date in the LTFU study.

Significant infections (either requiring IV antimicrobials or hospitalization) were markedly (90.7%) reduced from pre-infusion through the following 91 days post-engraftment up to the end of the study. RP-L201 was well-tolerated with no discontinuations or RP-L201-related adverse events. ISA demonstrated highly polyclonal integration patterns without evidence of predominant clones.

Summary/Conclusion: Treatment with RP-L201 results in durable phenotypic correction across all relevant clinical and laboratory parameters of severe LAD-I patients. The long-term benefit-risk profile for RP-L201 remains favorable, with no RP-L201-related adverse events and 100% alloHSCT-free survival.

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Bespoke Base and Prime Editing Approaches for STING-Associated Vasculopathy with Onset in Infancy (SAVI)

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Introduction: STING-associated vasculopathy with onset in infancy (SAVI) is a rare, severe type I interferonopathy caused by gain-of-function mutations in STING1, leading to early-onset systemic inflammation, cutaneous vasculopathy, and life-threatening interstitial lung disease. Current treatments attenuate downstream inflammation without fully addressing the pathogenic driver and carry significant adverse effects. Recently, gene editing has emerged as a paradigm-shifting approach for IEI, with substantial potential for gain-of-function disorders that require allele-specific correction. We present a highly efficient and specific base- and prime-editing strategy that supports both ex vivo and in vivo therapeutic applications.

Results: K562 were transduced to generate stable STING1-WT and STING1-V155M lines (K562wt, K562mut). 8 sgRNAs were screened for base editing across PAM-flexible nucleases (SpCas9-NG, SpRY) in K562mut, and sgRNA2 and sgRNA5 were selected based on on-target editing. Given the high bystander activity observed with sgRNA5, we leveraged a previously developed library-derived in silico TadA design tool to identify >15 variants for testing. The TadA variant prioritized after experimental screening (var_17) reduced bystander editing ($p<0.05$). To overcome bystander constraints, PEGsm was selected for prime editing after comprehensive screening. Top-performing guides and selected editor variants were delivered by electroporation as in vitro–transcribed mRNA, achieving high on-target editing (90.10% ± 2.73%) for sgRNA5 and PEGsm (PE2 and PE3) and 53.48% ± 2.02% for sgRNA2. To functionally assess editing, interferon-stimulated gene transcripts (IFIT1, ISG15, and IFI44L) were quantified by droplet digital PCR (ddPCR) before and after 2′3′-cGAMP stimulation. ISG15 and IFIT1 were significantly reduced in unstimulated K562mut-edited cells (sgRNA2, PEGsm) versus K562mut, while after stimulation, K562wt and K562mut-edited reached the K562mut plateau as expected. In healthy donor hematopoietic stem and progenitor cells (HSPCs), a surrogate sgRNA was used to benchmark editing efficiency within the target window.

Surrogate sgRNA achieved a mean bystander editing rate of 75.0% ± 4.4%. Finally, peripheral blood mononuclear cells (PBMCs) were reprogrammed into patient-derived induced pluripotent stem cells (iPSCs) using non-integrating Sendai vectors. iPSCs were prime edited to generate fully corrected isogenic single-cell–derived clones.

Conclusion: We developed a comprehensive, bespoke base- and prime-editing platform for SAVI, enabling efficient and specific STING1 variant correction with functional normalization of interferon-stimulated genes (ISGs) expression, paving the way for future therapeutic applications. We also generated multiple fully corrected isogenic iPSC clones to support mechanistic studies of SAVI pathogenesis.

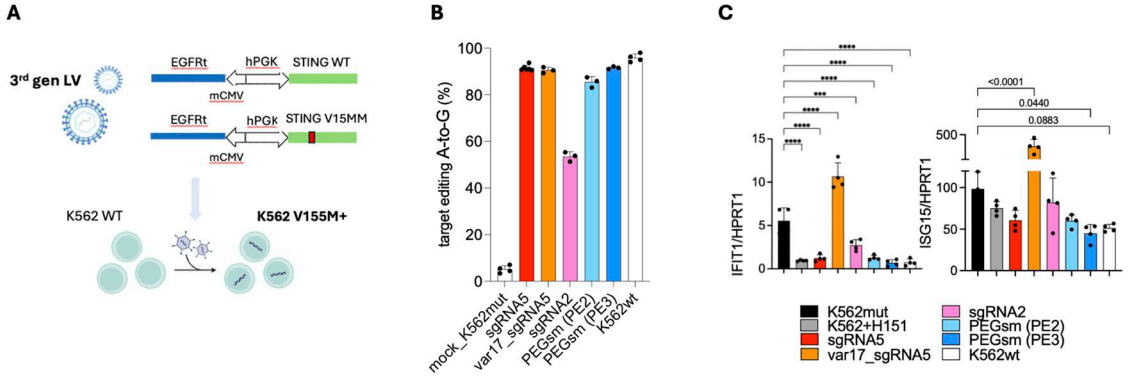

Figure 1. **Engineering of a STING1-V155M K562 model and functional assessment of bespoke base and prime editing. (A)** Bidirectional third-generation lentiviral (LV) vector used to generate stable K562wt and K562mut lines expressing STING1-WT or STING1-V155M together with an EGFRt surface marker.

(B) In vitro transcription (IVT) mRNA electroporation of top guide–editor pairs yields high A-to-G editing in K562mut, including base editing with sgRNA2/sgRNA5, a bystander-reducing TadA variant (var17) with sgRNA5, and prime editing with PEGsm in PE2 and PE3 configurations; editing was quantified by Sanger sequencing (EditR). **(C)** Functional readout by ddPCR showing IFIT1 and ISG15 expression (normalized to HPRT1) in K562mut across editing conditions and after STING inhibition (H-151). Statistics were computed by one-way ANOVA with multiple comparisons correction; significance is indicated, and where not otherwise specified, **** denotes $p < 0.0001$.

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Coexistent Alterations of BAFF and B Cell Biology Associated with CVID Complications

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Background: Common variable immunodeficiency (CVID) is a primary immunodeficiency marked by impaired antibody production and infection susceptibility, with about half developing noninfectious complications. B cell activating factor (BAFF) elevation and genetic variants in a BAFF receptor, transmembrane activator, and CAML interactor (TACI) frequently occur in CVID. While these findings associate with autoimmune and lymphoproliferative complications, pathogenic mechanisms remain incompletely defined.
Objective: This work explored how coexistent changes in BAFF, its receptors, and B cell subsets may shape CVID.
Methods: Plasma protein measurement, spectral flow cytometry, and single-cell RNA sequencing were applied.
Results: CVID with autoimmune cytopenias and lymphoid hyperplasia had elevated plasma BAFF:TACI ratio and increased transitional and activated naïve B cells. Activated naïve B cells from CVID patients had increased mRNA of genes downstream of BAFF receptor (BAFF-R) that promote B cell survival. Also on these expanded subsets, BAFF-R surface protein decreased, consistent with negative feedback, while autoreactive B cell receptor (BCR) VH4-34 clonality increased.
Conclusions: Novel application of spectral flow cytometry, paired BCR sequencing RNA sequencing, and measurement of BAFF and related proteins in plasma found CVID with autoimmune and lymphoproliferative complications to be marked by coexistent BAFF and B cell subset dysregulation. This included increased plasma BAFF, BAFF:TACI ratio, and transitional and activated naïve B cells with reduced BAFF-R expression and BCR repertoire diversity. The expanded activated naïve B cell subset in CVID had increased expression of BAFF-R-driven genes that subvert B cell tolerance, as well as increased autoreactive VH4-34 clonality. Convergence of BAFF, its receptors, and B cell subset dysregulation should be further explored in CVID.

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Decoding RELA-Related Disease: A Spectrum of Immune Dysregulation in a Large Global Cohort

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RELA-related disease is a rare, autosomal-dominant condition presenting with immune dysregulation and immunodeficiency. RELA encodes the p65 subunit, a component of the canonical NFκB pathway. The underlying pathogenesis, at least in part, involves impaired NFκB activation, increased susceptibility to TNFα-induced apoptosis, and hyperinflammation. To date, only a modest number of cases have been documented worldwide, and the full clinical and functional spectrum of disease remains incompletely defined. This study represents a large global cohort identified with RELA variants, comprising 40 patients from 30 institutions, expanding our previous report of a single large kindred (1). The clinical spectrum includes arthritis, mucocutaneous ulcers, uveitis, dermatitis, irritable bowel disease, recurrent infections, lymphopenia, hypogammaglobulinemia, recurrent fevers, and susceptibility to neoplasia. The patients represent 36 kindreds with 28 unique RELA variants, of which 15 are missense, 7 nonsense, and 6 frameshift variants. Fifteen are in the Rel homology domain, 7 in the transcriptional activation domain, and 6 in the C-terminal region proximal to TAD (Fig. 1). Functional studies assessed the canonical NFκB pathway in 27% of the cohort (n = 11; healthy controls = 40). Patient peripheral blood mononuclear cells (PBMCs) were used to quantify total and phosphorylated p65 (ph-p65, Ser529) by flow cytometry after stimulation with PMA (100 ng/ml) and ionomycin (1 uM). In 8 patients, we assessed the kinetics of IκBα degradation, required for p65 phosphorylation and nuclear translocation of p65/p50. All patients tested had decreased total p65, while 64% had decreased ph-p65 with altered phosphorylation kinetics. Nearly 45% had impaired IκBα degradation. One patient (P4) demonstrated increased IκBα degradation and ph-p65, while a related proband (P1) had decreased ph-p65. Additionally, P4 did not have the same mucocutaneous clinical phenotype as P1 despite sharing the same RELA variant. This could reflect the effect of other genetic modifiers, epigenetic, environmental, or stochastic variations, which could lead to variable expressivity and/or incomplete penetrance. All patients appeared to have haploinsufficiency, as none had normal levels of p65. This study expands the clinical and genetic spectrum of RELA-related disease and provides mechanistic insights into the impact of these variants on p65 phosphorylation and downstream function, resulting in variable expressivity.

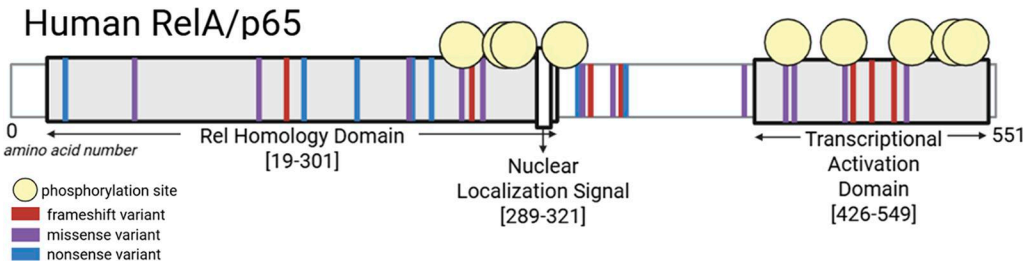

Figure 1. **RelA protein structure.** Represents unique variant locations and categories, key domains, and phosphorylation sites. Source: UniProt. Adapted from (2). BioRender.

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Derivation of Mesenchymal Stem Cells from Induced Pluripotent Stem Cells and Their Application in Genetic Disease Modeling

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Thymic stromal cells drive T cell development by supplying key cues for progenitor proliferation and differentiation. Although thymic epithelial cells are well characterized, recent studies highlight crucial functions of non-epithelial stromal populations, especially neural crest–derived mesenchymal cells. Mesenchymal defects underlie thymic abnormalities in mouse models of DiGeorge syndrome (DGS) and contribute to pathology in CHARGE syndrome, trisomy 21 (T21), and other disorders affecting mesoderm-derived structures. Human studies remain limited due to the rarity of these conditions and restricted access to thymic tissue.

To address this, we generated induced pluripotent stem cells (iSPCs) from individuals with mutations in TBX1, CHD7, HOXA3, and PAX1, as well as from DGS and T21 patients. Control and patient iPSCs, generated from peripheral blood mononuclear cells (PBMCs) or skin biopsies, were differentiated into mesenchymal stem cells (MSCs). Primary thymic mesenchymal cells (ThyMCs) were also isolated directly from thymi. All populations were assessed by flow cytometry and bulk RNA sequencing (RNA-seq).

Flow cytometry confirmed robust induction of MSC markers (CD73, CD146, and CD105) in all MSC and ThyMC samples, with no expression in undifferentiated iPSCs. Principal component analysis showed clear segregation of iPSCs, MSCs, and ThyMCs. Transcriptomic profiling revealed that although all patient-derived MSCs achieved a mesenchymal identity, each disease group displayed distinct transcriptional alterations. MSCs with TBX1, HOXA3, or PAX1 mutations exhibited the highest number of differentially expressed genes, consistent with their upstream roles in thymus development. Dysregulated genes mapped to several clinically relevant pathways, including extracellular matrix (ECM) and cartilage development. Particularly, DGS-derived MSCs and ThyMCs showed marked upregulation of ECM and collagen genes such as FBLN5, PCOLCE, EMILIN1, COL3A1, and COL1A2.

Ongoing tri-lineage (adipogenic, chondrogenic, and osteogenic) differentiation assays continue to uncover pathway defects relevant to T21 and CHARGE syndromes. Overall, these findings provide new insight into thymic development and immune dysfunction in congenital syndromes and establish a platform for probing thymic stromal defects.

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Determinants of Fate Progression Beyond the Human Tfh Cell Stage

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T follicular helper (Tfh) cells have been reported to have multiple trajectories, including terminally differentiated Tfh, memory-like circulatory Tfh (cTfh), and, most recently, induced T follicular regulatory (iTfr) cells (1, 2, 3). While sufficient data have validated the presence of each of these paths, the molecular machinery determining Tfh cell fate remains unclear due to the complex temporal and spatial influences within tissues. To bridge this gap in knowledge, we have applied the human tonsillar organoid (TO) system to study Tfh cell development longitudinally in a tissue-like setting. TOs are an all-human model system containing a range of cell types and stimulatory molecules that recapitulate key features of human follicular biology (4, 2). Our preliminary data suggest that when cultured alone, human tonsillar Tfh cells appear terminally differentiated, but when incorporated into autologous TOs, the same cells spontaneously divide and differentiate. Using intravital labeling of Tfh cells cultured in TOs combined with single-cell analysis, we have mapped the transcriptome of differentiating cells for each cell fate on a per-division basis. We have found that Tfh cells can either: 1) remain undivided and maintain their identities, 2) divide and upregulate markers associated with tissue egress (CCR6, S1PR1, and KLF2) and memory (CCR7), or 3) divide and differentiate into FOXP3-expressing iTfr cells. Using spatial transcriptomics of healthy tonsils, we have verified that each Tfh developmental trajectory maps to a distinct anatomic niche, linking cellular fate decisions to specific tissue microenvironments. In common variable immunodeficiency (CVID) and likely other immunodeficiencies, Tfh cell fate decisions appear to be disrupted (5). Patients often display skewed Tfh subset ratios and impaired humoral responses, suggesting a breakdown in the spatial and molecular

cues that normally guide Tfh development. A better understanding of these developmental pathways and their drivers could inform translational strategies to improve therapeutic targeting and enhance humoral immunity.

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Disseminated Fungal Infection, Hypercalcemia, and Portal Hypertension After Vaginal Seeding in a Neonate with Underlying Chronic Granulomatous Disease

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Introduction: Vaginal seeding has been proposed to restore the microbiome of babies born via caesarean section, but the associated risk of infection is unknown. We present the first case of disseminated candidiasis after vaginal seeding in an infant with chronic granulomatous disease and the challenges faced in controlling the early-onset infection.
Case Presentation: A 15-day-old Chinese-Caucasian male presented with fever, hepatitis, and generalized maculopapular rash that was refractory to antibiotics. His older brother was recently transplanted for chronic granulomatous disease (CGD), and his mother carried the CYBB c.674+1G>A mutation. Routine Bacille Calmette-Guérin (BCG) vaccination was omitted in view of family history, but vaginal seeding was performed due to caesarean delivery. Blood cultures grew Candida species (*Meyerozyma guilliermondii*), and the infection was controlled with intravenous amphotericin-B; however, fever was recurrent on oral voriconazole until subcutaneous interferon-gamma was added. He developed symptomatic hypercalcemia and nephrocalcinosis presumably from excessive macrophage conversion of vitamin D to the active form within granulomas, requiring special low-calcium formula milk for control. He also developed massive hepatosplenomegaly, transaminitis, and portal hypertension. At 7 months old, he received a TCRαβ/CD45RA-depleted haploidentical stem cell transplantation from his father with myeloablative conditioning (alemtuzumab, fludarabine, thiotepa, and treosulfan). Post-transplant, he required CD3+ donor lymphocyte infusions for silent graft rejection and low CD3 chimerism, with eventual full chimerism and resolution of infection, hepatosplenomegaly, and portal hypertension.
Discussion: This early presentation with disseminated candidiasis highlights the pitfalls of vaginal seeding in neonates with underlying immunodeficiency. Vaginal seeding should be avoided if there is a family history of immunodeficiency or other risk factors. Hypercalcemia is common in granulomatous inflammation, though not previously reported in CGD; it can also be exacerbated by initiation of interferon-gamma. Early diagnosis of CGD and stem cell transplant can potentially reverse complications from disseminated fungal infection, including portal hypertension.
Conclusion: Family history of immunodeficiency or early deaths from infection should be listed as a contraindication to vaginal seeding, and this history should be actively sought and documented during consent taking. Although interferon-gamma is typically used prophylactically in CGD, there may be an adjunct role for control of active fungal infections in CGD patients, which warrants further investigation.

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Human Germline Biallelic Loss-of-Function OSMR Variants Cause Severe Allergic Disease

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Introduction: OSMR encodes oncostatin M receptor beta (OSMRβ), a cell surface receptor of the gp130 family that binds OSM and IL-31, and is highly expressed on fibroblasts. The gp130 family comprises signaling proteins, many of which have been linked to primary atopic disorders (PAD).
Methods: We have been performing genetic evaluations on patients with suspected PADs, and we have identified a cohort with biallelic variants in OSMR. Functionally, we defined the localization of OSMR variants in fibroblasts and in HEK293 cells using flow cytometry. We measured transcriptional signatures and protein signaling in patients' fibroblasts after stimulation with IL-6 family cytokines. We linked OSMR genotype to phenotype using UK Biobank data.
Results: We have now identified six probands from six different kindreds worldwide with biallelic, damaging OSMR variants, including a compound heterozygote p.[(V436D)];[(A349D)] and the following homozygous variants: p.(V436D) (n = 2), p.(Y660fs*16), p.(Q270*), and p.(Q51Tfs*23). All patients had a core phenotype of severe atopic dermatitis, peripheral eosinophilia, and markedly elevated serum IgE. The OSMR variants prevented OSMRβ from localizing to the cell surface, as demonstrated in patients' fibroblasts and in HEK293 cells overexpressing the variants. Stimulation of fibroblasts with OSM resulted in decreased levels of pSTAT1 and pSTAT3; no decrease was noted after stimulation with IL-6 or IL-27. Inflammatory transcriptional signatures were noted in fibroblasts by RNA sequencing, which were restored by WT-OSMR transduction.

The p.(V436D) variant has been reported in gnomAD (v4.1), with 14 homozygous individuals identified, 9 of whom are from the UK Biobank. We obtained clinical data from the UK Biobank, which showed that 7/9 (78%) individuals had either elevated eosinophil levels, allergic manifestations, or a skin phenotype. We systematically tested all homozygous coding OSMR variants reported in gnomAD with a minor allele frequency greater than the p.(V436D) variant (minor allele frequency [MAF]=0.00339). These population variants, localized to the cell surface at the same frequency as WT-OSMR, β and were predicted to be benign by AlphaMissense, unlike the patients' OSMR variants.
Conclusion: We expand our understanding of the role of OSMRβ in human health and disease by describing patients with biallelic loss-of-function variants in OSMR.

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Human Herpesvirus 6 (HHV-6) Infection Impairs T Cell Development in Children with Congenital Athymia Who Have Received Allogeneic Processed Thymus Tissue–agdc (RETHYMIC)

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Background: Congenital athymia (CA) is a rare T cell immune deficiency, fatal without curative treatment with allogeneic processed thymus tissue–agdc (RETHYMIC) implantation (here termed CTTI). The rate and extent of T cell reconstitution following CTTI are variable and may be influenced by infection or autoimmunity prior to implantation. Human herpesvirus 6 (HHV-6), the cause of roseola infantum, is a common infection affecting infants under age 2 years. HHV-6 demonstrates thymocyte tropism and impairs T cell development in murine models. We hypothesize that HHV-6 infection prior to CTTI results in lower T cell reconstitution in children with CA.
Methods: Prospective, single-center study included 29 children with CA who received allogeneic processed thymus tissue–agdc at Duke University between March 2022 and April 2024. Following consent (NCT05329935), participants received similar immune suppression (anti-thymocyte globulin and calcineurin inhibitor) prior to, and following CTTI. HHV-6 PCR test results prior to CTTI categorized the cohorts into HHV-6(positive) or HHV-6(negative). Lymphocyte enumeration at 3, 6, 9, and 12 months post CTTI for CD3+, CD4+, CD8+, and naïve CD4+ T cells was compared in the HHV-6 groups using a Mann-Whitney U test. Outcomes included survival at 24 months post CTTI.
Results: A total of 23 children were characterized as HHV-6(negative) and six as HHV-6(positive). Groups were similar in sex, ethnicity, and etiology of CA. Two participants in the HHV-6(negative) group had prior infection with varicella and EBV, and one participant in the HHV-6(positive) group had dual infection with HHV-6 and EBV. Median age at CTTI was similar among the two groups. At 12 months, median CD3+ counts were significantly lower in HHV-6(positive), 190 cells/mm^3, compared to 512 cells/mm^3 in HHV-6(negative), also with lower CD4+, CD8+, and naïve T cells (p = 0.016, 0.011, 0.04, and 0.029, respectively). Overall mortality at 24 months was higher in HHV-6(positive) compared to HHV-6(negative) but did not reach significance (0.099).
Conclusion: HHV-6 infection prior to CTTI is associated with delayed T cell immune recovery after CTTI and potentially reduced survival. Children with CA should adhere to strict isolation, regular surveillance, and have aggressive treatment for HHV-6.

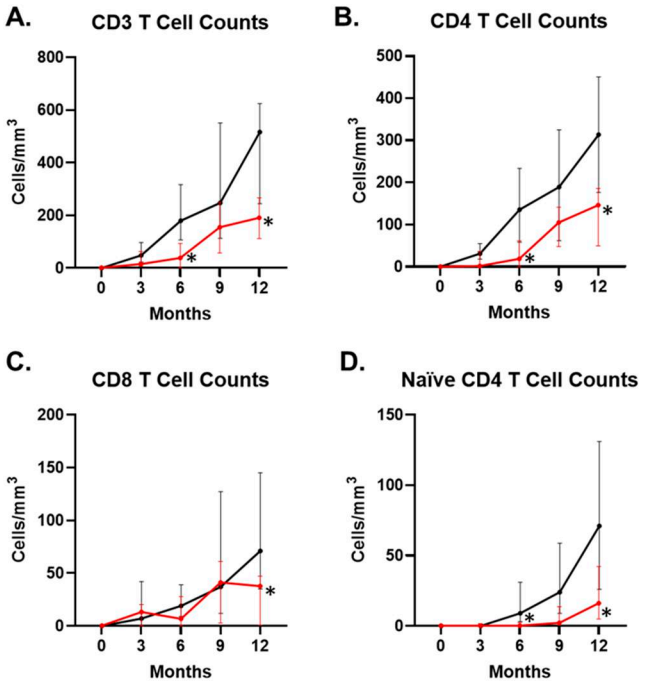

Figure 1. **Changes in T cell subpopulations over time following cultured thymus tissue implantation (CTTI) for infants with congenital athymia.** HHV-$6^{positive}$ are shown as a black line and HHV-$6^{negative}$ in red. The y axis shows median T cell numbers (cells/mm^3), with interquartile ranges of 3 months, 6 months, 9 months, and 12 months post CTTI (x axis). Panel A is $CD3^+$ T cells, panel B $CD4^+$ T cells, panel C $CD8^+$ T cells, and panel D naïve CD4 CD45RA and either CD62L, CCR7, CD27, or CD31 T cells. (*) denotes p< 0.05 Mann-Whitney U test.

Tabular data are included as downloadable supplement files.

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IEI Subphenotype Recognition Using Unsupervised Machine Learning on a National IEI Cohort with Clinical Validation

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Inborn errors of immunity (IEI) are increasing in number, and prompt recognition and diagnosis remain a challenge for clinicians. Use of machine learning (ML) for clinical pattern recognition is promising but has been limited to date. Unsupervised ML presents a methodology for systematic disease pattern recognition with voluminous and complex medical data. We hypothesize that clustering national laboratory data for IEIs will uncover disease subphenotypes guiding further treatment courses.

We extracted laboratory and demographic data for 26,760 IEI patients from Cerner Real World Data, a de-identified US national dataset. Five clustering algorithms (Density-Based Spatial Clustering of Applications with Noise [DBSCAN], Hierarchical DBSCAN [HDBSCAN], Hierarchical, K-means, and K-modes) were implemented for 7 IEI disease groups using lymphocyte measurements and analyzed across 6 age groups. We exemplify our approach here by focusing on DiGeorge syndrome (DGS) within the first year of life. Clusters were scored, ranked, and clinically validated using health record data and domain expertise.

A total of 3,144 experiments were implemented across IEI disease states. We used standard ML evaluation metrics and a custom composite score to identify phenotype clusters for clinical validation. Preliminary results demonstrated rapid discovery of IEI subphenotypes (e.g., DGS; Figure 1). Cluster clinical validation for DGS delineated the following subphenotypes based on frequent diagnostic codes within a cluster: gastrointestinal, cardiac/lung, and gastrointestinal/cardiac pathology. Feature importance analysis revealed significant differences among helper T cell distributions, lifetime leukocyte counts, and mean platelet volumes for patient data (Figure 2). The cluster with greater lung disease diagnostic codes demonstrated the lowest T lymphocyte distributions, while the cluster with a combined gastrointestinal (GI)/cardiac signature

was the only one with patients having qualitative platelet defect codes, while the mean platelet volume (MPV) laboratory distribution was among the highest for the clusters evaluated. These cluster validations may indicate complete versus partial DGS subphenotypes.

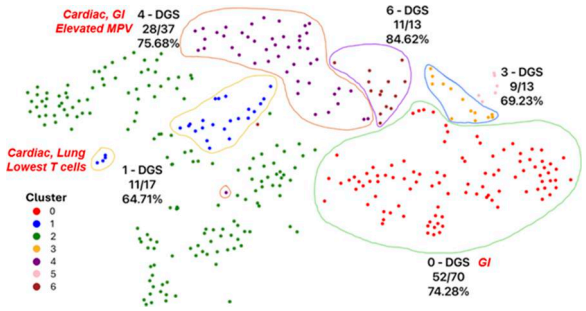

Figure 1. **High-performing clusters for 0–1-year-old agglomerative hierarchical clustering experiment.** Each patient data point is a 5-dimensional vector reduced through principal component analysis (PCA), followed by further reduction via the t-Distributed Stochastic Neighbor Embedding (t-SNE) algorithm to project on a 2D space. The illustrations show the dominant disease group (DGS) in the enclosed cluster and its fractional proportions. The cluster phenotypes based on diagnostic codes and laboratory data are labeled in red italics for clusters 0, 1, and 4. Clusters 3 and 6 had no immune phenotype of relevance.

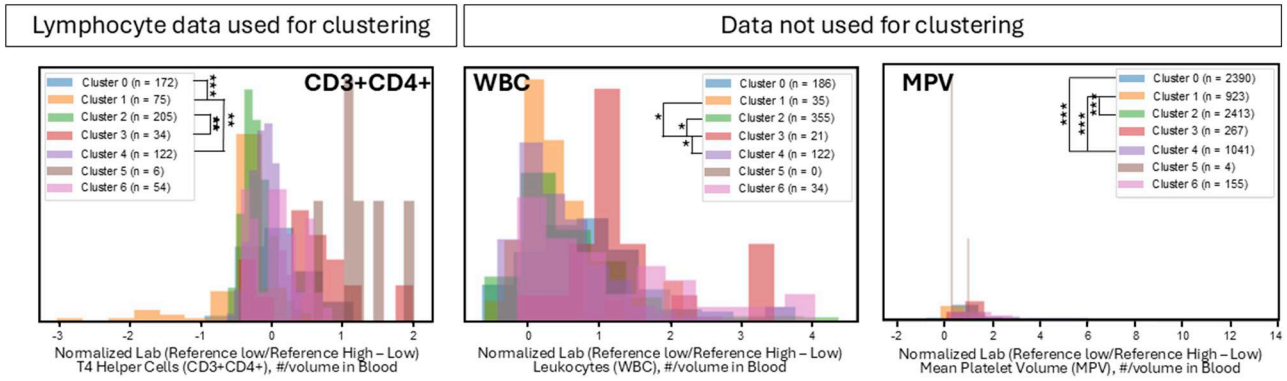

Figure 2. **Clinical validation of DGS clusters using laboratory studies.** Examples of laboratory studies with highly significant differences between DGS patients clustered separately. Distributions for lifetime laboratory data were evaluated for DGS patients across laboratory studies used in clustering algorithms and additional serum studies. Kolmogorov-Smirnov pairwise analyses based on Bonferroni adjustment. *p < 1e-5, **p < 1e-10, and ***p < 1e-15.

We present an unbiased ML approach for IEI subphenotype discovery. Agglomerative clustering using national lymphocyte data of 0–1-year-olds revealed separate DGS phenotype clusters and significant differences in laboratory data. For DGS, our findings may indicate differences in lifetime infection burden and immune health. Downstream evaluation of IEI patient subphenotypes could serve as a basis for multi-omic evaluation, risk screening, and targeted therapies.

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Inborn Errors of T Cell Topographic Memory Underlie Organ-Selective Infectious Diseases

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Background and Aim: Most infections are innocuous in most individuals, and most infectious diseases are confined to specific organs. Inborn errors of tissue-intrinsic, non-leukocytic immunity underlie some organ-specific infectious diseases, but most severe infections remain unexplained. We hypothesize that inherited "lacunar" defects of tissue-homing memory T cells can underlie organ-selective infections.
Methods: We screened >20,000 genomes from patients with severe, unexplained organ-specific infections for candidate variants potentially affecting T cell trafficking. We then performed extensive functional studies to validate disease-causing mutations and define their impact on memory T cell compartmentalization and local immune surveillance.

Results: We identified autosomal recessive deficiency of integrin αL (CD11a), due to biallelic loss-of-function mutations in ITGAL, in otherwise healthy adults of various ancestries with severe, persistent cutaneous lesions due to commensal papillomaviruses. The absence of CD11a does not compromise the development or function of any leukocyte subset, including CD4+ helper and CD8+ cytotoxic T cells. However, the trafficking of skin-tropic memory T cells is severely impaired, resulting in their selective sequestration in the blood and compromising the establishment of tissue-resident memory T cells in the skin. Conversely, alternative integrins mediate the extravasation of other leukocytes, including other T cell subsets, to other tissues. This leads to a skin-restricted T cell immunodeficiency characterized by the expansion of the commensal viral flora, including β-HPV, and a predisposition to skin cancers.
Conclusion: Human integrin αL is essential for steady-state T cell homing to the skin but largely redundant for protective immunity in other tissues. Our study provides proof of concept that severe organ-selective viral diseases can result from lacunar defects in tissue-specific memory T cell homing in patients whose immunity is otherwise intact.

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Multiomic Characterization of Treatment Response to JAK Inhibition in Patients with APECED

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Background: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an inborn error of immunity caused by loss-of-function of the AIRE gene. Lack of AIRE impairs thymic negative selection of T cells, causing multiorgan autoimmunity, making APECED a prototypical disease for failed central tolerance. IFNγ secreted by T cells drives inflammation in APECED, and targeting IFNγ downstream signaling with JAK1/2 inhibitor ruxolitinib remits autoimmunity in the patients. How JAK inhibition affects tissue-specific responses at the single-cell level remains unclear.
Methods: In longitudinal samples from four APECED patients treated with ruxolitinib on a phase-II clinical trial at National Institutes of Health, we combined single-cell RNA sequencing (scRNAseq) from blood, enteritis-affected duodenum, and scalp skin affected by alopecia with serum proteome, autoantibody microarray, and metabolome to characterize tissue-specific autoimmune responses and their normalization upon JAK inhibition.
Results: In tissues affected by autoimmunity, we detected multifaceted cross talk between immune and stromal cells, ushering IFNγ-driven inflammation. Ruxolitinib downregulated expression of tissue-homing chemokines and antigen presentation by stromal cells and resulted in decreased accumulation of immune cells to the tissues, as well as dampening of pro-inflammatory responses. Normalization of tissue homeostasis ensued; for example, hair keratinocytes became detectable, aligning with clinical hair regrowth.

Many of the transcriptional tissue changes were discernible by the serum proteome, and the treatment response was apparent in rejuvenation of proteome-based organ age. However, treatment was also associated with subclinical proteomic changes reflecting potential side effects of JAK inhibitors, including anemia, weight gain, and hypercoagulability.

We expanded the proteome evaluation to 89 additional APECED patients affected by autoimmunity, identifying a patient cluster with the most severe clinical phenotype, highest autoantibody burden, and proteome-based premature aging of multiple organs. These patients had a distinct inflammatory profile, which, in addition to excess IFNγ, was characterized by heightened IL6 responses and TGFβ resistance, partly driven by alterations in sex hormone production.
Conclusions: Multiomic characterization of treatment response to JAK inhibition uncovers pathogenesis and normalization of tissue-specific autoimmunity. JAK inhibitors are increasingly used to target various immune pathways in inborn errors of immunity, and understanding their complex effects systemically and in the tissues is a prerequisite for safe and successful therapy.

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MYB Haploinsufficiency Causes Familial Autoimmune Cytopenias

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MYB is a transcription factor and master regulator of hematopoiesis with a central role at multiple stages of B and T cell development. We identified ten heterozygous germline MYB variants in seven families and four unrelated singletons. The variants segregated with autoimmune cytopenias, including Evans syndrome, in three five-generation pedigrees. In our cohort of 41 carriers, 22 were affected by autoimmune cytopenias, while one had isolated B cell lymphopenia and neutropenia. All ten variants are absent or ultra-rare in population databases and segregate with disease in the kindreds in an autosomal-dominant pattern with incomplete penetrance. In silico analyses predict that the variants are likely to perturb MYB function. Carriers of select alleles (p.R81X, c.1587+1G>C, p.S407Vfs*13, and c.528-1G>T) from whom biospecimens were available exhibited elevated fetal hemoglobin levels, consistent with reduced MYB function given its established role as a fetal hemoglobin repressor. For the p.R81X and p.S407Vfs*13 alleles, we demonstrated reduced protein expression in activated CD8+ T cells, supporting MYB haploinsufficiency as the underlying mechanism. High-resolution immunophenotyping of carriers of the p.R81X, c.1587+1G>C, and p.S407Vfs*13 alleles revealed expanded T-bet-positive B cells and expanded CD4+ and CD8+ terminal effector T cells, suggesting that reduced MYB function affects lymphocyte differentiation pathways relevant to immune regulation. Together, the segregation, computational, functional, and immunophenotypic data establish damaging germline MYB variants as a dominantly inherited cause of autoimmune cytopenias, expand the spectrum of inborn errors of immunity, and support an immunoregulatory role for MYB in activated lymphocytes.

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On-Demand Personalized Gene Editing to Treat IRF4 p.T95A Immunodeficiency

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Background: On-demand gene editing of autologous cells offers a novel therapeutic option for inborn errors of immunity (IEIs) caused by dominant-negative variants, which are often poorly addressed by conventional viral gene addition or hematopoietic stem cell transplantation (HSCT). IRF4 encodes a transcription factor critical for T cell differentiation, Th17 polarization, memory formation, and tissue homing via integrins such as α4β7. Heterozygous neomorphic variants at T95 disrupt IRF4 DNA binding, leading to combined immunodeficiency with susceptibility to severe infections.

Objectives: We aimed to develop an allele-specific editing strategy targeting the pathogenic IRF4 p.T95A variant and to evaluate genomic precision, safety, and functional rescue in edited T cells.
Methods: Base and prime editing (PE) strategies were designed in a K562 reporter line, prioritizing allele-specific PE to minimize bystander and off-target effects. Patient-derived naïve T cells were selected and edited ex vivo via electroporation of PE and PE guide RNAs (pegRNAs). Functional rescue was assessed by flow cytometry and cytokine profiling of effector memory differentiation, Th17 polarization, and α4β7 expression. Genomic precision was evaluated with methods such as variant-aware in silico modeling and amplicon sequencing.
Results: The proband is a 24-year-old man with a de novo IRF4 T95A variant, multidrug-resistant *Mycobacterium avium* colitis, recurrent candidiasis, and EBV-driven lymphoproliferation, for whom HSCT carries prohibitive risk. His T cells exhibit reduced effector memory differentiation, impaired Th17 responses, and diminished α4β7 expression. In the K562 reporter with the patient's IRF4 allele, PE achieved efficient double-digit on-target correction with selective mutant-allele knockout while preserving the wild-type allele. Ongoing work focuses on optimizing PE in primary patient naïve T cells and evaluating phenotypic rescue and genome-wide specificity.
Conclusion: This study demonstrates the feasibility of nonviral, allele-specific prime editing to correct a de novo IRF4 variant in autologous T cells, representing a promising personalized therapy for dominant IEIs.

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SHP1 (PTPN6) Deficiency Defines a New PIRD with Infant-Onset Anemia and Severe Hyperinflammatory Lung Disease

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Primary immune regulatory disorder (PIRD) is a subset of inborn errors of immunity (IEIs) caused by disruption of genes involved in regulating the immune response. PIRDs are predominantly characterized by dysregulated immune activation that leads to organ damage, but may also include susceptibility to infections due to the intrinsic immune gene defect. We identified a novel PIRD in six children from four unrelated families from different ancestries presenting with severe infant-onset hemolytic anemia, life-threatening inflammatory lung disease, and severe pulmonary infections. All but one patient succumbed to disease.

Exome sequencing revealed biallelic coding variants in PTPN6, which encodes SHP1, a protein phosphatase primarily expressed in hematopoietic cells that functions as a critical negative regulator of both adaptive and innate immune signaling. All SHP1 variants are absent from gnomAD and are predicted to be damaging by multiple prediction algorithms (Combined Annotation Dependent Depletion [CADD], Rare Exome Variant Ensemble Learner [REVEL], and AlphaMissense). The variants are all clustered within the SHP1 phosphatase domain, which mediates the removal of phosphate groups from signaling proteins. Functional studies demonstrate that these variants destabilize SHP1 protein levels and markedly reduce or abolish the SHP1 phosphatase activity. These mutant SHP1 proteins also fail to appropriately downregulate ERK signaling following cell stimulation. Bulk RNA sequencing (RNA-seq) from one affected patient showed profoundly heightened inflammatory gene signatures, placing this individual as an outlier relative to a pediatric septic shock cohort, particularly within IL-6/STAT3, TNFα/NFkB, and general inflammatory pathways. These findings parallel phenotypes observed in SHP1-deficient mouse models, which also develop hyperinflammatory disease and anemia due to loss of SHP1-mediated negative regulation.

Collectively, these clinical and experimental data establish PTPN6 loss-of-function as the cause of a severe, newly recognized PIRD characterized by infant-onset severe anemia and life-threatening inflammatory pulmonary disease. Data from SHP1-deficient mice suggest SYK inhibition can prevent the development of inflammatory disease, suggesting potential therapeutic benefit with SYK inhibitors such as fostamatinib. Ongoing studies aim to further define the immunologic consequences of SHP1 deficiency and evaluate targeted therapeutic strategies for patients with this newly recognized disorder.

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The Role of IFNγ in the Pathogenesis of Good Syndrome

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Background: Thymoma, a neoplasm of the thymus, leads to hypogammaglobulinemia in ∼10% of affected patients, resulting in Good syndrome that frequently coexists with autoimmunity and mucosal candidiasis. Thymomas lose the expression of autoimmune regulator (AIRE), causing thymic escape of autoreactive T cells, mirroring the inherited AIRE deficiency Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED). However, the pathogenesis of Good syndrome and the mechanism-based treatment for hypogammaglobulinemia are poorly understood.
Results: We investigated B cell development in 12 patients with Good syndrome. Hypogammaglobulinemia was associated with a block at two stages of B cell development. The majority (n = 9) of Good syndrome patients had an absence of circulating B cells. Their bone marrow revealed lymphocyte aggregates, increased effector T cells with heightened clonality and IFNγ secretion, and associated arrest in B cell development. In the remaining three patients, bone marrow B cell production was intact; instead, peripheral diversion of B cell maturation to inflammatory CD21loCD38- B cells appeared to underlie hypogammaglobulinemia. Notably, these changes were not limited to patients with Good syndrome, as B cell lymphopenia was seen in half of the additional 21 patients with thymoma-associated autoimmunity. In addition to the bone marrow, IFNγ-driven T cell inflammation was present in 9 different tissues affected by thymoma-associated autoimmunity. These included mucosae affected by candidiasis, whereas anti-IL17 antibodies were present in only half of the thymoma patients with candidiasis. Based on these findings, we targeted bone marrow IFNγ responses with cyclosporine in a patient with Good syndrome and associated pure white cell aplasia and depleted infiltrating T cells with alemtuzumab in a patient with APECED-associated pure red cell aplasia and paucity of B cell production. Both treatments led to suppression of bone marrow IFNγ-associated inflammation with normalization of B cell production in the bone marrow.
Conclusions: In thymoma, a shared IFNγ-driven immunopathology in tissues affected by autoimmunity—including the bone marrow and mucosa affected by candidiasis—helps explain how a neoplasm at the site of T cell development may cause both autoimmunity and immunodeficiency. Good syndrome accounts for ∼5% of adult-onset primary hypogammaglobulinemia. Early recognition and intervention could potentially change the trajectory of developing immunodeficiency, avoiding both infectious complications and expensive immunoglobulin replacement.

Thursday Poster Hall

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A Survey-Based Study of Reproductive Health Practices by Immunologists of the Clinical Immunology Society in Patients with Inborn Errors of Immunity

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Introduction: Individuals with inborn errors of immunity (IEI) are increasingly reaching reproductive age, yet guidance on fertility preservation, genetic counseling, medication adjustments in pregnancy and breastfeeding, monitoring for complications, and multidisciplinary coordination is lacking. This joint effort between two committees of the Clinical Immunology Society (CIS), the Women of the Clinical Immunology Society (WCIS) and the Adult Immune Deficiency Committee (AID) survey aimed to characterize current reproductive care practices for IEI patients.

Methods: A survey was disseminated to 809 CIS members. The response rate was 6.43% (52 respondents). The 24-item questionnaire addressed management of pregnancy in IEI, medications adjustment, participation in hematopoietic stem cell transplant (HSCT) care and fertility preservation, and maternal/neonatal outcomes.

Results: Because survey items were optional, the number of respondents varies by question. Forty-two participants completed core items: 64% (27/42) allergists/immunologists, 71% (30/42) practicing at academic centers, and 48% (20/42) with >50% immunology-focused practices. Most respondents (78%, 41/52) currently or previously cared for pregnant/planning IEI patients. Preconception counseling was common (90%, 37/41), yet only 2% (1/41) have access to a formal reproductive multidisciplinary team. Among clinicians involved in HSCT care, 45% (13/29) referred patients for fertility preservation. More than half, 52% (22/42), observed reduced fertility in IEI patients, and 56% (20/36) observed adverse maternal outcomes. Medication management varied: 61% (24/39) discontinued known teratogenic medications, and 64% (25/39) adjusted dosing during pregnancy. Regarding immunoglobulin replacement therapy, 79% adjusted dosing based on IgG levels and 42% increased dosing by trimester.

Conclusions: This CIS survey reveals practice variability and notable gaps in reproductive health support for individuals with IEIs. Due to the relatively low response rate, generalizability across providers and practice settings is challenging. However, the results of this survey suggest that although most clinicians provide preconception counseling and manage IgG and immunomodulatory therapy during pregnancy, formal multidisciplinary structures are rare. High rates of reported fertility concerns and maternal complications underscore the need for enhanced collaboration with obstetrics/gynecology and the development of structured, evidence-based, multidisciplinary guidelines for reproductive care in IEI.

Tabular data are included as downloadable supplement files.

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A 5-Year-Old Female with Neutropenia and Compound Heterozygous Variants in CXCR2

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A 5-year-old female presented at age 2 with recurrent respiratory and ear infections, aphthous ulcers, and severe neutropenia (absolute neutrophil count [ANC] = 400 cells/mcl). Immunological testing at age 4 showed neutropenia, normal T cell, B cell, and natural killer (NK) cell numbers, normal immunoglobulin G/A/M, normal total hemolytic complement, protective tetanus titer, and 3/23 protective pneumococcal titers. The ANC exceeded 1,000 cells/mcl during infections. Bone marrow biopsy demonstrated normal trilineage hematopoiesis, suggesting a neutrophil egress problem.

Genetic testing of immunodeficiency genes revealed two variants of uncertain significance in trans in the gene encoding the neutrophil-selective chemokine receptor CXCR2: c.191T>G and c.865C>T. Both variants are in CXCR2 transmembrane regions and have a gnomAD prevalence of <0.01%.

AlphaMissense in silico prediction scores are 0.86 for c.191T>G and 0.852 for c.865C>T, indicating they are likely deleterious. Each parent was heterozygous for one mutation. c.865C>T has been reported previously in a patient with CXCR2 deficiency and chronic neutropenia.

Functional testing of cells transfected separately with plasmids encoding each variant showed that while each CXCR2 protein was expressed intracellularly, neither variant was expressed on the cell surface, explaining the lack of signaling upon CXCR2 agonist stimulation. Primary patient neutrophils also lacked surface CXCR2 and did not respond in vitro to the CXCR2-selective agonist CXCL2.

To our knowledge, this patient is the 7th identified with severe selective neutropenia, recurrent infections, and complete CXCR2 deficiency caused by biallelic loss-of-function mutations in CXCR2. Neutropenia despite normal neutrophil development is also found in Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome, an inborn error of immunity caused by hyperfunctional mutations in the panleukocyte chemokine receptor CXCR4. Neutrophil distribution is normally a balance of CXCR4-mediated retention in bone marrow and CXCR2-mediated egress from bone marrow. Unlike CXCR2-deficient patients, WHIM patients typically also have severe lymphopenia, may have hypogammaglobulinemia and warts, and do not present with mucositis. Dysmorphic neutrophils are often found in WHIM patient bone marrow but not in CXCR2-deficient marrow.

This case illustrates the crucial value of genetic testing for developing a complete mechanism-based taxonomy of severe congenital neutropenia and other congenital conditions.

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A Biallelic HELIOS Nonsense Mutation Disrupting Dimerization Is Associated with a Novel Syndromic Immunodeficiency

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HELIOS is an IKAROS-family zinc-finger transcription factor that plays an important role in regulatory T cell function and conventional T cell homoeostasis. HELIOS shares a conserved N-terminal DNA-binding and C-terminal dimerization domain with other IKAROS family members. Recent studies have identified germline HELIOS variants in inborn errors of immunity. Most variants are autosomal dominant, with one reported biallelic missense case. HELIOS dysfunction results in a spectrum of clinical manifestations depending on the underlying pathophysiology. Loss-of-function (LOF) variants impairing DNA binding and dimerization functions are associated with combined immunodeficiency and/or immune dysregulation (immune thrombocytopenia [ITP], autoimmune hemolytic anemia [AIHA], systemic lupus erythematosus [SLE], etc.), whereas dominant-negative variants (e.g., G153R, Exon5 duplication) are linked to syndromic presentations, including developmental abnormalities and immune dysregulation. Here, we investigated a patient born to consanguineous parents, carrying a biallelic nonsense variant (R477*) and presenting with immunodeficiency, lymphoproliferation, autoimmune cytopenias, craniofacial anomalies, sensorineural hearing loss, and developmental delay. HELIOS expression was almost absent in the patient's regulatory T cells (Tregs), whereas the mutant protein was detectable in EBV-transformed B cells. The mutant lacked both homo- and heterodimerization due to the absence of the dimerization domain and showed reduced protein stability, suggesting that the loss of HELIOS observed in patient Tregs is likely due to decreased protein stability. Further functional analyses revealed that the mutant failed to localize to pericentromeric-heterochromatin and exhibited abnormal monomeric, rather than canonical dimeric/multimeric DNA binding, features resembling IKAROS dimerization-defective mutations.

Immunophenotyping showed that the patient exhibited an abnormal lymphocyte immunophenotype characterized by decreased Treg and naïve T cells, increased T folicular helper (Tfh) and $CD8^+$-TEMRA cells, and reduced B cell number with low memory B cells. The patient's parents and three siblings are R477* heterozygous carriers. While the parents are healthy, the two siblings exhibit features of immune dysregulation (celiac disease, asthma), which may or may not be associated with the variant. Consistent with previous reports in patients with LOF variants, heterozygous family members show reduced Treg and mucosal associated invariant T (MAIT) cell frequencies, while overall lymphocyte phenotypes remain largely unaffected.

This novel HELIOS-associated disease expands the understanding of pathogenic HELIOS allelic variants, their genotype–phenotype correlation, and mechanisms of disease, while highlighting their impact on lymphocyte subset development and nonimmune manifestations.

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A Novel Immunomodulatory Strategy to Control Multiple Immune Dysregulation Disorders in a Pediatric Patient

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Immune dysregulation can lead to autoimmunity and autoinflammation. The goal of treatment is to balance targeted therapies while avoiding infections or other side effects, which becomes complicated with multiple diagnoses. We present an adolescent female patient

with coexisting systemic lupus erythematosus (SLE), Crohn's disease (CD), psoriasis, and hidradenitis suppurativa (HS) treated with a unique combination of immune suppression.

The patient was initially diagnosed with juvenile idiopathic arthritis at four years of age, with subsequent diagnosis of SLE with cerebritis and nephritis at age 14 years. This prompted treatment with plasmapheresis, corticosteroids, and cyclophosphamide, followed by mycophenolate mofetil (MMF).

Around the same time, she was hospitalized for a severe, widespread rash, with subsequent diagnoses of psoriasis and hidradenitis suppurativa. She was then initiated on treatment with belimumab for SLE, in combination with MMF and steroids. This resulted in initial improvement of her skin inflammation; however, she then developed severe diffuse dermatitis, hematochezia, and *Strep intermedius* necrotizing lymphadenitis. The MMF was subsequently discontinued, with ongoing hydroxychloroquine and steroids.

Colonoscopy demonstrated pancolitis, consistent with Crohn's disease. She was started on infliximab, with partial improvement in gastrointestinal (GI) symptoms, but severe ongoing psoriasis. Immune phenotyping was significant for elevated soluble IL2R, IL-17, and IL-6, in addition to T cell lymphopenia with nearly absent B cells post-belimumab. Genetic testing was unrevealing of a monogenic etiology.

With ongoing GI and cutaneous symptoms, the patient was started on ustekinumab to target IL-12/IL-23 signaling pathways; however, GI symptoms persisted. She was therefore started on upadacitinib, with the goal of targeting broader T cell and innate inflammation beyond the function of ustekinumab.

Antibacterial prophylaxis was also prescribed. On this regimen, all conditions remain well-controlled, without infectious complications.

Multidisciplinary collaboration facilitated an individualized treatment strategy incorporating hydroxychloroquine, upadacitinib, and ustekinumab to treat a combination of SLE, HS, psoriasis, and CD, which can lead to Th1/Th17, innate, and type I interferon-mediated inflammation. While each pairwise combination has been described, the simultaneous use of all three medications, post-belimumab, is novel. This underscores the possibility of safely targeting shared and distinct immune pathways between multiple disorders in patients requiring polypharmaceutical immune modulation.

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A Novel STAT3 N-Terminal Domain Variant Reveals an Alternative Mechanism of Disease Pathogenesis in Hyper-IgE Syndrome

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Autosomal-dominant hyper-IgE syndrome (AD-HIES) is characterized by chronic mucocutaneous candidiasis, recurrent sinopulmonary pneumonias, noninflammatory atopic dermatitis, extremely high levels of serum IgE, and non-immunological manifestations affecting the musculoskeletal and vascular systems. Most cases are caused by heterozygous dominant-negative (DN) variants in STAT3. Approximately 150 unique pathogenic STAT3 variants have been identified in hundreds of ethnically diverse kindreds who present with AD-HIES. Most variants are missense, affecting the DNA binding, SH2, and transactivation domains of STAT3. Remarkably, very few pathogenic variants affecting the N-terminal domain (NTD) have been identified. Here, we present a patient, P1, with a novel variant affecting the STAT3 NTD (R31Q) who presented with disseminated invasive aspergillosis affecting the brain and lung, bronchiectasis, and high serum IgE, but lacking non-immune disease manifestations. Biochemical analyses established that R31Q reduces expression and transcriptional activity of STAT3 and exhibits negative dominance on wild-type (WT) STAT3. We implemented Alphafold3 to predictively model the impact this variant had on STAT3 dimer formation and tested our hypotheses using in vitro biomolecular tests. We found that this variant resulted in enhanced basal dimerization with WT STAT3, thus sequestering STAT3 WT/STAT3 R31Q dimers in the cytosol, dampening nuclear translocation and subsequent transcriptional activity. Lymphocytes from P1 exhibited some typical defects observed in canonical STAT3 LOF/DN HIES (reduced memory B cells, mucosal associated invariant T [MAIT] cells, and Th17 cytokines). However, P1's naïve B cells had only a partial impairment in in vitro Ig secretion to IL-21. More striking were intact Th2 cells and circulating T follicular helper (Tfh) cells. Our findings reveal a hitherto unknown function of the NTD in regulating STAT3 dimer formation and function. This expands our understanding of JAK/STAT signaling, provides a novel biochemical mechanism of disease pathogenesis in STAT3 LOF/DN HIES, and extends the clinical spectrum of patients with STAT3 variants.

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A Site-Specific LLM-Based PHI Redaction Tool to Support Note De-Identification for the United States Immunodeficiency Network (USIDNET)

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The United States Immunodeficiency Network (USIDNET) is a registry that collects de-identified patient data from hospitals across the country to study rare immune conditions, including inborn errors of immunity (IEI). This registry contains both structured data and clinical notes, such as pathology reports and imaging narratives. These text fields may include protected health information (PHI), which must be removed before the data can be added to the registry. To address this, we have developed a tool called "PHIdentifier." Unlike manual de-identification, which is time-consuming and error prone, this tool is designed specifically for clinical notes and automatically removes PHI from the text. It allows valuable clinical details to remain available for research while still protecting patient privacy and supporting better patient care.

PHIdentifier runs on a secure, high-performance computing (HPC) environment to efficiently process large volumes of text data. It uses the Qwen-2.5-7B-Instruct large language model (LLM), combined with rule-based checks, to handle complex text patterns and ensure consistent de-identification across different types of note fields. The workflow starts with standard text preprocessing by organizing and preparing notes to ensure they are clean, structured, and ready for further analysis. The tool then performs a multilayered de-identification process, using carefully crafted prompts to instruct the model to detect PHI from the text. The model's responses are combined with rule-based checks to ensure that only sensitive information is replaced with placeholders, preserving all other clinical content. We perform additional quality checks to ensure data accuracy and consistency across notes, creating a reliable process that converts unstructured text into fully de-identified information.

PHIdentifier was tested on 3,000 narrative and pathology notes, achieving a precision of approximately 97.9–98.1% and a recall of 95.7–97.1%. Nearly all flagged items were true PHI, with only a moderate number of nonsensitive elements over-redacted, and very few direct identifiers, such as hospital names, locations, or years, were missed. This strong performance enables the tool to improve the overall quality and completeness of the registry dataset for rare immunodeficiency disorders. These results show how an LLM de-identification tool can make data collection more efficient and help protect patient privacy.

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Adenine Ribonucleotide (AXP) Depletion Due to Inherited Deficiency of Adenosine Deaminase 1 (ADA)

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Adenosine deaminase 1-deficient severe combined immune deficiency (ADA-SCID) has widely been attributed to the toxic accumulation of adenine deoxyribonucleotides (dAXP) derived from 2'-deoxyadenosine (dAdo). The presence of dAXP in red blood cells (RBC) is pathognomonic, and higher dAXP levels track with phenotypic severity. A less well-known consequence of ADA1 deficiency, depletion of adenine ribonucleotides (AXP), was discovered >40 years ago and documented in RBC of several patients with ADA-SCID. To better characterize the degree of AXP depletion and relationship to dAXP levels and phenotype, we have assessed adenine nucleotide levels in RBC of >700 patients from North America tested for ADA1 deficiency in our laboratory since 2010.

AXP and dAXP were measured in RBC from EDTA blood sent overnight at ambient temperature. AXP in RBC of the 120 ADA patients averaged 35% lower than in 592 who were not deficient (ND), $P < 0.00001$. dAXP were absent in ND RBC, but in ADA-RBC,

they averaged 1.1 ± 0.5 µmol/mL, or 48.4 ± 20% of total adenine nucleotides (TAN = [AXP] + [dAXP]). AXP and dAXP levels were reciprocal, with a stronger negative correlation between AXP and %dAXP than with absolute dAXP concentration. TAN in ADA patients averaged ∼29% higher than in ND patients (in whom dAXP = 0). AXP depletion was restricted to infants <1 year old and patients with >20-25% dAXP—characteristics of ADA-SCID. Older ADA patients and those with <20% dAXP, typical of delayed or late onset, showed minimal AXP depletion. In 68 ADA patients who received enzyme replacement therapy, RBC AXP levels normalized with dAXP clearance.

Our findings show that RBC AXP depletion is a biomarker for ADA-SCID and are consistent with in vitro evidence that dAXP accumulation activates AXP catabolism. ADA-SCID has been widely attributed to dATP-mediated allosteric inhibition of ribonucleotide diphosphate reductase, an enzyme essential for DNA replication. As ATP is an activator and binds to the same site as dATP, AXP depletion should synergize with increased dATP to potentiate reductase inhibition. Thus, the combined effects of elevated dAXP and depleted AXP may account for the more profound lymphocytopenia associated with ADA-SCID than with later onset phenotypes.

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Age Alters Host Innate Immunity and Microbial Subcommunities in the Adult Upper Respiratory Tract

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The composition of the upper respiratory tract (URT) microbiota is shaped by both anatomical niches and host immune defenses. Older adults (>65 years) are at greatest risk of acquiring severe URT infections. However, very little is known about whether age-related changes in the composition of the URT microbiota and host innate immunity contribute to this susceptibility to respiratory infection. We aimed to characterize age-related changes to the composition of the URT microbiota and investigate the modulation of host immune gene expression by microbiota community composition.

The mid-turbinate microbiotas of 270 adults between 20 and 100 years old were interrogated by 16S rRNA sequencing of nasal swabs. We identified dominant microbial subcommunities by latent Dirichlet allocation topic modeling. Dominant microbes, age, and nasal epithelium gene expression were correlated by mixed-effect models. Gene clusters examined include core macrophage markers, inflammatory macrophage genes, chemotaxis and migration genes, and neutrophil-associated genes.

Topic alignment identified 10 subcommunities in the URT microbiome dominated by the following species: *Staphylococcus aureus*, *Staphylococcus caprae*, *Corynebacterium accolens* 1, *C. accolens* 2, *C. accolens* 3, *Corynebacterium propinquum*, *Moraxella catarrhalis*, *Moraxella catarrhalis*, *Corynebacterium tuberculostearicum*, and *Peptoniphilus grossensis*. Subcommunities dominated by *S. aureus* and *C. accolens* had decreasing relative abundance with increasing age, though this was not statistically significant. The *C. accolens* 2-dominated subcommunity was more likely to be dominant and had higher relative abundance with increasing age. The nasal epithelium became more secretory and structurally robust with age, with a reduced expression of cellular plasticity and immune regulation genes. Inflammatory cytokine gene (IL1B, IL16, OSM, and SRGN) expression was significantly upregulated in microbial communities dominated by *S. aureus*, *C. accolens* 2, *C. accolens* 3, and *C. propinquum*. *S. aureus*- and *C. propinquum*-dominated communities also demonstrated significant upregulation of macrophage- and neutrophil-associated genes. In contrast, significant downregulation of macrophage- and neutrophil-associated genes was seen in *S. caprae*-dominated communities. We conclude that increasing age is associated with compositional changes in the adult URT microbiota, which further alter host innate immunity. Understanding age-related changes to the URT microbiota and immune defenses is essential to reduce susceptibility to respiratory infections.

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An Atypical Case of X-Linked Agammaglobulinemia: A Male Child with a Pathogenic Variant in BTK with Preserved IgG and IgM Production and Responsiveness to Tetanus Vaccine

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Background: X-Linked agammaglobulinemia (XLA) is characterized by absent B cell development due to defects in the BTK gene. Patients with this condition have B cell aplasia as well as agammaglobulinemia and impaired vaccine responsiveness. Here, we present an unusual case of a male child found to have a pathogenic variant in BTK with absent circulating B cells and absent IgA but with preserved IgG and IgM production and responsiveness to tetanus toxoid prior to initiation of immunoglobulin therapy.
Case Description: A 6-year-old fully vaccinated male referred to immunology due to a history of *Haemophilus influenzae* bacteremia as well as recurrent cellulitis requiring hospital admission and IV antibiotics to clear. He had one lifetime episode of pneumonia.
Results: Patient was initially found to have undetectable IgA, normal IgG and IgM, and absent tetanus, *H. influenzae*, and pneumococcal titers. Patient underwent a vaccine response assessment where he demonstrated a normal response to tetanus toxoid (2.83 IU/ml), suboptimal response to pneumococcal conjugate PCV-20 (3/20 serotypes protective), and an absent response to *H. influenzae* (<0.15 mcg/ml). Lymphocyte subset analysis by flow cytometry surprisingly showed absent CD19+ cells. We evaluated CD20 as an additional B cell marker, which was also absent. CD3+ cells and CD16/56+ cells were normal. Genetic testing demonstrated a hemizygous pathogenic variant in BTK (c.1517G>A, p.Cys506Tyr). This missense change has previously been observed in individuals with agammaglobulinemia. The patient's mother was unavailable to pursue familial variant analysis. Insurance constraints prohibited our ability to evaluate BTK expression in monocytes.
Conclusion: This case demonstrates a rather unusual presentation of XLA. We postulate his mutation to be hypomorphic and presume there is a small population of B cells that have developed and entered lymphoid tissues and are able to mount some degree of antibody response to particularly immunogenic antigens. Further testing has been limited due to insurance constraints. Atypical presentations of inborn errors of immunity should be considered during the evaluation of individuals with unusual infectious histories.

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An Interpretable, Artificial Intelligence-Empowered Mortality Risk Score for Inborn Errors of Immunity

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One foundational goal of global health and a shared inspiration for all humankind is to reduce premature mortality from preventable and treatable conditions. This imperative becomes markedly more urgent for the uniquely vulnerable population of patients with inborn errors of immunity (IEI), among whom mortality rates exceed the global average by a staggering 27-fold margin over the past 47 years. To reduce this profound mortality burden requires accurate individualized mortality risk prediction and identification of underlying risk factors, yet such tools remain lacking in the IEI field. Here, we developed an interpretable, artificial intelligence (AI)-empowered mortality risk score for IEI patients (IEIMRS) using machine learning and explainable AI techniques on large-scale, real-world US national Electronic Health Records (68,408 patients included with 5,685 deceased and 62,723 censored). IEIMRS outperformed existing intensive care unit (ICU), hospital, and all-cause mortality risk scores in individualized risk prediction (area under the receiver operating characteristic curve [AUROC] of 0.96, 95% confidence interval [CI] = [0.95, 0.97], and Delong test $p < 0.001$) with rigorous calibration (Brier score = 0.03), demonstrating stable and consistently superior performance across patient clinical and demographic subgroups (Delong test $p < 0.05$ for ethnicity, sex, age, and certain IEI subtypes and race). To facilitate broader implementation in diverse clinical settings, a simplified version of IEIMRS with comparable performance using merely 30 features was introduced as well (AUROC of 0.95, 95% CI = [0.94, 0.96], and Delong test $p > 0.05$).

Critically, IEIMRS moved beyond outstanding prediction alone by offering transparent contributing risk factors to interpret each risk estimate. Analysis of these risk factors verified well-established mortality risk factors and identified novel risk factors enriched in IEI patients. Interestingly, at the subtype level, IEIMRS revealed heterogeneity in both mortality risk pattern and risk factor profile across IEI subtypes ($F[1, 42] = 41.54$, $p < 0.001$). As the first mortality risk score specifically designed for IEI populations, IEIMRS enables clinicians to confidently identify high-risk patients through accurate, interpretable predictions. Beyond clinical applications, the identified risk factors

and risk patterns at both cohort and subtype levels offer insight into IEI mortality mechanisms and may inform fundamental immunology research on how specific pathophysiology and manifestations progress to fatal outcomes.

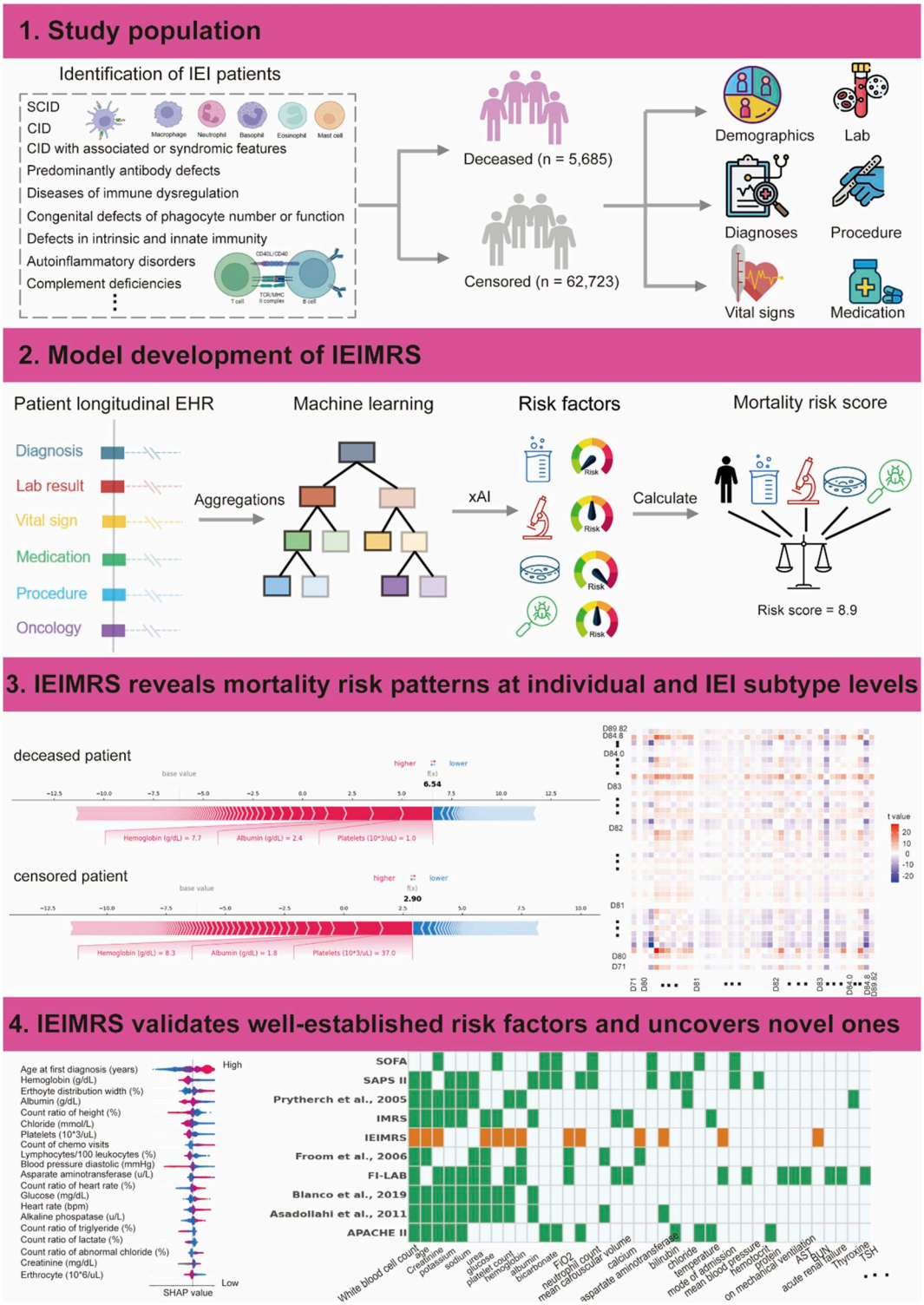

Figure 1.

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Antibiotic Allergies in Pediatric Patients Diagnosed with Hypogammaglobulinemia

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Rationale: Hypogammaglobulinemia increases the risk of life-threatening bacterial infections that require antibiotic treatment in pediatric patients. Only a handful of studies have looked at the prevalence of allergies in patients with hypogammaglobulinemia. Even fewer have characterized antibiotic drug allergies in these patients. This study reports observed outcomes for patients at Lurie Children's Hospital diagnosed with primary hypogammaglobulinemia and antibiotic allergy.
Methods: Using SlicerDicer built into Epic, pediatric patients were selected if they had a diagnosis of primary hypogammaglobulinemia, a low IgG level adjusted for age, and were seen between January 2015 and 2025 at Lurie Children's Hospital. The charts of the patients with listed antibiotic allergies were analyzed.
Results: Our search yielded 243 patients with primary hypogammaglobulinemia, 46 (19%) of whom had an allergy to at least one antibiotic (31 male, 15 female). This was significantly higher than the prevalence of antibiotic allergies across all Lurie Children's Hospital patients at 5% ($p<<0.01$). The most common antibiotic allergies were to amoxicillin (23), cephalosporins (15), and other penicillins (13). The most frequent reaction types were rashes (46%) and hives (35%) (see Figure 1). For patients with antibiotic allergies, the average age of hypogammaglobulinemia diagnosis was 7 years old. 12 (26%) of these patients had a diagnosis of recurrent infections. One patient had a documented drug challenge.

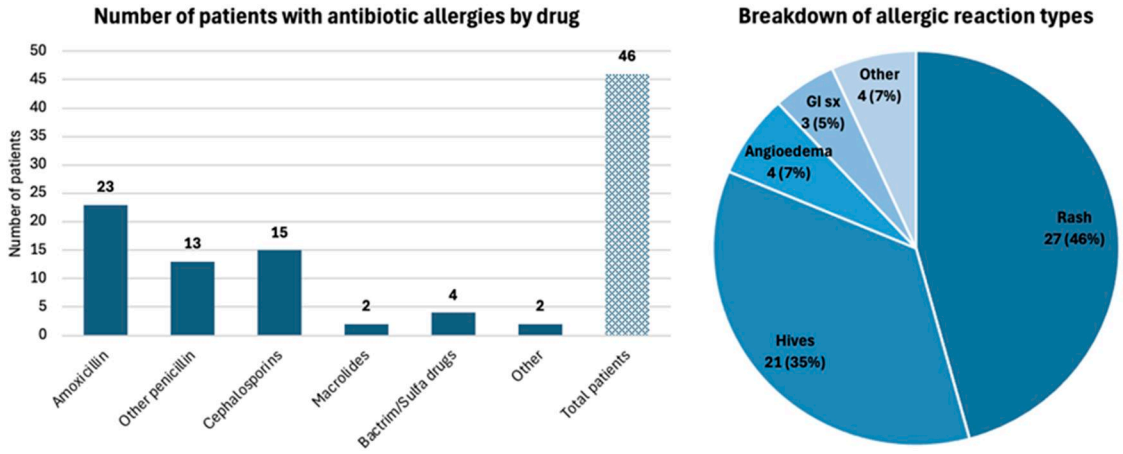

Figure 1. **Number of patients with an allergy to each antibiotic type, with a breakdown of the reaction types.** There were 46 total patients with an antibiotic allergy, but some patients had an allergy to more than one drug type. Allergic reaction types did not differ significantly by drug. Within reaction types, GI sx refers to vomiting and/or diarrhea.

Discussion: Our findings suggest that pediatric hypogammaglobulinemia is associated with an increased frequency of antibiotic allergies, despite low levels of immunoglobulins. A potential explanation is that due to increased infections, patients with hypogammaglobulinemia have frequent exposure to antibiotics and develop adverse reactions. Further research is needed to elucidate the mechanisms behind these allergies in the setting of low immunoglobulins, considering drug allergies are thought to be IgE mediated. Many hypogammaglobulinemia patients will go through several courses of antibiotics throughout their lifetime. Having to revert to second- and third-line antibiotics can increase cost and medical burden for these patients and their families. Thus, antibiotic stewardship is especially important. Despite 46% of the drug allergic reactions being rashes, only one patient underwent a drug challenge, highlighting the need for more robust drug allergy evaluation.

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Beyond Inborn Errors of Immunity: Brazilian Newborn Screening with KRECs Enabling Early Diagnosis of Hematologic Disorders

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Background: Newborn screening (NBS) with kappa-deleting recombination excision circles (KRECs) is primarily used to detect B cell lymphopenia and agammaglobulinemia as markers of inborn errors of immunity (IEIs). However, reduced B cell output on KREC testing may also represent an early sentinel of hematological disorders. Brazil currently implements NBS with both T cell receptor excision circles (TRECs) and KRECs, providing a unique opportunity to characterize disorders uncovered by isolated KREC abnormalities.
Objective: To describe the Brazilian experience using KREC-based NBS, identifying hematologic disorders, and to highlight the role of KRECs as an early marker of diseases affecting B cell production.
Methods: We conducted a prospective review of newborns referred to a Brazilian reference center following abnormal KREC results on NBS. Clinical, immunologic, and hematologic data were collected (complete blood counts, immunophenotyping, immunoglobulin levels, and bone marrow aspirate). After confirmation of B cell lymphopenia, patients underwent panel-based genetic testing. Final diagnoses and time from NBS referral to etiologic definition were recorded.
Results: Among infants referred for abnormal KRECs, distinct hematologic conditions were identified: 10 G6PD mutations (7/10 G6PD c.[202G>A(;)376A>G]), one GATA2 deficiency (GATA2 c.1348G>A; KREC 1copy/μL), one Shwachman–Diamond syndrome [SBDS c.258+2T>C(intron), c.184A>T; KREC 47copies/μL], and one juvenile myelomonocytic leukemia (NRAS c.35G>A; KRECs 6 copies/μL). In all cases, abnormal KRECs were the first abnormal finding and preceded clinical manifestations, as the confirmed B cell lymphopenia guided early hematologic assessment and subsequent genetic testing, establishing the final diagnosis. The KREC abnormality expedited diagnostic evaluation, facilitated recognition of the associated conditions, and guided early multidisciplinary follow-up with immunology and hematology when indicated. These diagnoses would likely have been substantially delayed in the absence of a KREC-based screening abnormality.
Conclusion: The Brazilian experience illustrates that KREC-based NBS can function as a powerful entry point not only to agammaglobulinemia but also to hematologic disorders that impair B cell lymphopoiesis, including bone marrow failure syndromes and myeloid neoplasms. The association between low KRECs and G6PD variants in our cohort is under investigation to clarify links with B cell impairment. Integrating KRECs into NBS programs and strengthening immunology–hematology collaboration can expand the impact of NBS beyond classical B cell IEIs, enabling earlier diagnosis.

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Biological Understanding of Spondyloenchondrodysplasia (SPENCD) Caused by Damaging ACP5 Variants

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Introduction: Inborn errors of immunity are genetic disorders that result in the absence or dysfunction of critical components of the immune system. Spondyloenchondrodysplasia (SPENCD) is one of these diseases, causing immune dysfunction, abnormal bone development, and neurological changes. SPENCD is caused by damaging variants in ACP5, which encodes tartaric acid-resistant acid phosphatase (TRAP). TRAP has dual roles, acting as a phosphatase and generating reactive oxygen species (ROS). While previous studies have shown that some SPENCD variants impair phosphatase activity, the impact of these variants on ROS production has not, to our knowledge, been investigated.

Methods: Clinical assessments and panel sequencing were performed. ACP5 variant-expressing constructs were generated using site-directed mutagenesis and expressed in HEK293 cells. Immunoblotting and p-nitrophenyl phosphate (PNPP) assay were performed on cells transfected with wild-type, patient, or known SPENCD variants. Flow cytometry was performed on PBMCs and THP-1 cells treated with the TRAP inhibitor AubipyOMe and stained for ROS with H2DCF.
Results: We report a novel case, elucidating the functional impact of two ACP5 variants: ACP5 (NM_001611.5) c. 550C>T, p.Q184* and c. 740T>G, p.L247R. This patient presented with hallmark SPENCD characteristics, including autoimmune hemolytic anemia, autism, intracranial calcification, radiolucent lesions, and short stature. In silico variant assessment confirmed a high likelihood of each variant being damaging with deleterious scores in multiple models. TRAP protein expression was comparable to wild type for patient and known SPENCD variants, except for truncating variants, which resulted in higher levels of truncated protein. Phosphatase activity was abolished for both the patient and known SPENCD variants. ROS production was impaired in cells treated with the TRAP inhibitor.
Conclusion: This work describes a newly identified SPENCD case, demonstrating the damaging effects of two ACP5 variants (p.Q184* and p.L247R) on TRAP production and function, reclassifying p.L247R as pathogenic. We also show impairment of ROS production with TRAP inhibition and are assessing how the patient's ACP5 variants influence ROS production. These findings elucidate the dual roles of TRAP in dephosphorylation and ROS production, showing TRAP's physiological role and SPENCD's biological mechanism.

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Cardiac Complexity Predicts Increased Immune Diagnostic Burden in 22q11.2 Deletion Syndrome

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Background: 22q11.2 deletion syndrome (DS) is the second most common cause of congenital heart disease (CHD) and a multisystem disorder that contributes to substantial overall disease burden. Additionally, 22q11.2DS is the most common cause of DiGeorge syndrome and the second most common chromosomal abnormality after Down syndrome, found in 1/2,148 live births. Up to 75–80% of 22q11.2DS patients have immune system abnormalities. We aim to determine whether CHD complexity is associated with a higher burden of allergic, immunologic, and autoimmune diagnoses.
Methods: We performed a retrospective chart review of adults (>18 years) with confirmed 22q11.2DS seen at the 22q and You Center at Children's Hospital of Philadelphia (CHOP). Exclusion criteria included 22q11.2 duplication, residence more than 100 miles from CHOP, and no documented visit between 2001 and 2025. We assessed CHD severity (based on structural complexity) and its association with allergic, immunologic, and autoimmune disorders identified through diagnosis codes. These variables were compared by chi-square analysis.
Results: A total of 419 adults met the inclusion criteria; 54 of 419 (13%) had a documented autoimmune diagnosis, 118 (28%) had an allergic condition, and 121 (29%) had an immune disorder. Twenty-five patients (6%) had an unknown cardiac history—so presumed normal/mild CHD. Of those with CHD, 37 individuals (9%) had a documented autoimmune diagnosis, 75 (18%) had an allergic diagnosis, and 87 (21%) had an immune condition.

Analysis of CHD complexity revealed no statistically significant association with lifetime autoimmune diagnoses ($p = 0.08$) or allergic diagnoses ($p = 0.32$). In contrast, CHD complexity was significantly associated with immune diagnoses ($p = 0.001$), suggesting that individuals with more structurally complex congenital heart disease experience a higher burden of immune-related conditions over their lifetime.
Conclusion: These findings highlight a potential link between cardiac severity and immune system involvement in adults with 22q11.2DS, underscoring the importance of longitudinal cardiovascular and immunologic care in this population.

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Caregiver- and Clinician-Reported Symptoms in Pediatric Patients with Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS) Receiving Leniolisib

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Introduction: Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS) is a rare disease characterized by early-onset, progressive symptoms. Delayed diagnosis and inadequate treatment in childhood may exacerbate disease manifestations and negatively impact health-related quality of life. In a 2-part, open-label, single-arm international study (NCT05438407) evaluating the safety and efficacy of leniolisib in pediatric patients (aged 4–11 years) with APDS, leniolisib was well tolerated, reduced lymphoproliferation, and increased naïve B cells to total B cells at 12 months. Here, we evaluated clinician- and caregiver-reported changes in symptom severity and global impression of change from this study, reporting 3- and 12-month data.
Methods: Caregiver- and clinician-reported outcomes were assessed at baseline and after 3 and 12 months of leniolisib treatment. Caregiver assessments included the Caregiver Global Impression of Change-APDS (CaGIC-APDS), APDS-Symptom Severity Scale (APDS-SSS), and Caregiver Overall Treatment Evaluation-APDS (CaOTE-APDS). Clinician assessments included Clinician Global Impression of Change-APDS (CGIC-APDS), Clinician Global Impression of Severity-APDS (CGIS-APDS), and Physician's Global Assessment (PGA). Study documents received institutional review board approval.
Results: Twenty-one patients were enrolled with a median (range) age of 7 (4–11) years; 61.9% were male. Median (range) treatment compliance baseline to 12 months was 98.7% (25.9%–100.0%). Following 3 and 12 months of treatment, caregiver-reported APDS symptom improvement was assessed with CaGIC-APDS (85.7% and 90.0% of patients, respectively), and clinician-reported improvement was assessed with CGIC-APDS (81.0% and 85.0% of patients, respectively) (supplementary table). Caregivers reported decreases in symptom severity across most APDS-SSS domains from baseline to 3 and 12 months; mean (SD) total symptom score change at 3 months was −0.15 (0.43). Caregivers reported the positive aspects of leniolisib outweighed the negative aspects in 85.7% of patients at 3 months, as assessed by CaOTE-APDS. At 3 and 12 months, clinician-reported mean (SD) changes from baseline indicated improvement, with PGA scores of −18.5 (18.1) and −22.7 (19.7), respectively, and CGIS-APDS scores of −0.5 (0.7) and −0.9 (0.8), respectively.
Conclusion: In pediatric patients receiving leniolisib, caregivers and clinicians reported improvements in symptoms. These findings demonstrated durable and clinically relevant progressive symptom improvement through 12 months.
Tabular data are included as downloadable supplement files.

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Cell-Free DNA Testing in Acute Infections in Chronic Granulomatous Disease

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Introduction: Chronic granulomatous disease (CGD) is an inborn error in immunity that results in increased infectious susceptibility to serious infections, often from catalase-positive organisms, due to defects in the NADPH oxidase activity. These microbes are difficult to culture and identify. Noninvasive cell-free DNA tests (Karius Test) are culture-free tools to identify microbes causing infections in CGD, but little published experience exists in CGD.
Methods: We performed a retrospective review of patients with CGD admitted at our institution for acute infection from 2020–2024 and had Karius testing done.
Results: Six patients were identified to be admitted eight different times for confirmed or strongly presumed infection. A Karius test was done during each of these admissions. Four admissions were for pneumonia, one for liver abscess, one for peri-rectal abscess, and two for lymphadenitis. In every admission, patients had negative fungal, aerobic/anaerobic, and mycobacterial peripheral blood cultures. All four patients with pneumonia had a bronchoscopy with bronchiolar alveolar lavage (BAL), with one patient undergoing a second bronchoscopy with BAL and transbronchial biopsy. This repeat BAL culture, biopsy tissue culture both grew *Burkholderia multivorans*, but 16s polymerase chain reaction (PCR) was unrevealing. All other BAL cultures were negative. The two patients with lymphadenitis had excisional lymph node biopsy with negative tissue cultures and 16s polymerase chain reaction on the tissue. The patient admitted for a liver abscess had a positive culture with *Staphylococcus aureus* growing on abscess drainage. This patient also had a positive Karius test showing *S. aureus*. The remaining seven Karius tests performed were negative.
Conclusion: Identifying the causative microorganism in acute infections in patients with CGD can be difficult but is imperative for the treatment of infection. Only 25% of our patients with acute infection had an organism identified through classic means. Noninvasive cell-

free DNA testing offers an option to overcome limitations of conventional and often invasive cultures. In our cohort, the only patient who resulted in a positive Karius also had positive cultures from liver abscess. There may be limitations in cell-free DNA testing in patients with CGD, but this does need to be studied further.

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Characteristics of Patients with Predominantly Antibody Deficiencies Undergoing Genetic Testing

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Rationale: Genetic testing can reveal a molecular diagnosis in 20–40% of patients with inborn errors of immunity (IEI) such as predominantly antibody deficiencies (PAD), though this varies by IEI type and other factors. In patients with PAD, we hypothesize that there are clinical and epidemiologic characteristics that predict the probability of determining a molecular etiology with genetic testing.
Methods: We analyzed clinical characteristics of all patients with PAD diagnoses seen by immunology at a tertiary care academic medical center who underwent genetic testing. Exclusion criteria included patients with other non-PAD IEI diagnoses and genetic testing that did not assess PAD genes. PAD diagnoses, infections, and comorbidities were determined using ICD9/10 codes.
Results: We identified 640 patients, of which 42% were female and 69% identified as white, non-Hispanic, or Latino. Median age at PAD diagnosis was 6.0 years (interquartile range [IQR] 2, 10). The first immunology evaluation was in the inpatient setting in 43% of patients. Patients had non-mutually exclusive PAD diagnoses of hypogammaglobulinemia (75%); antibody deficiency with near-normal immunoglobulins or hyperimmunoglobulinemia (28%); other immunodeficiencies with PAD (25%); common variable immunodeficiency (24%); selective IgA deficiency (15%); and immunodeficiency with PAD, unspecified (14%). Median age at genetic testing was 7 years (IQR 3,13) and included whole exome (64%), immunodeficiency panel (32%), whole genome (6%), and single gene (4%) sequencing. The number of patients with genetic testing has increased thirteen-fold over the last ten years. Evaluation with whole-genome sequencing has increased ten-fold over the last three years. Infection diagnoses were identified in the majority of patients with bacterial (15%), viral (13%), and fungal (6.3%) etiologies most classified. Acute otitis media (28%), pneumonia (24%), and acute sinusitis (9%) were identified. Most common comorbidity diagnoses by organ system were blood and blood-forming organs (75%), respiratory (38%), skin and subcutaneous tissue (18%), and nervous system (12%). Noninfectious complications were identified with lymphoproliferation (13%), autoimmune conditions (6.6%), bronchiectasis (5.6%), pulmonary fibrosis or interstitial lung disease (2.8%), and enteritis or colitis (0.9%). Hematologic malignancy was seen in 1.3% of patients.
Conclusion: Future investigation will include assessing clinical predictors of determining a molecular etiology for predominantly antibody deficiencies in those undergoing genetic testing.
Tabular data are included as downloadable supplement files.

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Characterizing Autoimmune and End-Organ Lympho-Infiltrative Disease Burden in Childhood-Onset Common Variable Immunodeficiency

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Background: Common variable immunodeficiency (CVID) is the most prevalent inborn error of immunity. Although CVID is most commonly diagnosed in adulthood, a subset of patients is diagnosed in childhood. Autoimmune and end-organ lympho-infiltrative

complications are common in adults with CVID and are associated with significant morbidity and mortality. Despite their clinical significance, the prevalence and timing of these complications in pediatric CVID remain poorly characterized.

Methods: We performed a retrospective analysis of clinical data from Beth Israel Lahey Health and Massachusetts General Hospital. We investigated the frequency, types, and natural history of autoimmune and inflammatory (AI) complications in patients diagnosed with CVID during childhood (<18 years old).

Results: We identified 36 patients (14 females, 22 males) diagnosed with CVID during childhood. The median age of diagnosis was 10 years old (interquartile range [IQR] 5–15). 56% (n = 19) of patients developed at least one AI complication during childhood. Cytopenias (anemia, neutropenia, lymphocytopenia, and thrombocytopenia) as well as gastrointestinal disease (enterocolitis, celiac disease, and other forms of malabsorption) were the most prevalent AI complications, each affecting 33% and 31% of patients, respectively. These complications typically appeared during childhood, often prior to CVID diagnosis. Interstitial lung disease, lymphadenopathy, splenomegaly, and liver disease were less common, each affecting <22% of patients; these complications tended to present later, into adulthood.

Conclusion: Our study demonstrated that AI complications—particularly cytopenias and gastrointestinal disease—occur frequently in patients diagnosed with CVID in childhood. Ongoing analyses will compare the prevalence, timing, and burden of these complications between pediatric- and adult-onset CVID and explore associated immunophenotypic differences. Our findings are limited by the small number of pediatric patients studied; larger studies are needed to better understand the natural history and risk factors for AI complications in childhood-onset CVID.

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Characterizing Pulmonary Gas Exchange in Inborn Errors of Immunity Using Hyperpolarized Xenon MRI

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Rationale: Inborn errors of immunity (IEIs) predispose individuals to recurrent respiratory infections and immune dysregulation, which together can drive inflammatory lung complications, including interstitial lung disease and thickening of the interstitial (alveolar–capillary) membrane. These changes are often subtle and may not be captured by conventional lung function testing. Hyperpolarized 129Xe MRI (XeMRI) is a novel, noninvasive technique that quantifies regional gas exchange by leveraging xenon's solubility in distinct pulmonary compartments: airspaces (Gas), interstitial membrane (Mem), and capillary red blood cells (RBC).

Objectives: Evaluate whether XeMRI can detect differences in pulmonary gas exchange in people with IEIs (pwIEIs) by comparing gas exchange ratios (Mem/Gas, RBC/Gas, and RBC/Mem) with healthy controls (HCs).

Methods: XeMRI was performed using a four-echo, 3D radial spectroscopic sequence to quantify compartment-specific signals (Gas, Mem, and RBC). All scans were acquired during a standardized breath-hold following inhalation of a hyperpolarized 129Xe/N_2 mixture. Carbon monoxide transfer coefficients (Kco), reported as GLI z-scores, were obtained from routine testing within three months of imaging for qualitative comparison. Group differences between pwIEIs and HCs were assessed using two-sided Mann–Whitney U tests for Mem/Gas (xenon uptake in membrane relative to gas), RBC/Gas (xenon uptake in RBCs relative to gas), and RBC/Mem (xenon uptake in RBCs relative to membrane).

Results: Seventeen pwIEIs (3F/14M; median age 28 years [Q1–Q3: 16–37]) and ten HC (3F/7M; median age 22 years [Q1–Q3: 15–23]) were included; HC recruitment is ongoing. Mem/Gas was significantly higher in pwIEIs than in HCs (0.0159 vs. 0.0134, p = 0.0459), while RBC/Mem was significantly lower in pwIEIs (0.4124 vs. 0.4624, p = 0.0355). RBC/Gas did not differ between groups (0.0057 vs. 0.0057, p=0.9019). Four pwIEIs (23.5%) had reduced Kco values (z < 1.3, <10th percentile); however, Kco showed no clear relationship with any gas-exchange ratios

Conclusions: pwIEIs, many of whom had normal lung function tests, showed increased xenon signal within the interstitial compartment with reduced transfer into the blood relative to the membrane signal. This pattern is consistent with mild interstitial pathology and suggests that XeMRI may provide a sensitive, noninvasive method for detecting interstitial pulmonary involvement in pwIEIs.

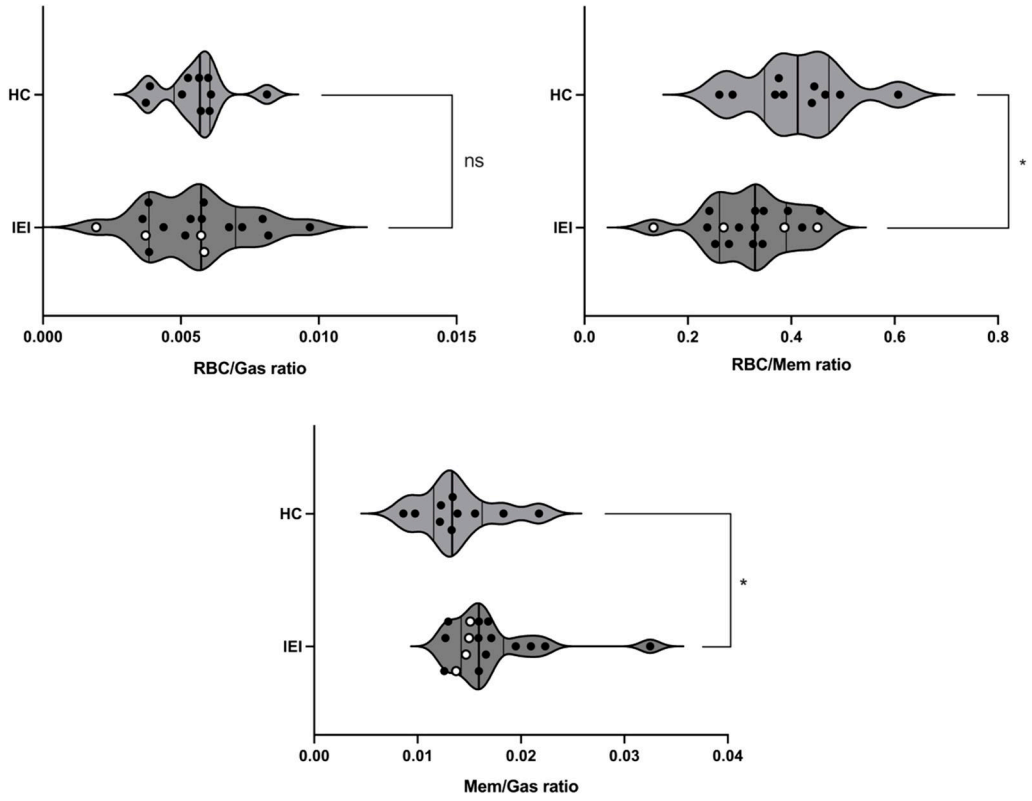

Figure 1. **XeMRI-derived gas-exchange ratios in people with inborn errors of immunity and healthy controls.** Violin plots show group differences in hyperpolarized XeMRI ratios: (A) RBC/Gas, (B) RBC/Mem, and (C) Mem/Gas. People with inborn errors of immunity had a higher Mem/Gas ratio (p=0.0459) and lower RBC/Mem ratio (p = 0.0355) compared to healthy controls, with no difference in RBC/Gas ratio (p=0.9019). White-filled points denote individuals with reduced Kco (z < −1.3, <10th percentile). RBC, red blood cell; Mem, interstitial (alveolar-capillary) membrane; Gas, airspaces; HC, healthy controls; IEI, inborn error of immunity; Kco, carbon monoxide transfer coefficient.

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Clinical and Genetic Spectrum of Autoimmune Lymphoproliferative Syndrome (ALPS) and ALPS-Like Disorders in Brazil: Insights from the First Year of the CNE3i National Cohort

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The recognition of disorders of immune dysregulation, particularly those presenting with lymphoproliferation and systemic autoimmunity (International Union of Immunological Societies [IUIS] Group 4.6), has markedly increased in recent years. Initially, many of these conditions were collectively classified as Autoimmune Lymphoproliferative Syndrome (ALPS); however, the advent and dissemination of next-generation sequencing enabled the identification of patients with distinct genetic etiologies despite sharing overlapping clinical and immunological features. Through a national collaborative effort, the Centro nacional de Erros Inatos da Imunidade e Imunodesregulação (CNE3i) has systematically collected data on ALPS and ALPS-related disorders across Brazil since 2024. Here, we report the first year of CNE3i's dataset on ALPS and ALPS-like diseases, highlighting their genetic diversity, clinical presentations, and immunological signatures within the Brazilian population. A total of 33 individuals were identified, 33.3% female (n = 11), from all 5 major regions of Brazil, with a mean age of 17 years (range 6–56 years) and a mean diagnostic delay of 5 years. Lymphadenopathy was the most common clinical finding (94%, n =31), followed by diffuse splenomegaly (72.7%, n = 24), hepatomegaly (54.6%, n = 18), and cytopenia (48.5%, n = 16), all present in a substantial proportion of patients. An elevated double-negative T cell (DNTs) was found in 14 individuals (42%), and diverse monogenic etiologies were identified (n = 15) (supplemental table). Despite extensive investigation, around 50% of the time, a causative gene could not be found. Most patients received corticosteroids as first-line therapy, followed by an mTOR inhibitor (41%) and mycophenolate mofetil (44%). The CNE3i Brazilian ALPS cohort reflects the complex phenotypic overlap between ALPS and ALPS-like disorders, underscoring the central role of autoimmune cytopenias and lymphoproliferation.

The identification of canonical FAS mutations and ALPS-like defects (e.g., LRBA, TNFAIP3, and CTLA4) reinforces the importance of broad genetic screening in cases of immune dysregulation. These findings contribute to a more refined understanding of the genetic and clinical heterogeneity of IEIs and support optimized therapeutic strategies, particularly involving mTOR inhibition and a selective PI3Kδ inhibitor.

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Clinical and Immunological Characteristics of Kabuki Syndrome Patients with Autoimmune Cytopenias

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Background: Kabuki syndrome (KS) is a multisystem genetic disorder caused predominantly by pathogenic variants in KMT2D or KDM6A, characterized by developmental delay, congenital anomalies, and immune dysregulation. Autoimmune cytopenias are an important hematologic manifestation in KS; however, their clinical and immunological correlations remain insufficiently defined. This study aimed to compare the clinical and immunological features of KS patients with and without autoimmune cytopenias.
Methods: This multicenter study included all patients with Kabuki syndrome who met the international consensus diagnostic criteria for KS. A total of 51 patients with genetically or clinically confirmed KS were enrolled. Among them, 11 had autoimmune cytopenias (autoimmune thrombocytopenia, autoimmune hemolytic anemia, or both) and 40 did not. Clinical manifestations, immune parameters, and comorbidities were compared between groups. Continuous variables were compared using the t test, while categorical variables were analyzed using the chi-square test.
Results: Patients with cytopenias were significantly older at diagnosis compared to those without cytopenias (10.5 ± 7.5 vs. 3.4 ± 4.9 years, $p = 0.005$). Gender distribution did not differ significantly between groups ($p = 0.477$). Hearing impairment was significantly more prevalent in patients without cytopenias (65.8%) than in those with cytopenias (18.2%) ($p = 0.005$). Conversely, hypogammaglobulinemia was markedly more common among patients with cytopenias (70%) compared to those without (22.9%) ($p = 0.005$). No statistically significant differences were observed in the prevalence of congenital cardiac abnormalities or endocrinopathies between the two groups. Regarding lymphocyte subsets, B cell lymphopenia and natural killer (NK) cell lymphopenia were significantly more frequent in the cytopenias group (33.3% vs. 6.7% for both, $p = 0.036$). Although T cell lymphopenia was more common in patients with cytopenias (55.6% vs. 30%), this difference did not reach statistical significance ($p = 0.161$).
Conclusion: Approximately 20% of KS patients exhibit autoimmune cytopenias. Autoimmune cytopenias in KS are associated with a higher frequency of hypogammaglobulinemia and B cell lymphopenia, indicating a more pronounced underlying immune dysfunction. These findings highlight the importance of proactive immunological evaluation and monitoring in KS patients presenting with cytopenias.
Tabular data are included as downloadable supplement files.

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Clinical Experience with Use of the PI3Kdelta Inhibitor Leniolisib to Treat Immune Dysregulation in Patients with CVID and CVID-Like Disorders

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Objective: Approximately half of common variable immunodeficiency (CVID) patients develop debilitating and life-threatening clinical manifestations of immune dysregulation, including lymphoproliferation, cytopenias, interstitial lung disease (ILD), nodular regenerative hyperplasia of the liver (NRH), and other complications. Recent research suggests a shared endotype among CVID patients with immune dysregulation and activated PI3 kinase delta syndrome (APDS). The objective of the current work was to summarize experience among clinicians treating patients with CVID and CVID-like disorders with investigational leniolisib via the appropriate expanded access pathways available in the USA, Italy, and Spain.
Methods: Information was collected from physicians treating 5 CVID patients and 1 patient with homozygous pathogenic variants in PRKCD (c.1352+1G>A).
Results: Five CVID patients and 1 PKCδ deficiency patient received leniolisib after failing multiple treatments. Ages ranged from 13 to 64 years with equal distribution of males and females. Predominant clinical manifestations of immune dysregulation included nonmalignant lymphoproliferation (6/6), cytopenias (5/6), ILD (4/6), and NRH (4/6). Leniolisib was initiated at 10 mg BID with escalation over 2–3 months to 40–70 mg BID. Median duration of treatment was 1.4 years (range 0.5–2.5 years). Leniolisib was well tolerated by most patients. Treatment was temporarily interrupted in 4 patients due to separate occurrences of rash and headache (patient 1), septic arthritis following a knee injury related to a fall (patient 2), worsening CMV colitis (Patient 5), or febrile neutropenia and spontaneous bacterial peritonitis with multiple bacteremias (patient 6). Patient 6 discontinued leniolisib related to difficult-to-control hyperglycemia and relapse of neutropenia. Favorable treatment responses were observed, including reductions in splenomegaly and/or lymphadenopathy (3/6), improvement in

cytopenias (5/5), and imaging and/or functional improvement in ILD (2/4). Decreases in IgM, reductions of transitional B cells, and reductions in CD21low B cells were reported in some patients. Five patients self-reported feeling better.
Conclusions: Experience suggests that PI3K inhibition may offer clinical benefit to CVID and other primary immunodeficiency patients suffering from complications of immune dysregulation. Two phase 2 clinical trials to formally evaluate safety and tolerability in CVID and other patients with clinical manifestations of immune dysregulation are underway in the USA, England, and Spain.

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Clinical Implications of Novel Monoallelic STAT6 Gain-of Function Variants

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Background: Primary atopic disorders (PADs) are monogenic inborn errors of immunity marked by severe allergic disease. Heterozygous gain-of-function (GOF) variants in STAT6 have recently been recognized as a PAD associated with severe atopy, gastrointestinal involvement, and, in some cases, lymphoma. The phenotypic spectrum remains incompletely defined. As genetic testing expands, more patients with atopy are found to carry variants of uncertain significance (VUS) in STAT6, and existing prediction tools often fail to identify GOF effects.
Methods: In previous work, we assembled an international STAT6-GOF cohort and performed functional testing using transient overexpression in HEK cells, IL-4 stimulation, and quantification of STAT6 phosphorylation as readout of pathway activation 1. Only recently, we evaluated the impact of other possible but so far not reported missense substitutions—particularly within previously reported GOF "hotspot" regions—using general pathogenicity tools (e.g., Combined Annotation Dependent Depletion [CADD]) and structure-informed prediction (Dynamut2, Alpha missense).
Results: Beyond published STAT6-GOF cases, we identified two VUS: p.Ala390Ser in a Japanese patient with clinical phenotype and p.Asp419Glu in Saudi individuals located within a recurrent GOF hotspot but without clinical manifestations. Multiple prediction tools—including structure-aware models—flagged both variants as likely pathogenic. However, functional testing for p.Ala390Ser and the absence of a phenotype for p.Asp419Glu argue against a GOF effect. Integrating both published and novel variants, we find that predictions tend to be stronger when substitutions alter amino acid residue charge and when variants appear in COSMIC (a catalog of somatic mutations found in tumor samples) but not in gnomAD (a database of germline variation from large-scale sequencing projects). It is important to keep in mind that not all somatic hotspot substitutions confer GOF, and in silico evidence alone is insufficient. Therefore, functional validation remains essential.
Conclusions: Our findings reinforce the notion that mechanistic validation remains essential for STAT6 monoallelic VUS, even within canonical GOF hotspots. Current computational tools have limited accuracy for predicting GOF apart from haploinsufficiency. We advocate a workflow that integrates targeted functional assays with clinical and genetic phenotyping to determine variant significance. Ongoing efforts within an international consortium to conduct an in-depth clinical evaluation aim to refine genotype–phenotype correlations and inform personalized management for patients with suspected STAT6-GOF.

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Coronary Artery Dilation and Tortuosity in STAT3DN Hyper IgE Syndrome

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Background: Hyper IgE syndrome from dominant-negative STAT3 mutations is a multisystem disease with vascular complications. Following a myocardial infarction (MI) from a coronary artery aneurysm in a 43-year-old patient, our center began MRI screening for coronary vessel changes. This project aims to identify the prevalence of coronary artery dilation or tortuosity in STAT3-HIES and changes over time.

Methods: We reviewed coronary artery MRIs of patients with STAT3-HIES, identifying 134 patients with 345 studies from 2006 to 2025, representing 70% of our cohort. We typically repeat imaging every 3 years.

Results: Patients were 7–64 years (median 21) at baseline imaging and ranged from 7 to 74 years, including all studies. Seventy-six of the patients were female (57%), 122 living. At baseline imaging, 56 patients (42%) had normal-appearing coronary arteries. Tortuosity of the right coronary artery (RCA) was seen in 56 patients (42 %), and dilation of the left anterior descending coronary artery (LAD) was seen in 19 patients (14%).

Eighty-eight patients had repeat imaging over 1–18 years (median 10), average 3.4 MRIs. 37 patients (42%) had imaging that worsened over time with either increased dilation or tortuosity. Three patients had myocardial infarctions related to coronary artery dilation/aneurysm; all were started on antiplatelet agents, and recurrence was seen in one patient.

Hypertension occurs in about one-third of patients with STAT3-HIES. In the patients with multiple images, 5 (19%) had hypertension with normal coronary arteries over time, compared to 11 (52%) with abnormal coronary arteries but no changes over time, and 16 (44%) with worsening changes. Six patients underwent hematopoietic stem cell transplant at ages 7–20 years (median 16); three of the five with post-transplant imaging had new RCA tortuosity.

Conclusions: Complications from middle-sized arterial abnormalities in STAT3-HIES include subarachnoid hemorrhage from cerebral aneurysm and myocardial infarction from clot in coronary artery aneurysms. Tortuosity and dilation of the coronary arteries are common in STAT3-HIES. Patients should be screened to allow for antiplatelet therapy if a coronary artery aneurysm is present. Further study is needed regarding the role of hypertension affecting coronary artery changes and whether hematopoietic stem cell transplantation (HSCT) provides additional vascular risk.

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Correlation of Activated-Inflammatory T Cell Subtypes in Patients Tested for Lymphocyte Immunodeficiency

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CD19negCD20dim T cells are mostly CD8+ and predominantly express memory markers. Based on the literature, they may be a subset of inflammatory T cells rather than a transient activated state. I postulated that CD19negCD20dim T cells would correlate with other signs of activated-inflammatory T cells. I examined blood from 100 consecutive patients referred for lymphocyte immune deficiency study, using the CD19negCD20dim expression on our B cell panel as a proxy for CD19negCD20dim T cells. I found a strong correlation between age and computed CD20dim T cells, which correlates with prior published findings. I separately analyzed 0–17-year-old children and 18–71-year-old adults. In both age groups, computed CD20dim T cells correlated well with age (Pearson p = 0.49 for pediatric, p = 0.45 for adult). Inspection of the data does not reveal any sharp inflection point in computed CD20dim T cells, and the percentage of computed CD20dim T cells did not differ by sex. When all subjects were examined, there was a weak positive correlation between computed CD20dim T cells and percentage of CD4+CD8+ "double-positive" (DP) T cells, percentage total T cells or CD8 T cells expressing HLA-DR, and an equally weak negative correlation with percentage TCRγδ T cells. However, none of the associations were statistically significant. Analyzing age groups separately, all correlations diminished in adults. However, in children, computed CD20dim T cells correlated well with T cell HLA-DR expression (Pearson p = 0.61) and with CD8 T cell HLA-DR expression (Pearson p = 0.52). I also compared the activated-inflammatory T cell markers with each other. Some weak correlations were noted (% DP T cells vs. % TCRγδ T cells in adults, p = -0.160; % HLA-DR vs. TCRγδ T cells in children, p = 0187), but none of the correlations was significant. The main conclusion is that computed CD20dim T cells correlated well with T cell HLA-DR expression and with CD8 T cell HLA-DR expression in children, but not in adults. Most markers of activated-inflammatory T cells did not correlate with each other and thus may represent distinct activation pathways.

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Cytokine Profile in Patients with Chronic Granulomatous Disease (CGD)

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Introduction: CGD is an inborn error of immunity that results in severe, recurrent bacterial and fungal infections, immune dysregulation, and chronic inflammation. Profiling the cytokine signature in CGD patients may inform allogeneic hematopoietic stem cell transplantation (allo-HSCT) or experimental gene therapy strategies.
Methods: A single blood draw was obtained in an observational clinical trial (NCT06605378) of patients in the United States and the United Kingdom confirmed to have CGD but had not previously undergone allo-HSCT or gene therapy. Serum cytokine levels were measured by Meso Scale Discovery (MSD) multiplex cytokine assay and enzyme-linked immunosorbent assay (ELISA) as a surrogate marker for cellular cytokine signatures.
Results: As of October 2025, 36 participants (median age 26, range 1–54 years; 33% under 18 years of age; 83% male, 11% Hispanic or Latino, 8% Asian, and 6% Black) with CGD (75% with mutations in CYBB) had cytokine results for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, and CXCL9. In adults (≥18 years of age), there were higher levels of CXCL9 (1.7-fold), IFN-γ (5.4-fold), IL-6 (4.8-fold), and IL-8 (1.1-fold) compared to pediatric participants (<18 years of age). In participants with mutations in CYBB, there were higher levels of CXCL9 (1.1-fold), IFN-γ (3.6-fold), and IL-6 (3.9-fold) with lower levels of IL-8 (0.6-fold) compared to those with mutations in other genes. Other cytokines did not appear different between groups. The impact of clinical status, including active infections or inflammatory complications, is still being analyzed. Small numbers prevented formal comparisons.
Conclusion: Cytokine profiles in CGD patients appear to vary with age and genotype. Further research is needed to compare these profiles with healthy controls and to elucidate the impact of these profiles on allo-HSCT or gene therapy outcomes. Understanding these differences may lead to more tailored therapeutic approaches for CGD patients.

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Defining Genotype to Phenotype Causality in Patients with Diverse FOXN1 Variants

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Background: Forkhead box N1 (FOXN1) is the master transcriptional regulator of thymic epithelial cells (TECs), quintessential for T cell development. Well-defined biallelic FOXN1 loss-of-function variants lead to congenital athymia. However, most patients who present with low T cell numbers due to FOXN1 mutations have single allelic variants, the majority of which are of unknown significance. For some individuals, their T cell numbers can improve over a prolonged period, often months to years. The mechanistic basis by which single-allele FOXN1 variants can disrupt thymopoiesis remains poorly understood. To address this knowledge gap, we developed a multi-platform strategy to define how specific human FOXN1 mutations cause T cell lymphopenia due to TEC dysfunctions.
Methods: Human FOXN1 variants were screened for transcriptional activity with reporter assays, cytoplasmic versus nuclear distributions, and the potential for aggregation or co-association. Allelic expression patterns are currently being assessed with mouse models developed to genocopy selected human FOXN1 mutations.
Results: Transcriptional reporter assays effectively categorize human FOXN1 variants into complete, partial, and gain-of-function mutations. Both partial loss- and gain-of-function can reduce thymic T cell output. A subset of the human FOXN1 variants function as dominant negatives, antagonizing the function of the wild-type allele. However, this accounts for the effects of a subset of variants, indicating that other mechanisms are involved. Current experiments are addressing whether particular human FOXN1 variants express more stable mRNA transcripts that compete with the normal transcript and/or whether this gene is governed by monoallelic expression.
Conclusions: Human FOXN1 mutations can be effectively categorized into loss- and gain-of-function, which explains the clinical phenotype of low T cell numbers due to thymic hypoplasia. However, other allelic variants can function as dominant negative or may undergo a monoallelic expression, also leading to a T cell lymphopenia. Such a combinatorial approach will lead to better classifications, enabling more informed clinical interventions.

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Development of a Disease Activity Score to Assess Treatment Success in Patients with NFKB1 Mutations

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Background: NFKB1 encodes for the p105/p50 nuclear factor-kappa-B (NF-kB1) transcription factors. Heterozygous mutations in NFKB1 may lead to NF-kB1 insufficiency, which may result in a multiorgan disease. Here, we aimed to develop a disease activity score to assess treatment success in patients with NF-kB1 insufficiency.
Methods: Based on phenotypic data of 179 patients with 77 distinct NFKB1 variants and clinical data from 41 patients with 22 distinct pathogenic NFKB1 variants, we identified the most relevant score parameters in a Leave-One-Out (LOO) analysis and developed the NFKB1-DAS. NFKB1-DAS values in patients with pathogenic variants in NFKB1 were compared to those of CTLA4-insufficient patients as a control group.
Results: Patients who spent at least one day in hospital in the last 6 months had a median NFKB1-DAS of 46% compared to 28% in patients without a hospital stay. In patients with pathogenic NFKB1 variants (n = 41), mean score values were 1.4-fold higher than in patients with CTLA4 deficiency (n = 31).
Discussion: We found the first indications that the newly developed NFKB1-DAS is able to measure disease activity. In a follow-up study, the NFKB1-DAS will be further validated and used to measure the effectiveness of treatment in a worldwide NFKB1 cohort.

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Development of a Yucatan Mini-Pig Model for Deficiency of Adenosine Deaminase 2 (DADA2)

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Deficiency of adenosine deaminase 2 (DADA2) was identified in 2014 as a novel inborn error of immunity caused by biallelic pathogenic variants in ADA2. DADA2 patients express two predominant clinical phenotypes: (1) autoinflammatory vasculitis/vasculopathy and (2) hematopoietic failure. These phenotypes may overlap, and immunodeficiency may occur in both. Like ADA1, the major ADA isozyme in humans, ADA2 can catalyze the deamination of adenosine (Ado) to inosine (Ino). However, differences in structure, Km, and tissue localization, as well as in the clinical and metabolic consequences of the inherited deficiencies of ADA1 and ADA2, suggest that the two isoenzymes are nonredundant. Many hypotheses regarding the biological function of ADA2 have been promoted, but no consensus has emerged.

ADA2 is evolutionarily conserved, and cerebral bleeding in ADA2-deficient zebrafish embryos has been likened to strokes that occur in a subset of DADA2 patients. However, rodents lack an ADA2 gene, rendering traditional knockout mouse models unfeasible. The absence of a mammalian model has been a major barrier to understanding ADA2 biologic function, the pathogenesis of DADA2, and evaluating targeted therapies.

Swine have been successfully used to model several human monogenic diseases, including cystic fibrosis and severe combined immunodeficiency, and offer substantial advantages in translational relevance compared with rodent systems. Importantly, pigs possess the ADA2 gene, and the porcine immune system closely mirrors that of humans in both development and function, supporting its utility as a preclinical DADA2 model. Thus, we have generated a viable CRISPR/Cas9-targeted ADA2-deficient ($ADA2^{-/-}$) Yucatan mini-pig in collaboration with Exemplar Genetics. Characterization of ADA2-deficient minipigs is at an early stage; however, consistent with observations in both asymptomatic and symptomatic DADA2 patients, $ADA2^{-/-}$ pigs exhibit an increased interferon signature. Yucatan mini-pigs, like humans, secrete ADA2 into the plasma; however, recombinant porcine ADA2 has markedly lower enzymatic activity with Ado as substrate than human ADA2. This interspecies difference supports the hypothesis that ADA2 evolved in higher vertebrates to mediate critical biological functions that extend beyond a catalytic role in Ado-to-Ino conversion.

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Diagnostic Utility of Genetic Testing in a Complex Multisystem Presentation: A Case of CTLA4 Haploinsufficiency

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CTLA4 haploinsufficiency is caused by mutations in the CTLA4 gene. The loss of this important immune checkpoint leads to uncontrolled production of lymphocytes, causing infiltration of T cells into multiple organs (gastrointestinal [GI], bone marrow, kidneys, lungs, and central nervous system [CNS]). The clinical manifestations include recurrent infections, enteropathy, lymphadenopathy, and hepatosplenomegaly.

13-year-old male with a history of recurrent respiratory infections, cough, and headaches. He was initially followed by neurology for headaches when he was found to have severe thrombocytopenia on screening labs. He eventually developed recurrent episodes of prolonged bleeding and was diagnosed with immune thrombocytopenia purpura, for which he was treated with transfusions, high-dose intravenous immunoglobulin [IVIG], and eltrombopag. Symptoms continued to worsen as he developed recurrent fevers, weight loss, decreased appetite, and diarrhea, and was found to have leukopenia, lymphadenopathy, splenomegaly, and bronchiectasis. Genetic testing was performed, which revealed a pathogenic variant in the CTLA4 gene, c.223 C> T p.(R75W), heterozygous, consistent with CTLA4-related immune dysregulation. The immune workup was notable for increased double-negative T (DNT) cells and sIL-2R, all of which are expected in CTLA4 haploinsufficiency. MRI of the brain did not demonstrate inflammation or demyelination. He initiated abatacept therapy, which binds to CD80/CD86 to downregulate T cell activation.

Trimethoprim/sulfamethoxazole prophylaxis was started due to abatacept therapy and immunodeficiency. Since starting abatacept treatment, immune monitoring labs have demonstrated improvement in markers of T cell activation, and the patient is also experiencing symptomatic improvement. Hematopoietic stem cell transplantation was also discussed; however, given high mortality and improvement with abatacept, deferred for now as a treatment option.

This case highlights the importance of early genetic testing in diagnosing complex patients with immunodysregulation, particularly in the presence of targeted therapies, such as those available for CTLA4 haploinsufficiency. Diagnostic delays are still common and may lead to ominous long-term consequences.

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Diagnostic Yield and Advantages of Exome/Genome Sequencing in Inborn Errors of Immunity

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The rapid annual increase in conditions classified as inborn errors of immunity (IEI), along with associated genetic variants, creates diagnostic challenges. The comprehensive nature of exome sequencing (ES) and genome sequencing (GS) makes these technologies suitable for diagnosing IEIs. We examined the diagnostic rate (Dx) of ES/GS in a cohort of individuals with suspected IEI.

Individuals were tested by ES/GS at a single clinical laboratory between 2013 and 2025 and were eligible for inclusion if testing was ordered by 1) an allergist/immunologist, or 2) any provider and containing at least one clinician-provided immune ICD-10 code (as defined by American Academy of Allergy, Asthma & Immunology [AAAAI]). Principal component analysis determined genetic ancestry.

A total of 2,044 individuals with suspected IEI received ES/GS, 38.3% of whom had known targeted gene panel testing prior to ES/GS. At least one molecular diagnosis (positive or possible finding) was identified in 33.7% of the cohort (689/2,044). Diagnostic findings were consistent with the individual's immune phenotype (immune-Dx) for 40.9% (282/689) of positive cases, including 47 individuals who had both immune and nonimmune diagnostic findings. The rate of immune-Dx findings was higher among individuals who were <18 at the time of testing (15.8%) compared to those who were ≥18 (10.7%; odds ratio [OR] 1.56; P = 0.001). There were no significant differences in the rate of immune-Dx findings among individuals of European (13.1%) and non-European (14.4%) ancestry (OR 1.11; P = 0.47). Diagnostic results in 275 cases were on the International Union of Immunological Societies (IUIS) 2024 classification list; the most prevalent categories were antibody deficiencies (26.6%) and CIDs with associated features (21.1%). The percentage of the cohort with candidate gene findings (6.0%) was larger than that found for all indications (4.4%) across ES/GS tested cases (OR 1.38; P = 0.001).

The use of ES/GS in individuals with suspected IEI at a single large laboratory demonstrates equity in immune-Dx across populations. ES/GS can provide additional information, such as nonimmune diagnoses that are relevant for the individual, dual diagnoses, and candidate gene findings that may be upgraded in the future. ES/GS is an equitable diagnostic approach, important in the context of the rapidly growing list of IEI-associated genes.

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Distinct EBV-Associated Phenotypes Due to a Novel Homozygous Missense Variant in CD27

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Biallelic deficiencies of CD27 and its ligand CD70 underlie selective susceptibility to Epstein-Barr virus (EBV) infection and its acute and chronic complications, underscoring their nonredundant roles in anti-EBV immunity. To date, 16 pathogenic CD27 variants have been reported. Here, we describe three patients from two unrelated families, homozygous for a new loss-of-function (LOF) CD27 variant, resulting in the substitution of serine 70 with proline (S70P). All three patients presented with EBV viremia and lymphoproliferative disease, with variable immune dysregulation or recurrent otosinopulmonary infections. One patient developed EBV-associated malignancy. Functional studies demonstrated that the S70P variant impaired surface expression of CD27 and abolished CD70 binding, rendering complete LOF when overexpressed in vitro. Endogenous CD27 expression from patients was absent ex vivo.

Together, S70P represents a novel pathogenic variant causing autosomal recessive (AR) CD27 deficiency, characterized by a unified susceptibility to EBV yet distinct clinical manifestations, ranging from chronic viremia to malignancy.

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Distinct Immunological Phenotype in Galactosemia Type 3 Patients with Biallelic GALE Mutations

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Galactosemia involves different forms of inborn errors of metabolism affecting galactose processing. Different from type 1 and type 2, respectively, related to GALT and GALK1 defects, type 3 galactosemia is due to biallelic mutations in UDP-galactose-4-epimerase (GALE), a transferase enzyme involved in the Leloir pathway. Here, we investigated two fraternal twins presenting with a syndromic disease characterized by intellectual disability, mild thrombocytopenia, fluctuating immunoglobulin levels, and T and B cell lymphopenia. The patients were diagnosed with type 3 galactosemia based on whole-exome sequence-detected compound heterozygous GALE variants, c.449C>T p.(T150M) and c.551G>A p. (R184H). Patients' peripheral blood mononuclear cells showed markedly reduced GALE protein abundance. In vitro overexpression studies demonstrated that the previously unreported GALE p. (R184H) variant showed increased ubiquitination and degradation, which, together with the previously reported/disease-causing p.(T150M) mutation, contribute to their disease. The patients' T cell phenotype was abnormal, showing low recent thymic emigrants as well as naive CD4+ and CD8+ T cells. CD4+ and CD8+ T cells also failed to properly proliferate after mitogen or T cell receptor stimulation, in addition to exhibiting increased apoptosis. The patients' B cell immunophenotyping in peripheral blood showed very low B cell numbers with relatively increased plasmablasts, increased apoptosis, and a markedly reduced CD19 mean fluorescence intensity (MFI), while CD20 MFI was within normal ranges.

Patient-derived EBV-transformed B cells also exhibited reduced GALE abundance, with a hyperglycosylated/higher molecular weight CD19 expression pattern.

Overall, our studies indicate that type 3 galactosemia due to GALE mutations can affect T cell thymic output, proliferation, and survival, altogether contributing to T cell lymphopenia. In terms of B cells, glycosylation defects on critical lineage-specific molecules, such as CD19, are affected, likely impacting B cell numbers, function, and/or trafficking. Further studies are underway for the in-depth evaluation of the GALE-specific immune glycosylated molecules/pathways involved (e.g., mass spectrometry, RNA-seq) and comparison with type 1 and type 2 galactosemia patients, none of whom are reported to have associated immune defects.

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Dominant-Negative FOXN1 Mutations: Clinical Variability and Omenn Syndrome Management in an International Cohort of 7 Families

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Background: Transcription factor forkhead box protein N1 (FOXN1) is the master transcription factor required for differentiation and maintenance of thymic epithelial cells (TECs) and is not only required for embryonic thymus development but also for postnatal thymic maintenance. Autosomal recessive FOXN1 deficiency leads to alopecia, nail dystrophy, and nude severe combined immune deficiency (SCID) due to athymia requiring thymus transplantation. Dominant-negative (DN) heterozygous variants, on the other hand, have incomplete and highly variable phenotypes. We hereby present an international cohort of families carrying dominant-negative mutations with variable clinical presentation, course, and outcomes.

Methods: Patient medical records and diagnosing physicians were consulted.

Results: We present 15 FOXN1 DN heterozygotes from 7 different families across the world, demonstrating highly variable intrafamilial clinical courses and management. Age at diagnosis ranged from 0.2 to 45 years. Eight patients were male, and seven were female. Four individuals were diagnosed through newborn screening (NBS) for SCID. Immunological phenotype included Omenn syndrome (OS) (6/15), SCID-like disease (1/15), combined immunodeficiency (CID) with autoimmunity complications (1/15), T cell lymphopenia (5/15) or antibody deficiency (2/15), and one asymptomatic individual. Herpesviridae-related complications were prominent, including EBV viremia (3/15), Varicella pneumonia (1/15), severe Varicella infection (1/15), and CMV disease (3/15), one of which presented with CMV retinitis. The severity and management of OS were variable: one patient was managed with monitoring alone, one received immunoglobulin replacement therapy (IgRT) alone, one received antimicrobial therapy only, two received IgRT and antimicrobial prophylaxis, and one was treated with prednisone, cyclosporine, IgRT, and broad antimicrobial prophylaxis. One patient underwent hematopoietic stem cell transplantation (HSCT) before the identification of DN-FOXN1 and died from transplant-related complications. No OS patient required HSCT. Up to date, no patient has received a thymic transplant.

Conclusions: Heterozygous FOXN1 variants have traditionally been considered mild, with immune function often improving over time and without the need for definitive therapies. However, DN-FOXN1 variants appear to carry a broader clinical spectrum, including OS. In our cohort, OS manifestations were variable and could often be managed with supportive care, including IgRT, antimicrobial prophylaxis, and, when indicated, immunosuppression, and none of the patients has required thymic transplantation to date.

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Expanded Clinical Spectrum of Artemis SCID: A Novel DCLRE1C c.545G>A Variant with Residual T Cell Function

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Artemis-deficient severe combined immunodeficiency (SCID) is a rare autosomal recessive disorder caused by pathogenic variants in DCLRE1C, which encodes ARTEMIS, a DNA repair endonuclease essential for V(D)J recombination. Loss of ARTEMIS function results in radiosensitivity and a characteristic T−/B−/NK+ SCID phenotype. Affected infants are highly vulnerable to life-threatening infections, and definitive therapy includes hematopoietic stem cell transplantation (HSCT) or gene therapy.

We report a two-week-old male identified through newborn screening for markedly low TRECs. Immunophenotyping revealed low T cells, absent B cells, and preserved natural killer (NK) cells. Rapid trio whole-genome sequencing identified a novel homozygous missense variant in DCLRE1C (c.545G>A; p.C182Y), currently classified as a variant of uncertain significance. The mutation lies within the β-CASP domain, a region in which pathogenic variants causing ARTEMIS SCID have been previously described. The variant is absent from gnomAD and has a REVEL score of 0.64, supporting potential deleteriousness.

Notably, the immunologic profile did not align with classic or leaky SCID. CD3 T cell counts were 1,600 cells/μL with 48% naïve CD4 and 92% naïve CD8 populations. Maternal engraftment was excluded, and T cell mitogen proliferation and TCR repertoire were preserved, suggesting partial ARTEMIS activity. This mixed phenotype—low but functional T cells with both naïve and memory subsets—is atypical for DCLRE1C-related SCID and suggests residual endonuclease function. Radiosensitivity testing showed increased T and B cell death but apparently normal repair of DNA double-strand breaks after low-dose irradiation.

A collaborating institution identified four additional patients with the same homozygous variant, all presenting with T low/B-/NK+ SCID, strengthening the evidence that c.545G>A (p.C182Y) is likely pathogenic. All four patients underwent successful HSCT.

This case describes a novel DCLRE1C variant associated with an unusual immunophenotype that broadens the clinical spectrum of ARTEMIS deficiency. Although the variant remains a variant of uncertain significance (VUS), accumulating multi-institutional data support

its pathogenicity. Our findings underscore the importance of collaborative genomic interpretation and detailed immune phenotyping to accurately classify rare variants and guide management in SCID.

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Expanded Phenotype, Outcome, and New Insights from the Largest Single-Country Cohort of ARPC1B Deficiency

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Genetic alteration of the genes of cytoskeletal regulatory proteins (e.g., actin-related protein complex-1 [ARPC1]) results in severe immune and hematological defects. ARPC1B deficiency (ARPC1BD) is an immune-actinopathy with combined immunodeficiency, allergy, inflammation, and bleeding tendency.

Only a few dozen cases have been reported worldwide. A single Nepalese center has diagnosed 20 cases (including 14 previously reported cases and 6 new cases) of ARPC1B deficiency so far. As far as published evidence shows, this is the largest single-country or single-center cohort. Eighteen cases had the same homozygous splice-site founder variant c.64+2T>A in intron 2 of the ARPC1B gene. Two cases had compound heterozygous mutation (c.64+2T>A and c.784-1G>A). This cohort proves this variant to be the most prevalent pathogenic variant resulting in ARPC1BD to date. Most of the cases were from 4 provinces. Haplotype analysis and homozygosity mapping proved this variant to be situated within a unique shared region of homozygosity, and all cases had similar haplotype around the variant, suggesting a founder gene effect. All of our cases had severe infective, allergic, autoimmune, and autoinflammatory features. Our cases (with the same founder variant) manifested a peculiar set of features, including frontal protuberance, a higher incidence of otitis, arthritis (including Rheumatoid factor positivity), recurrent skin vasculitis, severe skin hyperpigmentation, hyperkeratosis, distal phalangeal enlargement, inflammatory bowel disease-like features, gastroenteritis, elevated anti-tissue transglutaminase antibodies, immunoglobulin (Ig) A, and very high IgE. A lesser proportion had low IgG & CD3+ cells, but none had natural killer (NK) cell lymphopenia. A wide spectrum of microbial infections was noted.

Four patients did not receive specific therapy, and 5 underwent hematopoietic stem cell transplantation. Among these 5, 4 are doing well, whereas one died of vasculitis, pneumonia, and bowel obstruction. Among 20, a total of 4 patients died. Long-term morbidity in surviving patients included retinitis and severe pulmonary consequences. Nepal has a glaring lack of awareness, a nationalized healthcare system, and government support for complex immunological diseases, especially for their diagnostic, therapeutic, and research avenues. Comparatively soaring diagnosis of the cases with the same pathogenic variant of ARPC1BD in a small geographic area has provided many scientific insights about rare immune-actinopathy.

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Exploration of Clusters of Rare Disease: ARPC1B Deficiency with Founder Effect in Nepal

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Background: More than one-fourth of the world's burden of ARPC1B deficiency (ARPC1BD), a rare immune-actinopathy, is reported from Nepal, a resource-constrained Himalayan country with a single trained immunologist. The discovery of clusters indicates a potentially large, undiagnosed population. We conduct extensive immunophenotyping, functional, and genetic studies for ARPC1BD in a prospective cohort.

Methods: We established the core area of diagnosed cases with a c.64+2T>A splice site mutation of the ARPC1B gene. All cases are diagnosed by the lead author and enrolled after genetic evidence only. Investigations were performed at local labs or with the help of collaborators. A mixed-methods approach, involving both quantitative and qualitative data collection, will be continued over the next year.

Result: The study is in its initial phase. We have identified 20 ARPC1BD cases, of whom four died due to complications. Five patients have undergone hematopoietic stem cell transplantation, and two are preparing for it. Most cases are from Koshi, Gandaki, Lumbini, and Madhesh provinces of Nepal, with sporadic cases across peripheral regions. To date, 36 symptomatic siblings, relatives, or individuals from the same clan or kindred—presenting with recurrent allergy, infections, inflammatory or autoinflammatory features, bleeding, or combinations thereof—have been enrolled for initial evaluation. Genetic confirmation of ARPC1BD was achieved in three siblings of the probands and one child from the same kindred. Homozygosity mapping and haplotype analysis in eight patients identified the c.64+2T>A intronic splice-site mutation as a founder variant (of Nepalese origin), an analysis being extended to all new cases.

Sampling, immunophenotyping, and genetic analyses are ongoing. Planned next steps include expanded genetic screening of symptomatic family members and nearby individuals, analysis across clans and kindred, and detailed genotype–phenotype correlation, haplotype, linkage, and polymorphism studies to define the genetic landscape of ARPC1BD. This work contributes valuable data to the global understanding of ARPC1BD.

Conclusion: The findings from this research will provide comprehensive insights into the genetic and clinical features of ARPC1BD. This study will directly impact global immune-actinopathy literature, patient care, and serve as a foundation for future research on rare genetic disorders in similar settings.

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Fatal H5N1 Avian Influenza Pneumonia Associated with Autoantibodies Neutralizing Type I Interferons

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Highly pathogenic avian influenza A (H5N1) remains a major zoonotic threat, yet human infections continue to display striking heterogeneity in clinical severity. We report a fatal case of H5N1 pneumonia in an adult patient from Louisiana, highlighting the intersection between critical illness and impaired type I interferon (IFN) immunity.

A previously independent adult male presented with one week of dyspnea, fever, and confusion. He was hypoxemic on arrival and rapidly progressed to severe respiratory failure and moderate renal failure requiring intubation within 24 hours. Imaging revealed multifocal pneumonia, and repeat respiratory testing detected influenza A, later subtyped as H5. Clinical deterioration occurred despite guideline-directed antiviral therapy. History revealed multiple recently deceased pet and wild bird contacts. The patient's course was marked by refractory hypoxemia, right ventricular dysfunction with intracardiac shunting responsive to inhaled nitric oxide, and multiorgan failure. He required venovenous extracorporeal membrane oxygenation (ECMO), therapeutic plasma exchange, continuous renal replacement therapy, and adjunctive Seraph-100 blood purification. Despite maximal support, he developed recurrent vasoplegic shock and progressive respiratory failure and died following transition to comfort care.

Immunologic investigation demonstrated the presence of high-titer autoantibodies neutralizing type I IFNs (AAN-I-IFNs), including all 12 IFN-α subtypes and IFN-ω, at concentrations known to abolish antiviral signaling. Functional assays confirmed that the patient's serum blocked IFN-mediated restriction of influenza replication in vitro. These findings align with emerging evidence that AAN-I-IFNs underlie a proportion of severe viral pneumonias, including seasonal influenza, SARS-CoV-2, West Nile virus, and others. Their prevalence rises with age and may serve as a key determinant of susceptibility to severe disease. In this case, the coexistence of a zoonotic H5N1 infection with high-potency AAN-I-IFNs provides a biologically plausible mechanism for unchecked viral replication, fulminant respiratory failure, and poor response to antiviral therapies.

This case reinforces that impaired type I IFN immunity, whether genetic or acquired, should be considered in severe or atypical presentations of viral pneumonia, including emerging zoonoses. Early recognition may inform use of alternative IFN-β–based therapies, guide prognostication, and enhance understanding of host factors that shape viral pathogenesis and pandemic potential.

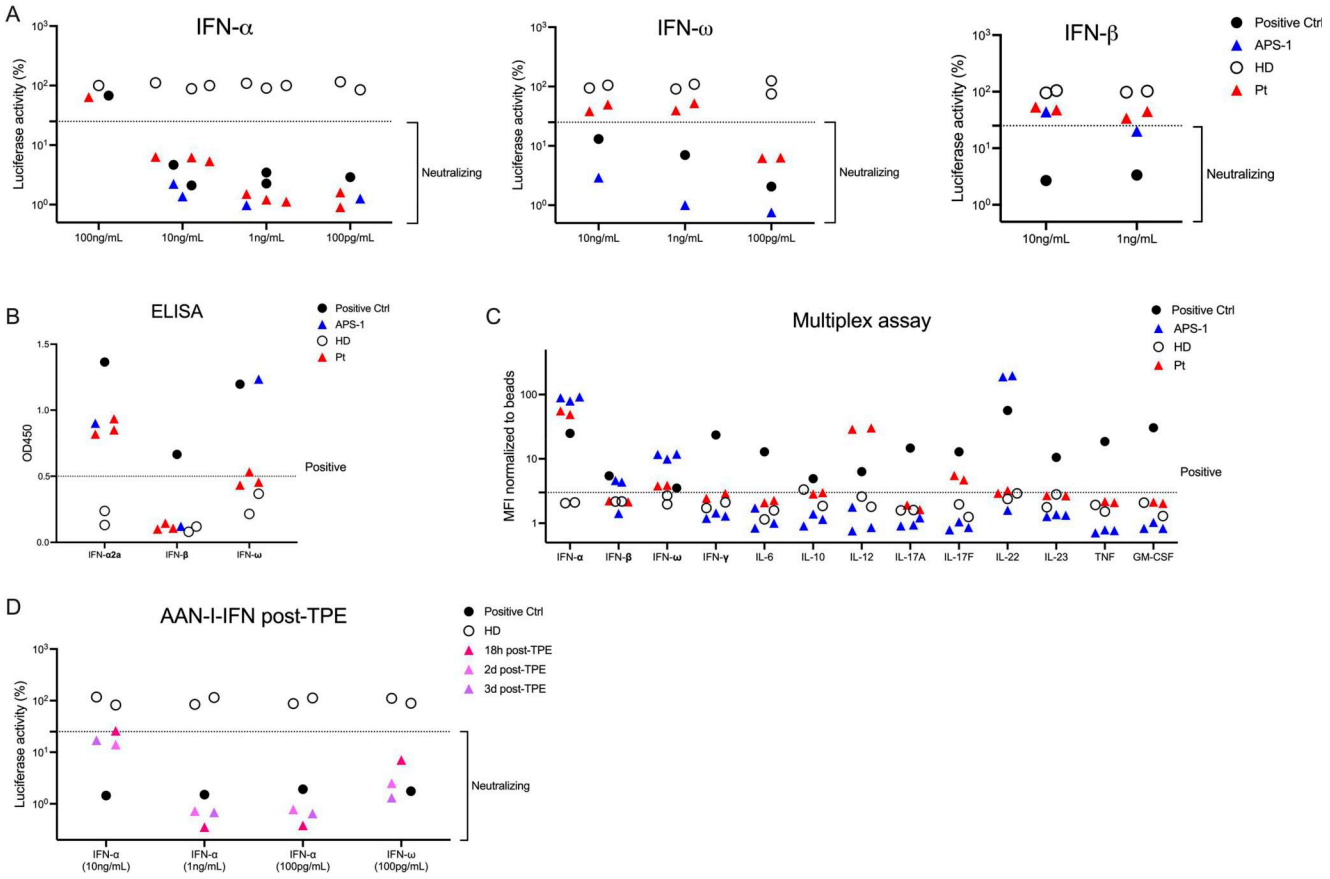

Figure 1.

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Foundational Analysis of the Impact of Mechanical Stress on Molecular Size Distribution in Immune Globulin Intravenous, Human-stwk, 10%

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Introduction: It is imperative to minimize protein aggregates in commercial intravenous immunoglobulin (IVIG) therapy as they have been implicated in adverse events and can enhance immunogenicity for patients receiving IVIG therapy. Shear stress, agitation, mixing speed, and filtration can impact aggregate formation during the manufacturing process, while shipping conditions and temperature excursions may contribute after manufacturing. A study was conducted to assess the impact of agitation on the molecular size distribution of Alyglo (immune globulin intravenous, human-stwk, 10% [IVIG-stwk 10%]).

Methods: 10 mL of IVIG-stwk 10% was dispensed into sterile washed vials, which were stoppered and sealed. Vials were then placed on a Green SSeriker shaker (Vision Science), and agitation started at 50 rpm in an upright position at a temperature of between 20 and 25°C to induce mechanical stress. On days 0, 1, 3, and 11, samples were withdrawn and diluted 1:16 with saline for analysis. The molecular size distribution of monomers, dimers, high-molecular weight aggregates, and fragments was quantified using size-exclusion high-performance liquid chromatography (SE-HPLC). For SE-HPLC, chromatographic separations were performed using a size exclusion column (TSKgel G3000SW) using a sample size of 50 mcL and a flow rate of 0.5 mL/min at a detection wavelength of 280 nm.

Results: The monomer + dimer percentage for IVIG-stwk 10% on day 0 was 99.576%; day 1 99.582%; day 3 99.591%; day 11 99.526%. The percentage of polymers and fragments remained below their respective validated limits of quantitation (0.3% and 0.5%) for each time point.

Conclusion: Mechanical agitation for up to 11 days shows minimal impact on IVIG-stwk 10% molecular size distribution. A very high percentage of monomers and dimers remained throughout the duration of the study, compared to polymers and fragments below quantifiable limits. Further assessments, more analogous to real-world conditions, along with additional measurements of opacity and particle size across multiple lots to assess variability, are warranted.

Tabular data are included as downloadable supplement files.

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Functional Defects in the NFκB pathway in Common Variable Immunodeficiency

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Common variable Immunodeficiency (CVID) is a heterogeneous immunodeficiency characterized by hypogammaglobulinemia and immune dysregulation. In up to 30% of cases, there is a monogenic defect, with a fraction of these familial. The majority, however, are sporadic. The nuclear factor kappa B (NFκB) cell-signalling pathway plays a vital role in normal B cell development and function. In fact, genetic variants affecting genes of the NFκB pathway are the most common cause of monogenic disease in CVID. Although these cases present a clear link between the NFκB pathway and CVID, it remains unclear how single-gene defects in NFκB lead to CVID. We compared the nuclear translocation and binding to the consensus κB DNA sequence of four transcription factors in the NFκB signalling pathway in B cells between patients with CVID and healthy controls upon stimulation. We found that nuclear NFκB DNA-binding activity was significantly reduced in CVID compared with healthy individuals. In patients with infections-only CVID, lower responses were observed only in p50/p52 activity, whereas in patients with CVID with additional complications, a reduction in responses to RelA and RelB was particularly pronounced. Noncanonical NFκB hyporesponsiveness was more frequently seen in CVID with autoimmune and granulomatous disease and, to a lesser extent, lymphadenopathy. In contrast, canonical hyporesponsiveness was associated with CVID with autoimmune cytopenias. We also noted an inverse relationship between the number of complications and the activity of the NFκB pathway in CVID. Taken together, these observations suggest a role for functional defects in the NFκB pathway in CVID.

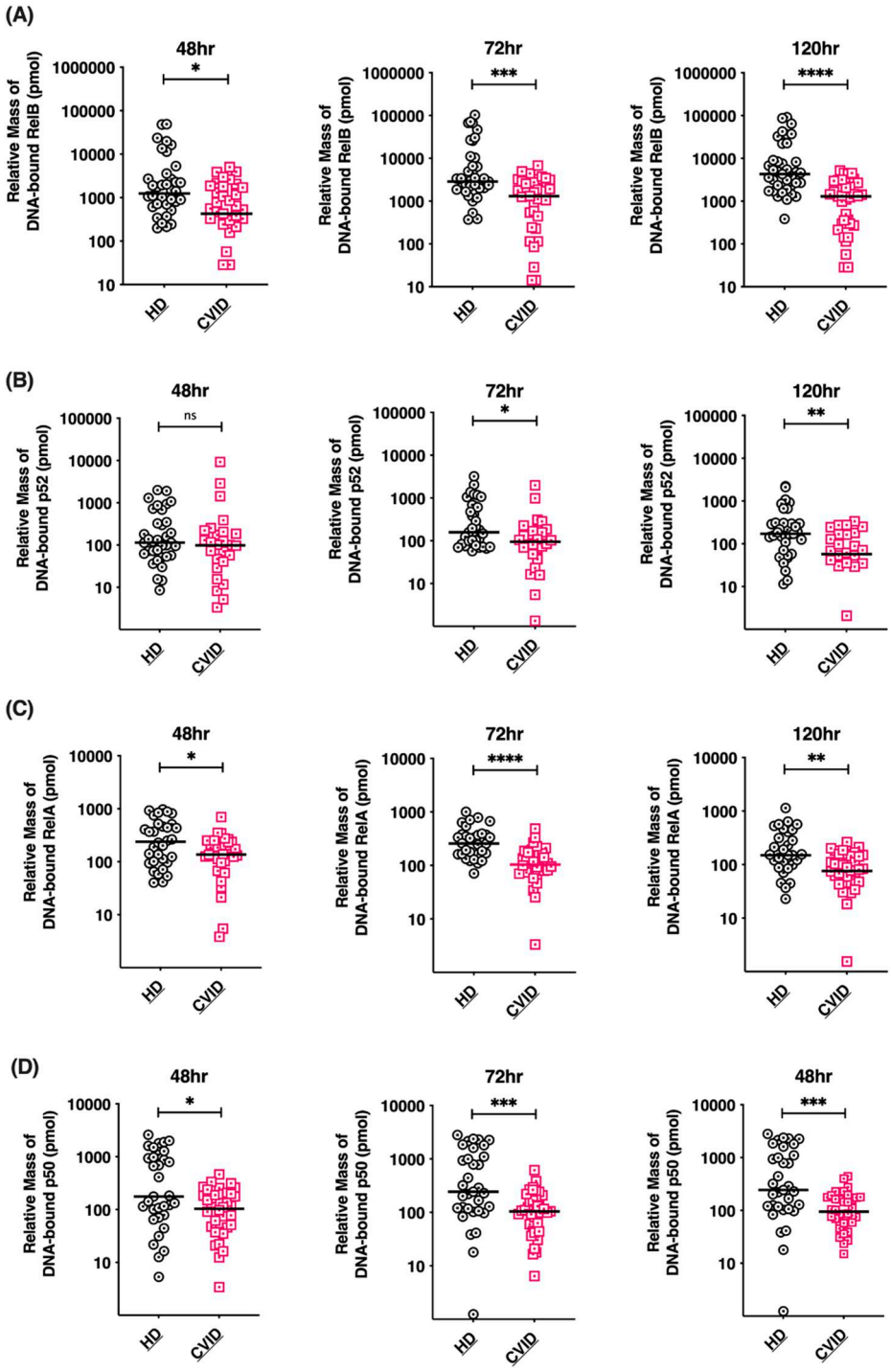

Figure 1.

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Functional Pneumococcal Assessment Using the Multiplexed Opsonophagocytosis Assay Improves Alignment with Clinical Diagnosis of Specific Antibody Deficiency

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Diagnosis of specific antibody deficiency (SAD) relies on serotype-specific IgG responses to PPSV23; however, IgG titers do not measure opsonophagocytic function and may misclassify patients due to pre-vaccine titers, variable serotype immunogenicity, and assay variability. The multiplexed opsonophagocytosis assay (MOPA) directly quantifies functional bacterial killing and may better reflect clinically meaningful antibody impairment. We evaluated how IgG versus MOPA-based interpretations aligned with clinician-diagnosed SAD.

Among 60 patients evaluated for recurrent infections, 26 had paired pre- and post-PPSV23 IgG levels and MOPA results across 18 pneumococcal serotypes. SAD was defined as >70% protective serotypes for patients ≥6 years and >50% for ages 2–5. IgG protection was determined using an operational algorithm incorporating absolute pre- and post-vaccine levels. Fold-rise criteria (2–3-fold) were applied for serotypes with low pre-vaccine levels. When pre-vaccine IgG levels were high, protection was based on post-vaccine concentration alone. IgG responses were interpreted by a physician blinded to clinical history.

For MOPA, opsonization indices, defined as the reciprocal serum dilution achieving 50% pneumococcal killing, were log standardized, and serotypes below a 0.1 SD Z-score threshold were classified as non-protective. Clinical SAD diagnosis was determined independently by the treating immunologist, blinded to all MOPA data. IgG- and MOPA-based SAD classifications were compared with clinician diagnosis.

Patients had a median age of 10.8 years (range 2–68), with 17 females and 9 males; 5 were Hispanic and 21 non-Hispanic, 1 black, and 1 Native American. All patients presented with recurrent sinopulmonary infections, and comorbidities included atopic disease (n = 12), autoimmune or immune-dysregulatory features (n = 6), quantitative immunoglobulin abnormalities (n = 4), and defined immunodeficiencies such as Wiskott–Aldrich syndrome or memory B cell defects.

Nine patients were diagnosed with SAD by the treating clinician. IgG captured 6/9 clinically confirmed SAD patients (sensitivity 0.667; specificity 0.882). Using the MOPA-derived threshold, MOPA correctly classified 8/9 clinician-diagnosed SAD cases (sensitivity 0.889; specificity 0.647).

MOPA aligned more closely with clinician-identified cases of clinically meaningful antibody dysfunction, although IgG maintained higher specificity; these differences reflect operational rule sets and may indicate complementary clinical utility. Establishing serotype-specific MOPA thresholds and correlating functional responses with clinical outcomes will be essential to refine SAD diagnostic criteria.

Tabular data are included as downloadable supplement files.

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Functional Validation of an ADA Variant in Secondary HLH Reveals Delayed Onset ADA-SCID

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Introduction: Hyperinflammatory and hemophagocytic lymphohistiocytosis (HLH)-like presentations are increasingly recognized as clinical "red flags" for inborn errors of immunity (IEI), including severe combined immunodeficiency (SCID). While standard newborn screening (NBS) using T cell receptor excision circles (TREC) allows for early detection of SCID, delayed presentations—particularly caused by defects in adenosine deaminase (ADA)—may be missed by NBS. Therefore, despite normal NBS, SCID should be considered in children presenting with HLH features.

Case Presentation: A 2-year-old male with normal NBS and a history of recurrent respiratory tract infections was admitted for fever and malaise. Laboratory evaluation demonstrated pancytopenia, elevated ferritin, hypertriglyceridemia, and hypofibrinogenemia, suggesting HLH. He subsequently developed multisystem organ failure and septicemia with *Escherichia coli*, *Candida*, adenovirus, and enterovirus. He quickly deteriorated despite aggressive therapy and passed. Genetic testing resulted postmortem and showed a heterozygous pathogenic variant in ADA, c.632G>A (p.Arg211His) and a variant of uncertain significance (VUS) in ADA, c.362+5G>C (intronic), which was not diagnostic for autosomal recessive ADA-SCID.

Methods: A CRISPR-engineered Jurkat T cell line carrying a homozygous patient-specific intronic splice variant was generated and compared to wild-type Jurkat controls for functional assessment of variant pathogenicity. Validation assays included: ADA enzyme activity measurement, western blot, evaluation of T cell activation/exhaustion through flow cytometry with stimulation, and bulk RNA sequencing to assess transcriptional signatures.

Results: ADA enzyme activity was absent in lysates from the variant Jurkat line compared with robust activity in wild-type cells. Western blot targeting the downstream epitope of the splice site revealed absent protein expression in variant cells and full-length product in wild-type controls. Compared with the wild type, the variant Jurkat line demonstrated attenuated upregulation of exhaustion marker, PD-1, despite elevated CD69 following stimulation. Bulk RNA sequencing showed upregulation of inflammatory pathways, including interferon gamma, IL-2, IL-6, and TNFα via NFκB in the variant.
Discussion: These findings confirm the variant's pathogenicity, enable variant reclassification, and demonstrate a hyperinflammatory T cell response in vitro that mirrors the patient's clinical phenotype. This integrated clinical-genetic-functional approach bridges gaps in genetic findings to actionable IEI diagnoses. Although not altering the patient's fatal outcome, it enabled early detection and ADA-enzyme replacement therapy for his affected brother.

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Genetics of B Cell Maturation in Common Variable Immunodeficiency in Brazil: A Joint Analysis of the CVID-Brazil Cohort and the CNE3I Program

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Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency and remains underdiagnosed in Brazil due to limited knowledge of its genetic landscape. Since 2024, the Centro Nacional dos Erros Inatos da Imunidade e Imunodesregulação (CNE3i) has led the first nationwide initiative to systematically collect clinical, immunological, and genomic data on Brazilian patients with CVID. A total of 30 patients underwent genetic reanalysis; 53% were female (n = 16) and 47% male (n = 14), with a median age at diagnosis of 44 years. Most patients originated from the Southeast region, predominantly São Paulo (n = 24). Genetic variants in genes related to B cell development and function were identified in 15 patients, while no relevant variants were detected in the remaining 15 individuals. The majority of identified variants were classified as variants of uncertain significance (VUS), underscoring the complexity of genetic interpretation in CVID. Only one patient carried a clearly pathogenic variant in a well-established CVID-associated gene, NFKB1. In addition, CFTR variants were detected in four patients, including one heterozygous pathogenic variant (c.3154T>G, p.Phe1052Val), one likely pathogenic variant (c.1210-11T>G), and two heterozygous VUS (c.489+3A>G), suggesting a potential modifying contribution to disease expression rather than a primary monogenic cause. In conclusion, this first-year analysis highlights the marked genetic heterogeneity of CVID in a Brazilian cohort and reveals a high proportion of inconclusive variants, reflecting the limited representation of admixed populations in current genomic reference databases. These findings emphasize the critical need for continued genomic reanalysis, expansion of ancestry-diverse datasets, and careful genotype–phenotype correlation to improve diagnostic accuracy and advance precision medicine approaches for CVID in underrepresented populations.

Tabular data are included as downloadable supplement files.

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Genome-Wide Association Study Implicates Immunogenetic Variation in Chemokine Signaling Pathways in Pediatric Tuberculosis Susceptibility

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Introduction: Although immune responses to Bacillus Calmette–Guérin (BCG) vaccination and susceptibility to mycobacterial infection vary across individuals, the underlying cellular mechanisms regulating this heterogeneity are poorly understood. We hypothesized that immunogenetic variation among common host variants contributes to susceptibility to pediatric tuberculosis (TB) disease.
Methods: We used a case-control study with a 12–36-month prospective observation period to examine pediatric TB susceptibility in children 2 mo–5 years with household *Mycobacterium tuberculosis* exposure in Worcester, South Africa. Low-pass whole-genome sequencing followed by imputation was completed for 212 TB cases and 184 controls. A genome-wide association study (GWAS) was performed to assess the association between genetic variants and pediatric TB susceptibility. Lead genetic variants were evaluated for their effect on BCG-induced innate and adaptive immune responses in 10-week-old South African infants using flow cytometry.
Results: We identified a genome-wide significant variant, rs4600676 (p = 3.7e-08), associated with increased pediatric TB susceptibility. Genetic variation at this risk locus is associated with differential expression of mitochondrial ribosomal protein MRPS9 (p < 1e-05), suggesting it may regulate cellular metabolism and stress response. We also identified an additional 18 risk loci mapping to 194 genes at a prespecified suggestive significance level (p < 1e-05) associated with pediatric TB susceptibility. MAGMA gene set analysis of these suggestive variants revealed the strongest enrichment for CXCL2 production (p = 4.1e-06) with suggestive variant rs79846470 (p = 1.9e-06) mapping to the CXCR1 and CXCR2 genes via chromatin association. Genetic variation at this locus is associated with increased IL6 production in myeloid dendritic cells following BCG vaccination (p = 0.007).
Conclusion: We identified a genome-wide significant variant, together with 18 additional loci, associated with increased pediatric susceptibility to mycobacterial disease. These findings highlight innate immune and metabolic pathways as key immunogenetic determinants of antimycobacterial host responses in children. By delineating these pathways, our work underscores the potential to leverage immunogenetic insights in advancing precision diagnostics and mechanism-based immunomodulatory strategies for children with inborn errors of immunity.

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Geranylgeraniol Modulates Inflammatory and Metabolic Pathways but Not IgD Biology in Mevalonate Kinase Deficiency

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Objectives: Mevalonate kinase deficiency (MKD) is a metabolic disorder caused by a block in the mevalonate pathway, leading to impaired synthesis of cholesterol and isoprenoids. Clinically, MKD presents with recurrent inflammatory attacks. A characteristic feature is elevated serum IgD, although the underlying mechanism remains unclear. This study assessed whether geranylgeraniol (GG) supplementation, which provides downstream isoprenoids missing due to the metabolic block, can modulate inflammatory and metabolic profiles in MKD. We also examined the plasma cell compartment, focusing on IgD-producing cells. Earlier reports described IgD-producing bone marrow plasma cells with strong cytoplasmic IgD. We extend these observations using new cellular, cytometric, and single-cell RNA sequencing data.
Methods: Six MKD patients (4 females, 2 males; age 12–51) were followed over 2 years. Treatments included on-demand anakinra (n = 4), continuous anakinra (n = 1), and nonsteroidal anti-inflammatory drugs (NSAIDs)/corticosteroid therapy (n = 1). Immunological assays, proteomics (SomaLogic SomaScan 7k), and metabolomics (gas chromatography–time-of-flight mass spectrometry [GC-TOF MS]) were performed before and after 3 months of GG supplementation (150 mg GGOH). Single-cell RNA sequencing in one patient not receiving IL-1 blockade revealed a subset of unusual IgD^+ cells with plasma cell features.
Results: GG supplementation was well-tolerated without significant adverse effects. Proteomic and metabolomic analyses indicated downregulation of innate immune pathways and metabolic adjustments consistent with an anti-inflammatory response, including partial normalization of protein and metabolite profiles. Serum IgD concentrations remained unchanged. A distinct population of plasma-like cells with high IGHD transcript levels was identified in the patient, not on IL-1 blockade, but was absent in healthy controls. These cells expressed XBP1, CD27, and CD38 yet showed aberrant expression of transcription factors involved in class-switch recombination and plasma cell differentiation. Unlike conventional plasma cells with broad IGHV/IGLV induction, this subset selectively upregulated IGHV4, IGHV6, and IGHD. Differential expression analysis highlighted a transcriptional signature linked to cell cycle regulation.

Conclusion: We describe a transcriptionally unique IgD$^+$ plasma-like population in MKD that may contribute to persistently elevated serum IgD, observed so far in one patient not receiving IL-1 blockade. GG supplementation modulates inflammatory and metabolic pathways but does not influence IgD. Further research is needed to define the origin and persistence of these atypical cells.

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Health-Related Quality of Life (HRQOL) in Pediatric and Adult Patients with X-Linked Hyper IgM

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Background: X-linked hyper IgM syndrome (XHIGM) is a rare primary immunodeficiency (PID) caused by pathogenic variants in the CD40 ligand (CD40LG) gene, resulting in defective immunoglobulin class-switch recombination, causing recurrent infections and malignancy. Treatment includes prophylactic antimicrobials, gammaglobulin replacement therapy (IGRT), and hematopoietic cell transplantation (HCT). To date, the impact of XHIGM on perceived quality of life has not been examined. The purpose of this study was to evaluate health-related quality of life (HRQoL) in individuals with XHIGM using validated Patient-Reported Outcomes Measurement Information System (PROMIS) instruments.
Methods: We conducted a prospective cross-sectional study of individuals self-identified as having XHIGM. Participants/caregivers completed REDCap surveys, including age-appropriate PROMIS HRQoL instruments in English or Spanish. Raw scores were converted to standardized T-scores (mean = 50, SD = 10) using standard reference data. A 3-point T-score difference was considered clinically meaningful. Statistical comparisons were performed using Kruskal–Wallis and Fisher's exact tests.
Results: Of 89 respondents, 63 (52 English and 11 Spanish) provided analyzable data (mean age 17.5 years, range 5–52; median age at diagnosis 13.0). 59% were post-HCT. 60% were receiving IGRT: 100% of non-transplanted respondents and 32% of post-HCT respondents. Three patients were diagnosed with malignancy; two were diagnosed after HCT. Compared to the general population, adult respondents reported worse global mental health, greater anxiety and depression, and reduced physical function. Proxy and pediatric self-reports indicated worse global health and reduced mobility (self-reports only). Compared to the general population, transplanted adults not receiving IGRT reported increased global physical health, physical function, and social participation. Transplanted pediatric respondents not receiving IGRT reported decreased depression, fatigue, and pain interference. Adult, pediatric, and parent proxy reports for those transplanted and still receiving IGRT reported worse HRQoL compared to the general population in more domains (8 of 9 adult, 5 of 9 pediatric, and 3 of 7 proxy domains) than any other treatment group.
Conclusions: Persons with XHIGM experience meaningful impairments in HRQoL. Those requiring IGRT after undergoing HCT reported worse HRQoL in more domains than the other treatment groups.

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HEM-1-Associated Inborn Error of Immunity: A Case Series

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NCKAP1L encodes hematopoietic protein-1 (HEM1), a component of the WASp family verproline-homologous protein (WAVE) actin regulatory complex, activated downstream of multiple immune receptors. HEM1 deficiency disrupts WAVE-mediated regulation of F-actin polymerization and actin capping in neutrophils and lymphocytes, resulting in impaired immune synapse formation, cell migration, and phagocytosis, and excessive cytokine release due to dysregulated granule exocytosis (1, 2). HEM1 deficiency also impacts mTORC2 signaling, T cell proliferation, and other T cell effector functions (3, 4). Thus, the totality of HEM1 deficiency is impaired specific immunity, in addition to nonspecific immune system hyperactivation.

Biallelic loss-of-function NCKAP1L variants, including the homozygous c.1076C>T (p.P359L) variant, were first described in 2020 and cause an inborn error of immunity marked by early-onset infection susceptibility, autoimmunity, and excessive inflammation (4). Only nine patients from seven kindreds with HEM1 deficiency have been reported (1, 3–5).

We describe two previously unreported patients and provide updated clinical information on two previously published patients, all homozygous for NCKAP1L c.1076C>T (p.P359L) (4, 6), comparing their features with prior cases. Three patients presented in early life with severe bacterial and viral infections accompanied by excessive inflammatory responses resembling hemophagocytic lymphohistiocytosis (HLH), but with uncharacteristic leukocytosis, and improving spontaneously without targeted immunosuppression. One fetus was identified at 25 weeks' gestation with hydrops, including cardiomegaly, pleural effusion, ascites, echogenic bowel, and Doppler findings consistent with severe anemia; subsequent imaging revealed hepatosplenomegaly, and fetal demise occurred at 31 weeks.

While hydrops fetalis has not been previously reported, it is noteworthy that the older sister of the two patients reported by Salzer et al. (3) died shortly after birth of unknown cause.

Over time, the three surviving patients experienced fewer infections, even without prophylaxis, but experienced lymphoproliferative, atopic, and immune-mediated organ disease, without classical autoimmunity. Three of the four patients are alive at ages 4–17 years and receive supportive care or immunomodulation; none have undergone hematopoietic stem cell transplantation.

This report expands the clinical and immunologic spectrum of HEM1-associated immune actinopathy and increases the total number of reported cases to 12. The shared homozygous c.1076C>T variant among unrelated Ojibway Indigenous Canadian families suggests a possible founder effect.

Tabular data are included as downloadable supplement files.

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Heterogeneous CD21low B Cell Subsets and Their Functional Impact in Common Variable Immunodeficiency

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Atypical CD21low B lymphocytes are a naturally occurring transient subset that has been increasingly recognized in chronic diseases, such as infections and immune dysregulation, where they may persist for long. Their fate and functional role among inborn errors of immunity, such as common variable immunodeficiency (CVID), is yet to be fully understood.

In this work, we provide a new perspective on atypical CD21low B cells by subdividing them into functionally relevant subsets that may differentially contribute to immune system dysregulation—namely naïve-like (IgD+ CD27-), double-negative-like (IgD- CD27-), and class-switch-like cells (IgD- CD27+).

Our cohort included 30 adult patients with CVID (age range: 23–67 years) followed at the Institute of Immunology, 2nd Faculty of Medicine, Charles University, and Motol University Hospital. CD21low B lymphocytes were assessed in peripheral blood. We noted an increased number of total CD21low B lymphocytes and significant higher amount of naïve-like CD21low B cells compared to age-matched healthy controls (HC).

Furthermore, to describe the involvement of individual CD21low B cell subpopulations in immune system dysregulation in CVID, we stimulated peripheral blood cells/isolated B cells from patients with TLR9 (CpG oligodeoxynucleotides [ODN]), TLR7/8 (R848—resiquimod), and B cell receptor ligands (anti-IgM and anti-CD40).

We observed increased expression of costimulatory markers CD80/86, CD40, HLA-DR, and chemokine receptor CCR7 on the surface of CD21low B lymphocytes and their subpopulations in these patients after their stimulation. In addition, we also found changes in the relative representation of CD21low B lymphocyte subpopulations after in vitro stimulation via BCR and TLR.

All of the above findings indicate that individual subpopulations of CD21low B lymphocytes contribute to immune system dysregulation in CVID patients, and further research is necessary to understand the exact mechanisms of CD21low B lymphocytes leading to the development of autoimmune or malignant diseases in these patients.

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Heterozygous Variants in DOCK2 Leading to Susceptibility to Viral Illnesses

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Background: Inborn errors of immunity (IEIs) are classically identified in infants and young children with severe or recurrent infections. However, hypomorphic variants with a partial loss-of-function can remain unrecognized until later in life and may underlie clinically significant susceptibility to infections in previously healthy individuals. We investigated how three novel heterozygous variants in DOCK2 contribute to impaired antiviral immunity, extending the understanding of DOCK2 deficiency beyond an autosomal recessive disease.
Methods: After identifying the first heterozygous DOCK2 variant in a family with 4 individuals with warts and T cell lymphopenia, we screened 1,109 exomes from three cohorts of patients with a history of at least one severe infection. We assessed the biologic impact of each variant via functional and transcriptional assays of the patients' primary peripheral blood mononuclear cells and in cell-based overexpression systems.
Results: Six individuals from three unrelated families, aged 3 months to 50 years, carried one of three heterozygous DOCK2 variants and experienced severe infections with human papillomavirus, respiratory syncytial virus, or SARS-CoV-2. All variants resided within the DOCK2 domain that binds and stabilizes ELMO1. Each variant reduced DOCK2 protein expression, ELMO1 binding, and DOCK2 function, as shown by diminished Rac1 activation and selective defects in Toll-like receptor signaling. Weekly IFN-alpha therapy led to complete resolution of severe, refractory warts in one patient, highlighting a potential therapeutic approach for DOCK2-associated immunodeficiency.
Conclusions: These findings expand the spectrum of DOCK2-related disease by showing that heterozygous pathogenic variants disrupting DOCK2–ELMO1 interactions impair protein stability and antiviral immunity, revealing a previously unrecognized IEI affecting otherwise healthy individuals.

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Human Inherited RORγT Deficiency: Genetic Heterogeneity, Immunological Impact, and Clinical Homogeneity

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We previously reported that inherited human retinoic acid-related orphan receptor gamma T (RORγT) deficiency underlies mycobacterial disease and chronic mucocutaneous candidiasis (CMC) in seven patients from three ancestries (Chilean, Palestinian, and Saudi Arabian). Here, we expand on the molecular, cellular, and clinical consequences of RORγT deficiency in these patients and identify five additional patients from different ancestries (Afghan, Indian, Iranian, Japanese, and Sri Lankan), each homozygous for a new loss-of-function RORC variant. All but one patient, who had received early prophylaxis (11/12), developed mycobacterial disease due to a near-complete depletion of innate-like adaptive T cells, including mucosal-associated invariant T (MAIT) and

invariant natural killer T (iNKT) cells, low counts of adaptive TH1* and CD8+ T cells, and impaired mycobacterium-induced IFN-γ production by the remaining cells of these subsets, and by NK cells, conventional CD4+ T, Vδ1, and Vδ2 γδT cells. Most patients (10/12) also displayed CMC due to their low counts of TH17 and TH1* cells. Additional phenotypes included anti-IL-4Rα-responsive eosinophilic disease in one patient and self-resolving skin warts in two patients, probably reflecting TH2-skewing and defective T cell development, respectively.

Finally, one patient (1/12) died from disseminated Bacille Calmette-Guérin (BCG) infection, whereas all the other patients remain alive and clinically stable at ages of 2 to 20 years. Thus, inherited human RORγT deficiency underlies mycobacterial disease with complete penetrance and CMC, with high but incomplete penetrance.

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Identification of a Novel Deleterious RIPK1 Variant

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Introduction: Receptor-interacting serine/threonine-protein kinase 1 (RIPK1), a cytosolic protein, plays an essential role in signaling pathways responsible for inflammation and programmed cell death. In humans, two main clinical syndromes associated with RIPK1 have been described. The first syndrome results from a loss-of-function in RIPK1, leading to immunodeficiency and auto-inflammatory conditions. The second syndrome involves a non-cleavable variant of RIPK1 and is characterized predominantly by auto-inflammation, manifesting as recurrent fevers and lymphadenopathy.

Case Presentation: The patient, a 3-month-old infant, was admitted for further evaluation following initial presentation of bloody diarrhea and abdominal pain, first suspected to be milk protein allergy. Over time, clinical symptoms worsened, including poor weight gain, persistent fever, and elevated inflammatory markers. Endoscopic evaluation with esophagogastroduodenoscopy (EGD) and colonoscopy raised concerns for very early onset-inflammatory bowel disease (VEO-IBD). Genetic testing revealed a homozygous variant of unknown clinical significance in RIPK1 (c.460-5C>A). This mutation is predicted to create a splice acceptor site upstream of exon 5, within the first domain of the protein, as indicated by Splice AI. Multiple in silico prediction tools suggest that this variant is likely deleterious. Further analysis with western blot showed no detectable RIPK1 protein, confirming a deficiency. To date, the patient has experienced CMV viremia; however, because he remains asymptomatic and continues to show clinical improvement, treatment for viremia has been deferred. Immunological evaluations have been normal and do not indicate combined immune deficiency. Initial treatment was anakinra, but has since been transitioned to infliximab.

Discussion: The variant identified in this patient has not previously been reported and was classified as a variant of uncertain significance (VUS). However, given the clinical diagnosis of VEO-IBD and the established association of RIPK1 deficiency with inflammatory bowel disease, there was strong suspicion that the mutation may be causative. However, as this specific variant is novel, functional validation was necessary. The absence of RIPK1 protein on western blot provided definitive confirmation of the deficiency.

Disclosures: Kathleen Sullivan: Relevant financial relationships with proprietary interests: Elsevier (royalties); Immune Deficiency Foundation (board member, consultant); UpToDate (royalties). The other authors have no financial relationships or conflicts of interest to report.

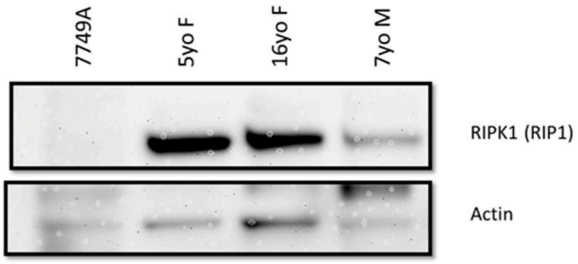

Figure 1.

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Immunological Aspects of CHARGE Syndrome on the Example of Four Clinical Case Reports

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Background and Aims: CHARGE syndrome (OMIM#214800) is a rare hereditary monogenic disease with an autosomal-dominant pattern of inheritance. It is characterized by multiple congenital malformations and is caused by pathogenic variants in the CHD7 gene. Immunological disorders are typically associated with thymic hypoplasia or aplasia and vary in their clinical manifestations. The diagnosis of immunological disorders in patients with CHARGE syndrome requires a comprehensive assessment that includes the analysis of immunoglobulin levels, the evaluation of T and B lymphocyte function, and the assessment of the response to vaccination. Early detection and appropriate treatment of immunodeficiencies in children with CHARGE syndrome are crucial for preventing severe infections and improving the prognosis.
Methods: The patients' phenotype was assessed based on the results of a clinical examination and instrumental and laboratory tests. The children's physical development was evaluated using the World Health Organization program Anthro. A cytogenetic study was conducted on lymphocytes using standard protocols (G-banding). A molecular genetic study was performed on the probands using full exome sequencing, and the segregation of the identified variants in the families was determined using Sanger sequencing. The functioning of the T and B cell immune system was assessed by determining the quantitative analysis of T cell receptor excision circles (TREC)/kappa-deleting recombination excision circles (KREC) using real-time quantitative (RQ) PCR.
Results: 4 patients from 4 families were diagnosed with CHARGE syndrome based on clinical data and genetically verified variants in the CHD7 gene. The family histories of these families were not affected. All patients had a normal karyotype. An immunological study showed that the absolute number of lymphocytes was low (1,050[1,010;1,400] cells/ml). Examination of blood samples from neonatal screening forms revealed a decrease in the TREC (0.0[0; 300] copies x10 6 leukocytes) at normal KREC 3,420[3,050–4,980] copies x10 6 leukocytes).
Conclusions: The results we obtained demonstrate the clinical significance of the TREC/KREC study within the framework of neonatal screening, not only in relation to the diagnosis of primary immunodeficiencies but also for syndromic diseases accompanied by immune system insufficiency. These data can serve as a basis for in-depth immunological examination of patients, timely initiation of preventive measures to prevent infectious diseases, and timely prescription of replacement therapy.

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Impact and Perspectives of Registry-Based Research in Inborn Errors of Immunity/Primary Immune Disorders: Insights from the ESID Registry of 36,681 Patients

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Clinical research and real-world observational studies are essential for advancing the diagnosis and treatment of rare diseases, such as inborn errors of immunity/primary immune disorders (IEI/PID). To support efficient study planning, it is crucial to estimate patient numbers and identify centers caring for specific IEI/PID. The European Society for Immunodeficiencies has maintained a dedicated patient registry (ESID-R) for over 30 years, now containing data from 36,681 patients. In 2024, the ESID-R was migrated to a professional clinical trials operator to streamline and decentralize studies conducted by academic groups.

Unlike cross-sectional health-economic or epidemiologic datasets, the ESID-R provides longitudinal follow-up (age range 0–97 years; mean follow-up 7.2 years), capturing diagnostic pathways, treatments, organ involvement, and major events such as hematopoietic stem cell transplantation, gene therapy, malignancies, and death. Data are manually extracted from electronic health records into structured case report forms (CRFs). Alongside baseline level 1 data, approximately 10–15 concurrent sub-studies use level 2 (diagnosis- or country-specific) or level 3 (more detailed, protocol-based) CRFs for non-interventional studies.

Over its first three decades, the ESID-R supported more than 85 publications with a mean citation rate of 95. Recent studies include analyses of initial manifestations or malignancies in IEI/PID, natural history of SOCS1 or JAGN1 deficiency, cartilage hair hypoplasia and activated PI3K-delta syndrome, machine-learning–based diagnosis classification using the Immune Deficiency and Dysregulation Activity (IDDA) score, and real-world experience with JAK inhibitors. Ongoing projects include sub-registries on familial hemophagocytic lymphohistiocytosis and immune reconstitution in adenosine deaminase 1-deficient severe combined immune deficiency (ADA-SCID).

The ESID-R enables rapid sub-study feasibility assessments and represents a valuable platform for clinical research in very rare diseases. While challenges remain—particularly in motivating consistent data entry and addressing legal or technical barriers to sub-study integration—many obstacles have been resolved through the new technical framework and harmonized center agreements. Despite progress in some countries, automated data extraction or widespread consent waivers remain unlikely in the near term across >30 participating countries. Future directions include integrating artificial intelligence to enhance both data acquisition and analysis. To maximize impact while minimizing burden on clinicians, patient registries for IEI/PID across the globe should remain interoperable, collaborative, and nonredundant, enabling broad access for joint research initiatives.

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Inborn Errors of Immunity Adolescents at School

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Background: Adolescents with inborn errors of immunity (IEI) experience disease-related absenteeism and psychosocial challenges that can compromise schooling. Evidence integrating perspectives across stakeholders is limited.
Objective: To map school-related strengths and gaps for adolescents with IEI across patients, caregivers, teachers, and classmates to inform actionable improvements.
Methods: Prospective cross-sectional study (May–June 2021) using multi-informant questionnaires co-created with researchers for Vall d'Hebron Research Institute and the Barcelona PID Foundation's patient council. Instruments covered five domains (knowledge, adaptation, school's understanding, coordination, and socialization) plus a cross-cutting prioritization of "most challenging areas."
Participants: 13 adolescents with confirmed IEI (13 schools), 21 parents, 13 tutor teachers, and 74 classmates. Descriptive analyses summarized agreement and free-text themes.
Results: Half of the students reported difficulty keeping up academically. Most teachers (11/13) wanted additional IEI training; 8/13 lacked detailed medical information, and 7/13 schools had no absenteeism action protocol. Parents frequently endorsed unmet academic/social needs and favored disclosure to staff/classmates. Classmates showed positive social acceptance and strong interest in learning about IEI, while perceiving insufficient disease-specific information. Free-text comments highlighted anxiety on returning after hospitalizations and the importance of role-specific guidance for school staff. Overall, supportive peer environments contrasted with system gaps in protocols and school–healthcare coordination.
Conclusions: IEI substantially affects schooling despite supportive peers. Priorities include co-developed, teacher-facing protocols for absenteeism, structured school–healthcare coordination pathways, and targeted educator training, disseminated via scientific societies and patient organizations. Future multicenter studies should validate stakeholder-aligned instruments and evaluate scalable implementation strategies to improve educational outcomes and quality of life in adolescents with IEI.

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Innovations in Care of Inborn Errors of Immunity in Brazil: CNE3I, the Brazilian National Center for Inborn Errors of Immunity and Immune Dysregulation Diseases

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Inborn errors of immunity (IEI), once considered rare, are more common than previously thought, affecting up to 1:1000 individuals, with 555 IEI identified involving variants in 546 genes. This expanded genetic and clinical understanding underscores the need for early detection and national centers to address diagnostic disparities and improve management. In this context, the Centro Nacional de Erros Inatos da Imunidade e Imunodesregulação (CNE3i) (Financiadora de Estudos e Projetos [FINEP] funded 0956/24) was established at Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (HCFMUSP) in 2024 as a genetic hub for linked centers collaborating with CoBEII (n = 63), historically supported by the Jeffrey Modell Foundation. The project has enhanced HCFMUSP's facilities, offering remote clinical assistance, genetic sequencing and validation, and the translational application of findings (Certificate of Presentation for Ethical Consideration [CAAE]: 73174223.1.1001.0068). Within a year, 56% of the target population (1,700 individuals) was included. A clinical registry, collecting 392 variables over ten years, confirmed the complex traits of IEI in 573 individuals. Telemedicine has prevented so far 126 lost workdays and 36 school absences, while saving 25.6 tons of CO_2. An artificial intelligence platform (EMEDGENE Illumina) supported the prioritization of rare variants. The project has already analyzed 320 sequencing, identifying at least one candidate variant in 50% of cases. Autoinflammatory diseases accounted for 35% of samples, with the MEFV gene most frequently prioritized. A notable finding was the IL1RN deletion (p.Asp72_Ile76del) acting as a founder effect for deficiency of IL-1receptor antagonist (DIRA) (n = 8) in Brazil. CoBEII also promoted health equity in Brazil by conducting an educational program on clinical advances across various regions. These innovative efforts have had a positive educational and socioeconomical impact on IEI care in Brazil, a populous nation of 213 million. The project's initial results highlight its ability to overcome racial biases, as Brazil is a trihybrid (Indian, African, and European ancestries) population, offering insights applicable to IEI diagnosis and research globally. Overall, the innovations introduced by CNE3I have significantly enhanced the care of IEI in Brazil, demonstrating that comprehensive genetic analysis and coordinated care can address longstanding disparities and improve outcomes for individuals with these conditions. The data are summarized in Figure 1.

Figure 1. **CNE3i Year 1.** Main results obtained in the first year of CNE3i (Centro Nacional de Erros Inatos da Imunidade e Imunodesregulação) in Brazil. The CNE3i is a collaborative effort of Brazilian Reference Centers for Inborn Errors of Immunity established through CoBEII, creating a technopole for innovations in the care of IEI in Brazil, located at the University of São Paulo. On the left, the drops on the Brazilian map represent reference centers, with colors indicating the number of samples included per state. On the right side, the summarized results include: i) telemedicine, ii) sequencing and analysis, iii) clinical registry, and iv) medical education and disease awareness.

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Investigation Into the Viscosity of Commercial IG 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% IGIV products.

Experiments were performed using: ALYGLO (immune globulin intravenous, human-stwk 10% liquid), GC Biopharma; OCTAGAM10% (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 concentrations for accurate viscosity comparison. Sample viscosities were determined using a Honeybun microvolume viscometer (Unchained Labs, USA) at 4, 10, 15, 20, 25, and 37°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: 2.587 cP; OCTAGAM: 2.646 cP; GAMUNEX-C: 2.598 cP; PRIVIGEN: 2.598 cP; GAMMAPLEX: 2.598 cP. At 37°C, viscosities were further reduced, ranging from 2.263–2.309 cP across all products. For reference, the viscosity of human plasma at 25°C generally ranges from 1.5 to 1.72 cP. All products showed consistent, sequential decreases in viscosity as temperatures increased, with the lowest values observed at 37°C. These findings suggest that IVIG infusions administered at room temperature (25°C) may be a safety consideration for the prevention of TEEs and that viscosity decreases even further once products equilibrate toward body temperature.

The consistency between the first and second analyses supports the robustness of these observations and warrants 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.

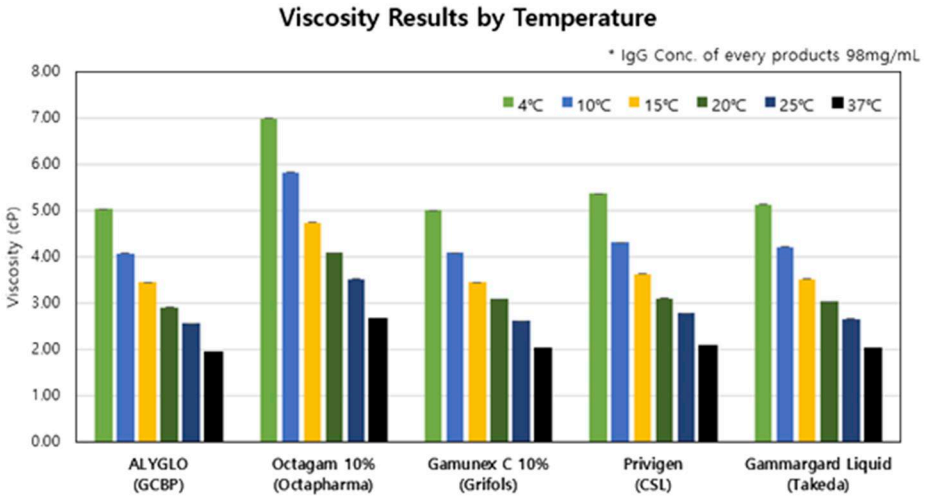

Figure 1.

Tabular data are included as downloadable supplement files.

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Janus Kinase Inhibitor Treatment Results in Rapid but Incomplete Immune Reconstitution and Resolution of Monocyte-Driven Hyperinflammation in STAT1 Gain-of-Function

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Autosomal-dominant STAT1 gain-of-function (GOF) is an inborn error of immunity characterized by chronic mucocutaneous candidiasis and variable autoimmune manifestations. Janus kinase (JAK) inhibitors are a promising treatment, but their efficacy remains variable and incompletely understood. We evaluated the impact of JAK inhibitors by studying two STAT1 GOF patients (harboring R321S and T385M mutations) longitudinally using Cellular Indexing of Transcriptomes and Epitopes by sequencing (CITE-seq), flow cytometry, and cytokine analysis in peripheral blood mononuclear cells and serum. Rapid, yet incomplete, immune reconstitution was observed after 1 week. T cells rebalanced from effector to naïve T cells, and T cell receptor diversity and abundance increased. Monocytes showed the most pronounced transcriptional dysregulation compared to healthy references, which markedly improved upon JAK-inhibitor treatment. Serum cytokine, cell–cell communication, and pathway analysis pointed toward an inflammatory phenotype in all cell types caused by monocytes and improved upon treatment. JAK inhibitors provided clinical and immunological benefit in STAT1 GOF but did not fully restore immune homeostasis, highlighting both its therapeutic potential and limitations.

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Lower Disease Severity in STAT3 GOF Patients with Mild Potency Variants

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Germline gain-of-function (GOF) variants in the transcription factor STAT3 are associated with early-onset, multisystem autoimmunity, lymphoproliferation, and immune dysregulation. Although STAT3 hyperactivation is a defining feature of this disorder, any relationship between the potency of STAT3 GOF variants and clinical presentations remains undefined. We hypothesized that variants with higher potency would result in more severe disease. Patients with STAT3 GOF were grouped into "mild" or "moderate to extreme" potency. Potency was determined by the fold increase in STAT3 transcriptional capacity of a variant relative to wild-type STAT3, determined using a standard luciferase. In a subset of patients for whom primary biosamples were available, lymphoblastoid cell lines (LCLs) were generated. LCLs were stimulated with IL-21 to assess STAT3 activation (phospho-Y705) using flow cytometry.

Transcription of the STAT3-driven gene SOCS3 following IL-21, in the absence or presence of JAK inhibitors, was also determined using real-time PCR. Clinical, immunophenotype, and treatment data for 191 previously reported patients with STAT3 GOF (1), representing 72 unique variants, were evaluated. STAT3 GOF variants ranged greatly in potency (median 16.6, interquartile range [IQR] 4.2, 46.5).

There were no high to extreme potency variants in the N-terminal or transactivation domains. In LCLs from 7 patients, activated STAT3 (MFI of phospho-STAT3) correlated with potency (r^2 = 0.78, $p < 0.0001$). Patients carrying low potency variants (<5x wild-type, 72/191 patients [38%]) were older at symptom onset (8 vs. 4 years, p = 0.001), had less total organ systems involved (4 vs. 4.8, p = 0.003), were given less cumulative medications (1.8 vs. 2.4, p = 0.022), and were less likely to be deceased (5.6% vs. 16%, p = 0.039). Patients with low potency variants in this historical cohort were also less likely to have been prescribed tocilizumab (13% vs. 36%, $p < 0.001$) or a JAK inhibitor (14% vs. 33%, p = 0.004).

Transcription of SOCS3 in 10 LCLs was terminated by the addition of a JAK inhibitor ($p < 0.01$ for most variants). In summary, STAT3 GOF variant potency varies widely compared to wild-type STAT3. Overall, patients carrying mild potency variants appeared to have less severe disease. Quantitative functional assessment of STAT3 variants may assist with the prognosis and management of STAT3 GOF syndrome.

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Multiple Bouts of Hypothermia and Shock in a Child with Gata-2 Mutation

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We are reporting a 14-year-old male who presented at 12 years of age with recurrent episodes of hypothermia and bradycardia (30s) secondary to culture-negative septic shock from presumed viral respiratory illnesses. His temperatures on presentation are frequently below the level of detection rectally, with the lowest recorded temperature of 95.2F. Infectious testing during these episodes has only ever been positive for common respiratory viruses, including rhino/enterovirus and SARS-CoV-2. His episodes of hypothermia and shock have responded to supportive care, including warming and vasopressors. He has had 7 admissions in the past two years, with a duration of stay ranging from 4 to 23 days. There has been no decrease in length or frequency of admissions.

He has also been found to have intermittent interstitial nodular lung disease on chest x-ray. A recent chest CT is normal. He has a kidney injury that has evolved into a nephrotic syndrome. No lymphedema.

He has had persistent lymphopenia with intermittent pancytopenia. His lymphocyte subset numbers are low with an absolute CD4 count of 105 cells/μL, CD3A of 422 cells/μL, and absolute natural killer (NK) cells of 64 cells/μL. GM-CSF plasma <15.0 pg/mL during an acute episode. A bone marrow biopsy was performed, which only revealed hypocellularity.

Concomitant problems include fetal alcohol syndrome and developmental delay. He has an intronic GATA2 c.1017+572C>T heterozygous mutation. He is on prophylaxis with atovaquone, voriconazole, and azithromycin and has received HPV vaccination. He was assessed for a stem cell transplant but was not considered a candidate.

Discussion: This patient's GATA2 mutation is a single-nucleotide substitution located within intron 5 within the +9.5-enhancer element. Quantitatively, this may result in 50% reduction in GATA2 transcript levels. Not much is known about this mutation in these patients. His phenotype is different from other mutations in this gene because of recurrent hypothermia and shock. These episodes seem mostly linked with respiratory viral infections. There has been no reduction in frequency of these episodes, and now he is on homebound education.

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Nibling of MHC Class II by Tfh Cells—Possible Role in Isotype Switching and Affinity Maturation

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Introduction: Trogocytosis is an intracellular transfer of membrane and membrane-associated proteins in a cell–cell contact manner. Trogocytosis plays an important role in immune regulation. We hypothesized that trogocytosis may play role in isotype switching and affinity maturation in the germinal center.

Trogocytosis of MHC-II by T follicular helper (Tfh) (CD4+CXCR5+CD45RA-) from dendritic cells (DCs) results in MHC-II-dressed Tfh to present antigen and stimulate B cells, resulting in B cell activation and proliferation with an important role in isotype switching and affinity maturation.

Methodology: Monocyte-derived DCs (moDCs) were prepared by culturing purified CD14+ monocytes isolated from peripheral blood mononuclear cells (PBMCs), enriched by immunomagnetic positive selection and addition of GM-CSF (50 ng/ml) and IL-4 (20 ng/ml) for 6 days. Purified CD4+T cells were enriched by immunomagnetic negative selection and were activated using anti-CD3/CD28 beads for 24 hours. MoDCs were co-cultured with activated CD4+T cells (1:1) for 4 hrs. Harvested co-cultured cells were stained with antihuman monoclonal antibodies and isotype controls. The cells were washed and acquired on FACS Calibur and analyzed using FlowJo.

Expression of MHC-II, co-stimulatory molecule (CD86), and mean fluorescence intensity (MFI) was measured on activated CD4+T, Tfh, and their subpopulations. Activated CD4+T cells and moDCs without co-culture served as controls. Statistical analysis was performed by a parametric t test, and a value of $p<0.05$ was considered significant.

Results: Our data show that following trogocytosis, MHC-II expression was significantly increased on activated CD4+T ($p = 0.002$), Tfh ($p = 0.0002$), Tfh1 ($p = 0.0002$), Tfh2 ($p = 0.0001$), and Tfh17 ($p = 0.0004$) cells. The MFI was also higher on total CD4+T ($p = 0.01$), Tfh ($p = 0.0007$), Tfh1 ($p = 0.001$), and Tfh2 ($p = 0.03$). The expression and MFI of CD86 were higher on total CD4+T, Tfh cells, and its subsets.

Conclusion: Trogocytosis results in MHC-II-dressed Tfh cells with Tfh1 showing a higher proportion of trogocytosed class MHC-II, followed by Tfh17 and Tfh2. Also, there is trogocytosis of CD86 on CD4T, Tfh, and its subsets. Future directions involve the exploration of the functional role of MHC-II-dressed Tfh cells as potent APCs and their contribution to isotype switching, affinity maturation, and restoration of immune function in patients with inborn errors of immunity.

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Nominating Genetically Driven Immune Disease Genes for BEACONS: The First U.S. Multistate Genomic Newborn Screening Initiative

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Background: T cell receptor excision circle (TREC)-based newborn screening (NBS) for severe combined immunodeficiency (SCID) has improved early diagnosis, treatment, and survival of SCID infants and identified additional cases of T lymphopenia requiring intervention. Early detection by whole-genome sequencing (WGS)-based NBS could benefit infants with many additional genetically driven immune diseases (GDIs) that lack traditional NBS screening biomarkers. Building Evidence and Collaboration for GenOmics in Nationwide Newborn Screening (BEACONS), the first research study to integrate WGS into multiple U.S. public health laboratories, will sequence up to 30,000 newborns with parental consent. An NBS-WGS task force established at the 2025 Clinical Immunology

Society (CIS) Meeting is collaborating with BEACONS to select early-onset, actionable GDIs to be identified by sequence analysis and reported.

Methods: Task force experts reviewed GDI disease mechanisms, penetrance, and expressivity to prioritize those requiring targeted surveillance or treatment in the first year of life to prevent morbidity and mortality. Candidate GDI gene sources included the U.S. Recommended Uniform Screening Panel (RUSP), 2024 International Union of Immunological Societies (IUIS) inborn errors of immunity tables, GenIA database, ClinGen Gene Curation Expert Panel (GCEP) curations, OMIM, prior NBS-WGS studies, and GDI clinicians and researchers. Inclusion in the GDI-associated gene list required published evidence for clinical manifestations by age 1 year and alignment with consensus criteria of the International Consortium of Newborn Sequencing (ICoNS).

Results: The initial BEACONS draft list of 100 immune genes (20 of them RUSP SCID genes) was circulated to NBS-WGS task force members from immunology, genetics, rheumatology, transplant, and related specialties. Thirty-five experts from 20 academic institutions augmented and curated the list, submitting 407 genes associated with early-onset GDI to the BEACONS Gene List Working Group and Steering Committee. The overall final BEACONS list (~800 genes) will be completed by January 2026, after additional review by participating public health laboratories and the public.

Conclusion: BEACONS is establishing a consensus-driven, evidence-based gene list as an initial research tool for multiple state public health laboratories, enabling prospective evaluation of the feasibility of population-wide NBS-WGS. The CIS NBS-WGS task force is now providing input regarding variant reporting, educational information sheets to accompany reports, and follow-up diagnostic evaluations and management measures required for each gene-disease relationship.

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Novel Pathogenic Variant in IL2RG Affecting the Signal Peptide Results in mRNA Instability, Decreased IL2RG Expression, and Atypical Late-Onset Immunodeficiency

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X-linked severe combined immunodeficiency (SCID-X1) presents as T-B+NK- SCID, due to mutations in the common γ chain (IL2RG/CD132), a shared component of several cytokine receptors. Without definitive therapy, SCID-X1 is fatal within two years due to severe recurrent infections. Atypical SCID-X1 can arise from hypomorphic variants that preserve partial immunity and delay diagnosis, sometimes into adulthood.

IL2RG is produced as a precursor with a 22-amino acid cleavable N-terminal signal peptide (SP), recognized by the signal recognition particle (SRP) during translation initiation. SRP engagement is essential for mRNA stability; when the SP fails to bind SRP efficiently, the corresponding mRNA is degraded through the regulation of aberrant protein production (RAPP) pathway. Because the SP is critical for proper protein expression, variants in this region have been linked to human disease. To date, however, none have been reported in association with SCID.

We studied a patient with a novel 25 bp deletion in exon 1 of the IL2RG (c.26_50del; p.Ser10Cysfs*6). Although this frameshift would be expected to generate a null allele and typical SCID-X1, he instead presented at age 17 with severe T cell lymphopenia (110 cells/uL), arthritis, disseminated zoster, and at age 22 developed progressive multifocal leukoencephalopathy due to the JC virus. We found that this mutation produces an IL2RG mRNA that enables in-frame translation from an upstream translation initiation site, generating a protein nearly identical to the wild-type except for the N-terminal 17 amino acids of the SP. Patient cells showed markedly reduced and variable expression of functional wild-type IL2RG, and proportionally defective cytokine response. The altered SP exhibited reduced hydrophobicity and an extremely low Bowman index, predicting impaired SP–SRP interaction and suggesting RAPP-mediated mRNA degradation as the cause of diminished and fluctuating protein levels. Assessment of mRNA turnover in patient versus healthy control EBV-transformed cells confirmed preferential degradation of the patient's IL2RG mRNA. We thus believe inefficient SP-SRP binding triggered IL2RG mRNA degradation, in turn causing low, variable IL2RG expression and atypical XSCID-X1.

These findings identify a novel SP-region mutation that disrupts mRNA stability and causes SCID-X1, underscoring the pathogenic impact of SP mutations in immunodeficiencies.

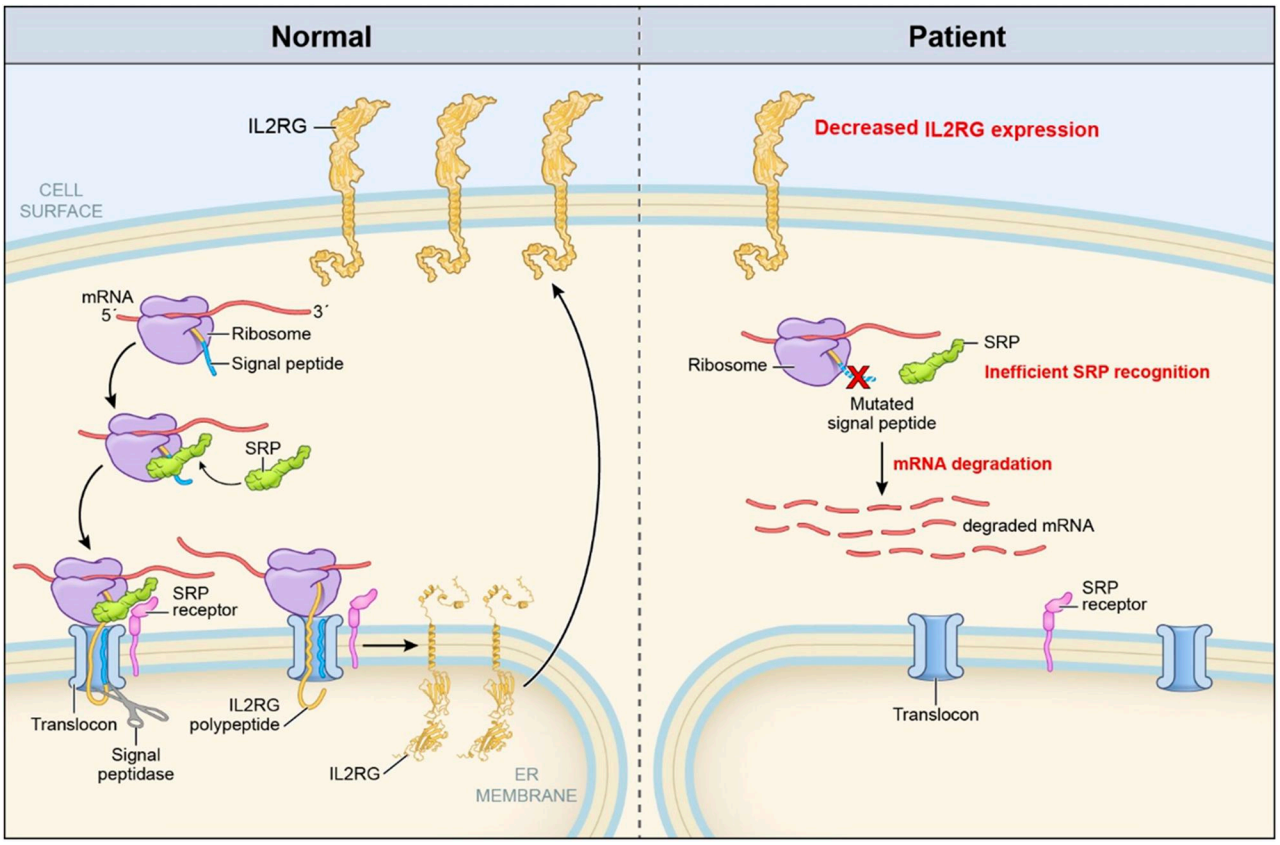

Figure 1. **Schematic representation of the mechanism of disease pathogenesis in the patient is shown.** Normally, the signal recognition particle (SRP) recognizes the signal peptide upon exiting from the ribosome exit tunnel, which halts translation of the protein until the ribosome–nascent chain complex (RNC) is translocated to the ER membrane. At the ER membrane, SRP binds to the SRP-receptor, and the RNC complex is transferred to the translocon, resuming translation. The translated protein is processed (signal peptide cleavage, protein folding, and post-translational modifications), and the protein is transported to the plasma membrane via the Golgi apparatus. In the patient, the mutation in the signal peptide results in inefficient SRP recognition during translation. SRP recognition protects the mRNA, and failure of signal peptide recognition by SRP triggers regulation of aberrant protein production (RAPP)-mediated mRNA degradation, resulting in reduced and variable IL2RG protein expression in the patient.

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One Solid Differential: Thyroid Cancer as a Hypereosinophilic Syndrome Trigger

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Hypereosinophilic syndrome (HES) is characterized by blood or tissue hypereosinophilia leading to organ damage or dysfunction. HES is most commonly secondary or idiopathic, but may be primary (myeloid) or familial. Here, we review a complex case of HES and discuss important diagnostic and therapeutic considerations.

A 19-year-old female with no significant past medical history presented to our hospital with respiratory failure, fevers, and generalized malaise. Three months prior to admission, she developed daily fevers, drenching night sweats, and 15 lbs of weight loss. One month prior to presentation, she was admitted with fevers and pancytopenia. Extensive hematologic, rheumatologic, and infectious workup revealed no infectious or rheumatologic trigger. She was found to have severe splenomegaly and a large thyroid nodule on CT imaging. Bone marrow biopsy revealed 42% eosinophils with relative myeloid hyperplasia but was otherwise normal. Fevers and pancytopenia resolved during admission without treatment, and she was discharged with close monitoring. An outpatient PET-CT completed two weeks later revealed only increased splenic and thyroid nodule uptake.

Prior to her current admission, she began to develop rapidly progressive eosinophilia and a resurgence of fevers. She presented to a local hospital, where she rapidly decompensated, was intubated, and transferred to our intensive care unit (ICU). Extensive evaluation

revealed concern for HES with multi-organ dysfunction, including neurologic, cardiac, and respiratory involvement. Eosinophil count prior to admission was 5,230/mm3, rising to 34,874/mm3 despite pulse-dose steroids. Benralizumab was started, but she had a slow response with ongoing organ dysfunction. Natural killer (NK) cell activity was undetectable. She was transitioned to mepolizumab with a rapid clinical response and was extubated shortly afterwards.

Following discharge, she underwent a thyroid biopsy, which was concerning for malignancy. Surgical thyroidectomy confirmed papillary and follicular thyroid cancer. Given suspicion of a possible malignant trigger of HES, her mepolizumab was discontinued two months after resection with close monitoring. Three months after discontinuation, her eosinophil count remained undetectable.

This case highlights solid organ malignancies as an unusual but recognized trigger for HES. Additionally, benralizumab activity depends on NK cell function; given markedly reduced NK cell function in some critically ill patients, mepolizumab may be a preferred agent for severe HES cases.

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Out of the TERT and Into the PARN: Sequential Telomere Biology Disorder Variants in a Single Patient

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Background: Telomere biology disorders (TBD) are rare multisystem disorders characterized by a wide array of clinical presentations, including bone marrow failure, pulmonary fibrosis, and malignancy predisposition due to premature telomere apoptosis. Definitive treatment requires allogenic bone marrow transplant (BMT), though it may not ameliorate organ-specific complications. Pathogenic variants in TERT and PARN have been described in both autosomal dominant (AD) and autosomal recessive (AR) inheritance patterns.
Objective: We describe a patient post-allogenic BMT for myelodysplastic syndrome (MDS) with both germline and donor-derived variants in TBD genes, presenting with recurrent EBV-associated lymphoproliferation and recurrent lymphomas.
Clinical Case Description: The patient is a 57-year-old male who was referred for recurrent EBV lymphoproliferation. The patient underwent an unrelated allogenic stem cell transplant in 2008 for myelodysplastic syndrome. Off immunosuppression, he developed Hodgkin lymphoma (2011) and EBV-positive polymorphic post-transplant lymphoproliferative disorders (PTLD) (2015). Later, diffuse large B cell lymphoma was discovered on colonic biopsy (2024). He received rituximab-containing chemoimmunotherapy with complete remission, and weekly rituximab for recurrent low-level EBV viremia with response. Genetic testing was sent in whole blood and fibroblasts to test for germline and donor-derived inborn error of immunity (IEI). He did not have antecedent evidence of pulmonary fibrosis, cirrhosis, or nail dystrophy.
Laboratory Investigations: DNA from skin fibroblast culture revealed a novel variant of uncertain significance (VUS) in TERT c.1148C>A p.Pro 383His. Whole blood demonstrated a likely pathogenic heterozygous variant in PARN c.1293del (P.Tyr432llefs*2). Flow fluorescence in situ hybridization (FISH) telomere testing from blood revealed lymphocytes <1st percentile, granulocytes 1–10th percentile, naive T cells <1st percentile, memory T cells 1–10th percentile, and natural killer (NK) cells in normal range; reduced telomere length was identified in multiple lineages. Flow revealed low CD4 (0.28 × 10E9/L), elevated CD8 (2.29 × 10E9/L), undetectable CD19 (<0.01 × 10E9/L; 4 months after rituximab), and normal CD16/56 cells (0.10 × 10E9/L). Chimerism was complete in whole blood and T cell compartments.
Discussion: While definitive treatment for many IEIs is a BMT, there is a very rare risk of donor-related immunogenic complications. While he has reduced telomere lengths, it is unclear if the EBV-associated lymphoproliferation is related to the PARN variant, TERT variant, or neither. This probable donor-acquired pathogenic variant is a highly unexpected finding and raises ethical and clinical considerations when found.

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Outcomes for Patients with CGD Undergoing HSCT Over the Past 2 Decades: A Single-Center Experience

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Introduction: Chronic granulomatous disease (CGD) is an inborn error of immunity (IEI) secondary to defects in the phagocyte oxidative burst. Patients mainly experience infections; however, many may also manifest inflammatory complications, both requiring medical management with antimicrobials and immunosuppression. Hematopoietic stem cell transplantation (HSCT) is a successful curative option.

Objectives: To report Texas Children's Hospital's experience performing HSCT in patients with CGD.

Methods and Characteristics: Forty-two patients who underwent HSCT from 2007–2025 were analyzed. The median age at transplantation was 4.6 years of age (range 0.5–17.1). All patients received a myeloablative conditioning regimen consisting of busulfan, fludarabine backbone, and either cyclophosphamide, cytarabine, or thiotepa with primarily alemtuzumab as serotherapy (n = 35, 83.3%). Donors were matched unrelated (n = 25, 59.5%), HLA-identical sibling (n = 11, 26.2%), HLA-mismatched unrelated (n = 3, 7.1%), mismatched unrelated (n = 2, 4.8%), and HLA-mismatched relative (n = 1, 2.4%). Cord blood unit recipients did not receive any serotherapy (n = 6, 14.3%). Most patients in our cohort were not Hispanic or Latino (n = 28, 66.7%). The median follow-up of these patients was 5.5 years (3.02–10.2).

Results: At a median follow-up of 5.6 years (0.17–17.11), 1-year and 5-year overall survival (OS) was 95.1% (95% confidence interval [CI] 88.7–100) and 89.4% (95% CI 80–99.8), respectively. Up to 97.6% of patients had neutrophil engraftment, and 87.8% had platelet engraftment. Six patients required an additional treatment at a median time of 167.5 days (95% CI 51.8–267.1). Of the 6 patients requiring additional treatment, 4 required a second transplant, and 2 required a CD34-selected stem cell top off. Acute graft-versus-host disease (GvHD) occurred in 12 patients (28.6%), only 3 of whom were grade II and 9 were grade I, none severe. There was only one case of chronic GvHD, which was mild. Five patients died, primarily from infections (60%), organ failure (20%), and respiratory failure (20%).

Conclusion: A myeloablative conditioning regimen can achieve excellent long-term survival, high engraftment, low graft failure, and low rates of severe GVHD in pediatric patients with CGD, including those from underrepresented populations.

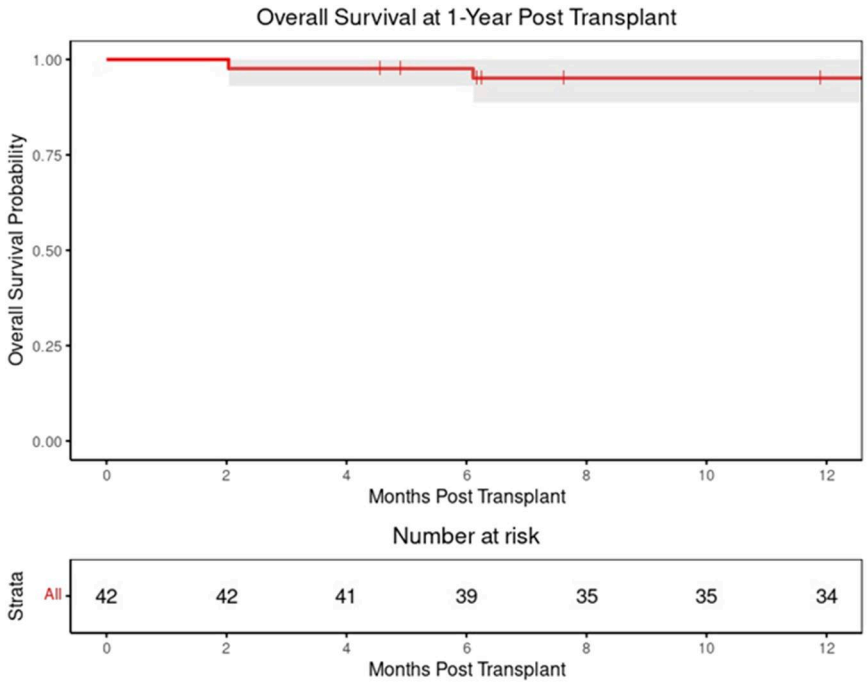

Figure 1. **Overall survival after 1 year.**

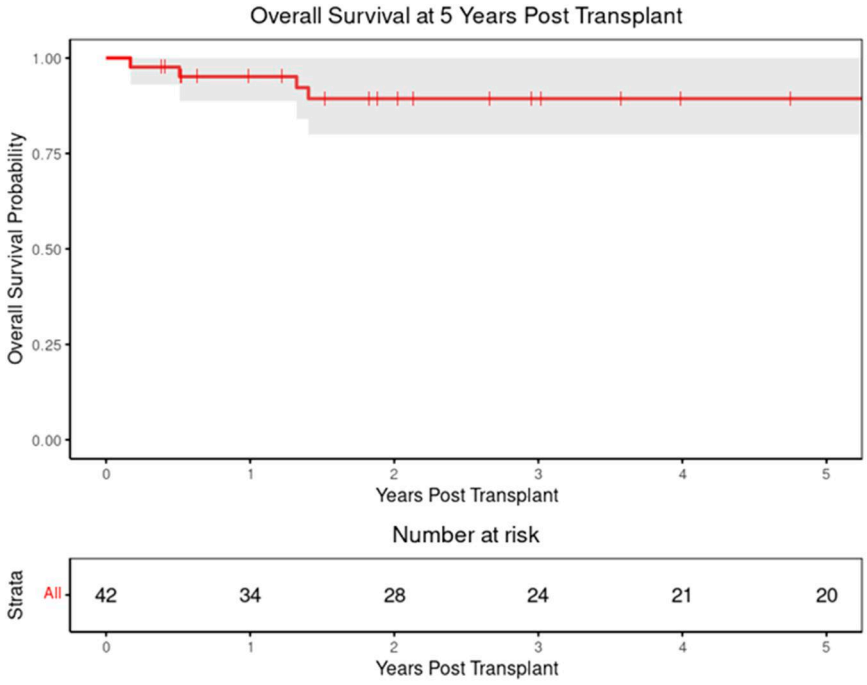

Figure 2. **Overall survival after 5 years.**

Tabular data are included as downloadable supplement files.

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Pediatric and Adolescent Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS): Demographic and Clinical Findings from the APDS-Characterization and Clinical Outcomes Immunologic Registry (APDS-CHOIR)

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Background: Activated phosphoinositide 3-kinase syndrome (APDS) is a rare inborn error of immunity with an autosomal-dominant inheritance pattern that leads to immune dysregulation. Presently, the natural history of disease for persons with APDS is incompletely understood, particularly among pediatric and adolescent individuals.
Methods: The APDS Characterization and Clinical Outcomes Immunologic Registry (APDS-CHOIR) follows participants in the United States with variants in PIK3CD or PIK3R1. The registry captures electronic health record (EHR) data historically and over time, including demographics, comorbidities, incident medical conditions, medications, medical procedures, and transplant history. In this study, we describe the demographic and clinical features of participants younger than 18 years at the time of enrollment over a one-year follow-up period.
Results: Participants were followed for at least one year (n = 14). Of those, 8 (57%) were female, and 43% were male; most self-identified as white (n = 10; 71%) and had pathogenic PIK3CD variants (n = 10; 71%). Age at diagnosis ranged from 2 to 12 years (median 7, interquartile range [IQR] 2–9, n = 11), and age at enrollment ranged from 2 to 14 years (median 9.5, IQR 7–14). Most participants had history at the time of enrollment of infections (n = 11; 79%), respiratory issues (n = 11; 79%), lymph node abnormalities (n = 9; 64%), splenomegaly (n = 8; 57%), and gastrointestinal issues (n = 8; 57%); detailed medical history is described in the supplementary table. Two participants

had a history of bone marrow transplants, and one participant underwent a bone marrow transplant during follow-up. Two mild infections were reported during follow-up. During the study period, 10 participants (71%) received immunoglobulin replacement therapy. Sirolimus was used by six participants (43%) and leniolisib by one participant (7%). One participant died during follow-up from multisystem complications related to a bone marrow transplant at the age of 14.

Conclusions: This study provides a detailed characterization of pediatric individuals with APDS over one year of follow-up, demonstrating variable clinical manifestations and management approaches. Given the paucity of clinical information regarding APDS in this population, these findings may improve the characterization of disease presentation and progression in children and adolescents.

Tabular data are included as downloadable supplement files.

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PI3K Signaling Pathway Abnormalities in Two Patients with PIK3CD (p110δ) Loss-of-Function (LOF) Variants

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Background: Phosphoinositide 3-kinase δ (PI3Kδ) is a lipid kinase that is composed of a catalytic subunit (p110δ, PIK3CD) and a regulatory subunit (p85, PIK3R1) and mediates signal transduction downstream of multiple immune receptors, making it essential for immune function.

PI3Kδ converts phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3), triggering activation of AKT and S6 in hematopoietic cells. Patients with PIK3CD (p110δ) loss-of-function (LOF) variants exhibit recurrent infection, immune dysregulation, with impaired T, B, and natural killer (NK) function and high mortality. In this study, we describe two patients (P1, P2) carrying novel PIK3CD (p110δ) LOF variants, their immune phenotype, and demonstrate IFNg-driven gastrointestinal inflammation, which resolved with JAK inhibition.

Methods: p110δ expression was evaluated by western blot in peripheral blood mononuclear cells (PBMCs), T cell blasts, and EBV-immortalized B cell lines. Downstream activation of AKT and S6 was assessed in primary B cells in response to human anti-IgM and in T cell blasts in the presence or absence of CD3/CD28 stimulation. RNAscope in situ hybridization for IFN-g, IL-12, IL-17, and CXCL9 was evaluated in gastrointestinal biopsies.

Results: Whole-exome sequencing of P1 revealed a novel homozygous PIK3CD frameshift variant (c.317dupA, p.D107Rfs23), whereas P2 carried compound heterozygous variants: c.2697delCAT (p.I899del) and c.346C>T (p.Q116*). Clinically, both individuals exhibited recurrent infection, immune dysregulation, and impaired T, B, and NK function, phenotypic features consistent with those previously documented in patients carrying p110δ variants. p110δ expression was absent in P2; interestingly, we observed a shorter protein in P1 (approximately 114 kDa). P1 exhibited aberrant activation of downstream mediators of PI3K activation (AKT and pS6), whereas P2 showed markedly reduced PI3K activity. Gastric biopsy in P1 demonstrated extensive lymphocytic infiltrates and a strong IFN-g signal that completely resolved after 8 weeks of ruxolitinib treatment.

Conclusions: Our results detail abnormal PI3K signaling caused by novel PIK3CD LOF mutations. Ruxolitinib treatment completely resolved gastrointestinal inflammation, providing further rationale for its use in patients with this autoimmune enteropathy associated with PIK3CD deficiency.

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Potential Association Between G6PD Deficiency and Severe B Cell Lymphopenia Identified by KREC-Based Newborn Screening (NBS) in Brazil

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Background: Glucose-6-phosphate dehydrogenase (G6PD) provides the main cellular source of NADPH through the pentose phosphate pathway, supporting antioxidant defenses and metabolic programs required for hematopoietic development. In leukocytes, NADPH is essential for maintaining redox balance during proliferation and differentiation, including in B cell ontogeny. Whether impaired NADPH generation could mechanistically contribute to low kappa-deleting recombination excision circles (KRECs) and early B cell lymphopenia in newborn screening remains unexplored.
Objective: To describe the relevance of KREC levels in Brazilian newborn screening (NBS), focusing on how impaired redox metabolism due to G6PD deficiency can contribute to severe B cell lymphopenia detected by KRECs.
Methods: From 2021 to 2025, the São Paulo, Brazil, NBS program screened nearly 500,000 infants. Those with abnormal results (750 neonates) were referred to our center. After confirmation of B cell lymphopenia (B cell counts below 100 cells/mm^3 or 2%), patients underwent panel-based genetic testing.
Results: Among infants referred for abnormal KRECs, we identified 66 patients with severe B cell lymphopenia, accounting for 9% of all B cell lymphopenias. Of these 66 neonates, a panel-based genetic testing was performed in 44 patients. Surprisingly, we identified 10 patients (27%) harboring three different G6PD mutations: 7/10 G6PD c.[202G>A(;)376A>G] (4 females, 3 males), a complex allele in hemizygosity, which can cause mild symptoms even in female carriers; 2/10 G6PD c.376A>G (1 homozygous female and 1 hemizygous male); and 1 male with hemizygous G6PD c.949G>A. Of these G6PD patients, 4 have no other genetically defined cause to date. The other 6 patients are under evaluation of heterozygous variants of uncertain significance (VUS) in IGLL1, CR2, IRF4, TRNT1, KMT2D, and PARN. These findings support the hypothesis that reduced enzymatic activity may affect early B cell development and result in lower KREC levels at birth.
Conclusion: The potential correlation between G6PD deficiency and severe B cell lymphopenia observed in NBS aligns with emerging biological evidence. To our knowledge, no prior study has specifically assessed the relationship between G6PD status and KREC-defined B cell lymphopenia in NBS programs. Investigating this potential correlation may clarify whether G6PD deficiency acts as a contributing factor or a disease modifier in the interpretation of B cell lymphopenia in KREC-based NBS for IEI.

Tabular data are included as downloadable supplement files.

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Preexisting Antibodies to Virus-Like Particles (VLP) Derived from Helper-Dependent Adenovirus (HDAd) in Patients with Chronic Granulomatous Disease (CGD)

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Introduction: Chronic Granulomatous Disease (CGD) is an inborn error of immunity that can be treated by allogeneic hematopoietic stem cell transplantation (allo-HSCT) or experimental gene therapy. For viral vector-based in vivo gene therapy, the presence of preexisting

antibodies to virus-llike particles (VLP) may have an impact on transduction. The prevalence of antibodies against VLPs that are derived from a chimeric Helper-Dependent Adenovirus (HDAd) is previously unknown.

Methods: A single blood draw was obtained in an observational clinical trial (NCT06605378) of patients in the United States and the United Kingdom confirmed to have CGD but had not previously undergone allo-HSCT or gene therapy. Total antibodies (TAb) were measured by an antibody bridging assay (capped to a titer of 2,048), and neutralizing antibodies (NAb) were measured by a transduction inhibition cell-based assay (capped to a titer of 1,024).

Results: As of October 2025, 36 participants (median age 26, range 1–54 years; 33% under 18 years of age; 83% male, 11% Hispanic or Latino, 8% Asian, and 6% Black) with CGD (75% with mutations in CYBB) had a median TAb titer of 1,024 (≤32 [n = 6], 128 [n = 4], 512 [n = 3], 1,024 [n = 8], and 2,048 [n = 15]) and median NAb titer of 128 (≤32 [n = 5], 64 [n = 10], 128 [7], 256 [3], 512 [4], and 1,024 [n = 7]). For pediatric participants (<18 years of age), 67% were at or below the median TAb titer, and 75% were at or below the median NAb titer. For adults (≥18 years of age), 54% were at or below the median TAb titer, and 54% were at or below the median NAb titer. Both TAb and NAb were above the median 33% of the time, and both were at or below the median 53% of the time (86% overall agreement). Small numbers prevented formal comparisons.

Conclusion: Patients with CGD have varying preexisting exposure to VLP that may increase with age. The concordance between TAb and NAb in CGD participants was high. Understanding these results may help to better inform gene therapy for CGD patients.

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Prevention of Irreversible Autoimmune Endocrinopathies in APECED with Ruxolitinib

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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED/APS-1) is a monogenic disorder of failed central tolerance caused by deleterious variants in the autoimmune regulator (AIRE) gene. Interferon-γ-driven inflammation in APECED underlies multi-organ autoimmunity and chronic mucocutaneous candidiasis and is targetable with JAK1/2 inhibition. Yet, whether early cytokine blockade can avert irreversible endocrine failure is currently unknown. Here, we describe two individuals with APECED who developed early autoimmune hypoparathyroidism and hypergonadotropic hypogonadism and in whom JAK1/2 inhibition halted progression and reversed biochemical and clinical abnormalities, preserving parathyroid and gonadal function. Specifically, patient 1 at the age of 2 years developed progressively declining intact parathyroid hormone (iPTH) levels that became undetectable within four months, while calcium and phosphorus levels remained normal, consistent with early, subclinical hypoparathyroidism. Ruxolitinib normalized iPTH levels and preserved calcium levels (Figure 1 A and B). Serum CXCL9 levels dropped and then increased, associated with a transient decline in iPTH levels; when the ruxolitinib dose was increased, iPTH increased, and CXCL9 dropped again and has remained normal after 18 months of treatment (Figure 1 C), suggesting that CXCL9 may be a potential biomarker of ruxolitinib efficacy in APECED. Ruxolitinib also remitted mycophenolate-refractory autoimmune hepatitis and recurrent oral candidiasis, which had occurred despite the absence of autoantibodies against IL-17A or IL-17F. Patient 2, at the age of 18 years, developed clinical and biochemical features of early hypergonadotropic hypogonadism. Screening labs showed declining anti-Müllerian hormone (AMH) and elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH). She reported severe hot flashes and oligomenorrhea with only three menses over five months, a reduction from her prior regular 28-day cycles. After initiation of ruxolitinib, hot flashes resolved while FSH, LH, and AMH normalized, and regular 28-day menstrual cycles were restored (Figure 2 A–C). Ruxolitinib caused no hematopoietic, hepatic, or renal toxicity in either patient. These findings provide, to our knowledge, the first clinical evidence that timely JAK–STAT pathway inhibition can intercept endocrine autoimmunity in APECED. More broadly, they advance a disease-interception paradigm in which early, pathway-directed cytokine blockade may alter the natural history of autoimmune endocrinopathies.

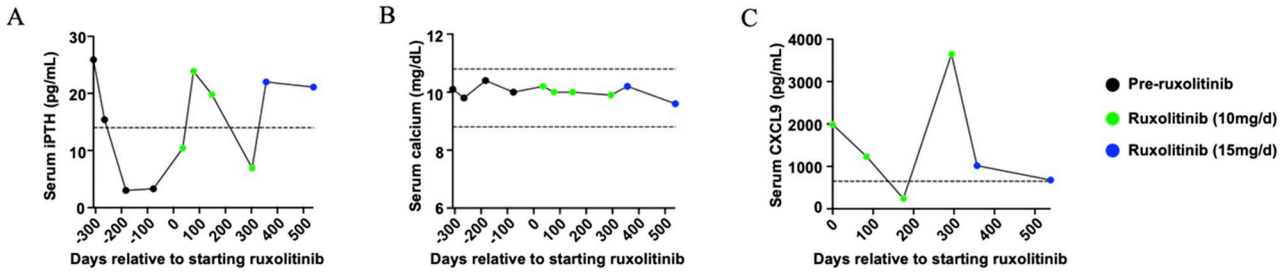

Figure 1. **Ruxolitinib reverses early hypoparathyroidism in patient 1.** Data points in black represent time points before ruxolitinib initiation, while those in green and blue represent time points while receiving ruxolitinib at the indicated dose. **A)** Serum iPTH over time relative to ruxolitinib initiation. The dashed horizontal line represents the lower limit of normal for this assay. **B)** Total calcium levels over time relative to ruxolitinib initiation. **C)** Serum CXCL9 levels over time relative to ruxolitinib initiation. The dashed horizontal line marks the upper limit of normal for this assay.

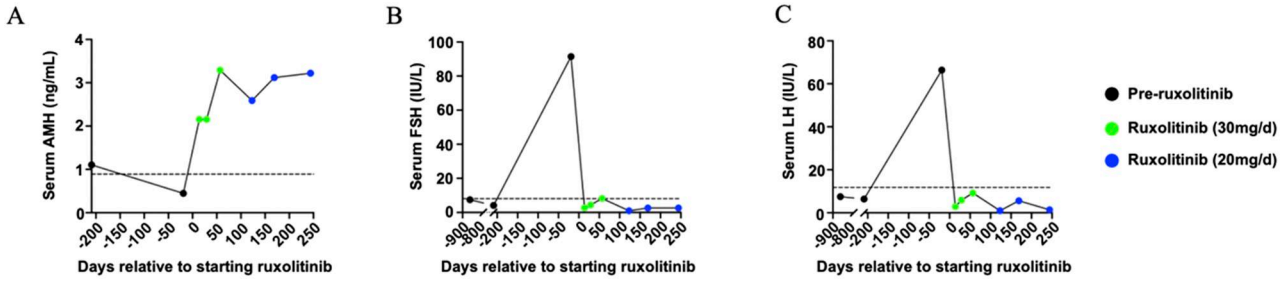

Figure 2. **Ruxolitinib reverses premature ovarian failure in patient 2.** Data points in black represent time points before ruxolitinib initiation, while those in green and blue represent time points while receiving ruxolitinib at the indicated dose. Serum AMH **(A)**, FSH **(B)**, and LH **(C)** levels over time relative to ruxolitinib initiation. The dashed lines represent the lower **(A)** or upper **(B and C)** limits of normal for these assays.

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Quality of Life in Patients with Severe Combined Immunodeficiency (SCID) Treated with Hematopoietic Cell Transplantation in the Modern Era: A Primary Immune Deficiency Consortium (PIDTC) Study

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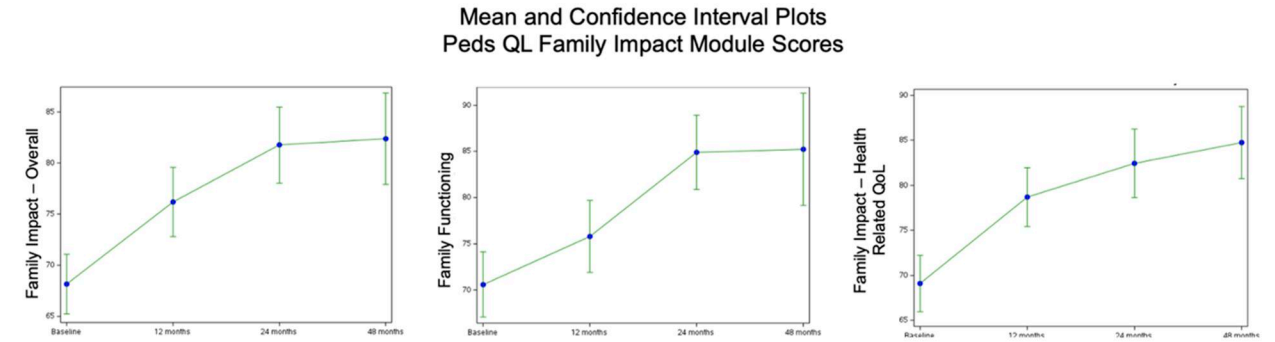
Introduction: Newborn screening (NBS) for severe combined immunodeficiency (SCID) leads to early diagnosis and hematopoietic cell transplant (HCT). Limited studies are available on the quality of life (QoL) of SCID patients treated with HCT. We prospectively evaluated the QoL of SCID patients and families to assess the overall impact of HCT at the time of transplant and in follow-up.

Methods: Primary Immune Deficiency Consortium (PIDTC) Protocol 6901 is a prospective natural history study of infants with SCID. The health-related QoL of infants/young children was measured using the Pediatric Quality of Life Inventory (PedsQL) completed by parent-proxy, while parental and family burden was assessed using the PedsQL Family Impact Module. Age-appropriate questionnaires were

offered at baseline (pre-HCT) and 12, 24, and 48 months post-HCT. Patients transplanted between 2010 and 2021 who completed ≥1 baseline or post-HCT survey were included in this analysis. Scores were transformed to a 0–100 scale, with higher scores indicating better QoL or family functioning.

Results: Of 249 families, 144 (57.8%) completed baseline QoL surveys (supplementary table). Population characteristics did not differ significantly between patients with completed QoL surveys and those without. At baseline, parent-proxy overall QoL mean was 78.75 (n = 141, SD = 15.36). The association of trigger for diagnosis with baseline overall QoL was significant (p = 0.0002). Lower overall QoL was reported by patients diagnosed by clinical symptoms such as infection compared with patients diagnosed by family history (95% confidence interval [CI]: -17.49, -1.76, p = 0.02) or by NBS (95% CI: -18.44, -6.77, p < 0.0001). Families reported significantly higher mean overall Family Impact scores, including subscales at 12, 24, and 48 months post-transplant, compared with baseline (Figure 1 A), reflective of decreased burden of chronic illness on parents and families. Improved mean parent-proxy overall QoL and physical health scores were reported at 12 months post-transplant (Figure 1 B).

A

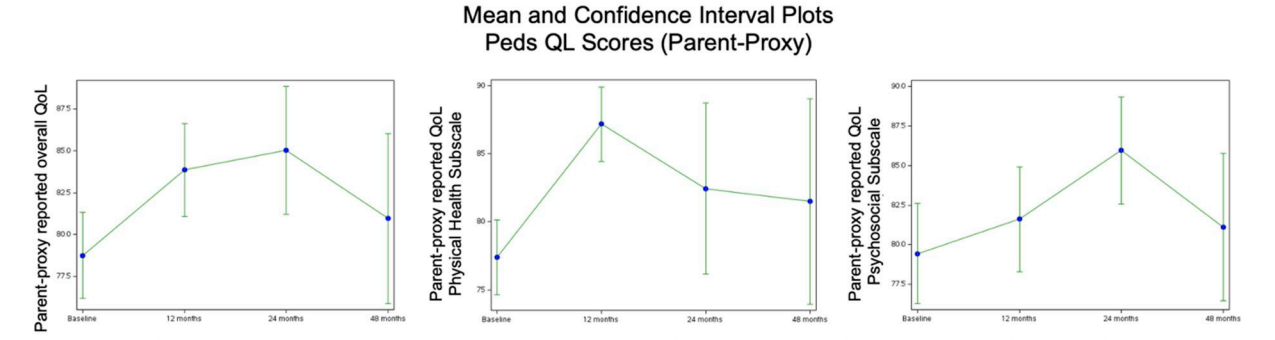


Comparison to baseline	N	Mean Difference	CI	P
12 mos	68	7.98	3.90-12.06	0.0002
24 mos	52	11.69	6.08-17.30	0.0001
48 mos	37	14.72	8.01-21.43	<0.0001

Comparison to baseline	N	Mean Difference	CI	P
12 mos	67	4.67	-0.69-10.03	0.0863
24 mos	52	12.12	5.41-18.82	0.0007
48 mos	37	15.44	6.87-24.02	0.0008

Comparison to baseline	N	Mean Difference	CI	P
12 mos	68	9.28	4.87-13.68	<0.0001
24 mos	52	10.76	4.84-16.69	0.0006
48 mos	37	15.96	9.39-22.53	<0.0001

B



Comparison to baseline	N	Mean Difference	CI	P
12 mos	65	5.05	1.28-8.82	0.0095
24 mos	47	3.91	-2.72-10.54	0.2417
48 mos	39	2.58	-4.45-9.61	0.4618

Comparison to baseline	N	Mean Difference	CI	P
12 mos	64	8.57	4.66-12.49	<0.0001
24 mos	47	3.67	-6.47-13.82	0.47
48 mos	39	6.34	-3.59-16.27	0.2042

Comparison to baseline	N	Mean Difference	CI	P
12 mos	63	3.02	-1.94-7.98	0.2278
24 mos	46	2.80	-3.45-9.04	0.3722
48 mos	39	0.86	-6.26-7.98	0.8084

Figure 1. **(A)** Mean and confidence interval plots for PedsQL Family Impact Module scores from pretransplant ("baseline") to 48 months post-transplant reported by families or caregivers of children with SCID. The PedsQL Family Impact Module is a tool used to measure the impact of chronic health conditions on parents/families. Scores are reported on a scale of 0–100, with higher scores indicating better family functioning. **(B)** Mean and confidence interval plots for PedsQL Scores (parent-proxy) from pretransplant ("baseline") to 48 months post-transplant reported by families/caregivers of children with SCID. The PedsQL (and PedsQL Infant scales in patients 0–24 months old) are tools designed to measure health-related QoL in infants and children. Scores are reported on a scale of 0–100, where higher values reflect better health-related QoL as reported by parents and/or patients.

Conclusion: Patients diagnosed with SCID through NBS reported higher pre-transplant QoL than those diagnosed by family history or clinical presentation. HCT was associated with sustained improved parent and family functioning, indicated by higher Family Impact scores post-transplant. Further analysis is forthcoming to identify pre- and peri-transplant variables as well as post-transplant complications, such as graft-versus-host disease, that may impact patient QoL following treatment.

Tabular data are included as downloadable supplement files.

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Recurrent Gluteal Abscesses in Infancy as an Early Presentation of A20 Haploinsufficiency

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Introduction: Haploinsufficiency of A20 (HA20) is a monogenic autoinflammatory disorder caused by heterozygous loss-of-function variants in TNFAIP3, resulting in dysregulated NF-κB activation. Clinical presentations are heterogeneous and often mimic Behçet disease with mucosal ulceration, fever, and systemic inflammation. Although cutaneous involvement is recognized, deep soft tissue abscesses as an initial manifestation in early infancy are rare. We present a 14-month-old boy whose evaluation for recurrent gluteal abscesses beginning at age 3 months led to the diagnosis of HA20.
Case Description: A 3-month-old boy was hospitalized for a painful right gluteal abscess. Prior infections included a febrile urinary tract infection and hand-foot-mouth disease. His mother initially noted a diaper rash before a progressive gluteal mass developed. He was treated with an incision and drainage, clindamycin, and amoxicillin-clavulanate with resolution; however, a new gluteal abscess recurred, prompting prescription for antibiotics, but improved with Epsom salt baths. Cultures were negative or yielded only skin commensals. Between episodes, he remained well without oral ulcers, gastrointestinal symptoms, or failure to thrive. Immunologic evaluation showed elevated quantitative immunoglobulins, normal neutrophil oxidative burst, and normal CD18/CD11b expression. Lymphocyte subsets demonstrated a persistently elevated CD8 and decreased CD4 T cell counts with an inverted CD4:CD8 ratio. Given persistent inflammation without a clear infectious etiology, a targeted immunodeficiency panel was obtained and identified a heterozygous, likely pathogenic TNFAIP3 variant (c.152_155delinsACAAA; p.Phe51TyrfsTer50), consistent with HA20.
Discussion: HA20 has a variable clinical presentation, but recurrent oral ulcers are the most consistent feature, seen in >70% of patients, with a median onset of ~6 years old. This case expands the phenotypic range, highlighting deep soft tissue abscesses as an early presenting sign, even without mucosal involvement. An inverted CD4:CD8 ratio, as seen in this patient, is frequently reported in HA20. Although our patient has not developed additional inflammatory manifestations, early genetic diagnosis was essential. Further evaluation, including expanded T/B cell phenotyping and inflammatory cytokines, may guide future targeted therapies such as TNF-inhibitors, IL-1 antagonists, and JAK inhibitors.
Conclusion: A20 haploinsufficiency should be considered in infants with recurrent soft tissue abscesses and unexplained inflammation. Early diagnosis facilitates tailored immunomodulatory treatment and may prevent disease progression.

Tabular data are included as downloadable supplement files.

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Recurrent Infections and EGID in CARMIL2 Deficiency

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CARMIL2 is a protein required for T cell activation, specifically for CD28 and CARMA-1/PKC coupling and NF-kB signaling. CARMIL2 deficiency has pleiotropic presentations, which can include recurrent viral and mucocutaneous infections and very early onset inflammatory bowel disease (VEO-IBD). Here, we present a 6-year-old Caucasian male with failure to thrive, recurrent infections, as well as eosinophil-associated gastrointestinal disorders (EGID). He was status post adenoidectomy x 3, bilateral myringotomy placement x 2, and

tonsillectomy x 1, presented for recurrent ear infection. He had an unremarkable newborn period. The patient developed ear infections at 6 months old that would persist despite antibiotics and surgeries. No known family history, and parents were not known to be consanguineous. He had a perianal skin infection that persisted for 12 months, despite adequate treatment. Outside allergist performed an immune workup at 2 years old, which showed low titers to pneumococcal vaccine and low IgG. Never had any overwhelming systemic infections. Due to the persistence and reoccurrence of infections despite surgeries and antibiotics, a repeat immune workup was performed. B and T cell flow cytometry, dihydrorhodamine (DHR) test, and complement were normal. DTaP and pneumococcal vaccine titers showed adequate post-vaccine response. However, he had low IgG (367), low class-switched B cells, absent T cell proliferation to tetanus, lymphocytosis, and eosinophilia. Genetic testing showed compound heterozygous CARMIL2 deficiency. The patient also had bloating and abdominal pain, and endoscopy showed 16 eosinophils per high-powered field in the distal esophagus, as well as eosinophilic gastritis. Most patients with CARMIL2 deficiency were noted to have consanguinity, poor vaccine response, and skin infection. Although both parents' genetic testing was found to have CARMIL2 mutations, the genomic variants were different, indicating less likelihood of consanguinity. Due to the rarity of CARMIL2 deficiency, specific treatment guidelines have yet to be established, but case reports noted improvement in disease process after immunoglobulin replacement. Our patient has started on immunoglobulin replacement and is on swallowed budesonide for his EGID.

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Recurrent Parvovirus B19 Infection in Pediatric Heart Transplant Recipients

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Introduction: Parvovirus B19 viremia has been reported as a cause of recurrent anemia in solid organ transplant (SOT) recipients. Many pediatric reports of this occurrence have been described in kidney transplant recipients, but less is known about this phenomenon in other pediatric SOT recipients. Furthermore, how immunosuppression may affect this outcome and how to manage chronic viremia remain to be studied.
Case Presentation: Here, we present a case series of three pediatric patients at a single institution (patients A, B, and C) who underwent orthotopic heart transplantation after which they developed parvovirus B19 viremia associated with recurrent episodes of aplastic anemia. Each patient required heart transplantation for dilated cardiomyopathy. Age at initial transplant ranged from 1 month, 19 days (patient A) to 6 months, 8 days (patient B). Patients A and B were both on tacrolimus and sirolimus dual therapy for immunosuppression, while patient C was on tacrolimus and mycophenolate for immunosuppression.

The average time to parvovirus viremia was 133 months (range: 124 months in patient B to 142 months in patient C). Patient A had two anemic crises due to high parvovirus B19 viral load, while patients B and C had three each. Each anemic crisis was managed with red blood cell transfusion and high-dose intravenous immunoglobulin therapy. In each case, all patients were unable to make specific parvovirus IgG responses following infection. Patient A had previously been on a long-standing immunoglobulin replacement therapy with acute anemic crises attributed to lapses in therapy. While on immunoglobulin replacement, patient A has had no further crises. Notably, patients A and C also had long-standing severe CD4+ and CD8+ T cell lymphopenia, while patient B had normal enumeration of lymphocyte subsets.
Discussion: Parvovirus B19 infection is a serious cause of morbidity and need for hospitalization and blood product transfusion among SOT recipients. Time to first infection and number of anemic crises may be influenced by the mode of immunosuppression. Immunosuppression may also affect class switching and production of an effective IgG antibody response following infection. As such, chronic immunoglobulin replacement therapy may be a viable option for management of parvovirus B19 viremia in SOT recipients.

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Risk Factors for Persistent Hypogammaglobulinemia in Pediatric and Young Adult Patients Receiving Rituximab

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Rationale: Rituximab is an anti-CD20 monoclonal antibody that can cause persistent hypogammaglobulinemia (PH) in 20–45% of patients, depending on the patient population. Risk factors for PH in pediatric patients following rituximab have been inconsistently identified. Prediction and timely identification of patients at risk for PH can enable earlier treatment with immunoglobulin replacement, preventing infectious complications.
Methods: We conducted a retrospective analysis of all patients who received rituximab (2017–2021) at an academic pediatric tertiary care center who had post-rituximab immunoglobulin G (IgG) assessed. Patients were excluded if they received rituximab for oncologic indications, underwent hematopoietic stem cell transplantation, received scheduled immunoglobulin replacement pre-rituximab, or had known humoral immunodeficiency. PH was defined as low IgG <2 standard deviations for age beyond one year from the most recent rituximab dose or, in the absence of a 1-year post-rituximab IgG level, new, continuous immunoglobulin replacement. We evaluated demographic, clinical, and laboratory characteristics that could predict PH using univariate and multivariate logistic regression. Post-rituximab absolute CD19 counts obtained greater than 1 year after the most recent rituximab dose were analyzed.
Results: A total of 206 patients met criteria, with the majority receiving rituximab for rheumatologic (34%), neurologic (33%), renal (14%), or hematologic (8%) indications. Median age at first dose of rituximab was 14.1 years (interquartile range [IQR] 8.7, 16.8), 59% were female, and 57% identified race as non-White. PH was observed in 42 (20.3%) patients. In univariate analysis, lower age (odds ratio [OR] 0.92, 95% confidence interval [CI]: 0.86, 0.97), Black race (OR 0.37, CI 0.13, 0.92), pre-rituximab IgM (OR 3.7, CI 1.2, 10.8), and post-rituximab absolute CD19 (OR 5.6, CI 2.5, 12.6) and IgA (OR 5.5, CI 2.4, 12.8) were associated with PH. Post-rituximab IgA was obtained at a median of 0.7 years (IQR 0.3, 2.2), and the first low absolute CD19 was obtained at median 1.3 years (IQR 1.1, 2.1) after the most recent rituximab dose. On multivariate analysis adjusting for age, post-rituximab low absolute CD19 (OR 6.5, CI 2.4, 19.3) and low IgA (OR 6.0, CI 2.5, 16.0) were associated with PH.
Conclusion: In a large, diverse cohort of pediatric and young adult patients, low post-rituximab absolute CD19 and IgA were risk factors for the development of persistent hypogammaglobulinemia.
Tabular data are included as downloadable supplement files.

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S220 Variants of Human CD48 Result in Aberrant Glycosylphosphatidylinositol (GPI) Linkage and Dominant-Negative CD48 Cellular Deficiency

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Introduction: CD48 is a coactivating receptor within the signaling lymphocytic activation molecule (SLAM) family that is important for the regulation of lymphocyte cytotoxicity and T cell activation. Volkmer et al. previously described a patient case with recurrent inflammatory disease secondary to a de novo heterozygous S220Y mutation in the CD48 gene (1). We also previously reported a novel, de novo, heterozygous S220F mutation with a similar clinical phenotype. As CD48 is tolerant of loss-of-function variants (probability of loss of function intolerance [pLI] = 0), CD48 haploinsufficiency could not explain the cellular derangements seen with S220 CD48 variants and investigated whether S220 causes immune disease through S220, which is the omega amino acid to which the glycosylphosphatidylinositol (GPI) is covalently linked. Further testing has demonstrated that these S220 variants are dominant-negative inborn error of immunity caused by impaired GPI anchor linkage.
Methods: Combinations of hCD48 expression vectors—either wild type (WT), S220Y, S220F, or empty—were transfected into the HEK-293 cell line, and surface or intracellular CD48 levels were measured by flow cytometry. Phospholipase C (PLC) from *Bacillus cereus* was used to cleave surface GPI anchors prior to flow cytometry. In separate experiments, an unfolded protein response (UPR) reporter was stably transduced prior to transfection with hCD48 expression vectors. pLVX-ATF4 mScarlet NLS was a gift from David Andrews (Addgene plasmid # 115969; http://n2t.net/addgene:115969; RRID:Addgene_115969).
Results: S220F and S220Y decreased surface CD48 when co-transfected with WT hCD48 ($p < 0.01$ compared to empty vector). PLC reduced surface CD48 by 73% for S220Y and 79% for S220F. UPR reporter activity was higher for S220F ($p = 0.01$) and S220Y ($p = 0.08$).

Conclusions: S220F/Y interacts with the GPI transamidase within the ER, but the efficiency of GPI linkage is severely reduced. This situation increases ER stress and induces the unfolded protein response. When monoallelic, S220 variants in CD48 dominantly impair surface expression of WT CD48, lower than levels seen with gene haploinsufficiency. Heterozygous S220 mutations are a new class of dominant-negative inborn error immunity with severely deficient surface expression and increased unfolded protein response as the mechanism of pathogenicity.

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Scoring Thoracic CT Scans of Patients with NFKB1-Related Disease for Clinical Management and Treatment Studies Using Four Parameters (Adapted from the Hartmann Score)

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Background: NFKB1 encodes the p105/p50 nuclear factor-kappa-B (NF-κB1) transcription factor. Heterozygous mutations in NFKB1 are associated with NFKB1-related disease, including granulomatous-lymphocytic interstitial lung disease (GLILD) or similar lung involvement. We aimed to characterize and score the severity of these pathologies in CT scans for the first time.
Methods: We evaluated clinical data and CT scans of 28 patients with 25 distinct NFKB1 variants (20 pathogenic and 8 variants of unknown significance [VUS]). CT scans were assessed by an experienced radiologist using the Hartmann and the modified Bhalla score.
Results: 15 of 20 patients with pathogenic NFKB1 variants showed pathological findings in their baseline CT. Three major phenotypes were identified: Slight bronchial wall thickening (n = 6), nodular phenotype (common variable immunodeficiency [CVID]-like) (n = 6), and bronchiectatic type (n = 3). Four parameters adapted from the Hartmann score were chosen to represent these qualities: Ground-glass opacities and consolidation (%), perilymphatic nodules (number), reticulation (%), and bronchial wall thickening (in relation to vessel diameter). The nodular type was not present in patients with a VUS in NFKB1, but a broad-spectrum of other pathological patterns.
Discussion: We identified three major radiological phenotypes in our NFKB1 cohort. The four parameters presented to analyze thoracic CT scans are currently validated in an unrelated worldwide NFKB1 cohort and can be used for clinical management and treatment evaluation.

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Severe B Cell Lymphocytosis with Autoimmune Cytopenia and Lymphoproliferative Disease in an Infant with a CARD11 Gain-of-Function Mutation

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Background: B cell Expansion with NF-κB Activation and T cell Anergy (BENTA) disease is a rare inborn error of immunity caused by gain-of-function (GOF) variants in CARD11. It is characterized by early-onset lymphadenopathy, splenomegaly, and profound polyclonal B cell lymphocytosis, with recurrent infections and immune dysregulation.

Case Presentation: We report a full-term female infant initially admitted with indirect hyperbilirubinemia, thrombocytopenia, and mild splenomegaly. At 6 months of age, she was hospitalized with fever, bilateral facial swelling, otomastoiditis, and urinary tract infection. Laboratory evaluation showed leukocytosis with progressive B cell lymphocytosis and evolving cytopenia with a positive direct Coombs test. Persistent splenomegaly and cervical lymphadenopathy were noted on the follow-up visit. Family history was significant for parental consanguinity and an older sibling with chronic mucocutaneous candidiasis and poor growth. Whole-exome sequencing identified a pathogenic missense variant in CARD11 (c.146G>A, p.Cys49Tyr), previously reported to cause BENTA disease due to a gain-of-function mechanism. During a subsequent admission. Her immunological evaluation showed marked lymphocytosis (absolute lymphocyte count [ALC] 51 × 10^9/L), increased $CD19^+$ B cells (12,309/μL), and reduced $CD3^+$ T cells (3,196/μL), including $CD4^+$ 1,846/μL and $CD8^+$ 1,208/μL. Double-negative T cells were elevated (6.3%), and natural killer (NK) cells were low ($CD16^+/56^+$ 180/μL). IgG 9.8 g/L, IgM 2.4 g/L, IgA 0.3 g/L, and total IgE <15. Tetanus antitoxin 0.25 IU/mL, diphtheria antibodies 0.02 IU/mL. Initially, she was clinically stable, but then she developed pancytopenia with Hgb 7 g/dL, platelets 30 × 10^9/L, absolute neutrophil count [ANC] 0.37 × 10^9/L, and ALC 10 × 10^9/L. EBV and hemophagocytic lymphohistiocytosis (HLH) were excluded, and she received intravenous immunoglobulin on two occasions. After discharge, the family stopped following up with the immunology clinic and elected to see traditional medicine. When they returned four months later, the patient had worsening lymphadenopathy and splenomegaly, along with more than twenty healed cautery marks on the abdomen. Plans for evaluation of B cell malignancy risk, initiation of sirolimus, and referral for hematopoietic stem cell transplantation were all declined by the family.

Conclusion: This case illustrates an early-severe phenotype of BENTA disease associated with significant lymphoproliferation, autoimmune cytopenia, and recurrent infections. It emphasizes the importance of early recognition and proactive management, while highlighting the impact of treatment refusal on patient outcomes.

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Severe Multisystem Autoimmunity and Atopy in a Child with a Loss-of-Function IKAROS Variant

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The IKAROS family of zinc finger transcription factors (IKZF1–4) plays a central role in lymphocyte development and immune regulation. Pathogenic IKZF1 variants produce a wide phenotypic spectrum related to whether the variant causes haploinsufficiency, dominant-negative effects, dimerization defects, or gain-of-function disease. Gain-of-function variants are typically associated with multisystem autoimmunity, allergic disease, and lymphoproliferation. Loss-of-function variants typically manifest with recurrent infections and hypogammaglobinemia. We describe a child with extensive autoimmunity and atopy who carried a novel loss-of-function IKZF1 variant, despite a clinical presentation that closely resembled gain-of-function disease.

A previously healthy girl with a benign family history presented to the gastroenterology clinic at age 6 for workup of frequent postprandial epigastric pain, diarrhea, and decreased appetite. She was previously diagnosed with polyarticular juvenile idiopathic arthritis (JIA) one month prior and was followed by allergy/immunology for eczema, asthma, and eosinophilic esophagitis. Laboratory evaluation demonstrated lymphopenia, reduced T, B, and natural killer (NK) cell subsets, elevated IgE, anemia, hypoalbuminemia, and elevated inflammatory markers. She was treated with infliximab, then transitioned to ustekinumab, methotrexate, and corticosteroids with partial improvement. At age 8, she developed periorbital, abdominal, and lower extremity edema. Renal biopsy confirmed class IV/V lupus nephritis, requiring therapy with corticosteroids, rituximab, and mycophenolate mofetil. Persistent secondary hypogammaglobulinemia led to the initiation of immunoglobulin replacement therapy.

Whole-exome sequencing identified a de novo IKZF1 c.378C>G (p.C126W) likely pathogenic variant affecting the first zinc finger DNA-binding domain. Functional testing showed diffuse nuclear localization on immunofluorescence and markedly reduced DNA binding on electrophoretic mobility shift assay, consistent with a loss-of-function mechanism through haploinsufficiency, as co-transfection of the wild-type and mutant constructs did not demonstrate a dominant-negative effect (Figure 1). Despite this, her clinical course was dominated by multisystem autoimmunity, severe allergic disease, and immune dysregulation, features which, in combination and severity, more closely resemble the gain-of-function IKZF1 phenotype.

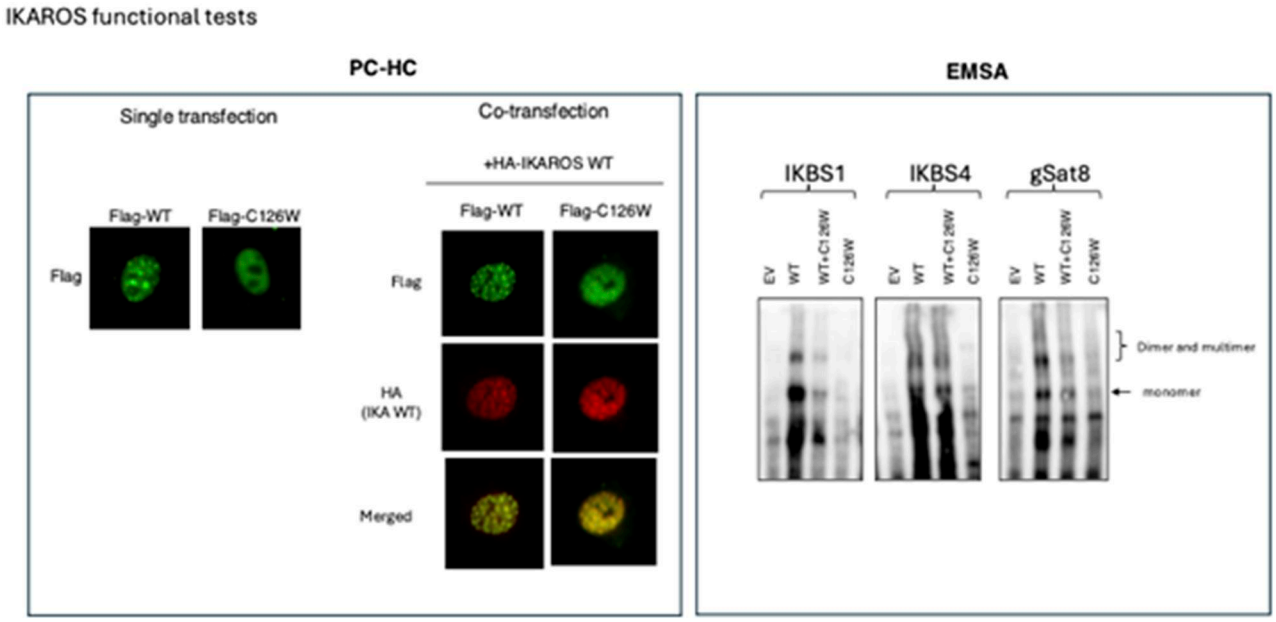

Figure 1. **Functional analysis of IKAROS C126W mutation. (Left)** Immunofluorescence analysis of pericentromeric heterochromatin localization (PC-HC) demonstrating nuclear distribution of wild-type (WT) and C126W IKAROS. WT IKAROS shows the characteristic punctate nuclear pattern, whereas the C126W variant displays diffuse nuclear staining, indicating impaired DNA binding and altered pericentromeric localization with no evidence of a dominant-negative effect on the WT/Mutant co-transfection experiment. **(Right)** Electrophoretic mobility-shift assay (EMSA) using IKBS1, IKBS4, and gSat8 probes demonstrates that wild-type IKAROS binds consensus DNA sequences, whereas the C126W variant fails to bind or is markedly reduced. Together, these findings confirm that the C126W mutation disrupts IKAROS pericentromeric heterochromatin localization and DNA-binding capacity, consistent with a loss-of-function, haploinsufficiency mechanism.

This case illustrates a gain-of-function-like phenotype arising from a confirmed loss-of-function IKZF1 allele. The discordance between molecular mechanism and clinical presentation suggests additional genetic or epigenetic modifiers and underscores the importance of early genetic testing and functional validation in children with unexplained multisystem autoimmunity.

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Shorter Distance to Main Academic Center Associated with Better Longitudinal Care and Follow-Up in Adult Patients with 22q11.2 Deletion Syndrome

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Background: 22q11.2 deletion syndrome (DS) is the most common chromosomal microdeletion syndrome and a leading cause of developmental delay, congenital heart disease, and varying degrees of T cell immunodeficiency. While most studies focus on diagnosis and childhood outcomes, understanding of adult complications and access to care remains limited. We explored the influence of geographic proximity vs. other socioeconomic factors on accessing complex specialty care and survival in adults.

Methods: We conducted a retrospective chart review of adults (>18 years) with confirmed 22q11.2DS seen at the 22q and You Center at Children's Hospital of Philadelphia (CHOP) between 2001 and 2025. Exclusions included 22q11.2 duplication, residence more than 100 miles from CHOP, and no documented visit between 2001 and 2025.

Results: Of 419 adults with 22q11.2DS, patients averaged 105 clinical visits over the 24-year study period and had a mean of 36 unique diagnoses. Most followed specialties (% of cohort, mean # visits) were cardiology (57%, 14), genetics (49%, 4), endocrinology (43%, 11), orthopedics (43%, 11), allergy/immunology (38%, 6), gastroenterology (26%, 13), pulmonology (14%, 11), and hematology/oncology (12%, 10). Over 60% of patients underwent diagnostic procedures, averaging 22 per patient. Our cohort demonstrated higher than national average rates of food allergy (21%, n = 86) and asthma (20%, n = 82), with allergic rhinitis occurring at rates comparable to national estimates (27%, n = 112). In contrast, eczema prevalence was lower at 3% (n = 11). Patients living within 25 miles of CHOP (n = 187) averaged 138 visits per patient, compared with 79 visits among those 26–100 miles of CHOP (n = 232; $p<0.001$). Overall, a shorter distance to CHOP was associated with an increased number of appointments, diagnoses, specialties involved, and diagnostic procedures. In contrast, socioeconomic status, measured by median household income for the zip code, was not associated with diagnostic burden or visit frequency.

Conclusion: Access to a tertiary comprehensive 22q center is associated with increased healthcare access and specialty longitudinal care. This is further emphasized by a lower mortality rate in our 22q11.2DS cohort (2%, n = 8) compared with the estimated overall mortality of 24% for inborn errors of immunity. Further study of adults with 22q11.2DS will describe the burden of persistent disease.

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Sirolimus as Successful Treatment in Children with Chronic/Refractory Primary Autoimmune Hemolytic Anemia

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Introduction: Autoimmune hemolytic anemia (AIHA) is a rare disorder that can follow a chronic/refractory course. Therapeutic management beyond first-line steroids remains challenging in children. Different immunosuppressive agents have been used as second/further-line treatments. Data supporting the use of sirolimus are limited to patients with autoimmune lymphoproliferative syndrome (ALPS) and Evans syndrome (ES).

Methods: We conducted a retrospective single-center study including children with chronic/refractory AIHA treated with sirolimus in our center. Patients with a diagnosis of ALPS or ES were excluded.

Complete response (CR) and partial response (PR) were defined as the normalization of hemoglobin levels according to age-adjusted reference values, with the absence of clinical signs of hemolysis and as the sustained increase in hemoglobin of ≥2 g/dL from baseline, reduced transfusion requirements, and persistence of minor signs of hemolysis, respectively. No response was defined as the absence of clinical and laboratory improvement, requiring additional therapies.

Results: Between 2002 and 2025, 15 patients (8 males, 7 females) with a median age at disease onset of 4.3 years (range 0.1–16.1) were included. AIHA was isolated in 60% of cases. The remaining patients presented signs of immune dysregulation. Median hemoglobin levels at diagnosis were 5.6 g/dL (range 2.1–11.3). Sirolimus was initiated after a median of 341 days from diagnosis and was used as second (5) or further-line (10) therapy. Steroids were given as first-line therapy in all cases. All patients achieved a response, which was complete and partial in 13 (87%) and 2 (13%) cases, respectively. Median follow-up was 6.4 years (range 2–23). Six patients experienced a disease relapse, successfully managed with steroid reintroduction, sirolimus reinitiation, or dose adjustment in all cases. Sirolimus was ongoing in 6 patients at the last follow-up. Adverse events were observed in 11 patients and consisted of dyslipidemia (4), infections (3), ovarian cysts (2), mild transaminase elevation (1), and oral aphthosis (1). No patients needed to discontinue the therapy due to toxicity.

Conclusions: Sirolimus proved to be an effective therapeutic option for children with chronic/refractory AIHA other than ALPS and ES. These findings support its role as a valuable treatment in this complex patient population.

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Structure-Guided Characterization of STAT1 Mutations: Integrating In Silico Modeling with Functional and Transcriptional Validation

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STAT1 gain-of-function (GoF) is an inborn error of immunity characterized by a common feature of chronic mucocutaneous candidiasis and variable additional clinical manifestations, including recurrent bacterial and viral infections, autoimmunity, lymphoproliferation, aneurysm formation, and bone fragility. Over 150 GoF mutations have been identified. However, the molecular mechanisms underlying individual STAT1 GoF mutations remain poorly understood. We developed an integrated approach combining computational prediction with functional characterization to validate STAT1 GoF variants and stratify variants based on their putative molecular mechanism toward a GoF. Single missense variants were screened in silico, and hits were analyzed using an in-house established semiautomatic molecular dynamics pipeline to predict STAT1 protein stability, activation dynamics, and DNA interaction.

Computational predictions were experimentally validated through stable expression of selected STAT1 variants in THP-1 monocytic cells. Functional characterization included analysis of STAT1 phosphorylation and dephosphorylation kinetics, together with transcriptomic profiling. Shared and mutation-specific characteristics were identified. Together, this integrated computational-experimental pipeline allows validation of STAT1 GoF variants and provides a framework for stratifying variants based on their putative molecular mechanism of action.

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Subgroup of 22q11.2 Deletion Syndrome Patients Have Blood-Borne 16S Bacterial DNA Signatures Associated with Gut Commensals

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Background: 22q11.2 deletion syndrome (22q11.2DS, also known as DiGeorge) affects 1/2,150 individuals. The deletion results in variable clinical phenotypes: thymic hypoplasia or aplasia, hypoparathyroidism, cardiac defects, dysmorphic facial features, and neurodivergent presentations. Vascular leakiness and a compromised blood–brain barrier is also evident in some. The immune consequences of 22q11.2DS are frequent and severe infections. Blood samples from a cohort of 22q11.2DS patients were screened for bacterial DNA signatures. This was assessed in conjunction with their clinical presentations, serum antibody specificities, and cytokine levels relative to normal healthy toddlers.

Methods: Blood samples were obtained from a cohort of 22q11.2DS patients (n = 82) along with normal healthy controls (n = 300). Bacterial 16S rRNA DNA sequencing was undertaken. Serum/plasma antibody specificities to pathogen, vaccine, and autoantigens were assessed, and clinical presentations were compiled. 16S sequencing data were analyzed using CLC Genomics microbial Module v25.0. Antibody and cytokine data analysis were performed using GraphPad Prism v10.0

Results: Based on the presence of 16S rRNA DNA signature patterns, the 2q11.2DS cohort was subclustered into 3 major groups. Subcluster 1 comprises bacterial DNA patterns related to the gut commensal species, including species *Akkermansia*, *Allobaculum*, *Bacteroides*, *Lactobacillus*, *Ruminococcus*, etc. Interestingly, this cluster was positively correlated with G-tube placement. On the other hand, subcluster 2 had a DNA signature of pathogens such as streptococcal and staphylococcal species. Subcluster 3 had no bacterial DNA. Interestingly, those with a positive gut-commensal pattern had reduced serum cytokine levels relative to subcluster 2. These findings differed significantly with normal healthy 1–4-year-old toddlers, wherein 12% showed a blood-borne DNA signature related to oral commensals and pathogenic species. Data analyses are ongoing, with information regarding antibody responses to various antigens and cytokine profiles being integrated.

Conclusion: A subset of 22q11.2DS patients have a bacterial DNA pattern in their blood related to species from the gut microbiome. This differed from the bacterial DNA patterns in blood from some "healthy toddler" group, which further differed from that reported for patients with common variable immunodeficiency [CVID] and acne inversa.

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Successful Allogeneic Hematopoietic Cell Transplantation in Two Patients with IL-12Rβ1 Deficiency

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IL-12Rβ1 deficiency is thought to be the most common etiology of Mendelian susceptibility to mycobacterial disease with incomplete penetrance and variable expressivity. Allogeneic hematopoietic cell transplantation (HCT) is potentially curative but has been rarely reported for this disease. We describe two affected patients successfully treated with HCT.

P1 was a 21-month-old female (homozygous, c.1623_1624delinsTT, p.Gln542*) who presented with disseminated *Mycobacterium avium* complex (MAC) infection. Her infection partially responded to antimycobacterial therapy and interferon (IFN)-γ. She underwent myeloablative HCT at age 3.5 years from a 12/12 HLA-matched unrelated donor. Conditioning consisted of busulfan, cyclophosphamide, thiotepa, and fludarabine. Graft-versus-host disease (GVHD) prophylaxis included anti-thymocyte globulin, methotrexate, tacrolimus, and mycophenolate mofetil. She achieved neutrophil engraftment on D+31 but required romiplostim for chronic thrombocytopenia. Post-HCT course was complicated by (1) engraftment syndrome with cytokine release syndrome and encephalitis, treated with anakinra and intravenous immunoglobulin (IVIg), and (2) MAC-immune reconstitution inflammatory syndrome (IRIS) with severe adenoviral infection and pulmonary hemorrhage requiring extracorporeal membrane oxygenation support. Late complications included acute immune thrombocytopenia, treated with corticosteroids. She is now 12 years old and well.

P2 was a 6-year-old female (homozygous, c.631C>T, p.Arg211*) who presented with disseminated *Mycobacterium bovis* infection (BCG-osis) despite antimycobacterial therapy and IFN-γ (NCT00018044). Her course was complicated by protein-losing enteropathy (PLE) from BCG mesenteric lymph node infection. She underwent HCT at age 11 years using peripheral blood stem cells from her 10/10 HLA-matched father after myeloablative conditioning with busulfan and fludarabine. GVHD prophylaxis included cyclophosphamide, tacrolimus, and mycophenolate mofetil. Post-HCT course was complicated by (1) engraftment syndrome, treated with corticosteroids and tocilizumab, and (2) BCG-IRIS managed with corticosteroids. Eltrombopag was given preemptively and empirically to mitigate the deleterious effects of an IFN-γ surge during IRIS on hematopoiesis; however, poor graft function still ensued, which resolved after emapalumab conditioning for a stem cell boost. She is currently well 5 years post-HCT with resolution of infection but persistent PLE.

In summary, allogeneic HCT is a viable therapeutic approach for IL-12Rβ1-deficient patients with refractory mycobacterial disease, but it can be complicated by IRIS and poor engraftment. Therapies such as eltrombopag and emapalumab may be considered.

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Suspected STAT3-Related Hyper-IgE Syndrome in a Toddler with a Novel STAT3 Variant of Uncertain Significance

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Background: Dominant-negative (DN) STAT3 defects (STAT3-DN) result in >75% loss of STAT3 function and lead to autosomal-dominant hyper-IgE syndrome (HIES) characterized by severe eczema, recurrent bacterial and fungal infections, elevated IgE,

eosinophilia, and skeletal and connective-tissue abnormalities. More recently, STAT3 haploinsufficiency (STAT3-HI), typically due to truncating or splice-site variants with partial preservation of STAT3 activity (>25%), has been associated with atopy, impaired Th17 differentiation, and possible increased susceptibility to fungal infections. When a STAT3 variant of uncertain significance (VUS) is identified, diagnosis of STAT3-related HIES in early childhood can be challenging without additional functional testing.

Case Presentation: A 22-month-old male presented with complex congenital and atopic disease. Congenital findings include a solitary kidney with cross-fused renal ectopia, Chiari malformation, vertebral anomalies, and gross motor delay. Atopic manifestations included early-onset eczema, multiple IgE-mediated food allergies, and recurrent wheezing. He experienced multiple respiratory illnesses, including status asthmaticus, recurrent croup, pneumonia, and bronchiolitis. Family history is notable for a sibling with specific antibody deficiency, intrauterine fetal demise of another sibling with bilateral renal agenesis, and a father with recurrent infections, bronchiectasis, and possible pneumatocele attributed to allergic bronchopulmonary aspergillosis (ABPA), treated with dupilumab. Immunologic evaluation demonstrated elevated IgE (569 IU/mL), otherwise normal quantitative immunoglobulins, and poor pneumococcal titers (4/14 protective), with repeat titers pending. A previously undescribed paternally inherited heterozygous STAT3 intronic VUS (c.1233+1_1233+3delinsCTTp.?) was identified on whole-genome sequencing. In silico analysis predicts a deleterious effect on splicing. His National Institutes of Health HIES score was 22, within the "possible" range for his age. Functional studies (RNA-sequencing testing) and Th17 enumeration are being pursued to clarify variant pathogenicity.

Discussion: Diagnostic uncertainty stems from his young age, incomplete evolution of classic HIES features, and lack of functional STAT3 testing. Nonetheless, primary diagnosis of STAT3-related HIES is suspected, with consideration of both classic STAT3-DN and emerging STAT3-HI as mechanistic possibilities. Further immunophenotyping and functional studies can facilitate diagnosis.

Conclusion: In young patients with complex congenital anomalies, atopic disease, and relevant family history, identification of a STAT3 VUS warrants comprehensive functional evaluation. Distinguishing STAT3-DN from STAT3-HI will have meaningful implications for prognosis and clinical management.

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Symptom Changes in Pediatric Patients with Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS) Receiving Leniolisib

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Introduction: Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS) is a rare disease characterized by progressive symptoms that begin early in life, including lymphoproliferation, recurrent and persistent infections, and early mortality compared with the global population. Delayed diagnosis and inadequate treatment in childhood may exacerbate disease manifestations. This post hoc analysis evaluated caregiver-reported changes in APDS symptoms in pediatric patients after 12 weeks of treatment with leniolisib.

Methods: Twenty-one pediatric patients aged 4–11 years with APDS received open-label leniolisib in a single-arm, multicenter, international study (NCT05438407). Study documents received institutional review board approval. In a post hoc analysis, worst-rated dimension scores on the APDS-Symptom Severity Scale (APDS-SSS) at baseline were compared with week 12 scores. Item-level symptom scores, assessed by APDS-SSS, rated moderate to very severe (≥2 on a 0–4 scale) at baseline, were also compared with week 12 scores. Multiple scores per participant were reported in the event of within-person ties.

Results: After 12 weeks of leniolisib treatment, APDS-SSS symptom severity scores for dimensions with the worst-rated baseline scores generally decreased, indicating improvement. All patients with infections (n = 4) or gastrointestinal symptoms (n = 3) as their worst baseline dimension improved after 12 weeks of treatment. Among patients with respiratory symptoms as their worst baseline dimension, 10 of 13 (77%) improved at week 12; 1 remained stable, and 2 worsened to mild/moderate severity over time.

Among patients with emotional impact as their worst baseline dimension, 3 of 6 (50%) improved at week 12; 1 remained stable, and 2 worsened to mild severity over time. Item-level symptom severity also generally decreased over time. For 3 symptoms, 1 patient each improved from severe/very severe at baseline to "none" at 12 weeks. All patients with visible swollen lymph nodes (n = 3) improved: 1 from severe to moderate and 2 from moderate to none.

Conclusion: According to caregiver ratings, the most severe APDS-related symptoms experienced by pediatric patients aged 4–11 years showed improvements after 12 weeks of leniolisib treatment. These results demonstrate the potential clinical benefit of leniolisib in most pediatric patients.

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TLR8 Gain-of-Function Syndrome Patient with Hemophagocytic Lymphohistiocytosis Treated with Emapalumab

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Introduction: Toll-like receptor 8 gain-of-function (TLR8 GOF) is a recently described inborn error of immunity caused by activating mutations in Tlr8. Pathogenic variants lead to constitutive signaling in myeloid cells and downstream overproduction of proinflammatory cytokines. Clinical features include recurrent infections, autoimmune cytopenias, lymphoproliferation, neutropenia, bone marrow failure, and hypogammaglobulinemia, although the full clinical spectrum and optimal management remain incompletely defined.
Case Description: An 8-year-old male presented with pancytopenia following respiratory syncytial virus and *Mycoplasma pneumonia*e infection. Laboratory evaluation revealed elevated inflammatory markers (ferritin 4,021 ng/mL, soluble IL-2 receptor 15,628 U/mL, and CXCL9 83,818 pg/mL). Bone marrow biopsy demonstrated hemophagocytic forms consistent with hemophagocytic lymphohistiocytosis (HLH). A targeted sequencing panel identified a maternally inherited hemizygous TLR8 variant of uncertain significance (VUS) (c.1299G>C; p.Leu433Phe). Functional studies confirmed gain-of-function activity, although of lesser magnitude than in previously reported pathogenic variants. The patient's mother, a carrier of the variant, had a history of adult-onset autoimmune hemolytic anemia. Immunophenotyping in the patient revealed hypogammaglobulinemia, B and natural killer (NK) cell lymphopenia, and absent class-switched memory B cells. He clinically improved with corticosteroids and etoposide, but persistent CXCL9 elevation prompted transition to emapalumab, which led to normalization of inflammatory markers as a bridge to planned hematopoietic stem cell transplantation.
Discussion: This case illustrates several important aspects of TLR8 GOF–associated disease. It highlights the value of genomic evaluation in HLH, where identifying underlying immune-dysregulation disorders can direct management and impact decisions on transplantation. In this patient, functional studies were essential for confirming the pathogenicity of a TLR8 variant initially classified as a VUS, thereby expanding the recognized clinical phenotype of TLR8 GOF to include HLH. The attenuated functional effect of this variant may explain the later onset compared with previously reported germline cases presenting in infancy. The mother's history of autoimmune cytopenia supports variable expressivity in heterozygous females, which is increasingly recognized, with two additional cases now identified independently. Finally, this is the first reported use of emapalumab for TLR8 GOF–associated HLH, suggesting that IFNγ blockade may serve as a rational targeted therapy and bridge to definitive therapy with transplantation.

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Treatment of Germline TET2 Deficiency with a Hypomethylating Agent

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Clinical Presentation: Patients with germline TET2 loss of function exhibit a syndrome of immunodeficiency, autoimmune lymphoproliferation, developmental delay, and predisposition to lymphoma. An 8-week-old infant was admitted with failure to thrive, ascites, respiratory failure, hepatosplenomegaly, lymphadenopathy, cytopenias, hypogammaglobulinemia, hypoalbuminemia, and nephrotic syndrome. The patient had chronic CMV and recurrent rhinovirus infections with secondary bacterial pneumonia requiring mechanical ventilation. Whole-genome sequencing revealed homozygous nonsense variants in TET2 (c.3075del p.(Ile1025MetfsTer8)). Studies

showed innumerably high lymphocyte subsets, elevated double-negative T (DNT) cells (2.7% lymphocytes), but no evidence of lymphoma. As TET2 deficiency causes global DNA hypermethylation, we hypothesized that treatment with a hypomethylating agent would ameliorate her symptoms.

Methods: After informed consent, the patient was initiated on decitabine, a cytosine analog and DNA methyltransferase inhibitor. For molecular characterization of TET2 deficiency and effects of decitabine, we collected peripheral blood mononuclear cells (PBMC) from the proband pre- and post-decitabine to compare with age-matched controls. Whole-genome sequencing with real-time methylation calling (5-methylcytosine [5mC] and 5-hydroxymethylcytosine [5hmC] is being performed on PromethION (Oxford Nanopore Technologies, ONT). Single-cell RNA sequencing will be performed with the 10X Genomics 3' Universal Gene Expression kit on a 10X Chromium. Data will be analyzed with ONT workflows.

Results: The patient was treated with intravenous decitabine 100 mg/m^2/month, which temporarily improved serum albumin from 1 g/dL to 2.5 g/dL with reversion between cycles. Despite transient lab changes, the patient was weaned off respiratory support with improved lymphadenopathy, ascites, and edema. For more consistent disease control, we attempted weekly infusions of 25 mg/m^2, causing serum albumin to normalize (3 g/dL), without exogenous albumin, and improved proteinuria (~100,000 to 1,100 mg protein/g creatinine). Lymphocyte subsets largely normalized, DNT cells improved to 2.2%, and CD27+ memory B cells increased (5.7% to 12.8%). The patient was discharged at 9 months old.

Conclusions: This is the first report of a patient with TET2 deficiency being treated safely and efficaciously with a hypomethylating agent. Ongoing studies will provide the first characterization of whole-genome DNA methylation and concomitant perturbations in RNA expression in TET2 deficiency and demonstrate how these are altered by decitabine.

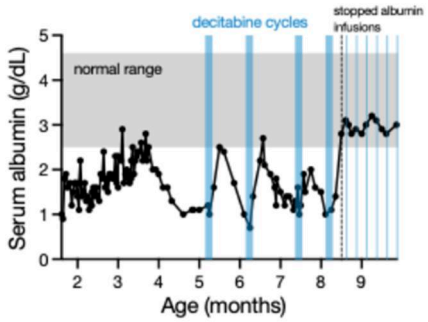

Figure 1. **Serum albumin in a patient with germline *TET2* deficiency pre- and post-decitabine.**

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Unmasking Primary Immunodeficiency After Rituximab

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Introduction: Rituximab, an anti-CD40 antibody, is a commonly used B cell-depleting therapy. We present a case that illustrates the unveiling of an underlying common variable immune deficiency (CVID) after completion of rituximab therapy.

Case Presentation: An 18-year-old female with a history of myelin oligodendrocyte antibody disorder (MOGAD) treated with rituximab for 1.5 years was referred for recurrent infections, chronic cough, and intermittent fevers persisting for five months despite multiple antibiotic courses. She had completed her rituximab therapy six years ago. Flow cytometry during therapy had shown complete B cell depletion. At the clinic visit, laboratory results revealed severe hypogammaglobulinemia (IgG 166 mg/dL, IgM 19 mg/dL, and IgA <20 mg/dL) and absent diphtheria protection and a pneumococcal response to only 2/23 serotypes, with preserved tetanus titers. Genetic testing was also performed and revealed a heterozygous likely pathogenic TNFRSF13B variant associated with autosomal recessive CVID. The literature indicates that single pathogenic variants may contribute to CVID risk. In the setting of persistent hypogammaglobulinemia, impaired vaccine responses, recurrent infections, and genetic findings, she was diagnosed with CVID.

Discussion: While rituximab usually causes transient hypogammaglobulinemia, in patients with unrecognized inborn errors of immunity, hypogammaglobulinemia may be persistent and severe. Hypogammaglobulinemia after rituximab typically persists for six to 12 months. Prolonged hypogammaglobulinemia lasting longer than six to 12 months and poor vaccine responses after rituximab warrant immunologic evaluation. Additionally, baseline testing prior to initiating therapy may help distinguish secondary from primary immunodeficiency.
Conclusion: This case highlights the importance of differentiating primary immunodeficiencies from rituximab-induced hypogammaglobulinemia. Early recognition of underlying primary immunodeficiency would enable more timely management and ultimately reduce CVID-associated morbidity. Genetic testing plays a key role in confirming clinical suspicion.

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Unraveling B Cell Lymphoma Presenting as AKI and Hypercalcemia in a Patient with BACH2 Variant and CVID

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Introduction: BACH2-related immunodeficiency and autoimmunity (BRIDA) increases the risk of developing B cell lymphoma. We present a case of a patient with a known history of common variable immunodeficiency (CVID) and BACH2 variant of uncertain significance, presenting with hypercalcemia and acute kidney injury (AKI), found to have T cell histiocyte-rich large B cell lymphoma of the spleen.
Case Description: 46-year-old male with CVID-like clinical picture with variant of uncertain significance in BACH2 (Combined Annotation Dependent Depletion [CADD] 25.2, allele frequency 2) and granulomatous-lymphocytic interstitial lung disease (GL-ILD), admitted for acute kidney injury with hypercalcemia. He is pancytopenic, hypercalcemic, with marked splenomegaly on CT. PET-CT showed retroperitoneal and iliac chain lymphadenopathy along with mixed changes of osseous/marrow lesions with new lesions in the thoracic spine and left mid femur. There is a notable improvement in GL-ILD on CT chest while the patient is on prednisone. Renal biopsy showed acute tubular injury with increased deposition of calcium phosphate, along with moderate interstitial fibrosis and tubular atrophy with mild fibrointimal thickening of arteries. No monoclonal protein detected in the serum, negative JC virus, BK virus, EBV, CMV, and HIV. Splenic biopsy showed B cell lymphoma with features of micronodular T cell/histiocyte-rich large B cell lymphoma of the spleen. Patient initiated on rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone treatment protocol.
Discussion: BACH2 is a regulator of T and B cell differentiation and maturation. The effect of BACH2 on T cells involves limiting the differentiation of regulatory T (Treg) cells, which aid in preventing autoimmunity. BACH2 mutations have been described in the literature in patients with CVID and autoimmunity, such as ulcerative colitis. Lymphoma can cause hypercalcemia, which can lead to acute kidney injury. This patient has a variant of uncertain significance in BACH2 with CADD 25.2, allele frequency 2. His clinical picture of CVID, acute kidney injury in the setting of hypercalcemia, and newfound B cell lymphoma of the spleen may be due to this variant of uncertain significance. Further studies need to be conducted to better understand this gene and its role in CVID and B cell lymphoma.

Tabular data are included as downloadable supplement files.

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Updated and Initial Validation of Warning Signs: Western Expert-Based Pidcap Delphi Project

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Objective: Early recognition of inborn errors of immunity (IEI) is critical to avoid morbidity and irreversible organ damage. Jeffrey Modell Foundation (JMF) warning signs have long guided and still guide clinical suspicion. However, the IEI phenotype has broadened substantially since 1993. We aimed to update and evaluate IEI warning signs using an international Delphi process, generating harmonized suspicion criteria that can serve as the basis for scalable, user-friendly tools and future data-driven technologies to support early detection.

Design and Methods: The Delphi study was carried out in two rounds in 2024/2025. Multidisciplinary IEI experts (including physicians, nurses, and patients from European Society for Immunodeficiencies [ESID], Clinical Immunology Society [CIS], International Nursing Group for Immunodeficiencies [INGID], and International Patient Organisation for Primary Immunodeficiencies [IPOPI] under the umbrella of the JMF) rated and weighted literature-derived candidate signs using a 9-point Likert scale. Consensus was defined as ≥66% of respondents scored 7–9. Dedicated pediatric and adult panels assessed age-specific signs. Outputs included consensus level and diagnostic weight matched with International Classification of Diseases (ICD) codes. To test the feasibility of an automated early-detection system for community-dwelling individuals at high risk of IEI, we ran the algorithm against primary care electronic health records (EHR) of a healthcare district (catchment population of 571,123; 91.9% adults and 8.1% children).

Results: Of 103 invited experts, 96 from 22 countries in Europe, Canada, and the U.S. completed round 1 (93% response rate) and 90 completed round 2 (94%). The pediatric panel (n = 68) reached consensus on 26 of 27 signs, and the adult panel (n = 49) on 17 of 24. High-consensus, high-weight items included ≥3 pneumonias, bronchiectasis, very early onset inflammatory bowel disease, positive family history, and multimorbidity (≥2 signs). When run against primary care EHRs: 14,519 individuals were considered at high-risk of IEI, eligible for considering referral: 14,174 adults (2.7%) and 345 children (0.75%).

Conclusions: This international Delphi provides the first harmonized, consensus-based update of IEI warning signs. The weighted, ICD-10–mapped signs support the implementation of early-detection screening strategies and facilitate federated learning frameworks. The pilot test of potential referrals suggests that the indicator would be feasible, although the potential overburdening of specialized services should be taken into consideration. Further testing is ongoing to validate the implementation strategy.

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Use of Sirolimus and Immunoglobulin Replacement Therapy (IRT) in Patients with Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS): A Systematic Literature Review (SLR)

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Introduction: Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS), a rare inborn error of immunity, is associated with immunodeficiency and immune dysregulation. Clinical management includes symptomatic treatment with immunoglobulin replacement therapy (IRT) and sirolimus, neither of which is approved by the U.S. Food and Drug Administration for the treatment of APDS. This systematic literature review (SLR) aimed to evaluate the effectiveness of IRT and/or sirolimus in patients with APDS.

Methods: An SLR was conducted to assess the evidence base and quality of literature specific to the impact of IRT and/or sirolimus on clinical outcomes in APDS, including manifestations, treatment utilization, and mortality. Searches were conducted in MEDLINE, Embase, and the Cochrane Library databases from database inception to July 2025. Grey literature searches included relevant conference proceedings and clinical trial registries; bibliography reviews were hand searched. Eligible publications included patients with clinically or genetically confirmed APDS; study types included clinical trials, observational studies, case series or reports, chart reviews, and real-world database analyses reporting IRT or sirolimus/rapamycin treatment outcomes. Publication quality assessment was performed using standard tools.

Results: Of the 79 studies identified, 90% (n = 71) were single-patient case reports (69 [87%]) or small (≤6 patients) case series (2 [3%]); 10% (n = 8) were retrospective cohorts. No prospective or controlled trials were available, and outcomes were inconsistently defined and quantified.

Conclusion: Quality evidence supporting the effectiveness of IRT and/or sirolimus in APDS is limited, with 90% of the data derived from case reports or case series involving ≤6 patients. These results highlight the need for quality prospective studies evaluating the effectiveness of these agents, specifically in APDS.

Friday Poster Hall

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A Case of HUPRA (Hyperuricemia, Pulmonary Hypertension, Renal failure, Alkalosis) with Immune Dysfunction

Payge Moraca[1], Whitney Shaffer[2], Michell Lozano Chinga[2], and Brenna LaBere[2]

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Introduction: Hyperuricemia, pulmonary hypertension, renal failure, alkalosis (HUPRA) syndrome is a mitochondrial disease caused by mutations in SARS2 (seryl-tRNA synthetase 2), which plays a role in protein synthesis. Limited case reports describe an association of HUPRA with immunodeficiency; however, no in-depth immune phenotyping has been described. We present a case of HUPRA with recurrent infections and lymphopenia, with clinical improvement on immunoglobulin replacement therapy (IgRT).
Case Description: An 11-month-old male born at 29 weeks' gestational age with pulmonary hypertension (PH) and tracheostomy dependence was admitted with recurrent fevers and worsening PH. History revealed prior *Enterococcus faecalis* bacteremia as well as *Staphylococcus aureus* and *Pseudomonas aeruginosa* tracheitis. Laboratory evaluation revealed mildly low IgG with normal IgM and IgA. Lymphocyte subsets revealed T cell, B cell, and natural killer cell lymphopenias, with CD4+ T cell compartment skewing to a memory phenotype, normal total switched memory B cells, and normal T follicular helper cells. Vaccine titers were not obtained, given receipt of only one set of vaccines. T cell proliferations were reassuring. Genetic testing revealed compound heterozygous mutations in SARS2, confirming a diagnosis of HUPRA. He is being treated with IgRT with significant clinical improvement.
Discussion: In case series, up to half of patients with HUPRA can present with increased infections, often with leukopenia. Multiple studies have shown that aminoacyl-tRNA synthetases can play a role in immune cell development, regulation, and autoimmunity through interactions with innate and adaptive immune responses. Additionally, hyperuricemia is known to induce innate and adaptive immune responses. It is difficult to know how these findings relate to the function of SARS2 or patients with HUPRA. Our patient was found to have multilineage lymphopenia with mildly low IgG, with significant clinical improvement on IgRT. More in-depth evaluations are needed to better understand the pathophysiology of immune dysfunction with SARS2 deficiency. This case provides in-depth immune phenotyping and a potential treatment option for others with HUPRA.

Tabular data are included as downloadable supplement files.

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A Case of T- B- NK+ SCID Without an Identifiable SCID Mutation

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[1]Northwell

Introduction: The T cell receptor excision circle (TREC) assay is an effective neonatal screening tool for severe combined immunodeficiency (SCID), enabling early diagnosis and timely intervention. While genetic analysis often confirms a causal mutation for T cell lymphopenia, challenges arise when patients phenotypically present with SCID despite lacking an identifiable genetic etiology. This scenario necessitates a high index of suspicion and decision-making regarding hematopoietic stem cell transplantation (HSCT).
Case Description: We present a 2-month-old female with a history of undetectable TREC levels (0,0,0) who presented with fever and confirmed influenza and coronavirus on viral swab. Initial lymphocyte phenotyping revealed severe CD4+, CD8+ T cell lymphopenia with very low B cells (supplemental table). Concern for maternal engraftment was suspected because of a markedly low absolute CD45RA number of 7 (nl = 1,200–5,300 cells/uL) and CD45RO of 84 (nl = 90–1,400 cells/uL). Whole-exon sequencing (WES) demonstrated a heterozygous autosomal recessive pathogenic mutation in the Ataxia-Telangiectasia mutated gene (ATM) (c.802C>T), with negative whole-genome sequencing, confirming that there was not a second ATM mutation. WES also identified a heterozygous pathogenic mutation in RNASEH2A (autosomal recessive Aicardi-Goutières syndrome). A variant of uncertain significance (VUS) was also present in autosomal recessive POLD2, which can cause non-severe combined immunodeficiency. Despite the absence of a

confirmed SCID gene, worsening T cell lymphopenia led to the decision of HSCT at age eight months using an allogeneic, unrelated cord blood donor.

Discussion: This case highlights that a definitive SCID phenotype, even in the absence of an identifiable genetic cause, warrants close management, including timely HSCT. Continued vigilance is crucial for preventing devastating infectious complications in patients with severe T cell lymphopenia, emphasizing the importance of clinical judgment when genetic findings are inconclusive.

Tabular data are included as downloadable supplement files.

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A Case of the Immune System Actin Up: DOCK11 Deficiency

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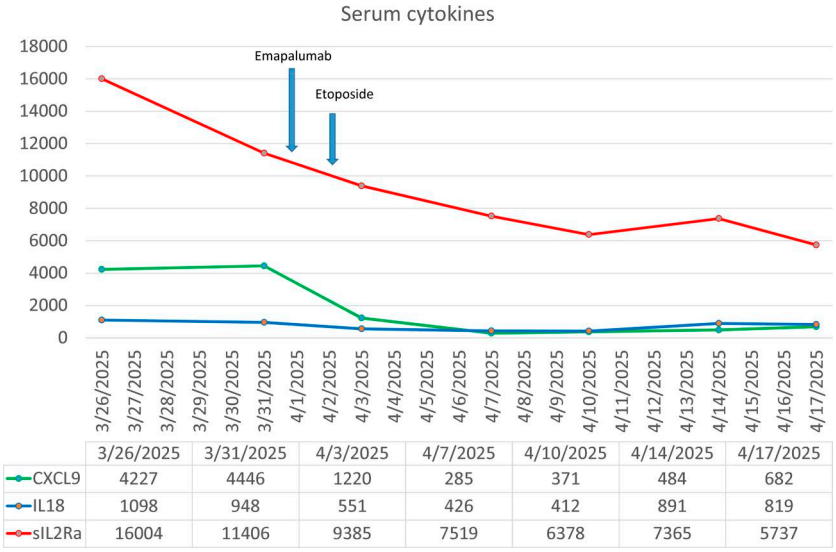
[1]UPMC Children's Hospital of Pittsburgh

A 12-day-old full-term (FT) male presented with one day of diarrhea and respiratory distress. The exam was notable for hypothermia, tachycardia, and hypoxemia. Initial bloodwork showed leukopenia (3,400 cells/uL, absolute neutrophil count [ANC] 710 cells/uL, absolute lymphocyte count [ALC] 1,460 cells/uL), thrombocytopenia (56 cells/uL), C-reactive protein (CRP) >19, procalcitonin 5.2, hyponatremia (126), and hypoalbuminemia (2.0). Chest x-ray revealed bilateral patchy opacities. Broad-spectrum antibiotics were initiated, and an extensive infectious workup was unrevealing. Within 24 hours, he required extracorporeal membrane oxygenation. On day 4, plasmapheresis was initiated. A reticular non-blanching rash developed. Intravenous (IV) methylprednisolone and IV immunoglobulin (IVIG) were started. Quantitative immunoglobulins and complements were normal. Lymphocyte subsets (CD3/4/8/19/56) showed a global reduction in absolute counts. Cytokine testing was notable for: CXCL9: 4,227 (ref:<769 pg/mL), IL-18: 1,098 (ref:82-344 pg/mL), IL-2RA, soluble: 16,004 (ref:325-1,785 pg/mL), IL-6: 6,407 (ref:<=9), IL-8: 10,505 (ref:<=7), and INF-y: 7 (ref:<=1) (Figure 1). Whole genome sequencing (WGS) identified a maternally inherited hemizygous variant of uncertain significance (VUS) in dedicator of cytokinesis 11 (DOCK11) c.4096 C>T p.(R1366W), predicted to be deleterious on in silico analysis (Figure 2). Treatment was escalated to anakinra, emapalumab, and etoposide with serologic improvement (Figure 1) and rash resolution. Legionella was identified on blood culture through Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) and confirmed with bronchoalveolar lavage (BAL). A second treatment course of levofloxacin was initiated, but unfortunately, his lung disease progressed with diffuse alveolar hemorrhage. Extracorporeal membrane oxygenation (ECMO) complications required premature decannulation and ultimately death.



	3/26/2025	3/31/2025	4/3/2025	4/7/2025	4/10/2025	4/14/2025	4/17/2025
CXCL9	4227	4446	1220	285	371	484	682
IL18	1098	948	551	426	412	891	819
sIL2Ra	16004	11406	9385	7519	6378	7365	5737

Figure 1.

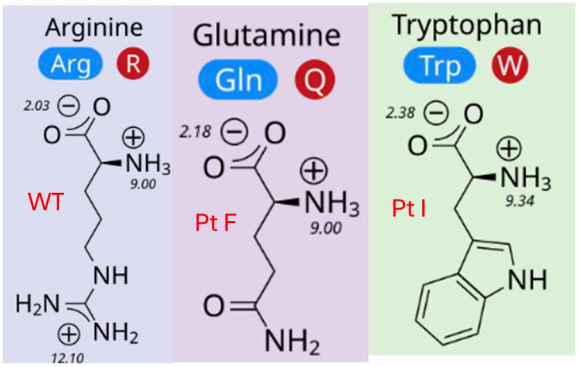


Figure 2. The first panel is the WT amino acid (AA) at 1336. The second panel is a patient reported with a pathogenic variant leading to AA substitution with glutamine, a similarly sized polar uncharged amino acid. The third panel is our patient, with a variant leading to AA substitution with tryptophan, a larger and hydrophobic AA.

DOCK11 is an activator of CDC42, a central regulator of actin cytoskeleton dynamics in hematologic cells. DOCK11 deficiency is an actinopathy resulting in impaired hematologic cell structure and function. Fewer than 20 cases have been reported. Complete loss of function is associated with a severe autoinflammatory phenotype and high-mortality risk. Partial loss-of-function is associated with polyautoimmunity and early-onset inflammatory bowel disease (IBD). Legionella is an extremely rare opportunistic organism in the first few months of life, even in those with immunodeficiency or structural lung disease. However, *Legionella* is an intracellular pathogen and inhibits the actin cytoskeleton. This double hit may have resulted in persistent disseminated infection and the state of cytokine storm.

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A Case Report of Serum Sickness Following Administration of Equine Anti-Thymocyte Globulin in a Patient with Severe Aplastic Anemia.

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Serum sickness is an immune complex-mediated hypersensitivity reaction, classically manifested by the triad of fever, rash, and arthralgias. It results from the formation and deposition of antigen–antibody complexes, leading to complement activation and small-vessel inflammation. Agents that commonly provoke serum sickness are heterologous proteins such as animal serums, antivenoms, and certain vaccines. The reaction typically occurs 7–21 days after antigen exposure, with resolution of symptoms within 2–3 weeks. Primary management is the discontinuation of the offending agent. Moderate reactions may be treated with steroids, while rare but severe reactions may necessitate hospitalization and/or plasmapheresis.

Herein, we present a 61-year-old male patient from Colombia with no previous medical history, who was diagnosed with severe aplastic anemia while undergoing a pancytopenia workup. He was admitted for initial therapy with equine anti-thymocyte globulin (ATG), cyclosporine, and eltrombopag. Post-discharge, he followed up in clinic with wrist pain and adenopathy and was prescribed Augmentin, only to be admitted the following day for neutropenic fever, rash, and worsening polyarthralgia. Symptoms resolved rapidly with supportive care alone. Following a thorough infectious workup and dermatology evaluation, the patient was discharged on a prolonged oral steroid taper with a diagnosis of serum sickness secondary to ATG therapy.

Serum sickness presents with nonspecific symptoms, and while objective data can be used to support a diagnosis, no standardized diagnostic criteria exist. Additionally, susceptible patient populations often harbor immuno-compromising comorbidities. Therefore, the initial differential should be broad, including infectious, autoimmune, and other drug-related etiologies, including serum sickness-like reaction (SSLR) and Stevens-Johnson syndrome (SJS). In this case, the timing of symptoms following ATG exposure and the absence of alternative infectious or autoimmune causes supported the diagnosis. Given the often self-limiting nature of the disease process, suppression of the immune system with steroids should only be initiated in the setting of sufficient infectious rule out and high clinical suspicion.

Furthermore, offending agents should be permanently discontinued given the risk of life-threatening reactions like anaphylaxis upon re-exposure.

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A De Novo Missense Variant in DKC1 Leading to Hoyeraal-Hreidarsson Syndrome

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Hoyeraal-Hreidarsson syndrome (HHS) represents the most severe form of dyskeratosis congenita (DC), a telomere biology disorder caused by pathogenic variants in genes involved in telomere maintenance. DKC1 encodes dyskerin, a component of the telomerase ribonucleoprotein complex. HHS typically presents with intrauterine growth retardation, microcephaly, cerebellar hypoplasia, developmental delay, bone marrow failure, and immunodeficiency.

A 12-month-old boy was admitted with failure to thrive and acute respiratory failure. His history included prematurity, intrauterine growth restriction, microcephaly, cerebellar vermis hypoplasia, and global developmental delay. Examination revealed profound growth failure (<0.01st percentile) without nail dysplasia, oral leukoplakia, or reticular skin hyperpigmentation. He tested positive for rhinovirus/enterovirus and adenovirus, complicated by adenoviremia. Laboratory evaluation showed pancytopenia and hypogammaglobulinemia. Bone marrow biopsy was negative for malignancy. Vaccine titers to tetanus, diphtheria, and pneumococcus were non-protective. Lymphocyte phenotyping revealed mild T cell lymphopenia with severely reduced B and natural killer (NK) cells; naïve-to-memory T cell ratios were normal. T cell proliferation to PHA was mildly decreased, and the T cell receptor repertoire was polyclonal.

He received intravenous immunoglobulin and prophylactic antimicrobial therapy with pentamidine, acyclovir, and fluconazole. Genetic testing identified a hemizygous DKC1 missense variant, c.229A>G (p.Asn77Asp), absent in his mother, confirming a de novo origin. Telomere length analysis demonstrated critically short telomeres (<1st percentile) across lymphocyte and granulocyte subsets. The patient recovered from acute illness with hematologic improvement and was discharged for outpatient bone marrow transplant (BMT) evaluation. Current concerns center on persistent feeding difficulties and poor weight gain. This case describes a novel de novo DKC1 missense variant associated with classical features of HHS. It underscores the early presentation of severe telomere biology disorders before the full mucocutaneous triad of DC is evident. Recognition of HHS in infancy is essential for anticipatory management of marrow failure and immunodeficiency and to guide the timing of hematopoietic stem cell transplantation.

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A Novel De Novo KMT2D Genetic Variant in Kabuki Syndrome: A Case Report

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Introduction: Kabuki syndrome (KS) is a rare, complex, multisystem, neurodevelopmental congenital disorder with characteristic phenotypic anomalies and pathogenic genetic variants of the KMT2D or KDM6A genes. KS is highly associated with dysregulation of terminal B cell differentiation, frequently leading to humoral immune deficiency and immunodysregulation. We present a novel heterozygous, de novo, pathogenic variant of KMT2D, c.6761del (p.N2254Tfs*10), identified on clinical trio whole-exome sequencing (WES) in a 7-month-old male with a recent KS diagnosis.

Case Presentation: A 7-month-old male, born prematurely at 33 weeks gestation, requiring prolonged neonatal intensive care unit (NICU) stay, with complex cardiac history including pulmonary atresia, ventricular septal defect status post-patent ductus arteriosus stenting, and pulmonary hypertension, initially admitted 3 months prior for management of severely excoriated diaper dermatitis, transferred to the pediatric cardiac ICU since, for chronic hypoxemic respiratory failure necessitating recent tracheostomy placement and mechanical ventilation, with recurrent bacterial tracheitis. He had been on dual antibiotic therapy for the management of persistent *Serratia marcescens* and *Pseudomonas aeruginosa* tracheitis and pneumonia. WES showed a pathogenic heterozygous KMT2D variant associated with KS, prompting a immunology consultation. Initial immune evaluation identified hypogammaglobulinemia, with serum IgG 127 mg/dL, mildly elevated IgA 67 mg/dL, and normal IgM 91 mg/DL. Intravenous immunoglobulin was initiated at 500 mg/kg every 4 weeks, with plans for close outpatient monitoring.

Discussion: KS is a rare, multisystem congenital neurodevelopmental disorder typically diagnosed between 3 and 12 years old, when its craniofacial anomalies become more recognizable. Our patient's prolonged hospitalization for management of complex congenital heart disease, chronic respiratory failure, and recurrent bacterial infections prompted inpatient genetics evaluation, which revealed KS with a novel KMT2D pathogenic variant. Our patient's hypogammaglobulinemia is a common humoral immune defect among patients with KS. His history of complex cardiopulmonary disease and recurrent bacterial infections prompted early genetics evaluation, with the identification of a novel variant associated with KS and prompt initiation of immunoglobulin replacement therapy for hypogammaglobulinemia. Initial and serial clinical immune evaluations are advised for all patients with known KS to offer early intervention and prevent sequela.

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A Novel IL6ST Variant in an Adolescent with Recurrent Abscesses and Eczema Treated with Dupilumab

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We present the case of a 17-year-old male with a long-standing history of recurrent and persistent cutaneous abscesses beginning at 6 years of age. Lesions were widespread, affecting the scalp, trunk, buttocks, and extremities, and characterized by painful, indurated nodules that drained purulent fluid spontaneously and resolved over 5–10 days, often with pruritus and residual scarring. He denied fevers or other systemic symptoms. Multiple antibiotic courses provided no sustained improvement. A punch biopsy at age 14 years demonstrated a suppurative granulomatous infiltrate. Bacterial cultures grew *Staphylococcus aureus* on two occasions, while fungal and Acid-Fast Bacillus (AFB) cultures remained negative. Partial clinical improvement on rifampin and azithromycin raised suspicion for an atypical acid-fast bacillary infection and potential underlying immunodeficiency; however, repeat cultures for nontuberculous mycobacteria were persistently negative, and the diagnosis was not confirmed.

Past medical history was also notable only for several otitis media episodes as a child. There was no history of pneumonia, fractures, dysmorphic features, delayed dentition, joint hypermobility, candida infections, or childhood eczema. Family history included severe acne and recurrent boils in the father, atopic disease in the mother, and two healthy siblings.

Immunologic evaluation revealed normal lymphocyte subsets, intact mitogen and antigen proliferation responses, normal neutrophil oxidative burst, and normal quantitative immunoglobulins. He had adequate vaccine responses to protein and polysaccharide antigens. IgE was markedly elevated at 6,757 IU/mL with mild eosinophilia.

A comprehensive primary immunodeficiency genetic panel identified a variant of uncertain significance in IL6ST at c.1405G>C (p.Asp469His), a gene associated with autosomal-dominant and autosomal recessive Hyper-IgE syndrome. This missense variant is absent from population databases and has not been previously reported in individuals with IL6ST-related disease. It is population frequency on gnomAD (v4.1.0) is 0.0000006199, Combined Annotation Dependent Depletion (CADD) score of 25.9, and a PolyPhen score of 0.940 (which categorizes it as probably damaging).

He subsequently developed atopic dermatitis involving the scalp and flexural regions of his extremities. Although never used in patients with IL6ST, dupilumab was initiated in light of emerging evidence that it can lead to marked improvement in cutaneous and systemic symptoms in select Hyper-IgE phenotypes. His clinical response is being closely monitored.

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A Novel Intronic Deletion Causing "Deficiency in ELF4, X-Linked"

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Deficiency in ELF4, X-linked (DEX) is a monogenic autoinflammatory disorder caused by loss-of-function (LOF) mutations in the ETS transcription factor ELF4. This rare disorder primarily affects young, male patients due to its X-linked expression. To date, the genetic aberrations causing disease in these patients have been (1) nonsense mutations leading to premature stop codons and a loss of ELF4

protein expression, and (2) missense mutations abrogating DNA-binding activity of ELF4. Here, we describe the case of an 11-year-old male harboring a de novo four-nucleotide deletion in the splice donor region following exon 5 (NM_001421.3:c.532+3_532+6del), which was discovered via trio whole-exome sequencing. The patient presented with characteristic DEX symptoms, including periodic fevers, oral ulcers, arthritis, and Crohn's disease. The mutation was confirmed at the DNA level via nanopore sequencing of the genomic region surrounding exon 5 of ELF4, and subsequent analyses of patient-derived peripheral blood mononuclear cells (PBMCs) revealed a loss of ELF4 protein expression, confirming that this patient suffers from DEX. Predictions of splicing outcomes caused by this variant suggested the possibility of partial intronic retention causing a frameshift and ultimately leading to a premature stop codon. RNA sequencing on patient-derived CD4+ and CD8+ T cell blasts confirmed the predicted splicing outcome, as well as a significant decrease in ELF4 transcript expression, likely due to nonsense-mediated decay. Here, we describe the first DEX patient with a de novo deletion in an intronic region of ELF4 that leads to a loss of ELF4 protein expression and autoinflammatory disease.

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A Single Institution Experience with Pediatric Hemophagocytic Lymphohistiocytosis (pHLH)

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Introduction: Pediatric hemophagocytic lymphohistiocytosis (pHLH) is a life-threatening condition characterized by aberrant immunopathology and systemic manifestations. The HLH-2004 protocol prioritizes urgent immunosuppressive therapy; however, timely diagnosis can be challenging due to rarity and symptom overlap with other pediatric pathologies. This study examines the outcome of pHLH at a tertiary care children's hospital in Canada and aims to identify gaps to inform an institutional protocol.
Methods: This retrospective cohort study reviewed medical records of pHLH at a Canadian tertiary care children's hospital between 2014 and 2025. Patients were identified using International Classification of Diseases (ICD) 10 diagnostic codes on discharge diagnosis and cross-referenced with oncology, immunology, and rheumatology clinic lists. Descriptive statistics were collected for the first admission with pHLH.
Results: Nineteen patients met the inclusion criteria. The median age at presentation was 7 years (range: 1–16). Of these patients, 3 cases were primary HLH, and 16 were secondary. Secondary causes included infections (3/19, 16%), inflammatory/rheumatologic conditions (10/19, 53%), and malignancy (3/19, 16%). The mean length of stay was 44 days, and 10 patients required pediatric intensive care unit (PICU) admission (mean: 5 days). Overall mortality was 21% (4/19). Diagnosis and treatment were initiated an average of 7 days after presentation (range: 1–26). Nine patients met 2004 HLH criteria, 7 patients were considered to have macrophage activation syndrome (MAS), and the remaining 3 had an overlap presentation or post-mortem confirmation of diagnosis. Treatments included HLH-2004 protocol (5/19, 26%), high-dose/pulse methylprednisolone (8/19, 42%), solely dexamethasone/prednisone (5/19, 26%), intravenous immunoglobulin (IVIG) (7/19, 37%), and small molecule immunomodulation (anakinra, tocilizumab, alemtuzumab, and rituximab) (7/19, 37%). Three patients received a hematopoietic stem cell transplant (HSCT), 2 of these being primary HLH cases—both died from complications. The final primary HLH case remains awaiting HSCT. Among secondary cases, 1 patient received HSCT and another was scheduled, but died prior to. Seven patients experienced recurrence, with 4 readmitted more than 3 times.
Conclusion: Despite prompt diagnosis among inpatients, HLH is a high-mortality condition. Patients with secondary conditions that were identified and treated showed considerable improvement without the use of the HLH 2004 protocol. These findings will help inform institutional diagnostic and treatment protocols for HLH.

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A Truncating NFKB1 Variant Presenting with Recurrent, Sterile Wound Inflammation, and Hypogammaglobulinemia

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The nuclear factor kappa light-chain enhancer of activated B cells (NFKB1) pathway is a central regulator of inflammatory gene expression. NFKB1 haploinsufficiency can present with common variable immunodeficiency (CVID) and autoimmunity. Recent publications report patients with necrotizing soft tissue inflammation who had truncating monoallelic loss-of-function variants in NFKB1.

We present a case of a 17-year-old male who had multiple episodes of sterile inflammatory responses to surgery or trauma in addition to recurrent infections. As an infant in the neonatal intensive care unit, he developed nasal columella erosion attributed to nasal respiratory support interfaces. At 15 years old, he underwent nasal reconstruction with a right ear graft that failed by 3 months postoperatively, resulting in nasal tip collapse and obstruction. A concurrent inguinal hernia repair was complicated by fevers and a purulent yet sterile abscess at the surgical site. Eight months later, reconstruction of the full-thickness columellar defect with left ear composite cartilage and cutaneous graft was complicated by a large, nonhealing graft site skin ulcer that was unresponsive to antibiotics and a surgical washout. Biopsy of this wound showed extensive, deep dermal and subcutaneous neutrophilic inflammation without identification of microorganisms consistent with pyoderma gangrenosum. The aforementioned, in conjunction with a history of recurrent oral ulcers and a new purulent scrotal ulcer, was felt to be consistent with Behçet disease. He was treated with pulse dose corticosteroids with subsequent taper, adalimumab, methotrexate, and colchicine with subsequent skin healing. He continued to have intermittent oral ulcers, fatigue, and increased frequency of upper respiratory infections.

Given his atypical clinical picture, a primary immunodeficiency-focused genetic panel was obtained and revealed a heterozygous pathogenic truncating NFKB1 variant (c.909dup, p.Thr304Hisfs*5). Given published evidence of truncating NFKB1 variants leading to impaired autophagy and type I interferon and NLRP3 inflammasome-mediated autoinflammation, canakinumab was started, and adalimumab, methotrexate, and colchicine were discontinued. Intravenous immunoglobulin replacement was initiated due to newly identified CVID. Frequency of oral ulcers, upper respiratory infections, and fatigue improved over the subsequent four months.

This case illustrates the autoinflammatory phenotype of NFKB1 deficiency with early truncating variants and highlights the prospect of targeted, personalized immunomodulatory therapy.

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Allogeneic Hematopoietic Cell Transplantation for SASH3 Deficiency

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SASH3 deficiency is an X-linked combined immunodeficiency characterized by recurrent sinopulmonary, cutaneous, and mucosal infections, refractory autoimmune cytopenia, and immune dysregulation. We report here the first two cases of allogeneic hematopoietic cell transplantation (HCT) for SASH3 deficiency.

Patient 1 was a 7-year-old with a history of refractory immune thrombocytopenia (ITP) who received bone marrow from his haploidentical mother. Conditioning was with alemtuzumab, busulfan (cumulative exposure 55.7 mg*h/L), fludarabine, and total body irradiation 200cGy. Graft-versus-host disease (GVHD) prophylaxis was with post-transplant cyclophosphamide, tacrolimus, and mycophenolate mofetil. His transplant course was complicated by severe veno-occlusive disease, adenovirus and CMV reactivation, grade I acute skin GVHD responsive to topical steroids, and presumed autoimmune neutropenia that resolved with high-dose intravenous immunoglobulin. Myeloid and T cell chimerism were 100% donor at all time points, and peripheral blood CD4 and CD8 T, CD19 B, and natural killer (NK) cell counts were normal at 1 year. He is alive and well 17 months post-HCT with no recurrence of ITP.

Patient 2 was a 55-year-old with a history of recurrent sinopulmonary infections, refractory ITP, nodular regenerative hyperplasia with portal hypertension and massive splenomegaly, and chronic norovirus infection. He received peripheral blood stem cells from a matched unrelated donor after alemtuzumab, busulfan (cumulative exposure 52.5 mg*h/L), and fludarabine conditioning. GVHD prophylaxis was the same as patient 1. His transplant course was complicated by worsening of chronic norovirus, ITP flare, ultimately treated with daratumumab, and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome treated with steroids and dupilumab. He developed a fungal pneumonia while on steroids for DRESS syndrome, as well as two episodes of bacterial pneumonia. Myeloid chimerism was 100% donor through 5 months post-HCT; T cell chimerism could not be assessed, given severe lymphopenia on steroids. He ultimately died on day +185 from multisystem organ failure in the setting of *E. coli* septic shock.

In conclusion, the immune defect of SASH3 deficiency can be corrected with allogeneic HCT, and HCT may be considered for patients with severe disease manifestations. The optimal HCT regimen to ensure durable engraftment while minimizing toxicity remains to be elucidated.

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Beyond Airway Clearance: Specific Antibody Deficiency as a Driver of Refractory Sinopulmonary Disease in Primary Ciliary Dyskinesia

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Background: Primary ciliary dyskinesia (PCD) management relies on mucociliary clearance to prevent bronchiectasis. While humoral immunodeficiencies have been reported in PCD, their clinical significance remains under-defined. We hypothesize that co-occurring specific antibody deficiency (SAD) creates a "refractory phenotype" where mechanical clearance alone is insufficient, necessitating additional treatment.

Case Description: We describe three pediatric patients with PCD, defined by genetics or persistent low nasal nitric oxide, who experienced recurrent exacerbations despite adherence to maximal airway clearance. Patient 1 (13-year-old female) developed recurrent and severe pneumonias 1–2 times per year and chronic wet cough, leading to suspicion for PCD. Testing revealed duplicate low nNO, although PCD genetics and cilia brushings were unrevealing. Immune evaluation revealed low IgA and non-protective pneumococcal titers, requiring immunoglobulin replacement therapy (IGRT). Patient 2 (18-year-old female) presented with congestion since birth and multiple episodes of pneumonia. The diagnosis of PCD was made by low nNO and genetic testing positive for two pathogenic mutations in CCDC65. Despite aggressive clearance and antibiotic prophylaxis, she had multiple admissions for breakthrough infections and declining pulmonary function. Workup revealed non-protective pneumococcal titers despite adequate vaccination. Initiation of IGRT and antibiotic prophylaxis improved her clinical status.

Patient 3 (17-year-old female) presented with chronic cough, sinusitis, and pneumonias from encapsulated organisms, frequently requiring intravenous antibiotics. She was found to have bronchiectasis and low nNO, nondiagnostic ciliary biopsy, and genetic testing confounded by chimerism. Inadequate post-booster pneumococcal titers suggested concomitant SAD that improved following initiation of antibiotic prophylaxis.

Discussion: These cases illustrate a unique phenotype of "treatment-refractory" PCD, characterized by breakthrough infections despite optimal clearance, warranting immune evaluation. All three patients were diagnosed with SAD and are routinely monitored for evolving humoral defects. Mechanical clearance addresses the mucociliary defect but fails to compensate for the lack of opsonization in concomitant SAD. Identification of this comorbidity allowed for targeted therapy (IGRT, prophylactic antibiotics) to stabilize pulmonary decline and improve quality of life. Thus, we recommend screening for humoral defects in PCD patients with recurrent infections despite adequate PCD supportive care.

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Caregivers of Children with APDS Balance Complex Medical Care, Family, and Work Responsibilities

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Rationale: Activated PI3K delta syndrome (APDS) is a rare primary immunodeficiency disease (PID) characterized in 2013. Caregivers of children with APDS juggle management of complex medical needs with family and work responsibilities. When their child gets sick, the balance is lost. Understanding the needs of caregivers and children living with APDS is important to help ensure resources and support needed are available.

Methods: Six caregivers of children ages 3–9 living with APDS participated in a virtual advisory board meeting in 2025. The meeting included polls, a chatroom, and pre-meeting questions.

Results: Caregivers reported their children experienced a broad-spectrum of APDS symptoms, with a combined total of 28 different symptoms. Recurrent infections were mostly commonly reported as impacting family life. Patients struggled with developmental delays; the most noted was speech delay (3). Four caregivers reported behavioral issues when their children experienced APDS symptoms of fatigue, illness, and speech/communication challenges. Issues included irritability (4), self-harm (2), and hitting other children (1). Two

were on intravenous immunoglobulin (IVIG) treatment, and parents noted increased irritability and behavior issues when the child was due for treatment. Caregivers were concerned about their children missing social interactions and social connections. For many, fatigue was a limiting factor in children's participation in social activities. Two caregivers reported frequent school absences; one child missed 65 school days. Missed work was a top challenge for some (3), while others had flexible work schedules that better accommodated frequent appointments and illness. Caregivers felt they needed to be available "constantly" and "immediately" for when their child got sick. Caregivers ranked worry as a top challenge as well. The constant worry their child will get sick, the stress of managing care, and the day-to-day responsibilities of caring for a child with APDS weigh heavily on caregivers.

Conclusions: Parents of children with APDS need information/support targeted at early intervention to help address speech delays, social-emotional needs, and behavioral issues. The needed resources and support identified were educational materials for children with APDS, opportunities for connection to other caregivers, and information about Family and Medical Leave Act (FMLA) and other legal protections for caregivers and their children.

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Chronic Spontaneous Urticaria with Angioedema Refractory to Standard Therapy: Insights Into the Protean Nature of a Common Presentation

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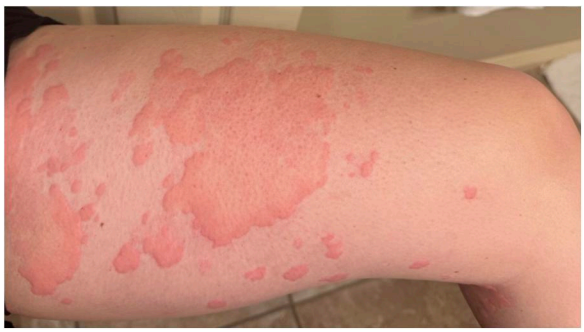
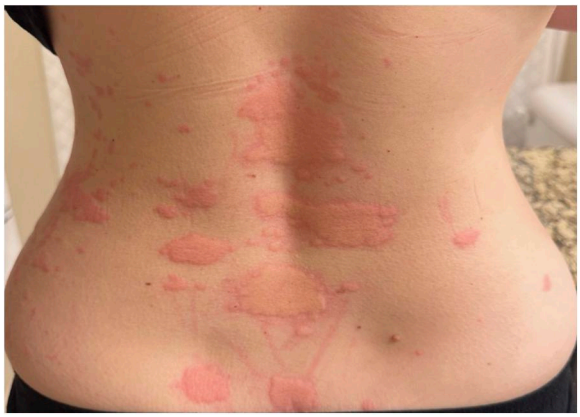
[1]ACH/UAMS

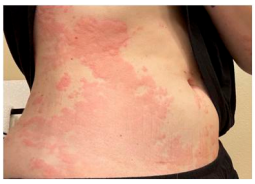
Introduction: Chronic spontaneous urticaria (CSU) is a clinical diagnosis managed according to American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) guidelines, which recommend high-dose second-generation antihistamines as first-line therapy, followed by biologics such as omalizumab, dupilumab, and, more recently, remibrutinib for refractory disease.

When patients fail standard and advanced therapies or develop systemic features, the differential diagnosis should expand to include autoimmune and autoinflammatory disorders. We present a case of refractory chronic urticaria with angioedema in which failure of multiple therapies and subsequent response to anakinra suggest an autoinflammatory component.

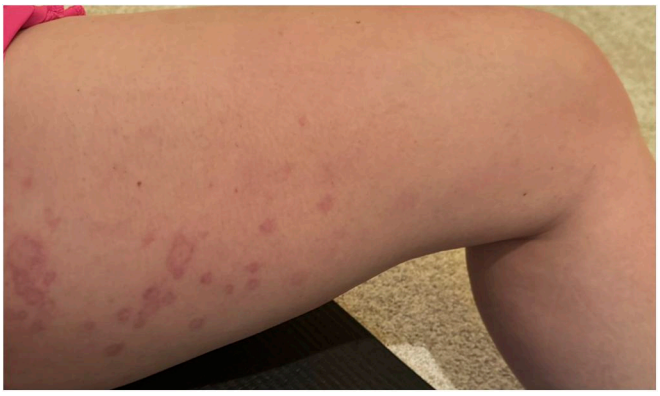
Case Presentation: A 34-year-old woman with no significant past medical history presented with a three-month history of recurrent urticaria (Figures 1–3). Initial treatment with high-dose antihistamines, H2 blockers, leukotriene antagonists, and systemic corticosteroids provided only transient relief. Omalizumab was initiated with minimal response, and cyclosporine was added for steroid-dependent disease, but discontinued due to alopecia. Skin biopsy demonstrated a superficial and interstitial dermal infiltrate predominantly composed of neutrophils, with scattered eosinophils and lymphocytes, and no evidence of vasculitis; direct immunofluorescence was normal. Laboratory evaluation, including complete blood count (CBC), erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP), tryptase, and serum protein electrophoresis, was unremarkable. A chronic urticaria index of 18.8 supported type IIb chronic spontaneous urticaria (CSU). Given the neutrophilic predominance on biopsy, dapsone and colchicine were trialed without improvement. The patient continued to experience severe flares requiring recurrent high-dose corticosteroids, resulting in steroid-induced metabolic syndrome requiring treatment with a GLP-1 receptor agonist. Additional therapies, including hydroxychloroquine, tacrolimus, and dupilumab, were ineffective. Lesions were annular and resolved with post-inflammatory hyperpigmentation (Figures 4 and 5).

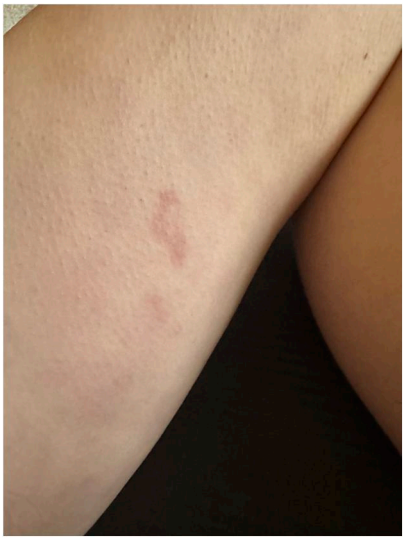






Figures 1–3. **Urticaria affecting the leg, upper and lower back, and abdomen, shown in Figures 1–3, respectively.**





Figures 4 and 5. **Postinflammatory hyperpigmentation affecting the thighs and legs.**

Based on histopathologic features and clinical refractoriness, daily anakinra was initiated, leading to marked improvement with near-complete resolution of urticaria and angioedema, though low-dose alternate-day prednisone remained necessary. Subsequent initiation of remibrutinib allowed for complete discontinuation of systemic corticosteroids. Informed consent for publication was obtained from the patient.

Discussion: This case highlights the heterogeneity underlying chronic urticaria. Neutrophil-predominant infiltrates, steroid dependence, and response to IL-1 blockade suggest an autoinflammatory mechanism rather than classic CSU.

Conclusion: In patients with refractory urticaria, neutrophilic histopathology, and systemic features, clinicians should consider auto-inflammatory syndromes and neutrophilic urticarial dermatoses, for which IL-1–targeted therapies may be more effective than standard CSU treatments.

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Clinical and Genetic Spectrum of Pyrinopathies in Brazilian Patients: Insights from the First Year of the CNE3i National Cohort

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Although Brazil has experienced substantial immigration from the Middle East and Italy, regions with a higher prevalence of pyrin-associated autoinflammatory diseases, pyrinopathies, remain under-investigated in the country. Through a national collaborative effort, the Centro Nacional de Erros Inatos da Imunidade e Imunodesregulação (CNE3i) has systematically collected data on pyrinopathies across Brazil since 2024. Here, we report the first-year dataset from CNE3i on pyrinopathies, highlighting their genetic diversity and clinical presentation within the Brazilian population. In this first-year report, we describe 47 individuals with pyrin-related diseases. Overall, 53% were female (n = 23), with a mean current age of 27 years (range 2–74). Most of them were from the state of São Paulo, and just one was a Syrian refugee. Consanguinity was documented in 4 families.

Among the patients for whom clinical information was available, periodic fever was the most common finding, present in 96.3% (n = 26/27), with 73.3% (n = 11/15) experiencing more than five episodes per year. Additionally, mucocutaneous involvement was observed in 64.5% (n = 20/31), arthralgia in 61.4% (n = 14/17), lymphoid involvement in 34.5% (n = 10/29), and thoracic pain in 84.1% (n = 6/7). The top three MEFV variants identified were those located at positions 744 (n = 5), 694 (n = 5), and 369 (n = 4) of the protein. One-third (n = 13; 27%) harbored biallelic mutations, and three patients, all with adult-onset disease and most (n = 2) with AAA (AA amyloidosis), were genetically negative through genome sequencing. Half of the individuals achieved a complete clinical and laboratory response with colchicine (n = 28; 59%). Biologics (anti-TNF, anti-IL6, and anti-IL1) were required for 31% (n = 15), whereas AAA was found in 12% (n = 6). Just one patient with a kidney-related AAA had a completely satisfactory response to colchicine. The results are summarized in the supplementary table. The initial findings regarding MEFV-related autoinflammatory diseases (commonly referred to as pyrinopathies) reflect the complex ancestry of the Brazilian population, with the most frequently found variants associated with Jewish (p.694) and Arab, Turkish, and Cypriot (p.744) ancestries. Moreover, we also noted a slightly higher frequency of AAA (usually 8.6%), which may be a result of delays in diagnosis of epigenetic interactions for the MEFV gene in the Brazilian population, such as gastrointestinal microbiota.

Tabular data are included as downloadable supplement files.

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Clinical Implications of Baseline-Corrected Total Immunoglobulin G Levels: Pharmacokinetic Data from a Phase 3, Open-Label Study of Patients with Primary Immunodeficiency Disease Treated with fSCIG 10%

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Dosing immunoglobulin G (IgG) replacement therapy in primary immunodeficiency disease (PIDD) depends on IgG pharmacokinetics (PK) and patients' clinical status. Conventionally, PK data used to determine dosing were based on total IgG levels, comprising both endogenous and exogenous IgG. However, this may overestimate IgG half-life (t1/2), which is a key parameter in determining steady-state IgG PK that informs dosing.

We assessed the PK and clinical implications of baseline correction of IgG in patients with PIDD receiving facilitated subcutaneous immunoglobulin (fSCIG) 10%, a hyaluronidase-facilitated subcutaneous IgG approved for PIDD.

PK data were analyzed for a subgroup of patients with PIDD (aged ≥12 years) receiving fSCIG 10% in a phase 3, open-label study (NCT00814320). Endogenous IgG levels were estimated from baseline values (before IgG infusion). Exogenous IgG levels were calculated by subtracting individual baseline IgG concentrations from measured IgG concentrations at each time point. Noncompartmental analysis (Phoenix WinNonlin version 8.5) was used for PK assessment and PK parameter calculation.

Baseline correction produced marked changes in mean (±SD) IgG PK parameters compared with uncorrected values: maximum plasma concentration (469 [±269] vs. 1,607 [±382] mg/dL) and area under the curve/week (13.4 [±12.0] vs. 89.7 [±22.9] g·days/L) were substantially reduced, reflecting exclusion of endogenous IgG. Mean (±SD) estimated IgG t1/2 showed clinically relevant reductions (baseline corrected, 8.9 [±7.3] days; uncorrected, 55.0 [±30.3] days). While baseline correction remains an approximation owing to individual fluctuations in endogenous IgG levels, it provides a more specific indication of exogenous IgG elimination. Given the shorter t1/2, steady-state IgG after fSCIG 10% initiation would be expected to be achieved within ∼3 months, conservatively, significantly earlier than the currently assumed 6-month period and consistent with other IgGs.

Baseline-corrected PK offers a practical estimation of exogenous IgG elimination for fSCIG 10%. Used alongside uncorrected PK, it provides better characterization of IgG PK. Baseline-corrected PK suggests steady-state IgG would be achieved within ∼3 months. Endogenous IgG variability and limitations of baseline correction should be acknowledged in clinical decision-making. Comprehensive dosing strategies should integrate PK approaches with patient-specific factors.

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Clinical Implications of Concurrent Heterozygous LRBA and RTEL1 Variants: A Case Study

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We present the case of a 43-year-old male who presented to pulmonology with 3 years of chronic cough and recurrent sinopulmonary infections. He was diagnosed with bronchiectasis and found to have mild thrombocytopenia and agammaglobulinemia (IgG 44 mg/dL, IgA and IgM undetectable). Further immunologic evaluation revealed normal lymphocyte subsets (T/B/NK), decreased class-switched memory B cells, and low specific antibody titers, consistent with common variable immune deficiency (CVID). Genetic testing identified heterozygous likely pathogenic variants in LRBA (c.216+1G>C) and RTEL1 variant (c.2869C>T; p.R957W). Patient's father was diagnosed with pulmonary fibrosis and carried the same variants. Patient's telomeres were <1st percentile in all leukocyte subsets.

Comprehensive organ evaluation of the patient revealed bone marrow hypocellularity, increased liver stiffness (9.6 kPa), further supporting a diagnosis of an inherited telomere biology disorder. Mature bone marrow plasma cells were essentially absent. CT chest showed interstitial changes most consistent with granulomatous lymphocytic interstitial lung disease (ILD) related to CVID. Additionally, he was found to have an expanded CD21lo B cell population (16.8%, risk ratio [RR] 0.2–8.6%) and an increased follicular helper T cell count (46%, RR 4–23%) for which a trial of abatacept has been suggested.

The two genetic variants in this case are noteworthy. The RTEL1 variant, short telomeres, cytopenia, hepatic fibrosis, and ILD are consistent with a telomere biology disorders (TBD) phenotype, though ILD and cytopenias can also be seen in CVID. However, while RTEL1 has been linked to hypogammaglobulinemia, it is usually in the setting of decreased B/T/NK cell numbers and bone marrow failure, not present in this case. While the clinical significance of the heterozygous LRBA variant remains uncertain, the numerous features of the patient's presentation mirror those seen in LRBA deficiency (hypogammaglobulinemia, lymphoproliferation, elevated CD21lo B cells, and elevated follicular helper T cells). This raises the provocative possibility of a digenic model to explain the patient's disease—with telomere dysfunction due to the RTEL1 variant exacerbating the immunologic aberrations of heterozygous loss of LBRA. Alternatively, the patient may have a second unidentified deleterious LBRA variant and additional genetic and functional testing is underway to evaluate this possibility.

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Combined B Cell Aplasia and Hypereosinophilia as a Complication of Lamotrigine Therapy

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Background: Although drug rash with eosinophilia and systemic symptoms (DRESS) and anticonvulsant hypersensitivity syndrome are well-known complications of anti-seizure medications (ASMs), lesser-known immunologic complications, including B cell loss and hypogammaglobulinemia, have been reported. Historically, the etiology and natural history of ASM-induced B cell injury have been incompletely understood.

Case: An otherwise healthy 20-year-old female with minimal infectious history presented with acute fatigue, fever, and upper respiratory tract infection symptoms. She had initiated lamotrigine therapy two months prior. One week after symptom onset, she developed severe abdominal pain and presented emergently to an outside hospital. Imaging demonstrated acute splenic infarction, with labs notable for leukocytosis, eosinophilia, lymphocytosis, near-absent B cells, and borderline low IgG. She was initiated on enoxaparin, but within five days developed a second splenic infarction and new maculopapular rash. The patient transitioned to rivaroxaban and was discharged home. The patient's condition progressed to include cough, mucositis, diarrhea, and unintentional weight loss, prompting admission for expedited workup.

Labs demonstrated new hypereosinophilia, with complete B cell aplasia and progressive immunoglobulin loss. Endoscopy revealed absent B cells and plasma cells throughout the small and large intestine. Bone marrow biopsy demonstrated near-complete loss of B cell precursors and mature B cells alike, with rare detectable plasma cells. Cytokine studies demonstrated elevated sIL-2R, CXCL9, IL-5, and IL-13. PET-CT was without evidence of malignancy. Whole genome sequencing (WGS) was negative for variants concerning inborn errors of immunity, but revealed a likely pathogenic heterozygous SLC4A1 variant compatible with hereditary spherocytosis. An extensive infectious disease workup was negative.

The patient tapered off lamotrigine, initiated immunoglobulin replacement, and completed two doses of mepolizumab, with significant symptomatic improvement. In the months following discharge, the patient has demonstrated recovery of B cell counts with evidence of emerging class switching and humoral output, without recurrence of eosinophilia.

Discussion: Drug hypersensitivity syndromes, B cell loss, and hypogammaglobulinemia may occur following ASM therapy. This case demonstrates for the first time that the mechanism may involve loss of developmentally diverse B cell populations, including precursors, mature B cells, and plasma cells across multiple compartments. Importantly, we observed B cell recovery after discontinuation of lamotrigine, suggesting that this loss may be reversible.

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Combined Immunodeficiency Manifests from S-Adenosylhomocysteine (SAH) Hydrolase Deficiency

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S-adenosylhomocysteine (SAH) hydrolase deficiency is a rare autosomal recessive disorder caused by pathogenic variants of the gene AHCY. Loss of SAH hydrolase causes SAH accumulation and impairs the methionine/S-adenosylmethionine (SAM) cycle that is integral to methylation reactions throughout the body. SAH hydrolase deficiency has been described in 16 patients with clinical features including intellectual disability, developmental delay, hypotonia, early mortality, and liver dysfunction. Although no immunologic sequelae have been previously noted, we report a 6-year-old boy with SAH hydrolase deficiency manifesting as combined immunodeficiency (CID).

Our patient had a longstanding diagnosis of SAH hydrolase deficiency with neurological manifestations including hypotonic quadriplegia, chronic static encephalopathy, and moyamoya vasculopathy complicated by a cerebral ischemic event. He initially presented to an outside hospital for *Klebsiella pneumoniae* sepsis and *Pneumocystis jirovecii* pneumonia (PJP). Infection history included recurrent upper respiratory infections. Following recovery, he was evaluated by our immunology department and was found to have persistent T cell lymphopenia (197; 700–4,200) with low numbers of CD4+ (97; 300–2,000) and CD8+ (90; 300–1,800) T cells, natural killer (NK) cells (45; 90–900), and B cells (70; 200–1,600). T cell receptor spectratyping demonstrated oligoclonal T cells and normal proliferative responses to anti-CD3. Humoral evaluation demonstrated hypogammaglobulinemia with normal IgA, IgM, and IgE, but absent vaccine responses. He was started on PJP prophylaxis and subcutaneous immunoglobulin. Hematopoietic cell transplantation (HCT) was considered but deferred due to the patient's comorbidities.

We hypothesize that loss of SAH hydrolase in lymphocytes impairs DNA replication and gene expression changes that rely on nucleotide synthesis and DNA/histone methylation. Impairment of these processes in proliferating B and T cells could then lead to cell cycle arrest or apoptosis. This is analogous to adenosine deaminase (ADA)-severe combined immunodeficiency, where DNA synthesis is impaired in rapidly dividing T and B cells, leading to accumulation of toxic metabolites and cell death.

In summary, we report that SAH hydrolase deficiency can cause CID. This represents a novel cause of immunodeficiency and suggests that other defects in the SAM cycle might present with immunologic defects. Additional studies are needed to determine if HCT could be a treatment.

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Community Immunologist-Led Multidisciplinary Approach to Secondary Hypogammaglobulinemia in Solid Organ Transplant Recipient with Recurrent Infections

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Background: Solid organ transplantation is an effective treatment for end-stage organ diseases, including renal, hepatic, cardiac, and pulmonary failure (1). Long-term graft survival depends on sustained immunosuppression; however, chronic exposure to immunosuppressive agents can impair humoral immunity and lead to secondary immune deficiencies (2). Secondary hypogammaglobulinemia, particularly with impaired specific antibody responses, increases vulnerability to recurrent or severe infections (3). Early recognition and coordinated management can significantly reduce morbidity and healthcare utilization.

Case Description: A 67-year-old woman with a history of end-stage renal disease (ESRD) secondary to lupus nephritis, status post kidney transplant 13 years prior, was referred by the renal transplant team to a community immunologist for evaluation of recurrent infections, including *Clostridioides difficile* colitis, recurrent bacterial pneumonias, bronchitis, and sinusitis over the preceding year. Her immunosuppressive regimen—mycophenolate, tacrolimus, and low-dose prednisone—had been stable for 13 years with excellent graft function. She had no personal or family history of primary immunodeficiency.

Immunologic evaluation revealed isolated hypogammaglobulinemia (IgG 563 mg/dL) with normal IgA, IgM, and IgE. Specific antibody testing demonstrated poor response to pneumococcal vaccines (Figure 1) but preserved responses to tetanus and diphtheria. Flow cytometry showed normal natural killer (NK), CD3, and CD8 T cell counts, mildly decreased CD4 counts (157 cells/uL), and reduced CD19 B cells (7 cells/uL), attributed to her chronic immunosuppressive regimen. Findings were consistent with secondary hypogammaglobulinemia related to prolonged immunosuppression.

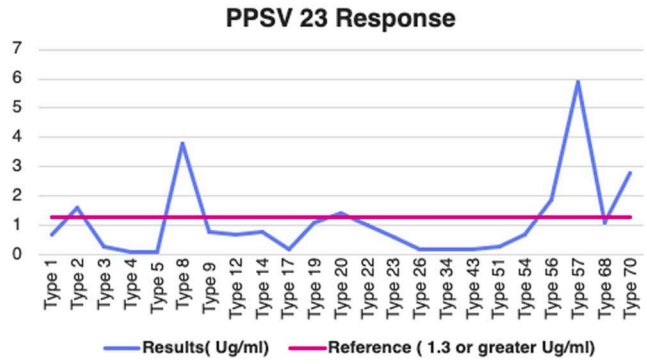

Figure 1. **Pneumococcal polysaccharide vaccine (PPSV) 23 vaccine response.**

The immunologist discussed management options with the patient and the renal transplant team. These included immunoglobulin replacement therapy (intravenous immunoglobulin [IVIG]/subcutaneous immunoglobulin [SCIG]) and/or modification of immunosuppressive therapy. Through shared decision-making, the patient opted for a dose reduction of mycophenolate (to 180 mg BID) with close monitoring. On subsequent follow-ups in the immunology clinic, her IgG levels gradually improved to 821 mg/dl (Figure 2). There was a marked reduction in infections with no further hospitalizations and stable graft function.

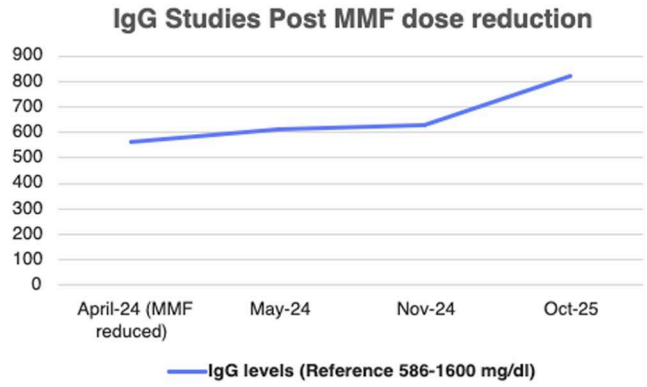

Figure 2. **IgG levels post mycophenolate mofetil (MMF) dose reduction.**

Conclusion: Secondary hypogammaglobulinemia remains an important and under-recognized cause of specific antibody deficiency in solid organ transplant recipients. Early diagnosis and timely intervention are essential to preventing recurrent and potentially life-threatening infections. This case highlights a community immunologist-led, multidisciplinary approach playing a pivotal role in identifying and managing acquired immune deficiencies, ultimately strengthening the continuum of transplant immunology care.

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COPA Syndrome and Its Many Flavors

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Introduction: Pathogenic variants in the COPA gene are associated with autosomal-dominant autoimmune interstitial lung, joint, and kidney disease, a condition known as COPA syndrome. It is associated with a type I interferon signature and with good response to JAK inhibitors in the literature. Not all variants present all the features.
Case Description: 6-year-old male with a history of recurrent pneumonia referred to immunology for bilateral leg and joint pain. For over a year, he experienced pain 3–4x per week upon awakening, which worsened with exertion. MRI showed no structural changes or evidence of arthropathy or myopathy. Orthopedics referred him to the immunology clinic for further evaluation due to the persistence of symptoms. History is also notable for 5–6 episodes of pneumonia successfully treated with outpatient antibiotics, presumed asthma, and allergic rhinoconjunctivitis. Family history is notable for a pathogenic RIPK1 variant in his sister (treated with tocilizumab) and Hashimoto's and celiac disease in his mother. His presentation and pertinent history raised concern for an inborn error of immunity, warranting further workup. Initial labs showed several signs of immunodysregulation, including a moderate type I IFN signature on a majority of Cd14bright monocytes, suggestive of a type I interferonopathy, and increased gamma delta double-negative T cells. Next-generation sequencing was obtained for further evaluation, revealing the presence of a heterozygous COPA variant, c.766G>T (p.Val256Phe). Additional autoantibody testing was negative, which would be atypical in the setting of COPA syndrome. However, given the different signs of immunodysregulation, the variant is undergoing further characterization on a research level.
Discussion: This case illustrates the importance of maintaining a broad differential to include in the presence of signs of autoimmunity and immunodysregulation. While he does not have overt kidney involvement, his arthralgias and pulmonary involvement further support the decision to explore the COPA variant with functional studies, given the potential therapeutic implications.

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Co-Segregation of Pyoderma Gangrenosum and a Heterozygous NFKB1 Variant in a Large Kindred: An Autoinflammatory CVID-Like Phenotype

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Background: Pyoderma gangrenosum (PG) is a rare ulcerative neutrophilic dermatosis that can be associated with primary immunodeficiencies. Its pathogenesis is incompletely understood, but it has been increasingly reported in a broad range of monogenic combined immunodeficiencies. NFKB1 variants are the most common genetic cause of common variable immunodeficiency (CVID), including in patients with prominent immune dysregulation, and some individuals can manifest significant autoinflammatory disease, including PG. The pathomechanism of PG in the context of NFKB1 deficiency remains poorly understood.
Objective: To characterize an immunophenotype of a kindred with a known history of PG and a recent diagnosis of a likely pathogenic NFKB1 variant.
Methods: We performed standardized clinical and immune phenotyping, including unique subsets of immune dysregulation such as T follicular helper (Tfh) cells, CD19^high21^low B cells, and monocyte subsets; targeted genetic testing; and pedigree analysis with cascade testing of at-risk relatives.
Results: The proband is a 33-year-old woman with childhood-onset refractory PG, recurrent sinopulmonary infections, and arthritis. She had hypogammaglobulinemia with absent pneumococcal vaccine responses. Following PPSV23, she mounted hyper-reactive titers, consistent with immune dysregulation rather than classic vaccine failure. Flow cytometry demonstrated CD19^high21^low expansion, low switched-memory B cells, Tfh expansion, and marked skewing toward atypical/nonclassical monocytes. A heterozygous likely pathogenic intronic NFKB1 variant was identified (c.1752+2T>C). Pedigree analysis revealed PG and immune dysregulation co-segregating with the familial NFKB1 variant. Among the seven family members with recurrent PG, the proband's mother and maternal uncle were confirmed to have the same variant. Genetic testing is pending in five additional family members. The proband's 3-year-old daughter is asymptomatic and carries the same variant.
Conclusions: In our family, the co-segregation of PG with NFKB1 variants underscores the importance of early recognition of immune dysregulation and timely genetic testing to refine diagnosis and anticipate complications. Both adaptive and innate immune

compartments are dysregulated in this context. Further pathomechanistic studies are needed to improve treatment options for refractory cases, such as those described in this family.

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CTLA-4 Variant Interpretation and Clinical Impact

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Background: The cytotoxic T lymphocyte-associated protein 4 (CTLA-4) is a well-known immune checkpoint inhibitor. Heterozygous germline mutations in CTLA4 in humans lead to immune deficiency, autoimmunity, auto-inflammation, lymphoproliferation, and infection. A reduced penetrance of approx. 70% is published. This project aims to classify all known variants of the human CTLA4 gene into five categories: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign.
Method: A comprehensive literature research was conducted and included 63 papers, along with unpublished patients that were referred to us by their treating physicians. We identified a total of 767 subjects with 133 different unique variants. Patient information was curated into the GenIA database (https://geniadb.net), focusing on demographic information, phenotypes, laboratory values, functional assays, and treatment.
Results: In this cohort, 84.76% of CTLA4 mutation carriers were affected or mildly affected. This penetrance of 84.76% is substantially higher than previously published. Moreover, 46.3% of patients were repeatedly reported in different studies. Disease-modifying antirheumatic drugs and systemic corticosteroids were the most used treatments. We found that GenIA is a suitable platform for comprehensive literature research. Not all variants had been tested or functionally validated.
Outlook: Our future work seeks to analyze genotype–phenotype correlation and advise medical professionals on typical presentation and treatment options for patients with CTLA-4 (haplo)insuffiency.

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Delayed Diagnosis of DOCK8 Deficiency Unmasked by Tuberculoid Leprosy and JC Virus Infection

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[1]Cleveland Clinic Abu Dhabi

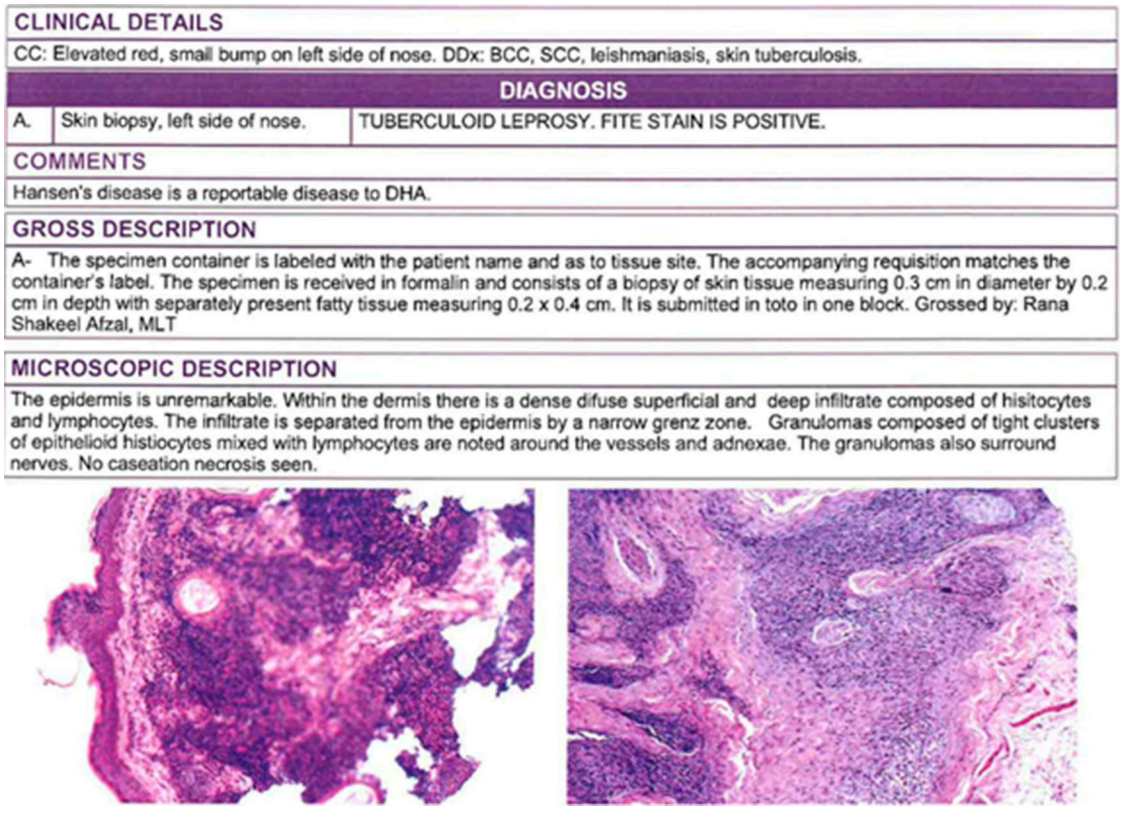
Dedicator of cytokinesis 8 (DOCK8) deficiency is a rare autosomal recessive combined immunodeficiency marked by severe atopy, recurrent viral and bacterial infections, high immunoglobulin E, eosinophilia, and lymphopenia. Although opportunistic infections may occur, central nervous system (CNS) involvement is uncommon, and susceptibility to *Mycobacterium leprae* has not previously been documented. We report the first recognized adult presentation of DOCK8 deficiency complicated by JC-virus encephalitis and biopsy-proven tuberculoid leprosy, representing an unreported infectious pattern.

A 21-year-old male came to clinical attention after two months of progressive neurological symptoms, including dysgraphia, dysarthria, headache, and right-sided ataxia. He had a background of long-standing but undiagnosed immune problems and severe atopy. MRI demonstrated T2/FLAIR hyperintense lesions in the pons and cerebellum, raising concern for rhombencephalitis. Cerebrospinal fluid showed lymphocytic pleocytosis with persistently positive JC-virus PCR. Immunological assessment revealed markedly low CD4 counts, low immunoglobulin M, raised immunoglobulin E and immunoglobulin G, and eosinophilia. Genetic testing confirmed compound heterozygous pathogenic variants in DOCK8, establishing the diagnosis at the age of 20.

A chronic nasal bridge lesion, originally nonspecific on biopsy, was resampled and showed granulomatous lymphohistiocytic inflammation consistent with tuberculoid leprosy. Screening for HIV and viral hepatitis was negative. The case was reviewed through a multidisciplinary approach, with continuation of antimicrobial prophylaxis and referral for assessment for hematopoietic stem cell transplantation (HSCT).

JC-virus infection of the CNS has been described in a small number of DOCK8-deficient patients but remains rare. Mycobacterial infection, usually tuberculosis, is reported infrequently in this condition. To date, leprosy has not been associated with DOCK8 deficiency and is more typically seen in defects affecting the interleukin-12/interferon-γ pathway. This case, therefore, widens the recognized infectious vulnerability of DOCK8 deficiency and illustrates that adult diagnosis remains possible despite longstanding symptoms.

This report underlines the need for early recognition of atypical infections in adults with suspected combined immunodeficiency and supports timely consideration of curative HSCT in DOCK8 deficiency.



CLINICAL DETAILS

CC: Elevated red, small bump on left side of nose. DDx: BCC, SCC, leishmaniasis, skin tuberculosis.

DIAGNOSIS

A.	Skin biopsy, left side of nose.	TUBERCULOID LEPROSY. FITE STAIN IS POSITIVE.

COMMENTS

Hansen's disease is a reportable disease to DHA.

GROSS DESCRIPTION

A- The specimen container is labeled with the patient name and as to tissue site. The accompanying requisition matches the container's label. The specimen is received in formalin and consists of a biopsy of skin tissue measuring 0.3 cm in diameter by 0.2 cm in depth with separately present fatty tissue measuring 0.2 x 0.4 cm. It is submitted in toto in one block. Grossed by: Rana Shakeel Afzal, MLT

MICROSCOPIC DESCRIPTION

The epidermis is unremarkable. Within the dermis there is a dense difuse superficial and deep infiltrate composed of hisitocytes and lymphocytes. The infiltrate is separated from the epidermis by a narrow grenz zone. Granulomas composed of tight clusters of epithelioid histiocytes mixed with lymphocytes are noted around the vessels and adnexae. The granulomas also surround nerves. No caseation necrosis seen.

Figure 1. **Histopathology report—FITE stain is positive.**

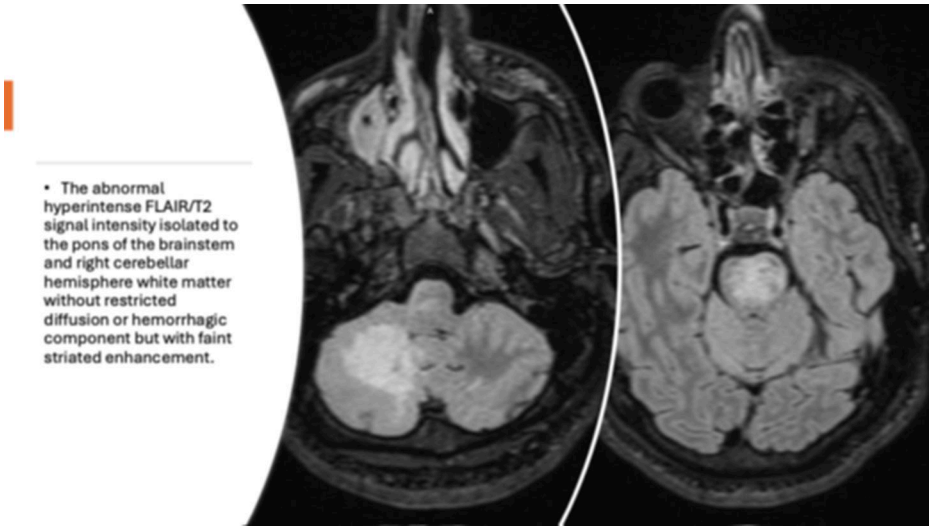


Figure 2. **MRI scans demonstrating T2/FLAIR hyperintense lesions in the pons and right cerebellar hemisphere.**

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Deletion of IRF2BP2 Presenting as Late-Onset Common Variable Immunodeficiency with Bronchiectasis

Samantha Shafer[1], Anahita Agharahimi[1], Chen Wang[1], and Alexandra Freeman[1]

[1]National Institutes of Health

Interferon regulatory factor-2-binding protein-2 (IRF2BP2) is a transcriptional regulator affecting diverse cellular functions, including cell differentiation and apoptosis. It plays an important role in lymphocyte and macrophage activation, positioning IRF2BP2 as a key regulator of the immune response. IRF2BP2 haploinsufficiency typically presents with common variable immunodeficiency (CVID) complicated by gastrointestinal and autoimmune features starting at a young age. Herein, we describe a case of late-onset CVID complicated by bronchiectasis associated with a heterozygous deletion in the IRF2BP2 gene.

A 67-year-old White female had an unremarkable childhood and early adult medical history presented to the National Institutes of Health (NIH) (NCT00001355). At age 58 years, she was found to have an elevated C-reactive protein (CRP) level without an identifiable etiology. At age 65 years, she had an episode of laryngitis with dyspnea, and chest imaging revealed bronchiectasis. She reported no prior history of invasive or opportunistic infections, gastrointestinal or autoimmune disorders. Her family history was notable for immune-mediated disorders: a brother with CVID and Crohn's disease, a nephew with CVID and Crohn's disease, and a niece with Crohn's disease. Further workup revealed pan-hypogammaglobulinemia (IgG 355, IgA 57, and IgM 11 mg/dL) with reduced class-switched memory B cells and an inadequate antibody response to pneumococcal polysaccharide vaccine, supporting a diagnosis of CVID. Whole-genome sequencing with chromosomal microarray analysis identified a heterozygous ~0.003 Mb deletion within 1q42.3 involving the entire sequence of IRF2BP2. Her clinical, immunologic, and genetic findings are compatible with autosomal-dominant CVID due to IRF2BP2 haploinsufficiency. She was started on immunoglobulin replacement therapy, but CRP levels have remained mildly elevated without other symptoms. This case highlights the variable expressivity of CVID caused by IRF2BP2 haploinsufficiency, even within the same family, and shows that disease onset may occur later in life.

Disclaimer: This research was supported by the Intramural Research Program of the NIH. The contributions of the NIH author(s) were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States Government. The findings presented are those of the author(s).

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Disseminated Fusariosis, Leukemia Cutis, and Acute Sinus Disease in Prolonged Neutropenia from Acute Myeloid Leukemia

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Background: Patients with acute myeloid leukemia (AML) and prolonged neutropenia are at high risk for invasive fungal infections such as fusariosis, which represents the second most common pathogenic mold infection in this population. Disseminated fusariosis carries mortality rates of 50–80% in immunocompromised patients, with persistent neutropenia being the most critical factor associated with poor outcomes.
Case Presentation: A 62-year-old man with systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and myelodysplastic syndrome (MDS) progressing to AML presented with two weeks of headache, sinus pressure, nasal congestion, right neck swelling, and worsening left lower-extremity pain. His hematologic disease was complicated by >6 months of transfusion-dependent pancytopenia, recurrent neutropenic infections, extended-spectrum-lactamase (ESBL) *Escherichia coli* bacteremia, liver abscess, nodular pneumonia, and neutropenic colitis. Prior therapies included avapritinib, decitabine/venetoclax, and enrollment in a vyxeos-gliteritinib clinical trial; he remained profoundly neutropenic (absolute neutrophil count [ANC] <20). Examination revealed numerous necrotic nodular skin lesions; biopsy grew *Fusarium*. Imaging showed new and worsening pulmonary nodules, and subsequently demonstrated multiple lung, spleen, and kidney lesions consistent with disseminated fusariosis, with the lungs suspected as the primary site of infection. Labs confirmed severe pancytopenia (WBC 0.28), mild acute kidney injury (AKI); blood cultures remained negative. Bronchoalveolar lavage (BAL) testing and Karius sequencing identified *Fusarium solani*. Concomitantly, multifocal painful nodules and right sternocleidomastoid enlargement were attributed to leukemia cutis, supported by progression of blasts to 30-35%. His presentation reflected overlapping disseminated mold infection and leukemic infiltration. He was managed with liposomal amphotericin B, voriconazole, and terbinafine, along with meropenem and vancomycin. Due to *Fusarium*'s high azole and amphotericin minimum inhibitory concentrations (MICs) at our institution, fosmanogepix was requested but anticipated to arrive in two weeks. GM-CSF was added to augment neutrophil recovery; however, despite maximal therapy, he developed progressive respiratory failure and expired on mechanical ventilation before fosmanogepix became available.
Conclusion: This case illustrates the devastating impact of invasive fusariosis in patients with hematologic malignancies and prolonged neutropenia. Early recognition of the clinical triad of respiratory involvement, severe myalgia, and skin lesions may suggest *Fusarium* etiology in severely neutropenic patients. Successful management requires prompt diagnosis, appropriate combination antifungal therapy, and most critically, neutrophil recovery, which represents the single most important prognostic factor.

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Effectiveness of Immunoglobulin-Replacement Therapy in Patients with Hematological Malignancies and Secondary Immunodeficiency: A Focus on COVID-19 Infections

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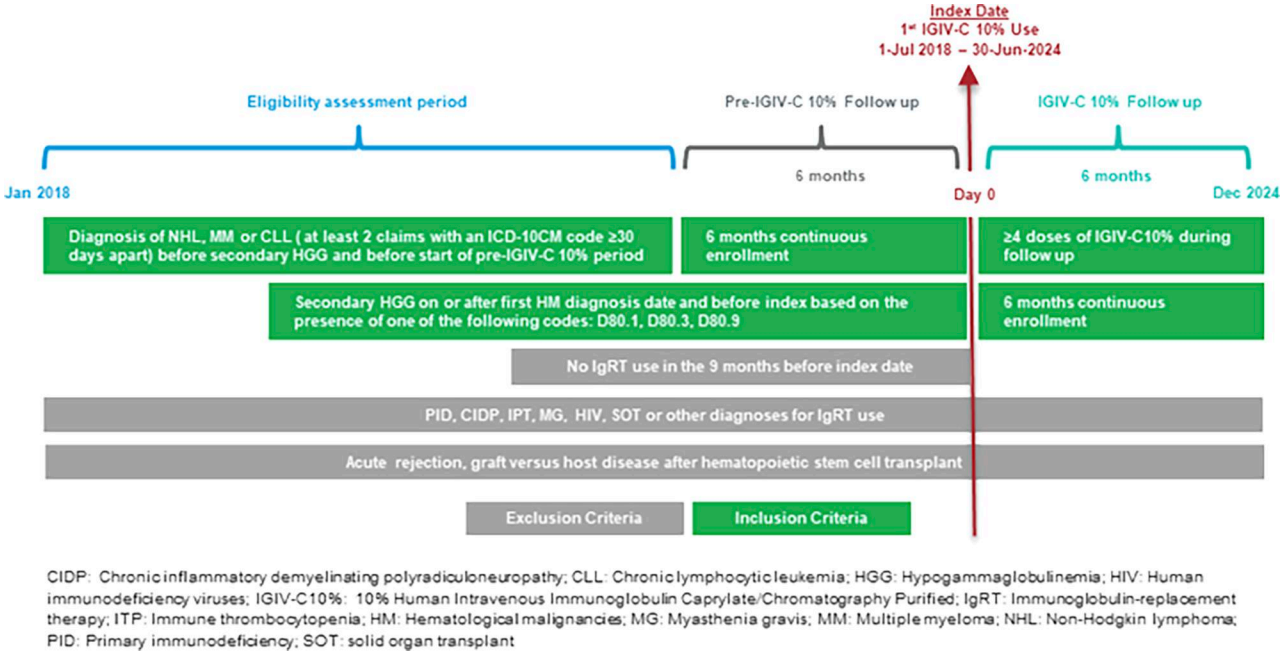
Introduction: Increased risk of infections in patients with hematological malignancies (HM) is a growing concern. Immunoglobulin-replacement therapy (IgRT) is used to reduce infection risk in patients who develop secondary hypogammaglobulinemia (HGG). The effectiveness of IgRT in preventing infections, including COVID-19, has not been fully assessed. This study aims to assess the effectiveness of 10% human intravenous immunoglobulin caprylate-chromatography purified (IGIV-C10%) in reducing infection risk in HM patients with secondary HGG, including COVID-19 infections.
Methods: A retrospective study was conducted using PharMetrics Plus. The study included patients with non-Hodgkin lymphoma (NHL), multiple myeloma (MM), or chronic lymphocytic leukemia (CLL) who developed HGG and initiated treatment with IGIV-C10% between July 2018 and June 2024. The index date was the first IGIV-C10% dose. Figure 1 includes additional details on study design and eligibility. The proportion of patients with severe infections and any infection over the post-index (exposed) period was compared to that during the pre-index (unexposed) period (including and excluding COVID-19 infections). A sensitivity analysis based on the month-year of the index was performed.



CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; CLL: Chronic lymphocytic leukemia; HGG: Hypogammaglobulinemia; HIV: Human immunodeficiency viruses; IGIV-C10%: 10% Human Intravenous Immunoglobulin Caprylate/Chromatography Purified; IgRT: Immunoglobulin-replacement therapy; ITP: Immune thrombocytopenia; HM: Hematological malignancies; MG: Myasthenia gravis; MM: Multiple myeloma; NHL: Non-Hodgkin lymphoma; PID: Primary immunodeficiency; SOT: solid organ transplant

Figure 1. **Study design.**

Results: Overall, 348 patients (NHL: 130, MM: 154, CLL: 64) were included, with a mean (SD) age of 64.6 (10.9) years; 53.2% were male. Of these, 62 (17.8%), 123 (35.3%), and 163 (46.8%) patients were identified during the pre-COVID-19, COVID-19, and post-COVID-19 periods, respectively. Patients received 5.8 (1.2) IGIV-C10% doses, with a mean of 21.8 (17.5) grams-encounter. When excluding COVID-19 infections, the adjusted odds of severe infection and any infection were 53% (OR: 0.47; 0.33, 0.66; p < 0.001) and 66% (odds ratio [OR]: 0.34; 0.23–0.50; p < 0.001) lower during the IGIV-C10% period, respectively. The same trend was observed when including COVID-19 infections in the definitions of severe infections (OR: 0.41; 0.28, 0.60; p < 0.001) and any infections (OR: 0.36; 0.24, 0.54, p < 0.001). Similarly, the odds of severe infection were significantly reduced regardless of whether patients initiated IGIV-C10% therapy before, during, or after the COVID-19 pandemic (Figure 2).

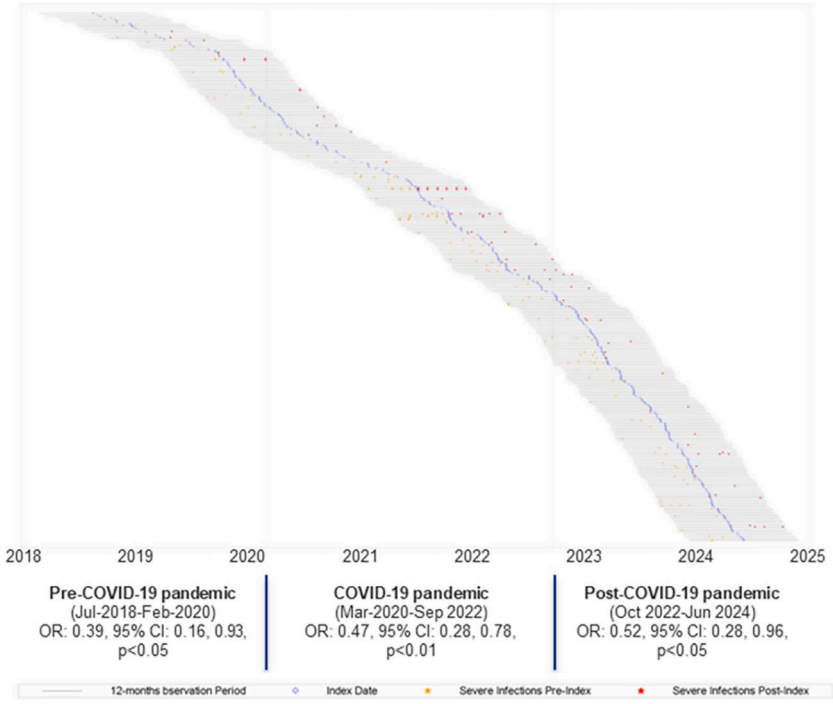


Figure 2. **Graphical representation of patients included in the study based on index day and presence of severe infections during the post-index and pre-index periods, and adjusted odds, 95% confidence intervals, and p-value of severe infections during the post-index (exposed to IGIV-C10%) compared to the pre-index (unexposed to IGIV-C10%).**

Conclusions: Regular IGIV-C10% infusions are effective in reducing infections in HM patients with HGG. Similar effects were observed when including COVID-19 infections as an outcome and when effectiveness was assessed before, during, and after the COVID-19 pandemic.

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Eosinophilic Lung Disease as the Initial Manifestation of X-Linked Hyper-IgM Syndrome in an Infant

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Background: X-linked hyper-IgM syndrome (XHIM) due to CD40L deficiency typically presents in early childhood with recurrent sinopulmonary or opportunistic infections, and its initial manifestations can be misleading. We report a 9-month-old boy with eosinophilic lung disease and severe *Pneumocystis jirovecii* pneumonia (PJP), whose evaluation revealed XHIM.
Objective: To highlight the diagnostic process of an infant with XHIM syndrome including atypical presentation and CD40L variant of uncertain significance (VUS).
Methods: We performed a retrospective chart review, immunophenotyping, CD40L studies, and genetic testing.
Case presentation: Our patient was born with normal newborn screening (NBS) results. He had multiple emergency visits at 4 months for viral infections and bronchiolitis, including one pediatric intensive care unit (PICU) admission for presumed *Mycoplasma pneumonia.* No total IgG level was obtained. At 9 months, he was readmitted to the PICU for respiratory distress, presenting with leukocytosis and marked eosinophilia. Chest computed tomography (CT) showed diffuse ground-glass opacities with subpleural sparing. BD-glucan was elevated, and both plasma cell-free DNA (Karius) and bronchoalveolar lavage were positive for PJP. Serum immunoglobulins showed absent IgG, IgA, and IgE, with elevated IgM. Flow cytometry revealed nearly absent class-switched memory B cells. Genetic testing identified a CD40L c.524T>G (p.V175G) VUS inherited from his mother, and further testing confirmed absent CD40L expression on activated T cells. The patient required 6 weeks to recover after prolonged mechanical ventilation and complex therapy with high-dose trimethoprim-sulfamethoxazole, corticosteroids, antifungals, and intravenous immunoglobulin.
Conclusion: This case highlights that atypical pneumonias complicated by eosinophilia may represent an initial manifestation of XHIM. Infants older than 6 months of age may experience diagnostic delays if serum immunoglobulin levels, particularly IgG, are not measured at the time of admission. Because XHIM is characterized by profound T cell dysfunction, NBS with T cell receptor excision circles (TRECs) may be normal and does not exclude the diagnosis. Early recognition of XHIM enables timely initiation of immunoglobulin replacement, PJP prophylaxis, and evaluation for curative hematopoietic stem cell transplantation or gene therapy before irreversible complications occur.

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Establishing Newborn Screening for SCID: The BC and Yukon Experience

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Background: Severe combined immunodeficiency (SCID) is a life-threatening condition that requires urgent medical attention. Newborn screening (NBS) using the T cell receptor excision circle (TREC) assay facilitates early diagnosis of SCID, which is crucial for improving outcomes.
Objectives: Describe the diagnoses and outcomes of the first 2.5 years of NBS for SCID in British Columbia and the Yukon, Canada.
Methods: An interdisciplinary working group of health professionals met at regular intervals prior to and after implementing NBS for SCID. We developed an algorithm for the evaluation and initial management of infants with an abnormal NBS for SCID based on a literature review and local expert consensus. The diagnoses and outcomes of infants with a positive NBS were monitored prospectively. TRECs were measured from dried blood spots of newborns, with the threshold for an abnormal NBS determined using multiples of the median to achieve a positivity rate of 0.1%. Absolute T cell counts less than 1,500 cells/mcL or naïve CD4 or CD8 T cell percentages less than 50% were considered abnormal and prompted immunology consultation.
Results and Discussion: A total of 110,156 infants were screened between October 2022 and April 2025. There were 2 infants diagnosed with SCID, resulting in a population-based incidence of 1 in 55,078. Both underwent stem cell transplantation within 4 months of life and had no infections at the time of transplant. There was one case of congenital athymia secondary to 22q11 microdeletion syndrome

identified by NBS for SCID, who underwent a successful thymic transplantation at 5 months of age. There were no cases of SCID diagnosed outside of the NBS program within this time frame.

Conclusion: Our experience supports the value of NBS using the TREC assay in facilitating early diagnosis and treatment of infants with SCID.

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Expanded Clinical Spectrum Associated with Heterozygous Variants of RNU4ATAC

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Introduction: RNU4ATAC-opathies are characterized by biallelic pathogenic variants and include three recognized phenotypes: autosomal recessive Roifman syndrome, microcephalic osteodysplastic primordial dwarfism (MOPD), and Lowry-Wood syndrome. These disorders exhibit overlapping features such as microcephaly, developmental delay, skeletal dysplasia, and immunodeficiency. We report two cases of heterozygous pathogenic RNU4ATAC variants with similar manifestations, distinct from classic RNU4ATAC-opathy presentations.

Case One: A 17-year-old male presented with severe persistent asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP). Laboratory workup revealed low IgG level (454 mg/dL), normal IgA and IgM, and non-protective titers to tetanus and pneumococcal vaccines. Genetic testing revealed a heterozygous pathogenic RNU4ATAC n.13C>T variant. Cystic fibrosis (CF) and primary ciliary dyskinesia workup were negative. The patient was started on dupilumab 300 mg every 2 weeks for severe asthma and CRSwNP and subcutaneous immunoglobulin therapy (SCIG) for immunodeficiency with significant clinical improvement.

Case Two: A 23-three-year-old male presented with severe persistent asthma, CRSwNP, bronchiectasis, recurrent bacterial and viral upper and lower respiratory tract infections since childhood, allergic rhinitis, and myofibrillar myopathy. Immune evaluation was significant for absent antibody titers to measles, varicella, and pneumococcal vaccines with normal immunoglobulin and lymphocyte phenotype. CFTR gene sequencing revealed R75Q and 7T/7T variant consistent with atypical CF. Family history was notable for a brother with atypical CF and a sister with asthma. Primary immunodeficiency diseases (PIDD) genetics revealed two heterozygous pathogenic variants: RNU4ATAC n.40C>T and PMM2 c.368G>A (p. Arg123Gln). The patient was started on dupilumab for asthma and CRSwNP and SCIG for recurrent infections with marked improvement in his symptoms.

Conclusion: These cases expand the phenotypic spectrum associated with heterozygous RNU4ATAC variants, diverging from classical autosomal recessive RNU4ATAC-opathies. Our patients predominantly presented with severe asthma and CRSwNP, atypical for RNU4ATAC-associated disorders. Notably, there are reported associations of asthma and CRSwNP with 2q14.2 polymorphisms, where the RNU4ATAC gene is located. Coexisting atypical CF in one patient underscores the phenotypic complexity of these presentations and suggests that heterozygous RNU4ATAC variants may predispose to multisystem respiratory and immunologic dysfunction. These findings warrant consideration of extended genetic testing, including CFTR analysis, in patients with severe overlapping respiratory phenotypes.

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Familial Reticular Dysgenesis Due to Adenylate Cyclase 2 (AK2) Deficiency: Insights from a Three-Sibling Case Series

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Reticular dysgenesis (RD) is a rare, severe form of severe combined immunodeficiency (SCID) caused by biallelic AK2 mutations, leading to profound defects in lymphoid and myeloid maturation. Unlike other SCID phenotypes, infants may present within days to weeks of life with infections due to profound neutropenia and sensorineural hearing loss. Hematopoietic stem cell transplantation (HSCT) remains the only curative therapy. We describe three siblings with genetically confirmed RD, highlighting phenotypic variability, immunologic features, and transplant outcomes.

Sibling A, born to Amish consanguineous parents, presented at 1 year with *Pseudomonas* and *Haemophilus influenzae* bacteremia, chronic diarrhea, and failure to thrive; sensorineural hearing loss was later identified. Immunologic evaluation revealed neutropenia (absolute neutrophil

count [ANC] 830 cells/uL), severe CD4 lymphopenia (CD4+ 15 cells/uL), and elevated IgA (281 mg/dL). SCID newborn screening (NBS) was not performed in 2011. He received antimicrobial prophylaxis with acyclovir, itraconazole, trimethoprim/sulfamethoxazole (TMP-SMX), and intravenous immunoglobulin (IVIG). Filgrastim was initiated but discontinued after rash and biopsy-confirmed Sweet syndrome. At age 4, he underwent a 7/8 HLA-matched maternal-donor HSCT using reduced-intensity conditioning (RIC) with alemtuzumab, fludarabine, melphalan, and ThioTepa. Complications included CMV viremia, steroid-refractory chronic cutaneous graft versus host disease (GVHD), disseminated non-mucor zygomycosis, and graft loss with partial donor T cell chimerism. A second 7/8 HLA-matched maternal-donor HSCT (CD3/CD19 depletion, busulfan-based conditioning) was performed 708 days later but was complicated by engraftment syndrome and severe hepatorenal failure; he died 22 days post-transplant. Postmortem exome sequencing confirmed homozygous AK2 c.622T>C (p.Ser208Pro).

Sibling B was diagnosed at birth through targeted genetic testing. He had neutropenia (ANC 1,600), panlymphopenia, hypogammaglobulinemia, and a failed newborn hearing screen with normal SCID NBS. Filgrastim was avoided due to concern for RD-associated myelodysplasia. He underwent an 8/8 sibling HSCT at 2 months using RIC (hydroxyurea, PK-guided busulfan, alemtuzumab, and fludarabine) and is now 5 years post-transplant with successful T and B cell reconstitution.

Sibling C, also identified at birth after a failed hearing screen, had panlymphopenia with mild neutropenia (ANC 3,000) and a normal SCID NBS. She remains clinically stable on antimicrobial prophylaxis while awaiting HSCT.

This series highlights marked phenotypic variability in RD, underscores limitations of SCID NBS in detecting RD, and emphasizes the importance of early genetic diagnosis and timely HSCT.

Tabular data are included as downloadable supplement files.

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Fatal Pneumococcal Meningitis in a 22-Month-Old with Classical Complement C2 Deficiency

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Background: Early complement pathway deficiencies predispose to invasive infections with encapsulated bacteria. C2 deficiency is the most common human complement deficiency, yet it may remain clinically silent until a life-threatening presentation. We describe a previously healthy 22-month-old male with fulminant pneumococcal meningitis and sepsis, diagnosed with C2 deficiency at the perimortem phase, with subsequent genetic confirmation in two asymptomatic siblings.

Case Presentation: A previously healthy, fully immunized 22-month-old male presented with 2 days of fever and irritability followed by rapid deterioration, lethargy, and tachycardia. Cerebrospinal fluid (CSF) demonstrated pleocytosis with gram-positive cocci, and pneumococcal PCR was positive. Despite broad-spectrum meningitic-dose antimicrobials, fluid resuscitation, and pediatric intensive care unit (PICU) management including seizure control and mechanical ventilation, he developed multiorgan failure, severe cerebral edema, and radiologic evidence of compromised cerebral perfusion. Brain death was confirmed within 48 hours of PICU admission. Complement evaluation at the perimortem phase revealed markedly decreased classical pathway activity, with preserved alternative pathway function, consistent with a deficiency in the classical component. Targeted complement gene testing identified C2 deficiency. Genetic testing of two clinically well siblings showed the same C2 deficiency; both remain asymptomatic to date.

Discussion: C2 deficiency may remain unrecognized until a sentinel, severe infection occurs. Children commonly present with invasive pneumococcal disease due to impaired opsonization of encapsulated organisms. While C2 deficiency is often associated with autoimmune features later in childhood, overwhelming infection remains the initial manifestation in a subset of cases. A fatal presentation in an otherwise healthy toddler highlights the importance of early complement testing in severe meningitis and the utility of family cascade screening.

Conclusion: Our patient emphasizes the importance of early recognition of complement deficiency in patients with fulminant pneumococcal meningitis despite vaccination and healthy preinfection status. Family screening enables anticipatory guidance, vaccination strategies, and prophylaxis considerations for relatives at risk.

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Functional Characterization of a Biallelic ITK D266H Variant Implicated in Infantile Fulminant and Giant Cell Hepatitis

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[1]UT Southwestern Medical Center

Background: Interleukin-2–inducible T cell kinase (ITK) deficiency classically presents with EBV-driven lymphoproliferation and lymphoma, but emerging data suggest broader phenotypes of immune dysregulation. The pathogenicity of novel ITK missense variants, particularly within the SH2 domain, often remains undefined.

Case: A previously healthy term 6-month-old girl presented with acute liver failure, marked hyper-transaminasemia, conjugated hyperbilirubinemia, coagulopathy, and liver biopsy showing giant cell hepatitis. Evaluation demonstrated hypergammaglobulinemia, elevated smooth muscle antibody, increased soluble IL-2 receptor, CD8 T cell expansion, reduced T cell proliferation to PHA and anti-CD3/anti-CD28 (with preserved responses to pokeweed mitogen and anti-CD3/IL-2), and impaired natural killer (NK) degranulation with decreased perforin-positive NK cells. Rapid whole exome sequencing (WES) revealed homozygous ITK p.D266H missense variants; NKT cells were markedly reduced, and progressive CD4 lymphopenia and hypogammaglobulinemia developed on follow-up.

Methods: To assess the pathogenicity of ITK D266H, SH2-domain GST-fusion constructs (wild type and D266H) were generated for GST pull-down and far western assays with SLP-76 and PLC-γ1. Full-length FLAG-tagged ITK constructs (wild-type, D266H, and a separate SH2 mutant R265G) are being introduced into T cells to determine the impact of the D266H mutation on ITK kinase activity before/after TCR engagement Jurkat cells, with planned TCR stimulation and in vitro kinase assays to evaluate ITK autophosphorylation.

Results: The ITK D266H SH2-domain fusion protein retained mildly diminished binding to SLP-76 and PLC-γ1s in GST pull-down. Far western assays suggested normal phosphotyrosine interactions. In ongoing work, in vitro kinase assays of wild-type, D266H, and R265G ITK will assess differences in the autophosphorylation activity as a mechanistic explanation for the patient's impaired T cell proliferation and NK cytotoxic function despite near-normal T cell counts.

Conclusion: This case expands the clinical spectrum of ITK-associated disease to include severe infantile immune-mediated hepatitis without classic EBV-lymphoproliferation and illustrates a strategy to functionally validate novel ITK SH2 domain variants. Early recognition of this phenotype has implications for hematopoietic stem cell transplantation (HSCT) timing, immunomodulatory therapy, and genetic counseling in families with suspected ITK-related immune dysregulation.

Figure 1. **Structure of the ITK kinase and mutation.**

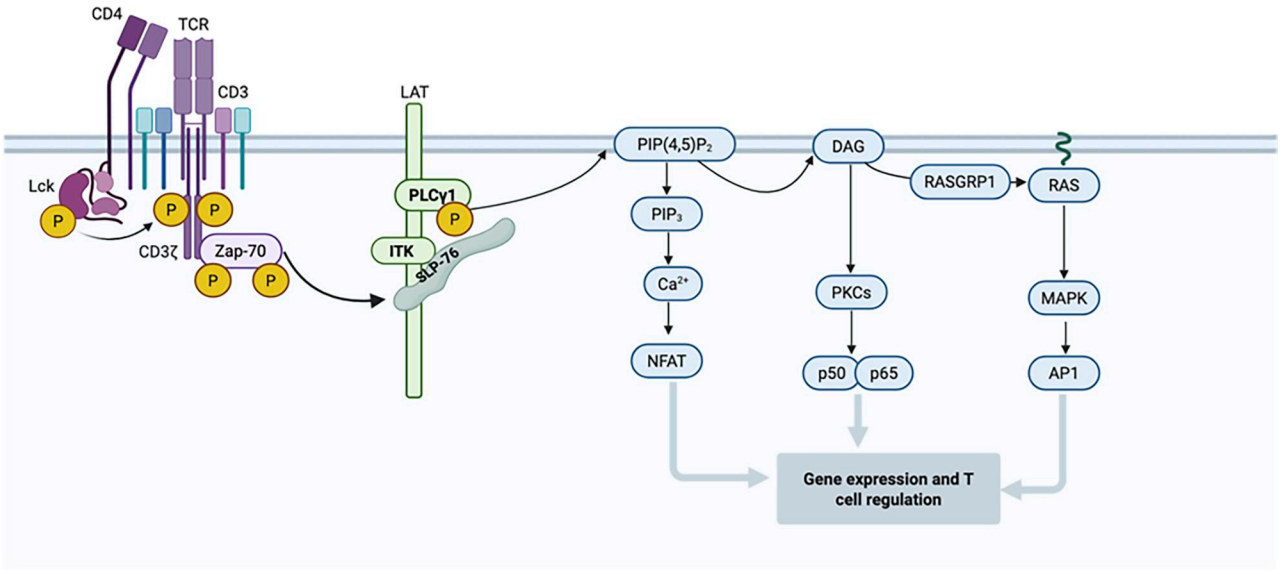

Figure 2. **ITK signaling.**

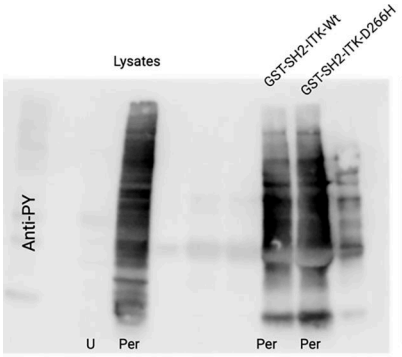

Figure A. GST-pulldown

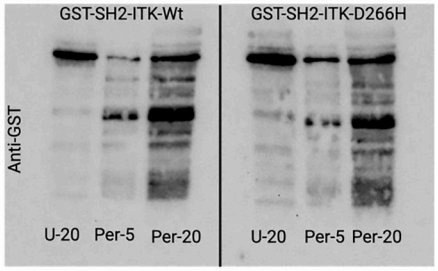

Figure B. Far Western Anti-GST.

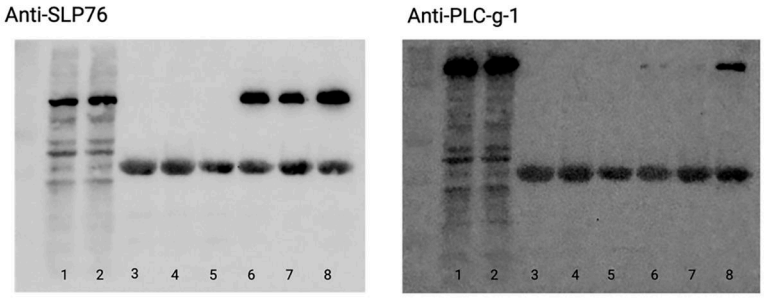

Figure C. Figure demontrated ITK SH2 domain mutants D266H and R265G retain SLP-76 and PLC-g1 binding.

1)Unstimulated, 2)Pervanadate (PO4 protein), 3)U-GST ITK PD, 4) U-GST ITK D266H PD, 5) U-GST ITK R265G PD, 6)Per-GST ITK PD, 7)Per-GST ITK D266H PD and 8)Per-GST ITK R265G PD

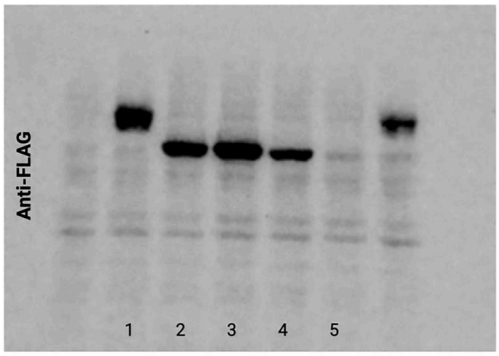

Figure D. Full-length FLAG-tagged ITK constructs 1) hFOXN-FLAG Wt, 2) hITK-FLAG Wt, 3)hITK-FLAG D266H, 4) hITK-FLAG R265G and 5) eGFP

Figure 3. **Results.**

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GATA2 Deficiency Presenting with Severe Immune Dysregulation

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Medicine, Providence Health Care, Providence Undiagnosed and Rare Conditions Clinic; [6]BMT Program of BC, BC Cancer; [7]UBC Department of Pediatrics, Division of Allergy & Immunology

Background: GATA2 deficiency results from heterozygous pathogenic variants in the GATA2 gene, which encodes a zinc-finger transcription factor essential for hematopoietic stem and progenitor cell development. It is a highly variable inborn error of immunity characterized by monocytopenia, B and natural killer (NK) cell lymphopenia, susceptibility to infections, increased risk of myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML), and pulmonary alveolar proteinosis. Autoimmune and inflammatory manifestations are increasingly recognized and include vasculitis, Sweet's syndrome, ankylosing spondylitis, seronegative erosive rheumatoid arthritis, and lupus-like rashes, among others. However, lupus nephritis has not been clearly documented in association with GATA2 deficiency.
Case Presentation: A 25-year-old male was referred to immunology for a history of multifaceted immune dysregulation, including systemic lupus erythematosus (SLE), severe atopic dermatitis, asthma, and necrotizing pancreatitis. The SLE was diagnosed at age 17, and he developed biopsy-proven class IV lupus nephritis that progressed to end-stage renal disease requiring hemodialysis. His disease course has been further complicated by autoimmune hemolytic anemia, thrombocytopenia, pleural effusions, and suspected pericarditis. Bone marrow aspirate was punctio sicca, limiting assessment for dysplasia, and biopsy was moderately hypocellular with bony changes associated with renal osteodystrophy, and no evidence of increased blasts. He has received extensive immunosuppression with tacrolimus, cyclophosphamide, mycophenolate mofetil, rituximab, azathioprine, and corticosteroids. Despite these therapies, his SLE remains poorly controlled.

The patient's infectious history was notable for serious infections that occurred during periods of immunosuppression: Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, *Staphylococcus epidermidis* endocarditis, *Candida parapsilosis* fungemia, *C. difficile* colitis, and shingles reactivation. Immune investigations revealed lymphopenia across all subsets with complete B cell absence despite discontinuing rituximab seven years prior. An immune and cytopenia gene panel identified a heterozygous pathogenic missense variant in GATA2 (NM_032638.5: c.1193G>A, p.(Arg398Gln)). Our patient lacks hallmark features of GATA2 deficiency: no monocytopenia, pulmonary alveolar proteinosis, or lymphedema.
Conclusion: This case expands the recognized variability of GATA2 deficiency, showing that severe autoimmune or atopic manifestations may predominate even when hallmark features are absent. Although GATA2 deficiency is an unlikely explanation for most cases of SLE, it may be worth considering in refractory or atypical presentations, especially those marked by unexplained lymphopenia or other deficits that prompt evaluation for underlying inborn errors of immunity.

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Genetic Prediction of Sepsis Severity Based on the Detection of MCP-1 Gene Polymorphism in Patients with Acquired Immunological Disorders

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Background and Aims: Acquired immunodeficiency in patients with hematological oncology is a serious and common complication, significantly impacting prognosis and quality of life. High doses of cytostatic drugs and the malignancy itself lead to suppression of the immune system, leaving the body vulnerable to various infectious agents. Sepsis, which develops in the setting of immunodeficiency, is characterized by a more aggressive course and high mortality. In the era of advancing sequencing technologies, identifying polymorphisms and changes in innate immune gene expression associated with the development and severity of sepsis, as well as their impact on outcome, is crucial.
Methods: We analyzed DNA samples (n = 155) from oncohematology patients with severe sepsis in the Department of Anesthesiology and Intensive Care at the Belarusian Research Center for Pediatric Oncology, Hematology and Immunology. The presence/absence of the rs1024611 polymorphism in the promoter region of the MCP-1 gene was determined using Sanger sequencing.
Results: The presence of homo- or heterozygous polymorphism was found to be associated with an increased risk of developing septic shock ($\chi^2 = 4.9$, $p = 0.013$). This supports the hypothesis that genetic factors influencing MCP-1 levels may be associated with a more pronounced systemic inflammatory response, leading to more severe clinical outcomes. In patients with the rs1024611 polymorphism, the

likelihood of developing sepsis-associated acute kidney injury requiring renal replacement therapy (RRT) was higher (χ^2 = 13.0, p = 0.00016) compared to patients without RRT. Patients with the rs1024611 polymorphism also have an increased risk of developing severe acute respiratory distress syndrome (ARDS) (χ^2 = 4.8, p = 0.014). Furthermore, the presence of homo- or heterozygous rs1024611 polymorphism increases the likelihood of an adverse outcome, such as 28-day mortality (χ^2 = 5.6, p = 0.009). This underscores the importance of genetic factors in determining the prognosis of patients with sepsis. High mortality may be associated with a more pronounced inflammatory response caused by the polymorphism, leading to more severe forms of sepsis and its complications.
Conclusions: The rs1024611 polymorphism in the MCP-1 gene promoter region is significantly associated with an increased risk of severe sepsis secondary to secondary immunodeficiency. These data highlight the importance of genetic testing for risk assessment and prognosis in patients with sepsis.

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Granulomatous-Lymphocytic Interstitial Lung Disease in Non-CVID Immune Dysregulation

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Background: Granulomatous-lymphocytic interstitial lung disease (GLILD) is a noninfectious interstitial lung disorder characterized by granulomatous inflammation and lymphoid proliferation. It is most frequently identified in individuals with common variable immunodeficiency (CVID) and has been reported less often in other primary immunodeficiencies. Characteristic histopathologic patterns include non-necrotizing granulomas, lymphocytic interstitial pneumonia, follicular bronchiolitis, and lymphoid hyperplasia. Accurate diagnosis requires multidisciplinary integration of clinical, radiologic, and pathological data to distinguish GLILD from other granulomatous or lymphoproliferative interstitial lung diseases.
Case Presentation: A 20-year-old man with isolated IgA deficiency developed GLILD following a long-standing history of immune dysregulation. His initial presentation at age nine included severe thrombocytopenia and a direct Coombs-positive test without hemolysis, consistent with immune thrombocytopenia. He subsequently developed neutropenia and experienced significant infectious morbidity, including recurrent otitis media, recurrent sinusitis, dental abscesses, skin and soft-tissue infections, and multiple pneumonias. Immunologic studies consistently showed normal IgG and IgM levels, absence of IgA, intact T cell subsets, and repeatedly negative evaluations for autoimmune lymphoproliferative syndrome (ALPS).

He underwent extensive immunomodulatory therapy—including intravenous immunoglobulin (IVIG), corticosteroids, granulocyte colony-stimulating factor, mycophenolate mofetil (MMF), rituximab, eltrombopag, and sirolimus—with minimal sustained benefit. Splenectomy was performed due to massive splenomegaly and transfusion dependence; however, he presented a year later with widespread lymphadenopathy. Progressive respiratory symptoms and evolving radiographic abnormalities led to a lung biopsy, which demonstrated follicular bronchiolitis, a pattern compatible with GLILD-associated pathology. Multidisciplinary review of clinical, imaging, and histologic findings supported a diagnosis of GLILD. He is currently being treated with rituximab in combination with MMF.
Discussion: This case highlights the diagnostic and therapeutic challenges encountered when GLILD develops in the context of a non-CVID primary immunodeficiency. As current understanding of GLILD is largely shaped by studies of CVID cohorts, evidence to guide diagnosis and management in non-CVID immune phenotypes remains limited. The patient's course underscores the need for heightened clinical awareness of GLILD and supports the development of tailored diagnostic pathways and individualized immunomodulatory strategies outside the context of CVID.

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Health-Related Quality of Life Reveals Distinct Fatigue and Functional Burden in Inflammatory Common Variable Immunodeficiency

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Rationale: Common variable immunodeficiency (CVID) is a chronic, multisystem immune disorder associated with substantial symptom burden beyond infections, particularly among individuals with noninfectious inflammatory complications (CVIDc). Fatigue and impaired functioning are frequently reported by patients but remain under-characterized using standardized, validated patient-reported outcome (PRO) instruments in major cohorts. Systematic assessment of health-related quality of life (HRQOL) using population-referenced tools may clarify patient-perceived disease impact across CVID phenotypes and inform patient-centered outcome assessment.
Methods: We conducted a cross-sectional observational study of CVID patients followed at Mount Sinai Hospital. Participants completed the PROMIS-29 Profile and the FACIT-Fatigue scale. PROMIS-29 domain scores were reported as T-scores standardized to the U.S. general population (mean 50, SD 10), with domain-specific directionality applied. FACIT-Fatigue scores were analyzed using standard scoring conventions, with higher scores indicating less fatigue. Participants were clinically categorized as uncomplicated CVID (CVIDu) or CVID with noninfectious inflammatory complications (CVIDc).
Results: Among 40 participants to date (CVIDu n = 15; CVIDc n = 25), fatigue burden and functional status differed by clinical phenotype. CVIDu participants reported better fatigue status on FACIT-Fatigue than CVIDc (median 46 vs. 36; mean 42.5 vs. 35.2), indicating greater fatigue in CVIDc. PROMIS-29 demonstrated a concordant pattern: domains reflecting symptom burden (fatigue, anxiety, depression, pain interference, and sleep disturbance) were directionally worse in CVIDc, while domains reflecting functioning (physical function and social participation) were lower, indicating reduced everyday functioning. Although not powered for formal statistical inference to date, the consistency of effect direction across PROMIS and FACIT instruments supports a coherent HRQOL profile characterized by greater fatigue and functional impairment in CVIDc. Exploratory analyses showed no consistent overall correlations between PROs and baseline immunologic parameters, including lymphocyte profiles and immunoglobulin levels.
Conclusion: CVID patients with inflammatory complications exhibit a consistent pattern of increased fatigue and impaired functioning across complementary PRO measures. These findings underscore HRQOL, and fatigue in particular, as a meaningful dimension of disease burden in CVIDc that is not fully captured by traditional clinical or immunologic assessments, supporting broader incorporation of standardized PROs into CVID research and outcome evaluation.

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Heart-Stopping Dilemma: Fever, Necrotic Skin Lesions, and Myocarditis in a Patient with XLA

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X-linked agammaglobulinemia (XLA) is an inherited inborn error of immunity caused by low or absent Bruton tyrosine kinase activity, resulting in impaired B cell development, poor immunoglobulin production, and severe, recurrent infections. Immunoglobulin replacement is the standard of care.

Despite adequate replacement, some patients experience severe infectious complications. In this report, a 19-year-old male with XLA on immunoglobulin replacement with sufficient IgG levels (~580) presented with fever of unknown origin (FOU). Physical exam notable for echthymic lesions of the anterior thighs near subcutaneous immunoglobulin injection sites.

During workup for FOU, an echocardiogram demonstrated a newly reduced left ventricular ejection fraction (25%) and pericardial effusion. He started cefepime, metronidazole, and vancomycin and was given high-dose intravenous immunoglobulin (IVIG).

He underwent right heart catheterization and endomyocardial biopsy. During cardiac MRI, he experienced cardiac arrest, ultimately requiring venoarterial extracorporeal membrane oxygenation.

Blood cultures and extensive infectious workup, including EBV/CMV PCR, were negative. Lyme screen was negative but results uninterpretable in this patient on IVIG, who cannot make IgM antibodies. A skin biopsy grew *Staphylococcus hominis*, *Corynebacterium striatum* group, and Gram-positive bacilli (probable *Dermabacter* species), consistent with normal skin flora. Given initial concern for non-*Helicobacter pylori Helicobacter* infection, skin and cardiac biopsies were submitted for Warthin-Starry stain and demonstrated abundant spirochetes. Microbial cell-free DNA sequencing was positive for *Borrelia burgdorferi* alone, without evidence of non-*pylori Helicobacter* species. Antibiotics were changed to gentamicin, doxycycline, and meropenem for a 6-week course.

He showed steady improvement, was subsequently extubated, and weaned off hemodynamic support. A repeat echocardiogram demonstrated recovery of his ejection fraction to 65%. Cardiac MRI at the end of therapy showed no residual myocardial enhancement to suggest scar, inflammation, or infiltration.

Patients with XLA are susceptible to fastidious organisms, including members of the Helicobacteraceae family. Increased susceptibility to spirochetes has not been described. Differentiating between spirochete and non-*pylori Helicobacter* infections can be challenging on Warthin-Starry stain if multiple helical bacteria cluster together, and both groups can have difficulties culturing from peripheral blood. This case is unique in that it describes severe Lyme myocarditis and represents a situation where cell-free DNA sequencing was critical in identifying the causative infectious organism.

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Hickam's Dictum, a Case of Chronic Granulomatous Disease and CVID-Like Hypogammaglobulinemia

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Background: Chronic granulomatous disease (CGD) is characterized by defective neutrophil oxidative burst activity with subsequent susceptibility to catalase-positive organisms, invasive fungal infections, in addition to inflammatory bowel disease (IBD)-like enteropathy. Autoimmune and inflammatory complications have also been less commonly described. Autosomal recessive CGD due to NCF1 is challenging to assess genetically through commercial IEI panels due to the presence of pseudogenes.
Objective: We describe a patient with presumed NCF1 CGD with a common variable immunodeficiency (CVID)-like pattern of hypogammaglobulinemia, immune thrombocytopenia (ITP), and recurrent sinopulmonary infections.
Case Description: The patient was found to have pancytopenia, splenomegaly, and mildly elevated IgG with low IgA on initial investigations at age 7. He was subsequently treated for suspected leishmaniasis with amphotericin B. CGD was later diagnosed after hospitalization with an empyema and cutaneous *Serratia* infection. He was found to have an NCF1 mutation on genetic testing. He was prescribed trimethoprim-sulfamethoxazole and itraconazole for prophylaxis. Years later, he developed chronic ITP treated with intermittent rituximab throughout his teenage years. He was referred six years after his last rituximab treatment for hypogammaglobulinemia and CGD.
Investigations: The neutrophil oxidative burst assay was very low at 3.1% activation. IgG level at age 7 was reportedly 1,600 mg/dL. In 2020, one year post-rituximab, this was low at 361. In 2025, repeat IgG level was found to be 116 mg/dL with an IgA <5 mg/dL. Invitae genetic testing demonstrated a pathogenic large deletion encompassing exons 21–34 in DUOX2.
Discussion: Hypogammaglobulinemia is an unexpected finding in CGD. The patient's previous low IgA and ITP preceding rituximab raises the question of a previous evolving CVID. However, rituximab use makes it impossible to differentiate this from post-rituximab persistent hypogammaglobulinemia.

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Homozygous C2 Deficiency with Hyper IgE Discovered in Adulthood After Persistently Low CH50

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Introduction: Complement C2 deficiency is a classical pathway defect associated with recurrent infections and autoimmunity. This case demonstrates the need for increased awareness amongst rheumatologists for the indications to suspect complement deficiency and also presents a unique presentation of C2 deficiency with hyper IgE.
Case: A 34-year-old woman with systemic lupus erythematosus and rheumatoid arthritis diagnosed in adolescence presented with lifelong recurrent infections. Her history included meningitis in infancy, recurrent otitis media and sinusitis during childhood, and multiple pneumonias requiring hospitalization in adulthood with the development of bronchiectasis. Complement testing demonstrated a CH50 less than 13 U/mL with normal AH50, low C4, and normal C3. Complement studies were repeated by a rheumatologist and noted that CH50 was persistently low despite optimal autoimmunity control with anifrolumab and hydroxychloroquine, so she was referred to immunology.

Immunologic testing showed IgE above 10,000 kU/L, IgM below 5 mg/dL, IgA 33 mg/dL, normal IgG with preserved subclasses except for low IgG4, and normal absolute eosinophil count. Absolute CD19 B cells were reduced at 58 cells/μL. Pneumococcal antibody titers were protective to only 8 of 23 serotypes above 1.3 mcg/L, while tetanus and diphtheria responses were intact. Serum protein electrophoresis was normal. Patient is not very atopic, with only slightly positive aeroallergen sensitization.

Commercial genetic testing using a 574-gene inborn errors of immunity panel identified homozygous known pathogenic variants in C2 (c.841_849+19del in the splice site). Management includes optimizing vaccines, antibiotic prophylaxis, and consideration of immunoglobulin replacement.

Discussion: This case demonstrates a unique finding of hyper-IgE in C2 deficiency. We do not know if the two findings are related, and we also cannot rule out that her hyper IgE is an immunologic consequence of anifrolumab targeting interferon, causing a downstream Th2 phenotype. This case also demonstrates that rheumatologists should always refer autoimmune patients with infectious histories and that persistently low CH50 is concerning for complement deficiency. Earlier identification of complement deficiencies may prevent diagnostic delays and improve clinical outcomes.

Tabular data are included as downloadable supplement files.

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Human FOXP3 Isoforms in Health and Disease

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Forkhead box P3 (FOXP3) is the master transcription factor of regulatory T cells (Tregs) and is essential for maintaining immune tolerance. FOXP3 is stably expressed in Tregs, driving their suppressive function, and it is transiently induced in conventional T cells (Tconv) upon activation, where it fine-tunes immune responses. In humans, but not in mice, FOXP3 is expressed as two major isoforms: the full-length protein (FOXP3FL) and an isoform lacking exon 2 (FOXP3Δ2), with additional variants such as FOXP3Δ7 and FOXP3Δ2Δ7 described. The precise contribution of each isoform to Treg development, stability, and function in health and disease remains incompletely defined, although clinical observations indicate that patients expressing only FOXP3Δ2 develop autoimmunity, highlighting a nonredundant role for FOXP3FL in Treg-mediated tolerance. Multiple studies have further associated increased FOXP3Δ2 expression with autoimmune disease and reduced Treg stability, suggesting that the relative abundance of FOXP3FL and FOXP3Δ2 may critically shape Treg function and the balance between tolerance and pathology. However, the physiological expression levels and ratios of FOXP3FL and FOXP3Δ2 in Tregs and activated Tconvs remain poorly characterized, hindering understanding of the distinct functions of these isoforms, the correlation of specific FOXP3 mutations with isoform expression patterns and disease severity, and the development of Treg-targeted and gene transfer–based therapies. To address this, we quantified isoform-specific expression in Tregs and activated Tconvs from healthy donors and in patients with loss-of-function mutations in FOXP3 that cause immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, a severe monogenic disorder that typically presents in early infancy, affects male patients, and is almost uniformly fatal without definitive therapy. Our data indicate that FOXP3Δ2 is the dominant isoform in activated Tconvs and Tregs across both cohorts, with a FOXP3FL:FOXP3Δ2 ratio of 0.52 ± 0.08, suggesting that regulated co-expression of FOXP3 isoforms but not exclusive expression of a single isoform underpins effective Treg development and function. Consequently, therapeutic strategies for IPEX and autoimmunity should aim to restore a physiologic FOXP3 isoform balance rather than solely achieving full-length FOXP3 expression.

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Hypogammaglobulinemia and Recurrent Tracheitis in a 4-Month-Old Male with RTEL1 Heterozygous Mutation

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Background: Mutations in the regulator of telomere elongation helicase 1 (RTEL1) gene cause excessive telomere shortening, leading to bone marrow failure, dyskeratosis congenita, pulmonary and liver fibrosis, and, in some severe cases, immunodeficiency. Most severe cases of RTEL1 deficiency leading to immunodeficiency are due to biallelic mutations; however, we present a 4-month-old male with a heterozygous RTEL1 mutation who presented with hypogammaglobulinemia and recurrent tracheitis.

Case Description: A 4-month-old male born at 37 weeks gestation with SCL2A and LMNA mutations, GLUT1 deficiency, seizure disorder, gastrojejunal and tracheostomy tube dependence, presented with recurrent tracheitis due to *Klebsiella pneumoniae* and *Enterococcus faecalis*. He had no history of otitis media, pneumonia, sinusitis, bacteremia, or urinary tract infections. However, at the initial consultation, all immunoglobulin levels were undetectable with normal lymphocyte subsets. Due to recurrent tracheitis and persistent hypogammaglobulinemia after 6 months of age, he was treated with monthly intravenous immunoglobulin replacement with an appropriate increase in IgG immunoglobulin levels and decreased frequency of infections. Eventually, a primary immunodeficiency genetic panel was completed and revealed two heterozygous variants of unknown significance in GUCY2C (c. 1735T>C, p.Tyr579His) and RTEL1 (c.2957G>A, p.Arg986Gln) genes, the latter of which has been associated with both cellular and humoral immunodeficiency in patients with homozygous mutations.

Discussion: This case highlights the possibility of severe immunodeficiency in patients with a heterozygous RTEL1 mutation and the need for long-term immunological monitoring in these patients. Although an RTEL1 mutation has not been described as pathogenic for immune dysfunction, this patient's clinical presentation, consisting of persistent hypogammaglobulinemia and recurrent infections, suggests that heterozygous mutations in RTEL1 should be considered as clinically significant when evaluating patients with immunodeficiency.

Tabular data are included as downloadable supplement files.

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Hypomorphic SCID Due to LIG4 Deficiency Not Detected on Newborn Screening

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DNA ligase IV (LIG4) is essential for repairing breaks in double-stranded DNA via nonhomologous end-joining in developing lymphocytes and is particularly important for V(D)J recombination. First described in the early 2000s, LIG4 deficiency is an autosomal recessive disorder characterized by hypomorphic T-B-NK+ severe combined immunodeficiency (SCID), as well as growth restriction with marked microcephaly, radiosensitivity, developmental delay, bone and skin abnormalities, and increased risk of hematologic malignancy. We describe a case of hypomorphic SCID due to LIG4 deficiency missed on newborn screening.

A 6-month-old male was referred to genetics given severe growth restriction, with microcephaly out of proportion to weight (weight Z-score –3.5, head circumference Z-score –7). He was born at 37 weeks' gestation after induction of labor for growth restriction, with a birth weight of 3 lb 14 oz. Pregnancy was otherwise uncomplicated. He had 2 normal Pennsylvania newborn screens for SCID. He had no infectious history and was meeting milestones. There was no family history of immunodeficiency or growth failure. Trio exome sequencing identified compound heterozygous likely pathogenic variants in LIG4: a maternally inherited missense variant (c.743C>T, p.(Pro248Leu) and a paternally inherited frameshift variant (c.1512_1513dup, p.(Arg505Leufs*9)).

He was then referred to immunology. Lymphocyte subsets revealed T and B cell lymphopenia: CD3 451 cells/μL, CD4 158 cells/μL (40% naive), CD8 222 cells/μL, and CD19 345 cells/μL, with normal natural killer (NK) cells. T cell proliferation to PHA mitogen stimulation and TCR V-beta spectratyping were normal. T cell receptor excision circles (TRECs) were low at 1,059 copies/μL, meeting criteria for hypomorphic SCID. DNA repair assessment in lymphocytes testing demonstrated defective repair in double-stranded DNA breaks at 24 hours post-irradiation, confirming radiosensitivity. He had no evidence of Omenn syndrome or maternal engraftment. He began immunoglobulin replacement therapy and fluconazole and trimethoprim-sulfamethoxazole prophylaxis.

He subsequently underwent maternal haploidentical TCRab/CD19-depleted peripheral stem cell transplant, conditioned with thymoglobulin, low-dose treosulfan, low-dose cyclophosphamide, and fludarabine, a modified regimen considering his DNA repair defect. He is approximately D+50 and recovering from a transplant outpatient.

This case highlights a case of SCID missed on newborn screening, despite low TRECs at diagnosis. We also report two previously unpublished variants leading to LIG4 deficiency.

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Idiopathic Combined Immunodeficiency Associated with Primary Pulmonary Sporotrichosis

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Introduction: Sporotrichosis is an uncommon but emerging opportunistic infection in immunocompromised patients. Primary pulmonary sporotrichosis can disseminate and result in significant morbidity and mortality, despite treatment. Pulmonary sporotrichosis has largely been associated with immunocompromised patients with human immunodeficiency virus (HIV) and disseminated infection. We present the first reported case of a patient with HIV-negative, idiopathic combined immunodeficiency (ICID) and primary pulmonary sporotrichosis.
Case Presentation: A 64-year-old male with a past medical history of prostate cancer, status post radiation, recurrent sinusitis, allergic rhinitis, and mild persistent asthma presented to our allergy/immunology clinic concerning recurrent sinopulmonary infections and a 4-month history of worsened chronic cough. An immunodeficiency workup revealed a B cell defect, given no pneumococcal polysaccharide vaccine response; a T cell defect, involving cluster of differentiation 4 T lymphocyte deficiency without HIV infection; no clinically significant genetic variants associated with primary immunodeficiency (PID); and diffuse bronchial wall thickening with bilateral mild central bronchiectasis, multifocal mucous plugging/mucoceles on high-resolution CT chest. Daily trimethoprim-sulfamethoxazole prophylaxis was initiated. Growth of *Sporotrichum* species on fungal culture prompted initiation of long-term oral itraconazole, which subsequently improved respiratory symptoms. Intravenous immunoglobulin was also initiated for the B cell defect and further infection prevention.
Discussion: The present literature is limited to case reports and small-scale retrospective cohort studies of patients with HIV and disseminated sporotrichosis, with very few case reports on associated primary immunodeficiency. This case contributed to the limited literature on pulmonary sporotrichosis and success with itraconazole. Optimizing pulmonary hygiene, infection precautions, and immediate initiation of pulmonary sporotrichosis treatment improved respiratory symptoms and quality of life.
Conclusion: Extracutaneous sporotrichosis primarily targets immunocompromised patients and is associated with significant morbidity and mortality. The present literature is limited to case reports and small-scale retrospective cohort studies of patients with HIV and disseminated sporotrichosis, with very few case reports on associated PIDs. We offer the first reported case of primary pulmonary sporotrichosis in a patient with ICID and have found success with long-term itraconazole therapy to date. A comprehensive approach to patient care guides accurate diagnosis and management of immunodeficiency and associated opportunistic infection.

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Immune Features of Chromosome 22q11.2 Deletion Syndrome

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Background: Chromosome 22q11.2 deletion syndrome is the most common microdeletion chromosomal anomaly. Frequent infections have been described as a major feature of immunodeficiency noted in 22qDS. Immune dysregulation is also noted in 22qDS, including autoimmunity. Recurrent fevers without infections are not typically well described in 22qDS. The aim of this project was to study the noninfectious issues in 22qDS patients.
Methods: This was a retrospective database report from USIDNet. We collected data about patients with an International Classification of Diseases (ICD) diagnostic code for chromosome 22q11.2 deletion syndrome, velocardiofacial syndrome, and DiGeorge syndrome. We studied these patients and their encounters with recurrent fevers, cytopenias, or autoimmunity. We performed descriptive analysis.
Results: USIDNet cohort from 2018–2024 included 1,456 patients with ICD codes: Q93.81, D82.1, Q92.2, Q93.88, Q21.3, and O35.19X0. This cohort includes chromosome 22q11.2 deletion (n = 1,428) and chromosome 22q11.2 duplication syndrome (n = 9, encounters 26). We reviewed 20,163 encounters for these patients. Patients had a range of encounters from 0 to 299 unique encounters (0 = no encounters,

diagnosis listed in problem list). Out of 1,456 patients, 134 patients had thrombocytopenia with 366 unique encounters and another 14 patients had easy bruising or bleeding accounting with 17 unique encounters, 145 patients reported recurrent fevers with 335 unique encounters, 27 patients reported arthritis or joint swelling redness with 246 unique encounters, 63 patients had neoplasms with 178 unique encounters, 77 patients had diarrhea with 142 unique encounters, and 34 patients were noted to have thyroiditis with 120 unique encounters.
Conclusions: Chromosome 22q11.2-related disorder deletion or duplication are associated with recurrent fevers, autoimmunity, cytopenias, and significantly contribute to the morbidity in these disorders.

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Immune Thrombocytopenic Purpura as a Herald of Underlying X-Linked Immunodeficiency with Magnesium Defect, Epstein-Barr Virus Infection, and Neoplasia (XMEN) Disease in a Pediatric Patient

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Background: Loss-of-function variants in magnesium transporter 1 (MAGT1) cause X-linked Immunodeficiency with Magnesium defect, Epstein-Barr virus infection, and Neoplasia (XMEN) disease through impaired glycosylation. The impaired glycosylation impacts several lymphocytic proteins, resulting in immune dysregulation (e.g., autoimmune cytopenias, hypogammaglobulinemia, recurrent infections, etc.) as well as platelet receptors leading to platelet function defects. Given the risk of both immune thrombocytopenia (ITP) and platelet dysfunction, successful treatment for ITP is critical to limiting bleeding risk. American Society of Hematology (ASH) ITP guidelines rely on thrombopoietin receptor (TPO) agonists if there is not an adequate response to first-line therapy. However, there are limited reports of the utility of standard ITP-directed therapies, particularly TPO agonists, in XMEN disease. Literature review identifies 7 cases of ITP in XMEN with variable response to TPO agonists and limited clinical details.
Case: Following a COVID-19 infection, a 10-year-old male presented with epistaxis and severe thrombocytopenia (platelets 8,000/μL), hypogammaglobulinemia (IgG 370 mg/dL, IgA <7 mg/dL, and IgM 18 mg/dL), and a normal bone marrow biopsy. He was diagnosed with ITP and treated with prednisolone and intravenous immunoglobulin (IVIG) with an adequate platelet rise. He required multiple courses of corticosteroids and IVIG and suffered a subgaleal hemorrhage after head trauma. Genetic testing via a commercial next generation sequencing (NGS) immune and cytopenia panel (642 genes) revealed a hemizygous variant of uncertain significance in MAGT1, denoted as c.628-2A>G. This variant was found to be maternally inherited, and ultimately reclassified as likely pathogenic, consistent with a diagnosis of XMEN disease. Due to persistence of thrombocytopenia and bleeding symptoms, he was started on a TPO agonist, eltrombopag, at age 11 years with a variable response. At age 14 years, he redeveloped severe thrombocytopenia refractory to escalated doses of eltrombopag. Of note, he remains EBV-naïve.
Conclusion: The optimal treatment for severe ITP associated with XMEN disease remains unclear. Urgency remains to determine efficacious treatment modalities given the compounding platelet dysfunction in XMEN disease exacerbates the bleeding risk.

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In Silico Hypersensitivity Risk Assessment of Product-Specific Human Contaminant Proteins in Commercial IVIg Products

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Background: Intravenous immunoglobulin (IVIg) products are widely used to treat immune deficiency and autoimmune disorders; however, infusion-related reactions remain a significant clinical concern. Differences in tolerability among commercial Ig products may be associated with variability in the number and types of human contaminant proteins (HCPs). HCPs may directly activate immune pathways or indirectly contribute to immune activation. We hypothesized that product-specific differences in HCP content may underlie patient-to-patient variability in infusion reactions and overall immunogenicity risk.

Methods: To assess this, we applied the ISPRI-HCP in silico immunogenicity platform, which integrates validated EpiVax tools (EpiMatrix, JanusMatrix, and ClustiMer) to evaluate T cell epitope density and human proteome cross-conservation in four commercial IVIg products. HCP were identified by liquid chromatography and mass spectrometry and assigned immunogenicity scores. Plotting the scores by epitope density (EpiMatrix) and humanness (JanusMatrix) enabled direct comparison of immunogenicity profiles across products.

Results: Substantial differences in HCP burden were observed: Products A, B, C, and D contained 7, 19, 14, and 31 HCPs, respectively (Figure 1). Some HCPs were shared among products, while others were unique, reflecting product-specific manufacturing or purification differences. Product A contained the fewest HCPs overall. Quadrant analyses showed that product A also had a greater proportion of HCP immunogenic regions (clusters) that were highly cross-conserved with other human T cell epitopes (quadrant 2) (Figure 2). In contrast, products B–D displayed higher frequencies (>66%) of HCP clusters in quadrant 1, indicating higher predicted immunogenic potential. Across products, certain shared HCPs—such as complement factor C3—that had high epitope density and limited cross-conservation, were also prevalent.

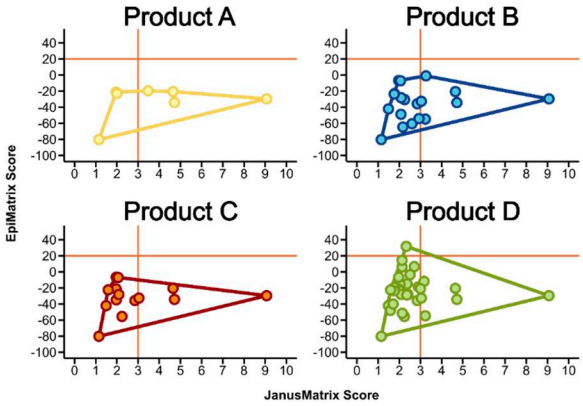

Figure 1. **IVIg products classified by immunogenic potential of HCP content. Characterization of host cell proteins (HCPs) by immunogenicity metrics.** Each subplot represents one of the four products. Within each subplot, the individual HCPs are plotted based on their JanusMatrix Score (x-axis) and EpiMatrix Score (y-axis). The outline of each product's HCP population is shown to facilitate visual comparison across subplots. EpiMatrix scores quantify epitope density normalized by protein length, enabling comparison across proteins of different sizes. JanusMatrix scores quantify the degree of cross-conservation between putative T cell epitopes and the human proteome. To obtain these scores, HCP proteins were parsed into overlapping 9-mer peptides, and each 9-mer was evaluated using the EpiMatrix algorithm for MHC class II-binding potential and using the JanusMatrix algorithm for sequence identity of TCR-facing residues to the human proteome.

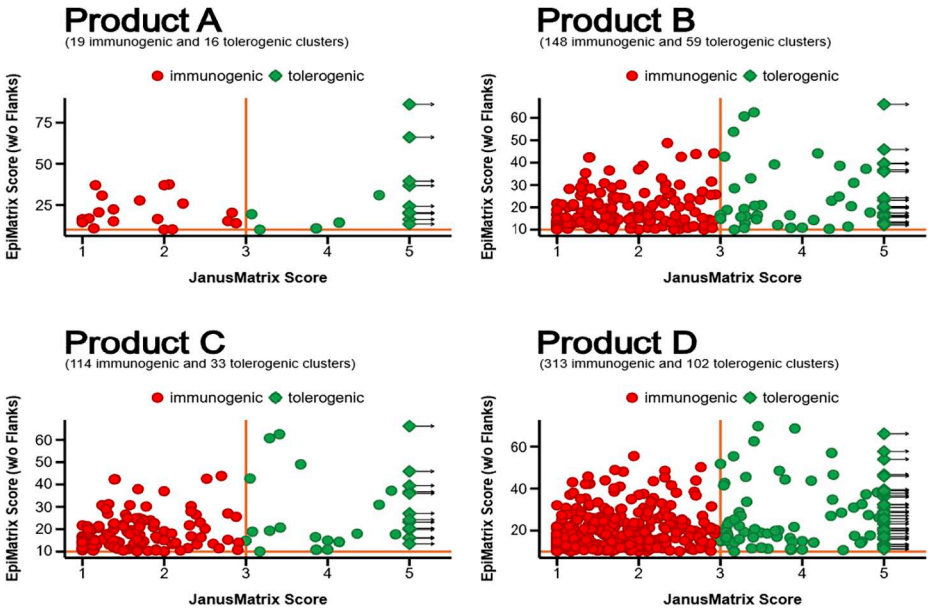

Figure 2. **IVIg Products classified by potential immunogenicity of class II "clusters" HCP sequences. Characterization of host cell proteins (HCPs) by immunogenicity metrics.** Each subplot represents one of the four products. Within each subplot, individual epitope clusters are plotted using the JanusMatrix

Score on the x-axis and the EpiMatrix Score on the y-axis. Clusters are epitope-dense regions within a protein. Each point represents a single cluster identified from any HCP sequence found in the product. Proteins containing multiple clusters contribute multiple points. To obtain cluster scores, proteins were first parsed into overlapping 9-mer peptides, and each 9-mer was evaluated using the EpiMatrix algorithm for MHC class II-binding potential. Epitope-dense regions (clusters) were then identified using ClustiMer. These were then characterized using the JanusMatrix algorithm to determine similarity to the human proteome. Red clusters have higher immunogenic potential than green clusters, which are highly conserved within the human proteome.

Conclusion: Product A demonstrated the lowest predicted in silico immunogenicity risk based on its reduced HCP burden, higher humanness of its HCPs, and fewer high-risk epitope clusters. This analysis highlights the value of in silico HCP screening for identifying product-specific immunogenicity drivers and informing future IVIg product optimization.

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In Utero Exposure to Azathioprine as Cause of Severe Newborn Lymphopenia

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Introduction: Low T cell receptor excision circles (TRECs) on newborn screen and severe T cell lymphopenia in a term newborn raise concern for severe combined immunodeficiency (SCID). Genetic polymorphisms in thiopurine methyltransferase (TPMT) can alter the metabolism of the purine analogue azathioprine to toxic metabolites, including 6-mercaptopurine, resulting in severe T cell apoptosis and deficiency. We present an infant with twice abnormal newborn screen for TRECs and severe lymphopenia resulting from in utero azathioprine exposure.

Case Presentation: A 9-day-old term newborn female with twice abnormal TREC screen appeared well with normal physical examination. Initial lymphocyte phenotyping demonstrated T cell lymphopenia (CD3+ 322/µL), absent B cells, and low natural killer (NK) cells (CD16+/CD56+ 8/µL), suspicious of T-/B-/NK- SCID. IgM and IgA were absent, with normal IgG (907 mg/dL). ADA1 and purine nucleoside phosphorylase (PNP) enzyme activity were normal. Further T cell phenotyping revealed age-appropriate thymic T cell output (recent thymic emigrant T cells 71%) with predominance of naïve (80%) over memory (20%) CD4 T cells, which was not consistent with SCID, thymus aplasia, or maternal T cell engraftment. The mother reported a diagnosis of myasthenia gravis and was on azathioprine therapy during pregnancy. She had normal numbers of T cells (CD3+ 1354/µL), low B cells (CD19+ 75/µL) and low NK cells (CD16+/CD56+ 19/µL), and normal serum immunoglobulins with protective antibodies to Rubella (113.8 IU/mL). Infant pharmacogenetic testing showed the TPMT *3A/*3A genotype (poor azathioprine metabolizer) with confirmed low TPMT enzyme activity (<2.3 EU). Both parents carry the TPMT*3A genotype without respective maternal pharmacogenetic testing prior to starting azathioprine. Infant lymphocytes are repopulating in a manner consistent with a diagnosis of neonatal azathioprine toxicity (Figure 1) with mild T cell lymphopenia (CD3+1400/µL), normal B cells (CD19+ 1083/µL), and normal NK cells (CD16+/CD56+ 312/µL) at age 84 days with normal IgM and IgG.

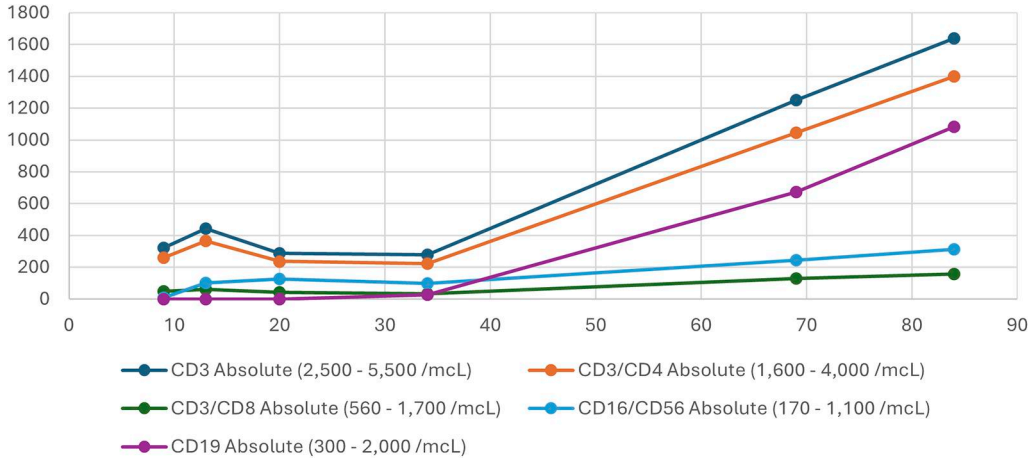

Figure 1. Postnatal lymphocyte development in an infant with twice abnormal newborn screen for SCID as a result of *in utero* exposure to azathioprine (reference ranges).

Discussion: This case underscores the importance of a detailed family and medication history for secondary causes of a SCID phenotype. Maternal TPMT genotyping and/or enzyme activity testing during pregnancy may inform about their infant's risk of lymphopenia through transplacental azathioprine exposure.

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Interferonopathies in Brazil: The Pivotal Role of the Interferon Signature for Diagnosis and for the Genetic Sequencing in the CNE3i

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Interferonopathies are rare autoinflammatory disorders driven by a constitutive upregulation of the type I interferon (IFN-I) pathway, leading to chronic activation of this cytokine. Despite advances, direct IFN-I measurement is challenging, making diagnosis reliant on clinical suspicion and genetic testing, which often yields inconclusive results due to a lack of established clinical criteria and the limited number of genes described as related to interferonopathies. Indirect methods, such as the "IFN signature" (expression of interferon-stimulated genes—ISGs), are used, but many patients still lack a confirmed genetic diagnosis. To this end, we aim to evaluate the clinical utility of the interferon signature as a diagnostic screening tool and to integrate it with genetic analysis in a cohort of Brazilian patients with suspected interferonopathy. We conducted a cross-sectional study within the Centro nacional de Erros Inatos da Imunidade e Imunodesregulação (CNE3i) (Certificate of Presentation for Ethical Consideration [CAAE]: 73174223.1.1001.0068). Patients with clinical suspicion of interferonopathy underwent peripheral blood collection for peripheral blood mononuclear cell (PBMC) isolation and RNA/DNA extraction. The IFN-I signature was assessed via quantitative PCR (qPCR) of a 6-gene panel (IFI27, ISG15, IFI44L, RSAD2, IFIT1, and SIGLEC1), and the IS (interferon score) was determined. All patients underwent exome sequencing (NovaSeqX), and Illumina EMEDGENE was used for secondary analysis. To date, 73 patients have been evaluated. The IS confirmed IFN-1 pathway activation (resulted positive) in 43/73 cases (59%). Among those with IS-positive patients, 27 (62%) remain without a definitive genetic diagnosis (Figure 1). Targeted reanalysis searching for genes involved in nucleic acid metabolism from exome data in 11 cases with positive IS identified potentially relevant variants of uncertain significance (VUS) in genes associated with interferonopathy (RNASEH2A, ADAR1, SAMHD1, PNPT1, and ATM). The interferon signature proved to be a highly effective front-line screening test, accurately stratifying 59% of clinically suspected cases. Its high positivity rate among undiagnosed patients (62%) underscores its critical role in confirming the pathophysiological

mechanism and prioritizing cases for advanced genomic investigation. The IS significantly aids in differentiating interferonopathies from other syndromes, reducing diagnostic delay, and providing a functional biomarker for future therapeutic monitoring. FINEP funding: 0956/24; FAPESP funding: 2023/09965-0; Instituto de Investigação em Imunologia funding CNPQ/MCTI: 408685/2024-7.

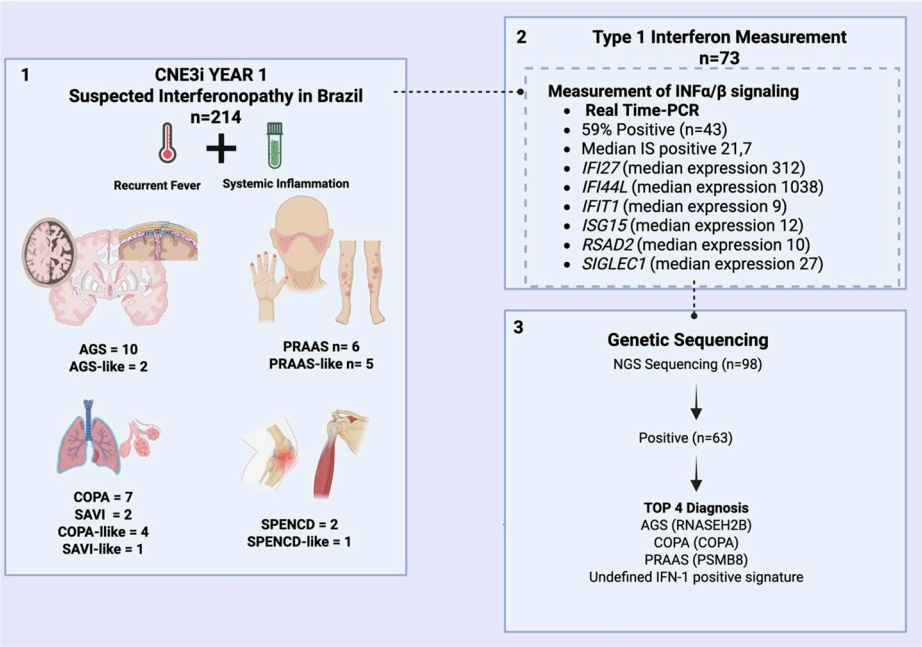

Figure 1. **Interferon signature in suspected interferonopathies at the CNE3i (Centro Nacional de Erros Inatos da Imunidade e Imunodesregulação) in Brazil.** (1) The number of samples received and the main clinical phenotypes. (2) The samples that have already been analyzed, along with the mean interferon score and the mean level of IFN gene expression. (3) The number of individuals who have already been sequenced and the top three diagnoses identified at the CNE3i. IS, interferon score; AGS, Aicardi-Goutières syndrome; PRAAS, proteasome-related autoinflammatory diseases; COPA, coatomer subunit alpha Protein; SAVI, STING-associated vasculopathy with infant onset; SPENCD, spondyloenchondrodysplasia with immune dysregulation.

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Invasive Haemophilus Influenzae Infection in a Neonate with an ERCC2-Related Disorder

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Introduction: The ERCC2 gene, located on chromosome 19, is essential for transcription and DNA repair via its protein product, XPD. Mutations in ERCC2 cause disorders such as trichothiodystrophy-1, xeroderma pigmentosum, Cockayne syndrome, or overlapping phenotypes. XPD functions as a helicase within the nucleotide excision repair pathway, correcting single-stranded DNA damage from ultraviolet radiation and chemical exposures. Immunologically, ERCC2 deficiency has been associated with increased infection susceptibility, potentially due to impaired adaptive immune responses.

Case Presentation: A female term infant was noted to be small for gestational age (2nd percentile) and microcephalic. She was admitted at 7 days of life (DOL) with acute hypoxemic respiratory failure secondary to Rhinovirus/Enterovirus infection. After initial improvement, she clinically worsened on DOL 12, requiring intubation, and was diagnosed with *Haemophilus influenzae* pneumonia and conjunctivitis. An immunologic evaluation on DOL 22 showed age-appropriate CD3, CD4, CD8, and CD19 counts but decreased CD16/56 cells, normal thymic T cell output (54% CD3+CD4+CD45RA+CD31+ cells), and a decrease in PHA-induced T cell proliferation. Immunoglobulins (mg/dL) were notable for elevated IgM and undetectable IgA (IgM 112, IgG 500). At DOL 36, infectious symptoms had improved on antibiotic therapy, and immunoglobulin levels normalized (IgM 58, IgG 292, IgA 11.6). Whole-genome sequencing, pursued due to neurologic concerns, revealed 2 inherited pathogenic ERCC2 variants in trans (c.1847 G>C; p.R616P and c.1996 C>T; p.R666W), consistent with compound heterozygosity and autosomal recessive ERCC2-related disorder.

Family history was largely unremarkable aside from reported adverse reactions to vaccines, resulting in reduced vaccinations of siblings (including no vaccines against *Haemophilus influenzae* B) who experienced upper respiratory infections at the time of her birth.

Discussion: This case describes an infant with an ERCC2-related disorder who developed an invasive *H. influenzae* infection. Given the patient's age, the infection was likely due to reduced herd immunity in her household rather than a direct consequence of ERCC2 dysfunction. However, early identification of the mutations is important, as ongoing immunologic assessment and characterization of her clinical phenotype will be required. Furthermore, impaired nucleotide excision repair increases long-term malignancy risk, underscoring the need for close multidisciplinary follow-up.

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Isolated Factor X Deficiency as an Immune-Mediated Complication of Waldenström Macroglobulinemia

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Unexplained coagulopathy with persistent anemia presents a significant diagnostic challenge and requires a broad differential. Isolated coagulation factor deficiencies are uncommon and described only sporadically in the literature. We present a case of Waldenström macroglobulinemia (WM) resulting in isolated factor X (FX) deficiency, causing bleeding diathesis and hemorrhagic shock. This case highlights a rare but severe immune-mediated complication of lymphoplasmacytic malignancy.

A 71-year-old woman with chronic kidney disease (CKD), insulin-dependent diabetes, and coronary artery disease (CAD) with recent stenting presented with weakness. She had multiple recent hospitalizations for similar symptoms, and prior evaluation revealed anemia and unexplained coagulopathy with elevated Prothrombin Time (PT)/International Normalized Ratio (INR). A hematologic workup was unrevealing until coagulation factor levels demonstrated isolated FX deficiency. An outpatient evaluation was planned, but she returned with worsening symptoms. On presentation, she had multiple hematomas involving the paraspinal muscles, abdomen, and flanks, along with gross hematuria.

Given the known association between FX deficiency and amyloidosis, a fat pad biopsy was obtained following aggressive correction with fresh frozen plasma. Despite this, she developed an expanding abdominal hematoma leading to hemodynamic instability requiring vasopressors, blood products, and prothrombin complex concentrate. She underwent surgical evacuation with subsequent stabilization of the bleeding. Further evaluation revealed an elevated serum IgM (1325 mg/dL), kappa light chain level of 355.2 mg/L, and a kappa/lambda ratio of 53.82. Urine immunofixation identified a free monoclonal kappa band. Although bone marrow biopsy was deferred, MYD88 L265P mutation testing returned positive, confirming WM. The patient's condition subsequently declined, and she was transitioned to hospice care.

WM is a lymphoplasmacytic disorder characterized by clonal IgM production, immune dysregulation, and multiorgan involvement. Acquired FX deficiency is a rare complication of hematologic malignancies, usually linked to amyloidosis or plasma cell dyscrasias. The combination of WM and FX deficiency is extremely uncommon, with only one prior case described, attributed to amyloid-related adsorption. This case demonstrates FX deficiency occurring in the absence of amyloidosis, suggesting alternative immunologic mechanisms such as antibody binding or paraprotein-mediated consumption. It expands the limited literature on immune-mediated coagulation abnormalities in WM and underscores the diagnostic and therapeutic challenges encountered.

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Learning From Loss: Early Identification of ADA-SCID After Sibling Mortality

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Introduction: Adenosine deaminase–deficient severe combined immunodeficiency (ADA-SCID) is an autosomal recessive disorder comprising ~15% of SCID cases. Newborn screening (NBS) relies on T cell receptor excision circle (TRECs) analysis, which may be normal at the time of testing. Once ADA-SCID is diagnosed, screening of family members is critical, as toxic metabolite accumulation leads to profound immunodeficiency, opportunistic infections, and multisystem organ dysfunction. We present an infant with a normal TRECs NBS who was diagnosed with ADA-SCID following post-mortem genetic testing of a deceased sibling.

Case Presentation: A previously healthy 2-month-old male presented with otitis media, oral thrush, and poor weight gain. TRECs NBS was normal. Family history was notable for an older brother who died at 2 years of age from fulminant hepatic failure attributed to hemophagocytic

lymphohistiocytosis (HLH). Given this history, soluble IL-2 receptor levels were evaluated in our patient and were markedly elevated (4,274 pg/mL), prompting evaluation for familial HLH. Initial laboratory studies demonstrated mildly decreased absolute lymphocyte count, elevated ferritin, hypertriglyceridemia, and normal hepatic function (supplemental table 1). HLH genetic sequencing panel was negative.

To clarify the diagnosis, post-mortem genetic testing of the sibling was performed and revealed compound heterozygous ADA variants: a pathogenic mutation, ADA1 c.632G>A (p.Arg211His), and a variant of uncertain significance, c.362+5G>C.

At 4 months of age, our patient's immunologic evaluation demonstrated worsening lymphopenia and eosinophilia (supplemental table 2). Flow cytometry showed declining CD4+ and CD8+ T cells, CD56+ natural killer (NK) cells, and CD19+ B cells over time (supplemental table 2). Genetic testing confirmed the same ADA variants in the patient associated with deficient ADA enzyme activity with elevated deoxyadenosine nucleotide levels (dAXP), confirming ADA-SCID (supplemental table 3).

Treatment included intravenous immunoglobulin (IVIG), antimicrobial prophylaxis, and PEGylated recombinant ADA (rADA) enzyme replacement therapy (ERT). By 8 weeks, ADA activity normalized, dAXP levels decreased, and lymphocyte counts improved. The patient remains clinically stable while awaiting hematopoietic stem cell transplantation.

Conclusion: This case underscores the importance of early recognition and a high index of suspicion for ADA-SCID, which may present with normal SCID NBS results. This case highlights the critical role of family genetic screening in enabling timely, life-saving intervention.

Tabular data are included as downloadable supplement files.

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Macrophage Activation Syndrome in MDA5-Positive Dermatomyositis: A Diagnostic and Therapeutic Odyssey in a Young Adult

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Introduction: Macrophage activation syndrome (MAS) is a rare, potentially fatal hyperinflammatory complication of autoimmune disease, characterized by fever, cytopenias, hyperferritinemia, and multiorgan involvement (1). In patients with inflammatory myopathies, MAS may mimic infection, pancreatitis, or medication reactions, posing diagnostic and management challenges (2).

Case Description: A 21-year-old male with atopic dermatitis and MDA5-positive dermatomyositis presented initially in October 2023 with fever, fatigue, lymphadenopathy, and rash; EBV serology suggested infectious mononucleosis. Over subsequent months, he developed daily fevers, unintentional weight loss, proximal muscle weakness, inflammatory arthritis, and evolving rash. Laboratory evaluation revealed elevated creatine kinase (CK) (~300s), ferritin 4,000–5,000 ng/mL, pancytopenia, elevated liver function tests (LFTs), and inflammatory markers. Imaging ruled out pancreatitis despite abdominal symptoms. Extensive workup included skin, liver, and bone marrow biopsies; autoimmune and infectious panels were otherwise unrevealing. MAS was suspected in February 2024 after worsening cytopenias and rising ferritin. The patient was admitted and treated with pulse IV methylprednisolone and intravenous immunoglobulin (IVIG), resulting in stabilization. Rituximab was attempted in April 2024 but discontinued due to an infusion reaction. Maintenance therapy included mycophenolic acid, hydroxychloroquine, and IVIG, with a gradual steroid taper. Long-term follow-up (through 2025) showed sustained remission, resolution of rash and systemic symptoms, and no evidence of active myositis or MAS flares.

Discussion: MAS complicating MDA5-positive dermatomyositis is rare, life-threatening, and diagnostically challenging (2, 3). High clinical suspicion is warranted in patients with fever, hyperferritinemia, cytopenias, and multisystem involvement. Prompt high-dose corticosteroids and IVIG can induce remission, while biologics may be required in refractory cases. Multidisciplinary care and longitudinal monitoring (labs, IVIG cycles, and pulmonary evaluation) optimize outcomes.

Conclusions: MAS should be considered in young adults with inflammatory myopathies presenting with persistent fever, cytopenias, and hyperferritinemia. Early recognition, aggressive immunosuppression, and coordinated care are essential to achieve remission and prevent long-term complications.

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Malignancy Is Associated with Disorders of Immunity in a Large U.S. Cohort: An All of Us Research Program Study

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[1]NIH/NIAID

Background: Although the association between disorders of immunity and cancer risk is recognized, the prevalence of different malignancies in this population remains incompletely characterized. Large electronic health record (EHR) databases such as the National Institutes of Health's All of Us Research Program (AOURP) offer the opportunity to evaluate the prevalence of malignancy in this population.

Methods: Diagnostic codes from the EHR of 393,601 participants in AOURP were analyzed. Diagnostic codes were queried for immune disorders (ID). The cohort of participants with ID was compared to a cohort of control participants. Participants were then queried for a diagnosis of malignancy. Control diagnoses with no biological association with ID were selected for comparison. The relative risk of these diagnoses for those with ID was calculated.

Results: Of 256,388 participants with at least one ICD9, ICD10, or SNOMED code in AOURP, 12,886 had at least one diagnostic code for ID (supplemental table 2). The control cohort of 243,502 remaining participants was well matched to the ID cohort for sex, race, and ethnicity (supplemental table 1). The ID cohort skewed slightly older than the controls, likely due to the inclusion of acquired ID and autoimmune conditions, which often develop with age. The median number of diagnoses in the ID cohort was 121 (interquartile range [IQR] 71–190), greater than 35 (IQR 13–76) in the control cohort, reflecting richer EHR data and medical complexity among those participants with ID.

Relative risk (RR) was low (<2) for all control diagnoses, as well as for prostate cancer (1.58) and breast cancer (1.96). However, RR increased for other solid tumors, including melanoma (2.67), lung cancer (3.43), and pancreatic cancer (3.58). Importantly, the highest risk for the ID cohort was for hematologic malignancy, with 8x lymphoma and 9x leukemia risk (Figure 1).

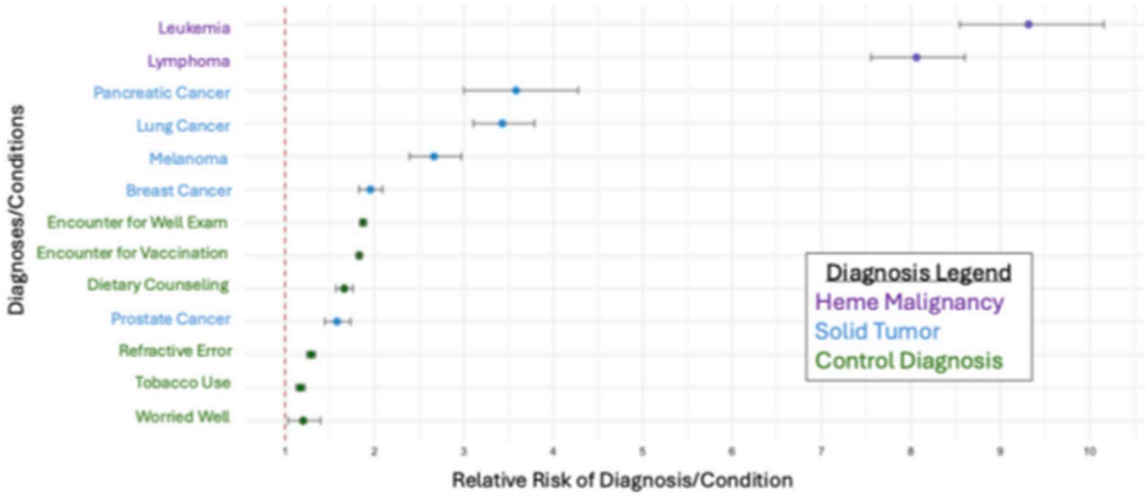

Figure 1. **Relative risk of control and malignancy diagnoses for immune disorder participants.**

Conclusions: In this cohort, disorders of immunity were strongly associated with lymphomas and leukemias. Notably, participants with an ID diagnosis also had a greater risk of some solid tumor malignancies such as lung cancer, melanoma, and pancreatic cancer. Conversely, risks for other common solid tumors, such as prostate and breast cancer, did not differ from those of control diagnoses.

Tabular data are included as downloadable supplement files.

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Mosaic KRAS Mutation Leading to RAS-Associated Autoimmune Leukoproliferative Disorder

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Background: RAS-associated autoimmune leukoproliferative disorder (RALD) is a rare immune-dysregulation syndrome caused by pathogenic mutations in RAS–MAPK pathway genes, most commonly KRAS. It is characterized by autoimmune cytopenias, monocytosis, hepatosplenomegaly, and chronic lymphoproliferation without malignant transformation.

Case Presentation: We report a case of a 3-year-old Saudi girl with a mosaic pathogenic variant in the KRAS gene. She was born at term with an unremarkable neonatal period and remained well until 1 year and 9 months of age, when she presented with fever, respiratory symptoms, skin rash, and epistaxis. Evaluation revealed splenomegaly, pancytopenia, and lobar pneumonia, for which she was treated with antibiotics and oral prednisolone 2 mg/kg/day for 4 weeks, followed by a gradual taper over 2 months targeting autoimmune cytopenias.

Following the initial episode, she experienced recurrent admissions every 2–3 months for respiratory or gastrointestinal infections. Her weight remained below the 3rd percentile; however, no dysmorphic features or lymphadenopathy were noted. Immunologic evaluation revealed B cell lymphocytosis (CD19: 3,127 cells/μL), persistent monocytosis (>1,500 cells/μL), and a positive Coombs test. Bone marrow analysis demonstrated left-shifted granulopoiesis with normal blast percentage. Serial abdominal ultrasounds showed progressive splenomegaly (10 → 11.3 → 13 cm within one year) and mild hepatomegaly.

Whole-exome sequencing identified a mosaic KRAS c.37G>T (p.Gly13Cys) pathological variant with a 14% allelic ratio. This variant has been previously reported to cause a gain-of-function KRAS, confirming the diagnosis of RALD. She also developed hypothyroidism, treated with levothyroxine.

Sirolimus was later initiated to control cytopenias and lymphoproliferation, with partial clinical response. She is currently undergoing evaluation for hematopoietic stem cell transplantation (HSCT) pending matched donor availability.

Conclusion: This case emphasizes the importance of considering molecular testing in children with early-onset autoimmune cytopenias and splenomegaly. Evaluation for mosaicism is critical in suspected RALD to ensure an accurate diagnosis and guide appropriate targeted management.

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Neonatal T Cell Lymphopenia as Presenting Finding in Bone Marrow Failure Syndrome

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Background: Newborn screening for severe combined immunodeficiency (SCID) using T cell receptor excision circles (TRECs) enables early detection of disorders affecting T cell development. While low TRECs typically indicate T cell lymphopenia due to primary immunodeficiency, other rare congenital or genetic conditions may also present with abnormal results. Fanconi anemia typically presents with a combination of progressive bone marrow failure, congenital physical abnormalities such as short stature, abnormal skin, and skeletal malformations, especially of the thumbs and forearms, and increased cancer risk, but the clinical spectrum is highly variable.

Case Presentation: A 2-week-old female was seen in the immunology clinic due to abnormal newborn TRECs screening. The infant was born at 37 weeks to non-consanguineous parents after a pregnancy complicated by maternal anemia and fetal intrauterine growth restriction (IUGR). Family history includes a maternal second cousin who has short stature and absent thumbs. The infant's parents and siblings were healthy. She had a normal physical exam, including the absence of skin lesions, microcephaly, or skeletal abnormalities. Her initial laboratory values included reduced WBC 4.61 x10e3/uL, reduced absolute neutrophil count (ANC) 1,040/ul. The remainder of her

complete blood count (CBC) was normal. Lymphocyte subset analysis revealed absolute CD3 count 1,018 (62%), CD4 count 622 (38%), CD8 count 369 (22%), CD19 count 397 (24%), CD16/56 count 490 (22.3%). The patient's genetic testing revealed a homozygous pathogenic variant in FANCD2 (c.2444 G>A), consistent with the diagnosis of Fanconi anemia (FA-D2).

Discussion: Fanconi anemia and other inherited bone marrow failure syndromes typically do not present with isolated T cell lymphopenia in the neonatal period, and their cytopenias often develop later in childhood. To our knowledge, this is the first report of Fanconi anemia being detected by newborn screen for SCID. Early diagnosis allows for surveillance for progressive bone marrow failure and malignancy.

Conclusion: This case highlights the value of obtaining genetic testing early in the evaluation of an infant with lymphopenia. Early diagnosis allows for anticipatory guidance, multidisciplinary management, surveillance for hematologic complications and family counseling regarding genetic risks.

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Newborn Screening Inborn Errors of Immunity in the Republic of Belarus: The First Pilot Study

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Background and Aims: The primary focus of neonatal screening is the early detection of asymptomatic infants with a range of serious diseases for which effective treatment is available and for which early diagnosis and intervention will prevent serious consequences. Severe combined immunodeficiency (SCID) is a congenital disorder of immune function that requires prompt diagnosis and treatment to prevent life-threatening infections, improving survival and quality of life. The absence of functional T and/or B lymphocytes in congenital immune disorders serves as a diagnostic criterion used for newborn screening. Currently, an early diagnostic method exists based on the detection of T and B lymphocyte receptor gene recombination products (TREC/KREC).

Methods: Newborn screening for inborn errors of immunity, characterized by T and/or B cell lymphopenia, was carried out in a pilot program in the 2 regions of the Republic of Belarus, over a 2-year period (2023–2025), encompassing 27,796 newborns. The number of T cell receptor excision circles (TREC) and kappa-deleting recombination excision circles (KREC) was measured using multiplex real-time quantitative PCR (RQ-PCR) on DNA isolated from dried blood spots of neonatal screening cards. The number of copies of TREC/KREC was calculated per 1 million leukocytes using the formula: [1,000,000 × SQ TREC (KREC)/SQ ALB/2].

Results: Fourteen children were recalled for re-examination due to low TREC and/or KREC levels. However, upon retesting, TREC and KREC values were within the normal range. During screening, one child was found to have a low TREC copy number—433 copies (2,200–45,000 copies)—with a normal KREC copy number. Upon examination, the child had DiGeorge syndrome. One child with a normal TREC copy number had absent B lymphocytes, which was also confirmed by lymphocyte immunophenotyping. Based on genetic testing, he was diagnosed with X-linked agammaglobulinemia with a mutation in the BTK gene.

Conclusions: This is the first large-scale screening study in the Republic of Belarus with simultaneous detection of TREC and KREC, allowing the identification of newborns with defects in both T and B cells.

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Novel FOXN1 Variant as Cause of Neonatal T Cell Lymphopenia

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In the last decade, diagnostic detection of severe combined immune deficiency (SCID) has improved with the widespread implementation of universal newborn screening (NBS) for SCID in the United States. Our case identifies a novel variant of forkhead box protein N1 (FOXN1) deficiency, identified after NBS.

A 1,683 g male infant, born at 31w2d by spontaneous vaginal delivery in the setting of preterm premature rupture of membranes and maternal chorioamnionitis, was found to have initial NBS inconclusive for SCID. Family history was unremarkable. He was admitted to the neonatal intensive care unit (NICU) for respiratory distress syndrome, prematurity, and hyperbilirubinemia. He developed *Enterococcus faecalis* urinary tract infection and was treated with piperacillin-tazobactam followed by ampicillin.

Both the second and third NBS remained inconclusive for SCID. Laboratory studies revealed markedly low T lymphocyte counts (cells/uL): CD3+ 208, CD4+ 119, CD8+ 89, CD45RA 67, and CD45RO 25, with normal CD19+ B cells (574) and normal natural killer (NK) cells (158). Eosinophil counts were normal, and the physical exam was unremarkable. CMV, EBV, HSV PCRs, and HIV-1 RNA PCR were negative. While awaiting additional workup, he was started on *Pneumocystis jirovecii* (PJP) and antifungal prophylaxis with pentamidine and fluconazole, respectively, as well as intravenous immune globulin. Isolation precautions were instituted, and maternal breast milk was initially withheld until maternal CMV resulted negative.

Maternal engraftment studies were negative. T cell proliferation assay with phytohemagglutinin (PHA) was normal. Ultimately, rapid targeted analysis of the genome (rTAG) revealed a heterozygous, paternally inherited variant of uncertain significance (VUS) in FOXN1 (supplemental table), deemed the likely cause of his presentation. Repeat lymphocyte subset enumeration two months later showed persistent T cell lymphopenia: CD3+ 318, CD4+ 184, CD8+ 95.

We herein present a novel heterozygous variant in FOXN1 associated with T cell lymphopenia not yet reported in large population databases (ClinVar, gnomAD). Patients with FOXN1 heterozygous haploinsufficiency have variable clinical presentations and trajectories, though generally, T lymphocyte enumeration and function are thought to improve over time. Our case may assist clinicians who encounter patients with similar phenotypes and demonstrates the value of NBS combined with immunogenetic testing to guide management prior to the onset of potentially fatal infection.

Tabular data are included as downloadable supplement files.

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Novel NLRC4 Variant in a Young Female with Recurrent Rash and Fever

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We report a previously healthy 4-year-old female presenting with a diffuse, recurrent, pruritic, erythematous rash involving the entire body with eight episodes over 2 years, each lasting 7–10 days. The rash reliably appears 2–3 days before the fever begins. Other symptoms include cough, rhinorrhea, or sore throat, and during her most recent episode, oral ulcers and conjunctivitis. The rash starts on the face and spreads caudally to involve the entire body. It intensifies during the febrile phase and persists for several days after the fever resolves. Individual lesions last longer than 24 hours, and antihistamines (loratadine, diphenhydramine) have provided minimal benefit.

Family denies noticing signs of joint pain or identifiable triggers for the rash. Her growth is normal with no weight loss, diarrhea, or bloody stools. She has no history of atopy or recurrent or severe infections. Family history is notable for psoriasis, eczema, and hypertension in an older sister, and lupus in a maternal cousin.

Immunologic evaluation showed normal T, B, and natural killer (NK) cell counts and normal IgG, IgA, and IgM levels. Tetanus IgG level was protective. *Streptococcus pneumoniae* IgG levels were nonprotective, with post-vaccination levels pending. HSV PCR and throat cultures for group A *Streptococcus* were repeatedly negative.

Genetic testing via a gene panel for autoinflammatory and autoimmune syndromes identified a variant of uncertain significance in NLR-family CARD domain-containing protein 4 (NLRC4) at c.1363C>T (p.Leu455Phe). NLRC4 mutations are associated with autosomal-dominant familial cold autoinflammatory syndrome 4 (FCAS 4) and periodic fever-infantile enterocolitis-autoinflammatory syndrome.

This is a missense variant that has not been previously reported; it has a gnomAD (v4.1.0) frequency of 0.000006815, a high Combined Annotation Dependent Depletion [CADD] score of 23.6, and a PolyPhen score of 0.994 (which categorizes it as probably damaging).

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Overlap in Immunologic Pathways Between Asthma and Primary Immunodeficiency Disorders

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Background: Asthma is traditionally conceptualized as a T helper 2 (Th2)-mediated inflammatory airway disease. However, increasing evidence suggests that primary immune dysregulation may underlie or phenotypically mimic asthma in a subset of patients. Overlap between atopy and primary immunodeficiency disorders (PIDs) complicates diagnosis, delays appropriate evaluation, and may lead to suboptimal therapy when immune defects are unrecognized.
Objective: To review the clinical phenotypes and immunologic mechanisms linking asthma with primary immunodeficiency disorders and to identify clinical and immunologic features that should prompt immune evaluation in patients with severe, refractory, or atypical asthma.
Methods: A narrative literature review was conducted using PubMed and Scopus databases, covering publications from 2020 to 2025. Studies describing asthma-like airway manifestations, immune pathways, and treatment responses in PIDs were identified. Disorders were categorized by underlying immunologic defect and associated clinical features.
Results: Several PIDs, including common variable immunodeficiency, selective IgA deficiency, hyper-IgE syndromes, and STAT3- or DOCK8-related disorders, are associated with asthma-like airway inflammation and recurrent wheezing. Shared immunologic mechanisms include Th2 polarization with elevated IL-4, IL-5, and IL-13 signaling; impaired regulatory T cell function; defective mucosal antibody production; and chronic airway epithelial inflammation. These abnormalities may coexist with immune deficiency rather than classic allergic sensitization alone. Clinically, recurrent or severe sinopulmonary infections, poor or incomplete response to inhaled or systemic corticosteroids, early-onset bronchiectasis, and multisystem involvement serve as key clues distinguishing immune dysregulation from isolated atopic asthma.
Conclusion: Asthma and primary immune dysregulation represent a spectrum of aberrant immune responses rather than discrete clinical entities. Recognition of immune deficiency patterns in patients with difficult-to-control or atypical asthma can facilitate earlier immunologic evaluation, guide decisions regarding immunoglobulin replacement, and inform selection of targeted biologic therapies. Increased awareness of these overlaps is essential for optimizing outcomes in patients with complex airway disease.

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Post-Covid-19 Rise in Postural Orthostatic Tachycardia Syndrome and Antibody Deficiency: Exploring Immunoglobulin Therapy for Symptom Management

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Since 2020, our clinic has observed a notable increase in primary immunodeficiency (PI) patients presenting with antibody deficiencies, despite previously reporting minimal illness or being clinically stable prior to the COVID-19 pandemic. Concurrently, we've documented a rapid rise in cases of Postural Orthostatic Tachycardia Syndrome (POTS) and related dysautonomia. Whereas only a handful of POTS patients were seen before 2020, our current clinic population exceeds 40, with roughly 80% also demonstrating antibody deficiency, most commonly Specific Antibody Deficiency (SAD). We conducted a retrospective review of five patients with SAD and POTS receiving intravenous immunoglobulin (IVIg) therapy in either the home infusion setting or our clinic. Comorbidities included other dysautonomia conditions, Lyme disease, and orthostatic hypotension. The cohort was all female, White, median age 25 years, and dosing of 0.62 g/kg/Q4Weeks over 10 months. Reported Adverse Drug Reactions (ADRs) were primarily headaches and fatigue, with one patient discontinuing

IVIg due to aseptic meningitis. Functional impact was substantial, with missed school, impaired work capacity, and reliance on online education. IgG levels improved in most patients. Patient-reported outcomes varied. Two described clear improvement in syncope, dizziness, and activity tolerance and one noted improved energy but no change in core POTS symptoms, one reported diminishing benefit over time, and one discontinued due to severe ADRs. Compared with other POTS treatments, IVIg was perceived superior by two patients, neutral by two, and intolerable by one. This review highlights a post-COVID-19 increase in patients presenting with both PI and POTS, with a notable overlap of SAD. While IVIg was associated with improved IgG levels and, in some cases, reduced syncope and fatigue, responses were heterogeneous. These findings suggest a possible immunologic contribution to POTS in the context of SAD, but the small sample size limits definitive conclusions. Future research should investigate correlations between new onset PI/SAD and POTS, the role of COVID-19 in triggering dysautonomia, and whether IVIg can be systematically evaluated as a therapeutic option. Larger, prospective studies are needed to clarify whether recurrent infections and immune dysfunction exacerbate POTS symptoms and to determine if IVIg can meaningfully improve quality of life.

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Paternal Inheritance of a Likely Pathogenic Variant of NFKB2 in the Setting of CVID in a 4-Year-Old

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Background: Common variable immunodeficiency (CVID) is diagnosed at ages ≥4 years with hypogammaglobulinemia across more than two immunoglobulin classes, leading to impaired vaccine responses, frequent infectious, autoimmune, and granulomatous complications. The underlying genetic mechanisms for CVID are poorly understood, and over 20 genetic causes have been described.

Importantly, NFKB2 is a central component of the non-canonical NFKB pathway, and its variants are among monogenic drivers of CVID-like phenotypes.

Case Presentation: A 4-year-old girl, born at 38w2d via spontaneous vaginal delivery, experienced near-weekly illnesses since 6 months of age, including croup, post-viral cough lasting 4–6 weeks, gastroenteritis, and recurrent bilateral otitis media refractory to four antibiotic courses. Immunologic testing revealed low IgG (343 mg/dL), low IgA (12 mg/dL), and low IgM (14 mg/dL), reduced B cells (244 cells/uL), and reduced responses to vaccines. Genetic testing identified a NFKB2 c.2594A>G (p.Asp865Gly) mutation. Patient's 38-year-old father was also found to have the same NFKB2 mutation and subsequently diagnosed with CVID. He also had a history of recurrent sinusitis, alopecia areata, and viral encephalitis. Labs showed low immunoglobulins of IgG (301 mg/dL), IgA (24 mg/dL), and IgM (9 mg/dL), low B cells (42 cells/uL), and an appropriate vaccine response. He received one dose of intravenous immunoglobulin (IVIG) following excision of newly diagnosed stage I colon cancer.

Discussion: Previous studies suggest this mutation causes an autosomal dominant syndrome of antibody deficiency. Although penetrance for NFKB2-related disorders is incomplete, the presentation in our patient and her father is supportive of an autosomal-dominant inheritance pattern. The patient's father was counseled on the 50% recurrence risk with strongly encouraged genetic testing for first-degree family members. The option of in vitro fertilization (IVF) with preimplantation genetic diagnosis was discussed, and the patient will also require adulthood counseling. Based on the father's diagnosis of colon cancer at age 38, all first-degree relatives were advised to start colorectal cancer screening at age 28. This case builds on previous studies of the hereditary nature of this NFKB2 mutation and its suspected role in the pathogenesis of familial inheritance of CVID, emphasizing the importance of timely genetic testing and counseling.

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Peripheral Expression of FOXP3 in Brazilian Patients with IPEX Syndrome: From FOXP3 Biomarker to Targeted FOXP3 Therapy Within the CNE3I

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Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a monogenic disorder caused by loss-of-function mutations in the FOXP3 gene, which is critical for the development of functional regulatory T cells (Tregs). In IPEX patients, Tregs are unable to inhibit effector T cell proliferation and cytokine production, leading to a loss of peripheral immune tolerance. The disease presents with heterogeneous clinical manifestations, severe early-onset autoimmunity, the classic triad (enteropathy, eczema, and type 1 diabetes), as well as atypical or late-onset symptoms. A clear genotype–phenotype correlation has not been established for IPEX, and immunological assessments that could contribute to the diagnosis are scarce. Therefore, we aim to characterize the peripheral Treg cells in IPEX patients in Brazil through combined quantitative and qualitative flow cytometry analysis. We enrolled 6 male patients with a confirmed IPEX diagnosis (clinical, genetic, and immunological). All patients exhibited autoimmunity (enteropathy: 5/6; arthritis: 3/6; hemolytic anemia: 2/6; type 1 diabetes: 2/6), and allergic manifestations (rhinitis: 6/6; asthma: 4/6), eczema (4/6), and recurrent sinusitis (4/6) were also observed. Up to the last follow-up, two patients were alive after bone marrow transplantation and one after gene therapy (Figure 1). Peripheral FOXP3 expression was assessed in peripheral blood mononuclear cells (PBMCs) by flow cytometry (CD3, CD4, CD25, CD127, and FOXP3). Quantitative analysis determined the frequency of Tregs (CD4+CD25+CD127-FOXP3+), while qualitative analysis measured FOXP3 protein expression via median fluorescence intensity (MFI). The frequency of circulating Tregs in IPEX patients from our cohort was highly variable (14.6%–81.2%; mean: 58.5%) and overlapped with the control range (59.6%–84.1%; mean: 72.4%). In contrast, FOXP3 MFI was significantly lower in patient Tregs (mean: 986, range: 863–1,276) compared to controls (mean: 1,937, range: 1,089–4,132; $p<0.05$), another indication of quantitative Treg defects. Different patterns of FOXP3 expression have been reported, depending on the type and location of the mutation. While Treg numbers can be preserved in IPEX syndrome, FOXP3 protein expression per cell is consistently and significantly reduced. This defect in the expression level of FOXP3 likely underlies Treg dysfunction and disease pathogenesis. Assessment of FOXP3 MFI emerges as an additional valuable complementary diagnostic tool, providing functional insight beyond genetic sequencing alone.

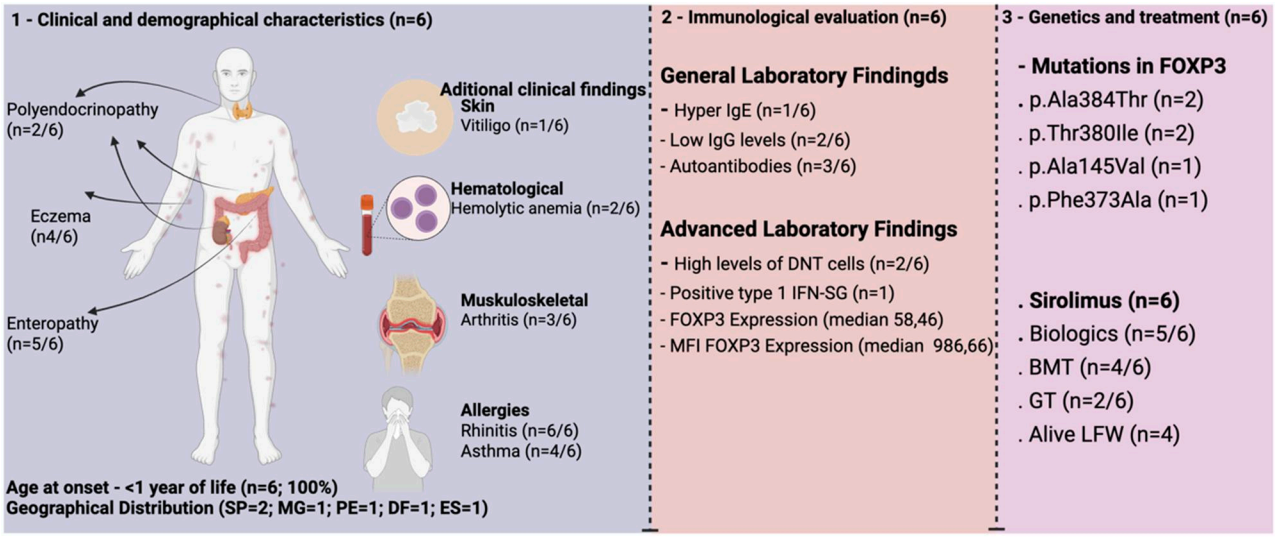

Figure 1. **Clinical, immunologic, genetic, and therapeutic findings for IPEX syndrome within the CNE3i (Centro Nacional de Erros Inatos da Imunidade e Imunodesregulação) in Brazil.** (1) Demonstrates the main clinical and geographical findings of the six IPEX patients; (2) general and advanced laboratory findings; and (3) genetics and therapeutics. SP, São Paulo; MG, Minas Gerais; PE, Pernambuco; DF, Distrito Federal; ES, Espírito Santo; IgE, immunoglobulin E; IgG immunoglobulin G; DNT, double negative T cells; IFN-SG, interferon-stimulated genes; MFI, median fluorescence intensity; BMT, bone marrow transplantation; GT, gene therapy; LFW, last follow-up.

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Primary Immune Regulatory Disorder with Features of Behçet's Disease: The Role of Persistent CMV Viremia in Inflammatory Bowel Disease Pathogenesis

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Background: Behçet's disease is a multisystem inflammatory disorder whose diagnosis can be challenging due to overlapping features with other inflammatory conditions and primary immunodeficiencies (1). In patients with immune dysregulation, the role of cytomegalovirus (CMV) in the development of inflammatory bowel disease remains poorly understood. We present a case of a patient initially diagnosed with Behçet's disease who subsequently developed Crohn's colitis in the setting of persistent CMV viremia and combined immunodeficiency.
Case Presentation: A 37-year-old woman was referred to our immunology service for recurrent sinopulmonary infections, hypogammaglobulinemia, and persistent CMV viremia. Her history included childhood varicella-zoster virus reactivation, chronic cytopenia, lymphadenopathy, hepatomegaly, and hypogammaglobulinemia. In 2017, she developed inflammatory arthralgias, oral ulcers, and biopsy-proven leukocytoclastic vasculitis, leading to a diagnosis of Behçet's disease. Her course was complicated by severe thrombocytopenia requiring rituximab and *Pneumocystis jirovecii* pneumonia, followed by neuro-Behçet's.

In 2022, she developed COVID-19 pneumonia, followed by CMV viremia. In 2024, she presented with chronic diarrhea, weight loss, and rising CMV viral loads. Immunologic evaluation demonstrated CD4+ lymphopenia, persistently low B cell counts, and absent CMV-specific T cell responses (supplementary table 1).

Colonoscopy confirmed Crohn's colitis with superimposed CMV colitis. A close temporal relationship was observed between gastrointestinal symptoms and CMV viral burden, with C-reactive protein (CRP) peaking at 226.90 mg/L, coinciding with CMV detection, improving following viral suppression (11.90 mg/L), and rebounding (73.20 mg/L) directly with CMV recurrence (supplementary table 2). Whole-exome sequencing identified a heterozygous likely pathogenic variant in the SLC46A1 gene (supplementary table 3).
Discussion: This case emphasizes the complex interplay between genetic predisposition, immune dysregulation, and viral triggers in the pathogenesis of inflammatory disease. Comprehensive immunological evaluation and serial viral monitoring may be critical in patients with atypical presentations of rheumatologic diseases, particularly when accompanied by recurrent infections or unusual laboratory findings.
Conclusion: Further investigation into the role of persistent viral infections and folate pathway abnormalities in immune dysregulation may provide insights into novel therapeutic approaches for patients with complex immune-mediated inflammatory disorders.

Tabular data are included as downloadable supplement files.

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PRIORITY Study: Baseline and Post-Rituximab Immune Profiles in a Pediatric Cohort

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Background: Pediatric utilization of rituximab encompasses autoimmune, renal, hematologic, and neurologic conditions. Its association with secondary hypogammaglobulinemia and unmasking of inborn errors of immunity is well recognized. However, incomplete pretreatment immune evaluation may lead to misattribution of preexisting immune abnormalities to rituximab or delayed recognition of underlying immune disorders. We conducted a quality improvement initiative to assess immune monitoring practices surrounding rituximab use at our institution.

Objectives: To evaluate the baseline frequency of pre- and post-rituximab immune testing and describe the prevalence of hypogammaglobulinemia before and after rituximab therapy using age-adjusted pediatric reference ranges. This was to identify potential care gaps and targets for quality improvement.
Methods: We conducted a retrospective chart review of pediatric patients treated with rituximab at McMaster Children's Hospital between 2022 and 2025. Extracted data included demographics, rituximab dosing, immunoglobulin levels (IgG, IgA, IgM, and IgE), and lymphocyte subsets (CD3, CD4, CD8, and natural killer [NK]) when available. Values were interpreted using age-specific reference ranges. Descriptive statistics were performed.
Results: Twenty-seven patients were included. Pre-rituximab IgG, IgA, and IgM levels were available in only 15/27 patients (55.6%). Post-rituximab IgG, IgA, and IgM levels were available in 16/27 patients (59.3%), with post-rituximab immunoglobulin measurements obtained at least one year after the final rituximab dose. Baseline lymphocyte subset analysis (CD3, CD4, CD8, and NK percentages) was available in 7/27 patients (25.9%), increasing to 13/27 (48.1%) post-rituximab. Among patients with available baseline IgG data, 6/15 (40.0%) had IgG levels below age-adjusted reference ranges prior to rituximab initiation, representing 22.2% of the total cohort. Post-rituximab, 9/16 patients (56.2%) had low IgG levels, representing 33.3% overall. Low baseline IgA was observed in 7/15 patients (46.7%), while low baseline IgM was uncommon, 1/15 (6.7%).
Conclusions: More than half of the children receiving rituximab lacked a complete baseline immune evaluation. A substantial proportion had hypogammaglobulinemia prior to therapy, particularly affecting IgG and IgA. These findings highlight gaps in immune monitoring and the risk of misattributing preexisting immune abnormalities to rituximab. Standardizing pre- and post-treatment immune testing across specialties is needed to improve the identification of treatment-associated immune complications and underlying inborn errors of immunity.

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Recurrent Aphthous Stomatitis, Gastrointestinal Inflammation, and Hyperinflammatory Features in a Child with IgA Deficiency: A Diagnostic Dilemma

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Background: Complex inflammatory phenotypes in children can pose significant diagnostic challenges, particularly when clinical, histopathologic, and immunologic findings do not conform to established diagnoses. We present a case of a child with recurrent severe aphthous stomatitis, abdominal pain, and constipation, with laboratory evidence of immune dysregulation and gastrointestinal inflammation on biopsy, whose underlying etiology remains undefined.
Case Presentation: A 6-year-old boy presented with a history of recurrent aphthous stomatitis, abdominal pain, and constipation since toddlerhood. Previously, oral lesions were mild, self-resolving, and occurred bimonthly without significantly impacting oral intake. Recently, he developed worsening and persistent symptoms with severe mucosal lesions limiting oral intake, low-grade fevers, and flares lasting weeks to months. Prior workup revealed IgA deficiency. Infectious workup, including herpes simplex virus (HSV) and varicella zoster virus (VZV), was negative. Trials of systemic corticosteroids and azithromycin provided no significant improvement.

Immunological evaluation revealed elevated inflammatory markers, including TNF-alpha, IFN-gamma, soluble IL-2 receptor, IL-12, IL-10, IL-8, and elevated CXCL9, suggesting innate or adaptive immune activation. Lymphocyte subsets were normal.

Esophagogastroduodenoscopy and colonoscopy revealed patchy mucosal congestion with aphthous lesions in the rectum and scattered erythematous areas throughout the colon. Histopathology demonstrated focal reactive changes with increased lamina propria fibrosis and mild basement membrane thickening—nonspecific findings suggestive of inflammatory etiology, though not diagnostic of inflammatory bowel disease. Magnetic resonance (MR) enterography showed no bowel wall inflammation.

Targeted genetic panel testing identified several variants, including a heterozygous NOD2 risk allele, a novel heterozygous SLC2A2 splice-site variant, and additional variants of uncertain significance (VUSs). However, their contribution to the phenotype remains unclear. Given the severity of symptoms, the patient is planned for a trial of anti-TNF to assess clinical response while comprehensive immunologic and genomic analysis continues.
Conclusions: This case illustrates the complexity and need to balance diagnostic workup and empiric treatment in pediatric patients presenting with recurrent mucosal inflammation, atypical histopathology, and systemic hyperinflammatory features without a unifying diagnosis. The findings suggest an autoinflammatory or immune dysregulatory process but do not conclusively support classical diagnoses

such as Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome, Behçet disease, or inflammatory bowel disease (IBD). Further genetic and functional studies are pending while clinical response to anti-TNF therapy is being evaluated.

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Regional and Racial Variations in IgGRT Use and Long-Term Disease Progression Among U.S. CVID Patients

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Common variable immunodeficiency (CVID) is characterized by recurrent infections due to impairments in antibody quantity and quality. As such, immunoglobulin G replacement therapy (IgGRT) is the standard-of-care (SOC) for CVID patients. However, national patterns of IgGRT use and variations in SOC receipt rates among demographic groups remain poorly characterized. Furthermore, there is a limited understanding of how disease burden evolves across age and gender at a cohort level.

Quantifying SOC receipt rates and characterizing the longitudinal disease progression are essential for identifying care variations and detecting high-risk disease accumulation points.

We aimed to quantify regional and racial differences in IgGRT utilization among CVID patients and to characterize longitudinal patterns of disease progression. We identified CVID patients within the TriNetX electronic health record (EHR) dataset via ICD-9/10 diagnostic codes. IgGRT receipt was defined as a binary SOC outcome and compared across U.S. regions (Midwest, West, Northeast, South, and other) and self-reported racial groups (White, Black, Asian, and other). We calculated multivariate logistic regression estimated odds ratios (ORs) with 95% confidence intervals (CI) to assess demographic differences in treatment receipt rates. To evaluate longitudinal disease progression, the cohort was stratified by age and gender, followed by the enumeration of cumulative disease categories over time.

White patients in the West had significantly higher odds of receiving IgGRT than White patients in the South (OR = 1.47, 95% CI: 1.33–1.63, $p < 0.05$), whereas Black patients in the Northeast had markedly lower SOC achievement odds (OR = 0.45, 95% CI: 0.31–0.65, $p < 0.05$) (Figure 1). Trajectory analysis showed distinct age- and gender-dependent patterns: females exhibited higher cumulative disease burden by ages 50–60, while males demonstrated increased burden in early childhood and in mid-adulthood (Figure 2). Across both genders, respiratory diseases and immune-related abnormalities increased substantially by age 50–60.

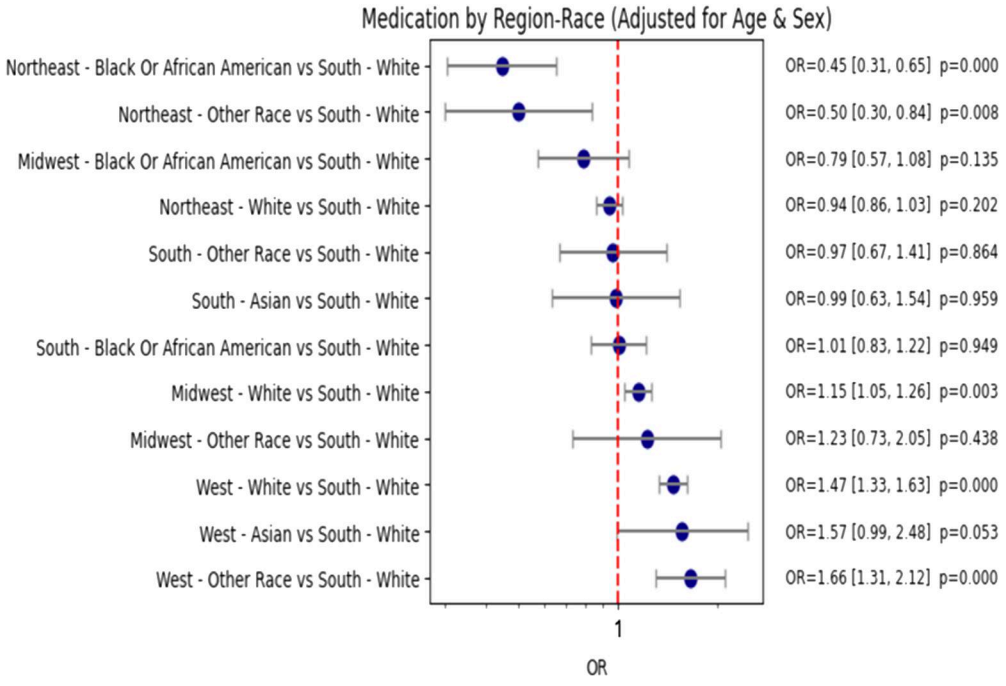

Figure 1. **Adjusted odds ratios (OR) for medication (IgGRT) receipt by region-race for the CVID cohort, shown with 95% confidence intervals.**

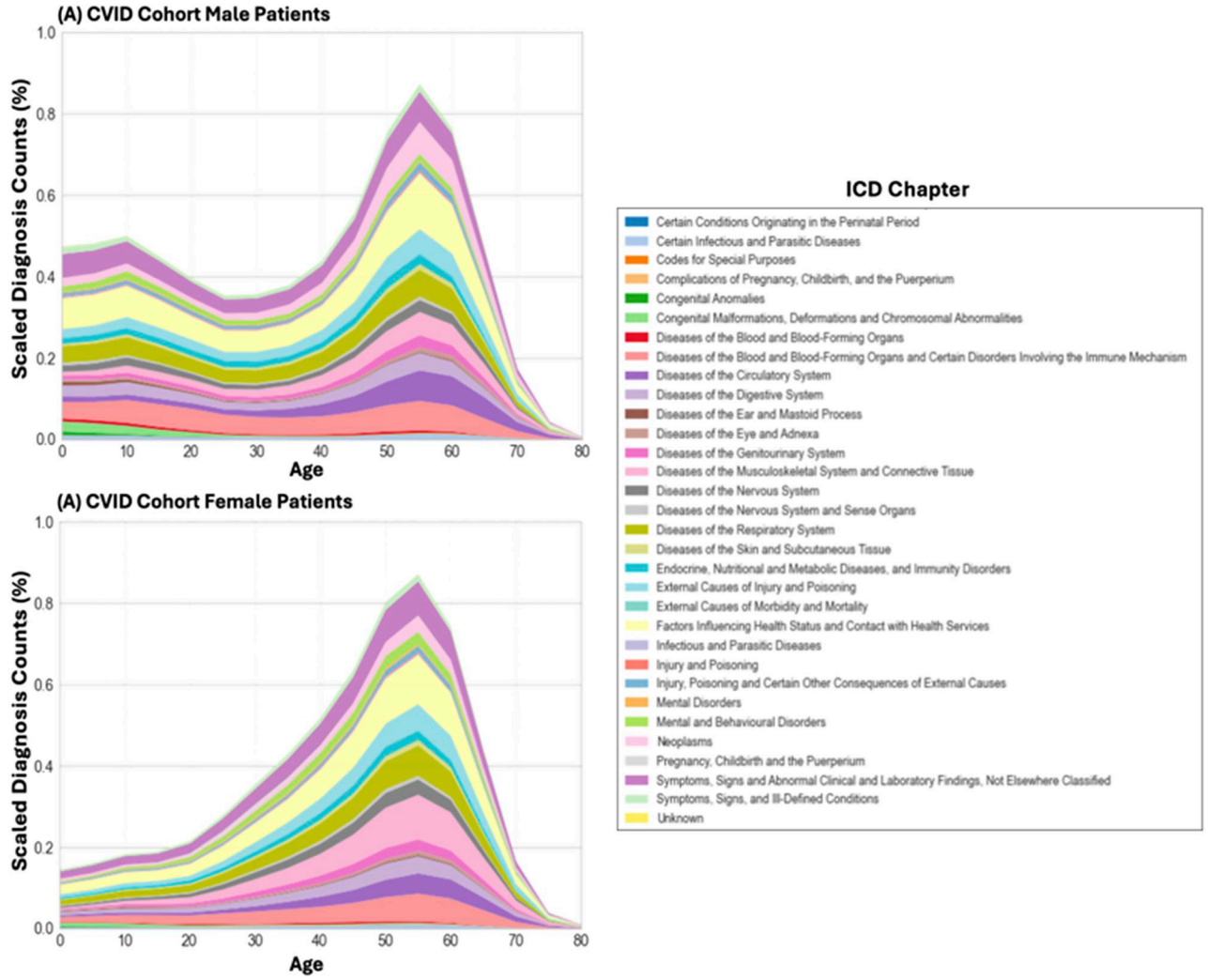

Figure 2. **Density plots stratified by age and gender, indicating disease trajectories for (A) CVID cohort.**

Using a U.S. national EHR-based analysis, we demonstrate significant demographic differences in IgGRT utilization and disease progression patterns among individuals with CVID. We have noted that these patterns indicate that CVID disease burden follows gender-specific trajectories early in life but accumulates by age 50–60. These findings inform the need for time-based intervention strategies to reduce treatment gaps, improve detection, and reduce morbidity.

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Retrospective Crossover of Patients with Primary Immunodeficiency Switching from Standard Immune Globulin Replacement Therapy to ASCENIV

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ASCENIV is a 10% intravenous immune globulin (IVIG) indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents (12 to 17 years of age). ASCENIV contains a blend of normal source plasma and plasma containing high antibody titers to respiratory syncytial virus (RSV). In the phase 3 trial, 59 PI patients were treated with ASCENIV 300–800 mg/kg every 3 or 4 weeks for 12 months. The study resulted in zero acute serious bacterial infections, meeting the primary endpoint.

Since the approval, case reports have described select clinical cases of patients with PI who have switched from standard immune globulin (IG) to ASCENIV due to recurrent respiratory infections and experienced fewer infections. The goal of this retrospective crossover was to investigate the changes in infections in patients with PI who transitioned from a previous IG product to ASCENIV.

Data were collected from de-identified medical records through Soleo Health using SoleMetrics from January 1, 2020, to December 31, 2024. Patients were included if they received ASCENIV for the treatment of PI for a minimum of 120 assessment days and received a different IG replacement therapy from the same specialty pharmacy prior to transitioning to ASCENIV. Medical records included data on reported infections from telephonic visits from the pharmacy care team or nursing visits for IG administration. The number of infections on previous IG products compared to the number of infections on ASCENIV was analyzed using Poisson regression.

Fourteen patients were included in the data collection. Patients were primarily female (n = 10, 83.3%) with an average age of 69.9 years. During the observation period on the previous IG product, a mean of 3.4 infections occurred (standard deviation [SD]: 3.94), whereas during the observation period of patients on ASCENIV, 1.2 infections occurred (SD: 0.89; p = 0.0169).

IG product selection should be individualized for each patient's clinical needs and comorbidities. This study suggests that ASCENIV may reduce infections in patients with PI who experience infections despite IG therapy. Larger, prospective studies are needed to confirm these results and further understand the select patient population that may benefit from ASCENIV.

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Roifman Revisited: Embracing the spectrum of RNU4ATAC-Opathies

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RNU4ATAC-opathies are genetic conditions that include growth restriction, skeletal dysplasia, and cognitive impairment. Historically, these have been divided phenotypically into microcephalic osteodysplastic primordial dwarfism type I (MOPDI), Roifman syndrome, and Lowry-Wood syndrome. In this case series, we highlight the variety of presentations of three novel patients with RNU4ATAC-opathy associated most closely with Roifman syndrome.

Patient 1 (female, 14y) had a history of skeletal dysplasia, short stature, and mild developmental delay. She developed hypothyroidism and had recurrent migraines. She had a history of recurrent otitis and pneumonia, along with recurrent HSV stomatitis and recurrent urinary tract infections (UTIs). Immune evaluation identified combined T and B cell immunodeficiency, and IgG replacement was initiated at age 3y. RMRP-targeted sequencing identified a variant of uncertain significance (VUS) for which she carried a diagnosis of presumed cartilage hair hypoplasia (CHH). More recent targeted gene panel found two heterozygous pathogenic variants in RNU4ATAC.

Patient 2 (female, 12y) is the sister of patient 1, also with presumed CHH due to the same VUS. She had a history of skeletal dysplasia, short stature, and cognitive delay. She had intrauterine growth restriction at birth as well as congenital hip dysplasia. In addition to recurrent otitis and pneumonia, she also had eczema and hypergonadotropic hypogonadism. At 18 months of age, immune evaluation revealed specific antibody deficiency managed with monthly IgG replacement. Genetic testing revealed the same two mutations in RNU4ATAC found in her sister.

Patient 3 (male, 36y) had a history of brachydactyly, partial syndactyly, short stature, and intellectual disability. Microcephaly and a flattened philtrum were noted at birth, though acetabular dysplasia and femoral head flattening were not identified until adulthood. After an episode of severe cardiomyopathy and subsequent renal failure, genetic testing revealed two mutations in RNU4ATAC as well. Subsequent immune evaluation revealed a profound combined immune deficiency with very low T cells and hypogammaglobulinemia, for which he is now on replacement IgG as well as prophylactic antimicrobials.

These cases illustrate the variability and overlap in the spectrum of RNU4ATAC-opathies and broaden the phenotypic range of these disorders.

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Ruxolitinib as a Targeted Therapy for Arthritis and Alopecia Universalis in a Child with APECED: A Case Report

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Background: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare monogenic autoimmune disorder caused by mutations in the AIRE gene and is characterized by immune dysregulation with multi-organ involvement. While several case reports in adults have demonstrated the successful use of Janus kinase (JAK) inhibitor in controlling autoimmune complications, its use in the pediatric age group remains poorly documented, particularly in the setting of concomitant rheumatologic and dermatologic manifestations.
Case Presentation: We report an 11-year-old boy with APECED who initially presented at the age of 3 years with alopecia universalis. At 5 years of age, he developed primary hypoparathyroidism and adrenal insufficiency. In 2020, the diagnosis of APECED was confirmed by genetic testing, which revealed a homozygous frameshift variant in the AIRE gene (c.1193del; p.Pro398Argfs*82). Subsequently, he developed nail pitting and dystrophy, recurrent episodes of oral candidiasis, and bilateral nephrocalcinosis.

At 10 years of age, he presented to the pediatric rheumatology clinic with symmetrical arthritis involving both wrists and the right knee, associated with pain and swelling. A clinical diagnosis of arthritis was made, with further investigations pending. He was initiated on ruxolitinib at a dose of 5 mg twice daily, which led to gradual improvement in joint symptoms. After three months, the dose was increased to 10 mg twice daily, resulting in marked clinical improvement of arthritis and noticeable regrowth of scalp hair and eyebrows. Residual bilateral limitation of wrist extension persisted. Methotrexate was subsequently added to further optimize arthritis control. Of note, he had 2 episodes of oral candidiasis since he was started on ruxolitinib, both resolved with oral nystatin.
Conclusion: This case demonstrates the potential therapeutic benefit and favorable safety profile of ruxolitinib in a pediatric patient with APECED, leading to improvement of both arthritis and alopecia universalis.

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Safety of Janus Kinase Inhibitors in Individuals with Down Syndrome: A Systematic Review

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Background: Down syndrome (DS) is associated with chronic hyperactivation of interferon signaling and downstream Janus kinase (JAK) and STAT pathways, contributing to increased susceptibility to autoimmunity, autoinflammation, immunodeficiency, and immune dysregulation. JAK inhibitors represent a mechanistically rational therapeutic option, but systematic safety data in this vulnerable population are limited. This review evaluates the safety profile of JAK inhibitors in individuals with DS.
Methods: A systematic search of MEDLINE, Embase, Web of Science, and ClinicalTrials.gov identified 147 records. After deduplication, title and abstract screening, and full text review, 12 studies met the inclusion criteria. Eligible studies included human subjects with DS receiving a JAK inhibitor for any indication. Extracted variables included demographics, indication, agent, dose, duration, adverse events, infections, laboratory abnormalities, and treatment discontinuation. Studies sharing overlapping cohorts were examined to avoid double counting. The review protocol was registered in PROSPERO (CRD420251231172).
Results: Twelve studies representing approximately 25 to 30 unique individuals with DS were included. JAK inhibitors used were tofacitinib, baricitinib, and ruxolitinib. Indications included DS-associated arthritis, alopecia areata, immune-mediated skin disease, DS regression disorder, and hemophagocytic lymphohistiocytosis. Treatment duration ranged from three months to more than two years. No deaths, venous thromboembolism, major cardiovascular events, or malignancies attributable to therapy were reported. Mild infections were the most common adverse events and generally resolved without treatment interruption. One child receiving baricitinib developed COVID-19 pneumonia but did not experience recurrence of hyperinflammatory disease. Laboratory abnormalities were infrequent, mild, and reversible. In the largest interventional dataset, no serious adverse events were attributed to tofacitinib during the sixteen-week primary analysis period. Long-term case reports similarly demonstrated stable monitoring without significant toxicity.
Conclusion: Current evidence suggests that short-term and intermediate-term use of JAK inhibitors in individuals with DS is associated with an acceptable safety profile. No increased signal for serious infection, thrombosis, malignancy, or cardiovascular events was observed. Larger prospective studies are required to define long-term safety and guide clinical use in this immunologically distinct population.

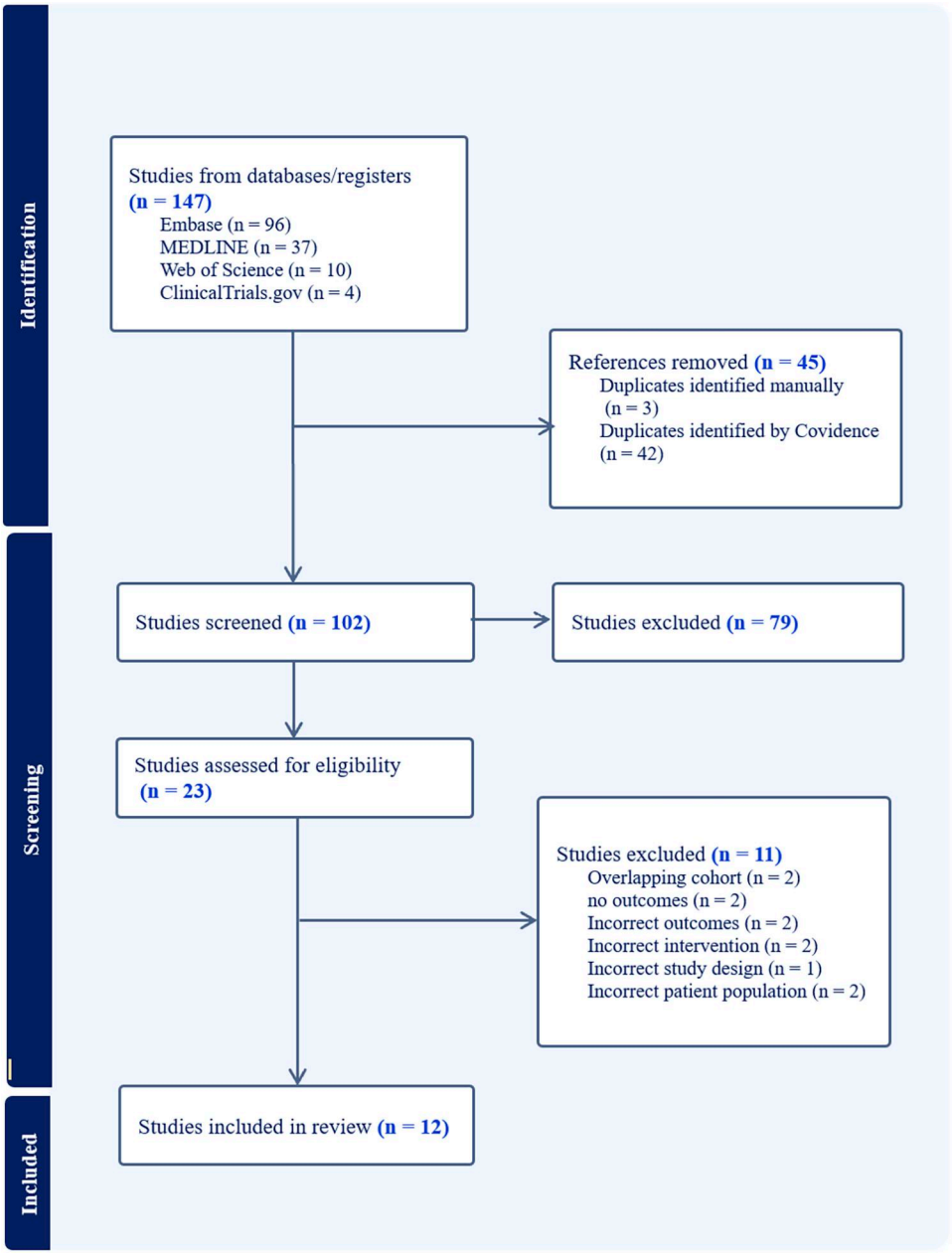

Figure 1. **PRISMA diagram.**

Tabular data are included as downloadable supplement files.

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Seasonal Surge of Steroid-Refractory T Cell–Mediated Hepatitis in Phoenix: A Cascade of Cases and Treatment Dilemmas

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Background: T cell–mediated hepatitis is an uncommon cause of acute pediatric liver injury. Most patients respond to steroids, but management of refractory disease remains challenging. We describe four patients with non-monogenic CD8+ T cell–mediated hepatitis with close temporal presentation and variable response to therapies.

All four patients had severe elevations in liver enzymes, synthetic dysfunction, hyperbilirubinemia, cytopenias, elevations in cytokines (supplemental table), and CD8+ T cell predominance on biopsy, without meeting criteria for autoimmune hepatitis. All underwent next-generation or whole-exome sequencing; no monogenic causes were elucidated. Broad infectious workup was unrevealing.

Case 1: A 17-year-old male with epilepsy presented with abdominal pain and jaundice, with labs and biopsy consistent with portal and lobular hepatitis with $CD8^+$ T cell predominance. Bone marrow aspirate (BMA) was reassuring. Hepatitis was refractory despite corticosteroids, tacrolimus, sirolimus, anakinra, intravenous immune globulin (IVIG), and anti-thymocyte globulin (ATG). Infliximab led to dramatic but incomplete improvement. He remains on steroids, tacrolimus, and infliximab, with planned hematopoietic stem cell transplantation (HSCT).

Case 2: A 7-year-old female with type 1 diabetes presented with jaundice and abdominal pain, with labs and biopsy consistent with CD8+ T cell hepatitis. Steroids induced a partial response, while infliximab led to marked improvement. She transitioned to azathioprine and maintains normal liver enzymes.

Case 3: A 5-year-old male with autism presented with fevers and abdominal distention, with labs and biopsy consistent with portal and lobular hepatitis with CD8+ T cell predominance. IVIG/steroids provided only a transient improvement. Tacrolimus normalized labs and enabled steroid discontinuation.

Case 4: An 11-month-old healthy female presented with jaundice. Labs and biopsy were consistent with giant cell hepatitis with CD8+ T cell predominance, and no evidence of autoimmune hemolytic anemia.

She was listed for liver transplantation. Partial steroid response prompted tacrolimus initiation, leading to normalization of labs and removal from transplant listing.

Conclusion: CD8+ T cell–mediated hepatitis may progress rapidly and be steroid refractory. Early initiation of infliximab or tacrolimus may prevent progression to liver failure. Case one represents a severe presentation with limited response; however, most avoided liver or hematopoietic stem cell transplantation. All cases presented within a three-month window, suggesting a possible infectious trigger.

Tabular data are included as downloadable supplement files.

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Selective IgM Deficiency with Combined Lymphocyte Abnormalities and Aortic Root Dilation: A Potential Novel Inborn Error of Immunity

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Background: Recurrent bacterial pneumonia accompanied by atypical systemic findings may indicate an uncharacterized inborn error of immunity (IEI). We report a 10-year-old male with recurrent pneumonias, mildly low but functional IgM, subtle combined immunologic abnormalities, and unexplained aortic root dilation, suggesting a potentially novel immunogenetic phenotype.

Case Presentation: The patient had four hospitalizations for bacterial pneumonia over the past year. His 7-year-old brother has had two pneumonias but is otherwise healthy. Parents are consanguineous, with no family history of connective tissue or immunologic disorders.

Pulmonary Findings: Chest CT revealed bilateral nodular and patchy opacities with early bronchiectasis. Bronchoscopy demonstrated a large amount of thick, purulent secretions, suggesting impaired airway clearance; fungal and mycobacterial studies were negative. He required inpatient airway clearance and now uses Aerobika and AffloVest at home. Sweat chloride and pancreatic elastase were normal.

Immunologic Evaluation: Quantitative IgG and IgA were normal; IgM was mildly low (41–47 mg/dL). Anti-blood group B isoagglutinin titer was 1:4, indicating low but detectable functional IgM. Initial pneumococcal serotype titers were low, but post-immunization responses were adequate (15/23 protective). Lymphocyte subsets showed low absolute CD8 counts, decreased memory (CD45RO+) T cells, and low natural killer (NK) cells, consistent with a subtle combined immunologic defect. Clinical whole-genome sequencing revealed no pathogenic, likely pathogenic, or variants of uncertain significance, leaving the etiology unexplained.

Cardiovascular and Connective Tissue Findings: Echocardiography showed a moderately dilated aortic root (Z +4.8), dilated sinotubular junction (Z+5.4), and ascending aortic dilation. The patient demonstrates flexibility and hypermobility, though not enough to meet criteria for hypermobile Ehlers-Danlos. No features of Marfan or Loeys-Dietz syndrome were present.

Conclusion: The combination of recurrent pneumonias, mildly low but functional IgM, mild T and NK cell abnormalities, early bronchiectasis, impaired airway clearance, and significant aortic dilation represents a phenotype not described in current IEI classifications or known connective tissue disorders. These findings raise suspicion for a novel or unclassified IEI with vascular involvement, highlighting the need for multidisciplinary management and research-level genomic and functional investigation.

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Serum IL-18 as a Predictive Biomarker for Systemic Inflammation in XIAP Deficiency: A Retrospective Analysis

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Background: X-linked inhibitor of apoptosis protein (XIAP) deficiency is a rare genetic disorder caused by pathogenic variants in the XIAP gene. It disrupts TNF-receptor signaling and NLRP3 inflammasome function, leading to chronically elevated interleukin-18 (IL-18). Patients present with diverse phenotypes and are predisposed to inflammatory complications such as hemophagocytic lymphohistiocytosis (HLH) and inflammatory bowel disease (IBD). A threshold for symptomatology based on IL-18 levels is unknown.

Methods: We retrospectively analyzed confirmed XIAP-deficient patients to evaluate the relationship between serum IL-18 levels and clinical status. IL-18 measurements were paired with contemporaneous clinical presentations, categorized as either clinically well (no active disease), as having systemic inflammation characterized by fever and/or cytopenia with or without other symptoms of HLH or infection, or as having active IBD. Receiver operating characteristic (ROC) curves were generated to evaluate the predictive value of IL-18 for systemic inflammation and IBD.

Results: Figure 1 presents the ROC curves derived from 26 XIAP-deficient patients (n = 122 samples). IL-18 levels demonstrated poor correlation with IBD. ROC analysis demonstrated that an IL-18 cutoff of 5,000 pg/mL yielded 100% sensitivity and 95% specificity for identifying patients with systemic inflammation.

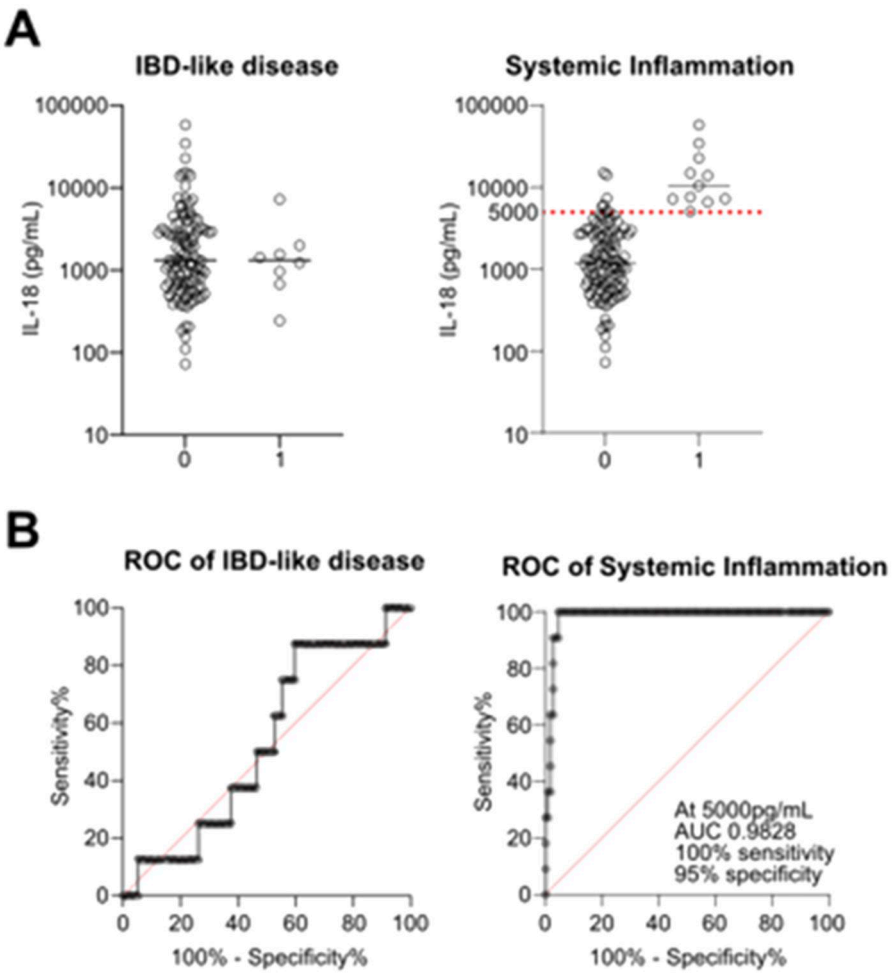

Figure 1.

Conclusion: Serum IL-18 levels greater than 5,000 pg/mL strongly correlate with systemic inflammation in XIAP-deficient patients, suggesting IL-18 as a robust biomarker for risk of systemic inflammatory disease. Incorporating IL-18 measurements into clinical evaluation may improve early detection and prevention of complications of systemic inflammation in this population.

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Severe Hyperinflammation and Evans Syndrome in Patient with RelA Deficiency Successfully Treated with Infliximab

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Introduction: RelA deficiency is a recently recognized inborn error of immunity (IEI) caused by mutations in the RELA gene. RelA is a transcriptional factor in the NF-kB pathway. Deficiency of RelA leads to impaired downregulation of anti-apoptosis in fibroblasts, leading to TNF-induced cell death. Clinical presentation includes mucocutaneous ulcerations and Bechet's-like disease along with autoimmunity.

Additionally, dominant-negative mutations can cause type 1 interferonopathy. Our case highlights effective treatment of RelA-associated autoimmune hemolytic anemia (AIHA)/Evans syndrome and severe dysregulated hyperinflammatory state with infliximab.

Case: A 20-year-old previously healthy female was diagnosed with severe and relapsing AIHA at age 12. AIHA was refractory to multiple immunomodulators, including prednisone, rituximab, mycophenolate mofetil, abatacept, and sirolimus. While on sirolimus and abatacept, she developed vaginal ulcerations resembling Bechet's disease requiring interruption of therapy. She was in full remission following 8 doses of daratumumab. Approximately 11 months into remission, she was hospitalized for a fever of unknown origin. Labs showed exacerbation of her AIHA, new immune thrombocytopenia, and markedly elevated inflammatory markers, including ferritin (125,803 ng/mL), CXCL9 (19,343 pg/mL), and Il-18 (188,985 pg/mL), consistent with macrophage activation syndrome. Infectious evaluation was negative. PET scan showed hypermetabolic lymphadenopathy in her neck/chest. Bone marrow biopsy was negative for malignancy but revealed hemophagocytosis.

Excisional lymph node biopsy showed reactive lymph nodes with paracortical expansion by macrophages. She received methylprednisolone (1,000 mg) for 3 days, followed by a prednisone wean with cessation of fevers after 13 consecutive days. Genetics revealed a heterozygous pathogenic variant in RELA c.592C>T (p.Arg198*). Given worsening cytopenias and inflammatory markers with steroid wean, she was initiated on Infliximab. Interestingly, her mother had a history of oral ulcers as a teenager, and her older sister was recently diagnosed with inflammatory bowel disease.

Conclusion: Evaluation of IEI should be pursued in patients with refractory/chronic cytopenias. Careful consideration of RelA deficiency should be taken in patients with autoimmunity. Our patient developed life-threatening hyperinflammation that was effectively treated with steroids followed by TNF inhibition. Additionally, she has had resolution of her ulcerations and cytopenias. She remains on monotherapy infliximab with stable disease.

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STAT1 Gain-of-Function with a Novel Clinical Manifestation: Recurrent Pancreatitis Associated with Hypertriglyceridemia and Anti-GPIHBP1 Autoantibodies

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Patients with STAT1 gain-of-function (GOF) variants may present not only with chronic mucocutaneous candidiasis and other forms of immunodeficiency but also with a broad-spectrum of autoimmune manifestations, for which Janus kinase (JAK) inhibitors have been reported to be effective. Here, we report a pediatric patient with STAT1 GOF who developed recurrent pancreatitis in association with hypertriglyceridemia, potentially mediated by autoimmune mechanisms.

The patient is a 6-year-old female who developed oral thrush and herpes zoster at 2 years of age. She had previously been diagnosed with neonatal lupus in the setting of maternal Sjögren's disease. There was no family history of primary immunodeficiency.

At 4 years of age, she developed autoimmune hypothyroidism, with positive thyroglobulin Ab and microsomal Ab. Further evaluations revealed hypertriglyceridemia accompanied by episodes of acute pancreatitis and spleen atrophy. She was treated with levothyroxine, omega-3 supplementation, and a low-fat diet. Despite these interventions, she developed three additional episodes of pancreatitis occurring in the context of hypertriglyceridemia, requiring intermittent fenofibrate therapy to control hypertriglyceridemia. However, fenofibrate was later discontinued because of drug-induced hepatitis. To explore the underlying mechanism of hypertriglyceridemia, anti-GPIHBP1 autoantibody testing was performed and yielded a positive result. She later developed cholestatic hepatitis without concurrent pancreatitis, and liver biopsy findings are consistent with autoimmune hepatitis, with positivity for anti-smooth muscle antibodies.

Whole-genome sequencing identified a de novo heterozygous STAT1 variant of unknown significance (c.1199T>C, p.Leu400Pro). Given the history of unusual infections, multiple autoimmune manifestations, and the localization of the variant to a region previously implicated in STAT1 GOF, treatment with ruxolitinib and oral prednisolone was initiated, while antifungal prophylaxis was continued.

To our knowledge, this is the first case of STAT1 GOF who presented with recurrent pancreatitis associated with hypertriglyceridemia and the presence of anti-GPIHBPI1 autoantibodies. This case highlights a possible autoimmune link among STAT1 GOF, dyslipidemia, and pancreatitis, warranting further investigation and long-term therapeutic monitoring.

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Steroid-Refractory Idiopathic Hypereosinophilic Syndrome with Prolonged Respiratory Failure Responsive to Mepolizumab

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Background and Literature Review: Hypereosinophilic syndrome (HES) is a rare, heterogeneous group of disorders defined by persistent hypereosinophilia (>1,500 cells/μL) with eosinophil-mediated end-organ damage. Its estimated prevalence ranges from 0.36 to 6.3 per 100,000 individuals. Pulmonary involvement occurs in 40–60% of cases and most commonly presents as chronic cough or dyspnea. Acute respiratory failure requiring mechanical ventilation is uncommon and represents a severe manifestation. Glucocorticoids remain the first-line therapy and induce remission in approximately 85% of patients. However, nearly 15% demonstrate steroid-refractory or steroid-dependent disease. Mepolizumab, an anti–IL-5 monoclonal antibody, reduces eosinophil production and survival and has shown efficacy in decreasing disease flares and corticosteroid dependence, with reported remission rates of 57–76%. It is currently used as rescue therapy in steroid-refractory HES.

Case Summary: A 73-year-old man presented with six weeks of progressive dyspnea and nonproductive cough. His medical history included coronary artery disease, stage 3 chronic kidney disease, and alcohol use disorder. Evaluation revealed a small pulmonary embolism, diffuse bilateral pulmonary opacities, lymphadenopathy, and marked eosinophilia peaking at 5,730/μL. His condition rapidly deteriorated, requiring intubation and intensive care unit (ICU) admission. He received pulse-dose methylprednisolone followed by high-dose oral prednisone.

Despite aggressive steroid therapy, eosinophil counts rebounded to 3,470/μL by hospital day eight, and he experienced repeated failures to wean from mechanical ventilation. A tracheostomy was performed on day 21. Persistent eosinophilia despite steroids prompted initiation of mepolizumab 300 mg on day 24 after exclusion of secondary causes. Following treatment, eosinophil counts stabilized, and respiratory status improved. By day 41, he was successfully transitioned to a tracheostomy collar.

Conclusion: This case illustrates a rare presentation of steroid-refractory idiopathic HES causing life-threatening respiratory failure. Mepolizumab resulted in hematologic stabilization and meaningful respiratory recovery. Early recognition of steroid resistance and timely initiation of biologic therapy may reduce morbidity and improve outcomes in severe HES.

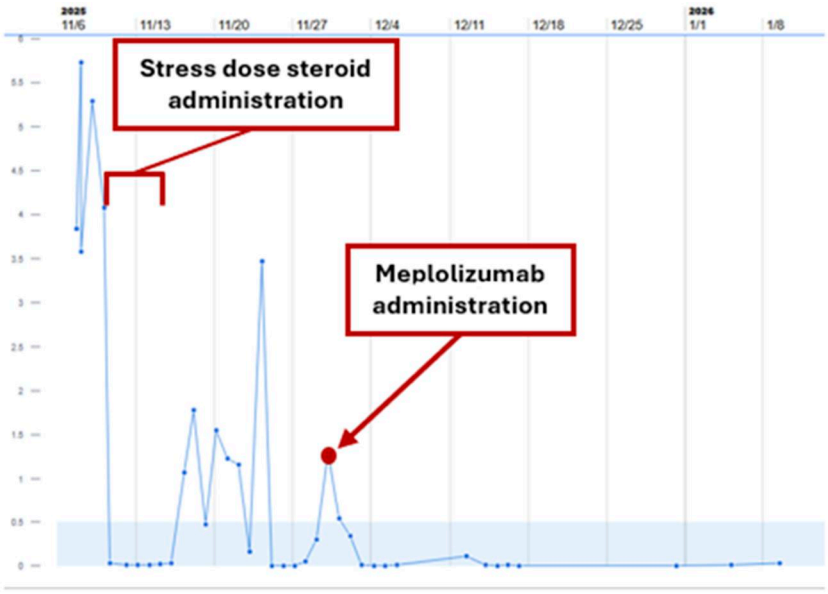

Figure 1. **Eosinophil count of the patient throughout the hospital course.** Stress dose steroids administered 11/10-11/15. Mepolizumab was administered 11/30.

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The Essential Role of Genetic Evaluation in Prepubertal Systemic Lupus Erythematosus

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Introduction: Systemic lupus erythematosus (SLE) in prepubertal children is rare and can indicate a monogenic cause. Although outcomes are variable, monogenic lupus is often difficult to treat with long-term complications related to the disease and treatment. Over thirty immune regulatory genes have been reported as a cause, including defects in the protein kinase C delta (PRKCD) gene. Promising preclinical studies suggest that mTOR inhibition can serve as a targeted therapy in SLE due to the PRKCD G510S mutation.
Case presentation: We describe a case of monogenic lupus in a two-year-old female who initially presented with photosensitive rashes, epistaxis, and thrombocytopenia. Evaluation revealed diffuse alopecia, hemolytic anemia (direct Coombs 3+ anti-C3d), severe thrombocytopenia (platelets 9K/μL), high-titer antinuclear antibody (>1:2,560), positive anti-double-stranded DNA (36 IU/mL) and anti-Smith antibodies (>8 AI), and hypocomplementemia (complement C4 6mg/dL, complement C3 71 mg/dL).

Findings fulfilled the 1997 American College of Rheumatology revised classification criteria. Whole-genome sequencing showed a heterozygous, likely pathogenic variant of the PRKCD gene: c.1840C>T, p.Arg614Trp. The patient did not have evidence of lymphoproliferation. The patient was treated with conventional lupus therapy, including mycophenolate mofetil and high-dose corticosteroids. The patient had an incomplete response to this regimen with subsequent evolution of lupus nephritis, necessitating 6 months of cyclophosphamide therapy. Additionally, she was not able to wean systemic steroids and developed multiple sequelae of long-term steroid use. One year after initial presentation, the patient's genome was reanalyzed, given significant suspicion for PRCKD-related immune dysregulation disorder. On reanalysis, an additional variant of uncertain significance was found on the PRCKD gene, c.-20.285delA p.? with paternal inheritance. Given the clinical presentation and the two inherited gene variants, a diagnosis of PRKCD deficiency was strongly suspected. The patient started on sirolimus as primary immunosuppressive therapy with remarkable improvement of symptoms and ability to wean steroids.
Discussion: Our report highlights the importance of genetic evaluation and interval reanalysis in prepubertal SLE. Furthermore, our case suggests use of sirolimus can be pivotal in PRKCD deficiency with monogenic lupus, including non-G510S variants. We propose considering genetic testing in all children with a prepubertal SLE diagnosis.

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The Role of TLR4 Gene Polymorphisms in the Development of Severe Sepsis in Oncohematological Patients with Acquired Immunological Disorders

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Background and Aims: Sepsis is a common complication in patients with hematological malignancies that occurs during chemotherapy treatment, which in turn leads to acquired immunodeficiency. In recent years, increasing attention has been paid to the role of genetic predisposition in the development of sepsis and its outcomes. Toll-like receptor 4 (TLR4), which plays a key role in the recognition of lipopolysaccharide, a component of the cell wall of gram-negative bacteria, is one of the most studied candidate genes for sepsis susceptibility. Genetic alterations in the TLR4 gene can influence the expression and functional activity of the receptor, modulate the intensity of the inflammatory response, and, consequently, determine the severity of the infection.

Methods: The study group consisted of oncohematological patient samples (n = 148) with severe sepsis in the Department of Anesthesiology and Intensive Care at the Belarusian Research Center for Pediatric Oncology, Hematology and Immunology. DNA samples isolated from peripheral blood and buccal epithelium, which were subjected to Sanger sequencing, were used as material for the study.
Results: The rs11536889 polymorphism in the noncoding region of the TLR4 gene was studied in 148 patients with sepsis, of whom 73 (49.4%) had sepsis and 75 (50.6%) had septic shock. The rs11536889 polymorphism of the TLR 4 gene was associated with the development of septic shock (χ^2 = 4.9; p = 0.027; odds ratio [OR] = 2.4 [1.1–5.3]; OR = 1.49 [1.1–2.1]).

Since this allelic variant is located in the noncoding region of the TLR4 gene, it should not directly alter protein conformation. However, polymorphisms in introns and/or UTRs (untranslated regions) may influence transcription and translation. This polymorphism may regulate TLR4 expression and influence the response to bacterial cell wall lipopolysaccharide, likely through binding to microRNA. Consequently, the rs11536889 genetic variation may influence the development of systemic inflammation.
Conclusions: Identification of the rs11536889 polymorphism in the TLR4 gene in patients with hematological malignancies scheduled for high-dose chemotherapy and/or prior to hematopoietic stem cell transplantation due to a high risk of developing acquired immune deficiency. This will allow for the identification of high-risk groups and patient stratification for more aggressive and personalized therapy.

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Thriving Without Transplant: A Case of X-Linked Hyper-IgM Syndrome with Near-Normal Quality of Life on IVIG

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Introduction: Hyper-IgM syndrome (HIGM) is a rare primary immunodeficiency characterized by impaired immunoglobulin class-switch recombination, most commonly due to mutations in the CD40 ligand (CD40L) gene. Affected patients typically present in early childhood with recurrent sinopulmonary infections and are at risk for opportunistic infections, chronic lung disease, and immune dysregulation. Hematopoietic stem cell transplantation (HSCT) is considered curative but carries significant risks. Long-term outcomes with immunoglobulin replacement therapy alone in selected patients remain an area of clinical interest.
Case Report: We present a male patient with X-linked HIGM (CD40L Thr254Met mutation) diagnosed at age 6 years. He initially developed recurrent otitis media by 1 year of age, followed by recurrent bacterial pneumonias and chronic sinusitis. Notably, he had no history of opportunistic infections. Initial immunologic evaluation revealed elevated IgM (431 mg/dL), markedly low IgG and IgA, and undetectable IgE levels.

He was started on intravenous immunoglobulin (IVIG) replacement therapy in 2011, resulting in significant clinical improvement and resolution of recurrent infections. He is currently 21 years of age, his immunoglobulin levels demonstrated therapeutic IgG (1,542 mg/dL), persistently low IgA (<5 mg/dL), and improved IgM (170 mg/dL). Over the subsequent years, he experienced only two mild, self-limited upper respiratory infections and was described by his family as healthier than most peers. He remained compliant with IVIG therapy (30 g every 3 weeks) and reported excellent quality of life.

A minor gastrointestinal concern consisting of intermittent passage of small amounts of mucus-like stool with flatus was reported but was infrequent, nonprogressive, and without systemic symptoms. Physical examination was unremarkable. Given his stable clinical course, lack of opportunistic infections, and excellent response to IVIG, HSCT was previously discussed but deferred in favor of continued immunoglobulin replacement.
Discussion: This case highlights the potential for excellent long-term clinical stability in selected patients with X-linked HIGM managed with IVIG alone. While HSCT remains the definitive therapy, careful patient selection is critical, particularly in those with mild phenotypes and excellent infection control. This case supports an individualized approach to management, emphasizing quality of life, treatment response, and shared decision-making in rare primary immunodeficiencies.

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Thrombotic Microangiopathy in a Child with C1q Deficiency and Lupus Nephritis

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C1q deficiency is an inheritable immune disorder attributed to biallelic pathogenic mutations in C1q genes (C1QA, C1QB, or C1QC). Patients with C1q deficiency demonstrate increased susceptibility to severe infections and systemic autoimmune conditions, particularly systemic lupus erythematosus (SLE) and lupus-like disease. Thrombotic microangiopathy (TMA) is a histopathologic finding of vascular endothelial injury often associated with hemolytic anemia, thrombocytopenia, and acute kidney injury. Patients with SLE are at risk for developing TMA due to excessive complement activation in the setting of autoantibody immune complexes. However, TMA has not been reported in a patient with C1q deficiency with SLE.

We report an 11-year-old child with known C1q deficiency and associated SLE who presented with hypertensive crisis, acute kidney injury, hemolytic anemia, and thrombocytopenia. A kidney biopsy demonstrated lupus nephritis. Additionally, glioblastoma (GBM) remodeling and an arteriolar fibrin thrombus were observed, consistent with TMA. Immunofluorescent staining for C4d, a marker of complement activation via the classical or lectin pathways, was negative. An abnormally elevated soluble C5b-9 complex was observed in plasma, suggestive of terminal complement activation. Genetic variants or autoantibodies that might cause a disorder of complement dysregulation, other than the known C1q deficiency, were excluded.

Treatment consisted of immunosuppression with steroids, mycophenolate mofetil, and tofacitinib for SLE and lupus nephritis, and aggressive blood pressure control, including continuous renal replacement therapy. For her TMA, she was started on eculizumab and anticoagulation with bivalirudin and ultimately required 12 rounds of therapeutic plasma exchange before indices of microangiopathic cell damage improved. The patient was discharged in stable condition on intermittent hemodialysis and is now undergoing evaluation for hematopoietic stem cell and renal transplantation.

Excessive complement activation contributes to TMA pathogenesis in patients with SLE and lupus nephritis. This case highlights that TMA can occur in the absence of classical complement activation and provides insight into the mechanisms that underlie TMA and lupus nephritis. In this patient, activation of the alternative complement pathway in the setting of systemic autoimmunity may have potentiated TMA. We provide a framework for therapeutic options that may include terminal complement inhibition, anticoagulation, and plasma exchange, in addition to SLE-directed therapies.

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Transforming Diagnosis of Primary Immunodeficiency: Global Impact of Jeffrey Modell Foundation's Genetic Sequencing Program, Jeffrey's Insights

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[1]Jeffrey Modell Foundation; [2]Veritas Intercontinental; [3]Labcorp (formerly Invitae Corp.); [4]CHOP and the Perelman School of Medicine at the University of Pennsylvania

Primary Immunodeficiencies (PI) include more than 550 monogenic disorders presenting with recurrent infections, autoimmunity, and significant morbidity. Early molecular diagnosis is essential for guiding targeted treatment, improving outcomes, and reducing the prolonged and costly diagnostic odyssey that many patients experience. To address global barriers to genetic testing, the Jeffrey Modell Foundation (JMF) established Jeffrey's Insights, a no-cost next-generation sequencing (NGS) program delivered through the global Jeffrey Modell Centers Network (JMCN). The program leverages expert immunologist selection to identify patients with a high pretest probability of PI and facilitate access to high-quality molecular diagnostics.

From January 2019 to June 2025, 5,991 individuals across 60 countries underwent targeted NGS through partnering clinical laboratories (Invitae, now a part of Labcorp, and Veritas Intercontinental). Across five progressively expanded PI gene panels (207–576 genes), the overall molecular diagnostic yield was 22.7%, with 1,357 patients receiving a confirmed or likely molecular diagnosis. Diagnostic yield remained statistically consistent across panel iterations, underscoring the value of expert clinician-guided patient selection. Regional diagnostic rates varied, with the highest yields observed in Australia/New Zealand (40.9%), Asia (31.6%), and the Middle East/Africa (31.3%). Among diagnosed individuals, 76.5% were children, and diagnostic yield was highest in patients younger than five years (26%), highlighting the importance of early testing. A subset of patients had dual or triple molecular diagnoses, emphasizing the complexity of blended phenotypes.

A total of 1,482 patients had clinician-reported follow-up. NGS altered clinical diagnosis in 38%, disease management in 37%, treatment in 33%, and genetic counseling in 51%. Relevant therapies were identified for 47% of patients, and 31% experienced improved clinical outcomes directly attributable to sequencing results. Questionnaire responses revealed substantial pretesting healthcare utilization,

including frequent emergency department visits, hospitalizations, and intensive care unit (ICU) admissions, as well as significant global barriers to accessing NGS, with cost and lack of insurance coverage identified as major limitations.

This global evaluation demonstrates that early, immunologist-guided NGS provides substantial diagnostic and clinical benefit for suspected PI. These findings strongly support the use of NGS as a first-tier diagnostic test for PI and emphasize the urgent need to expand access to genomic testing worldwide.

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Two Sides of the Same Coin, Pathogenic RTEL1 Mutations

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Background: Regulator of telomere elongation helicase 1 (RTEL1) is a gene that encodes a DNA helicase crucial for DNA repair and telomere maintenance. It belongs to a family of genes associated with telomere biology disorders (TBD). The phenotypic spectrum of RTEL1 mutations is highly variable, encompassing bone marrow failure, idiopathic pulmonary fibrosis, cirrhosis, and malignancy due to excessive telomere erosion.

Objective: We describe two patients at opposite ends of age, both with pathogenic variants in RTEL1.

Clinical Case Descriptions: Patient 1 was admitted to the hospital at 3 years of age due to failure to thrive and chronic diarrhea, found to have refractory CMV colitis and CMV and HHV6 viremia. She developed toxic megacolon secondary to CMV, requiring a subtotal colectomy. She underwent a reduced-intensity conditioning matched sibling donor bone marrow transplant (BMT) and ileorectal anastomosis. She was referred at age 4 for immune evaluation due to severe inflammatory bowel disease (IBD)-like gastrointestinal (GI) disease with suboptimal response to steroids and vedolizumab. She was treated with danazol with resolution of her diarrhea and, interestingly, hair regrowth.

Patient 2 is a 61-year-old female with leukopenia and recurrent fevers without infection. She was previously healthy with no history of autoimmunity or recurrent infections. She had atypical CD8-positive T cell lymphoid infiltration on liver biopsy with elevated inflammatory cytokines and was referred for immune dysregulation.

Investigations: Patient 1 had an elevated fecal calprotectin of 889 ug/g and had a homozygous pathogenic RTEL1 variant c.2869C>T (P.Arg957Trp).

Patient 2 had an expanded CD8+ T cell population (74%) with a low CD4/CD8 ratio (0.19) and reduced B cells (1%), while immunoglobulin levels remained within the normal range. Cytokine studies showed elevated IFN-y (49pg/mL), elevated CXCL9 (32, 454pg/mL), and elevated soluble IL-2 receptor (5,899 pg/mL) with no evidence of hemophagocytic lymphohistiocytosis (HLH) or granulomas on bone marrow biopsy. She had a heterozygous pathogenic RTEL1 variant: c.3791G>A (p.Arg1264His).

Discussion: These two cases highlight the phenotypically distinct presentations of pathogenic RTEL1 across the age spectrum. When discovered in older adults, it raises the question of somatic mutations, though germline heterozygous pathogenic variants have been described. Danazol and BMT are being considered in patient 2.

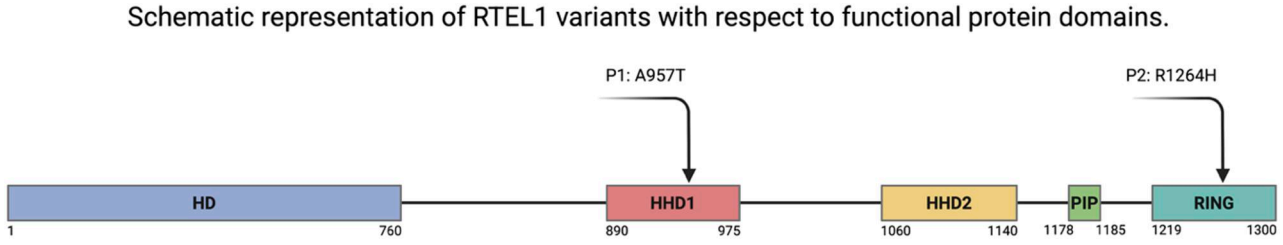

Figure 1. **Schematic representation of RTEL1 variants with respect to functional protein domains.** Variants in P1 and P2 with respect to the RTEL1 function protein domains. HD, N-terminal helicase domain; HHD1 and HHD2, harmonin homology domains 1 and 2; PIP, PCNA-interacting protein box; RING, C-terminal C4C4 type RING domain. Reference transcript NM_001283009.2, adapted from (1). Created using Biorender.com.

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Two TYK2-Deficient Cases with Divergent Clinical Presentations

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We describe two Turkish patients with tyrosine kinase 2 (TYK2) deficiency who experienced recurrent infections ranging from viral to bacterial and intracellular pathogens.

Case 1: An 8-year-old male patient was first admitted as a 2-year-old with fever, fatigue, and recurrent draining cervical, inguinal, and axillary lymph nodes (Figure 1). He was the third child of first-cousin parents. He was vaccinated with Bacillus Calmette-Guérin (BCG) at the age of two months. At eight months, left axillary lymphadenopathy was detected. Serum IgE concentration was 115 IU/ml (N: 1.2-52 IU/ml). Histologic examination of his left axillary lymph node showed a positive staining for acid-fast bacilli. *M. bovis* BCG was isolated from the discharging cervical sinuses. The patient was treated with a regimen of isoniazid (INH), rifampicin, streptomycin, and pyrazinamide.

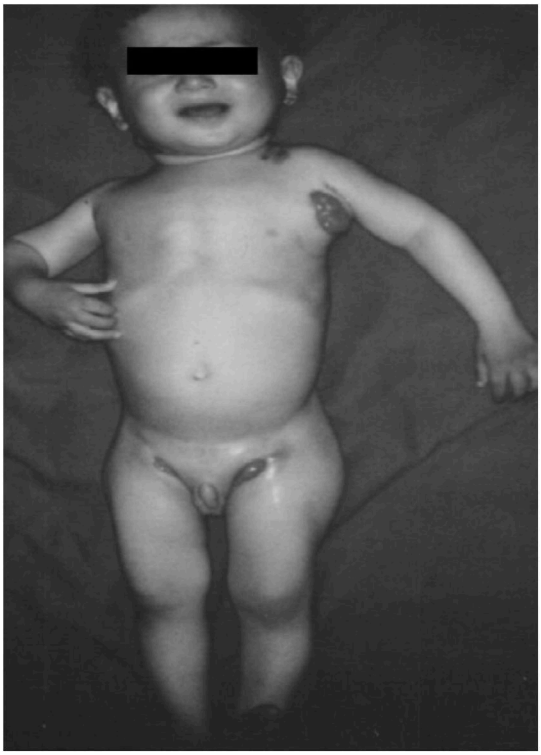

Figure 1. **Disseminated BCGitis.**

At eight years, he had brucella meningitis, and at 11 years, he suffered from herpes zoster of the right maxillary branch of the trigeminal nerve.

Genetic evaluation revealed a homozygous for a 9 bp deletion in exon 16 of TYK2, c.2302_2310del or 2302del9, which creates a premature termination codon at position 767. Informed consent for publication was obtained from the patient's parents.

Case 2: A 3-year-old female patient exhibited recurrent infections and oral candidiasis since early infancy. Febrile episodes are frequently accompanied by recurrent vesicular skin eruptions consistent with herpetic infections (Figure 2). The patient had a history of three hospitalizations due to bronchiolitis and pneumonia. She underwent a surgical correction for omphalocele when she was 5 days old.

The parents were cousins. Ig E level was: 570 IU/ml. Clinical exome sequencing (CES) identified a homozygous pathogenic variant in the TYK2 gene (p.Pro216ArgfsTer14). Intravenous immunoglobulin (IVIG) therapy was started every three weeks. Recurrent herpetic skin

infections were treated with acyclovir. However, due to organ involvement and resistance to prophylactic valacyclovir, hematopoietic stem cell transplantation was planned. Informed consent for publication was obtained from the patient's parents.

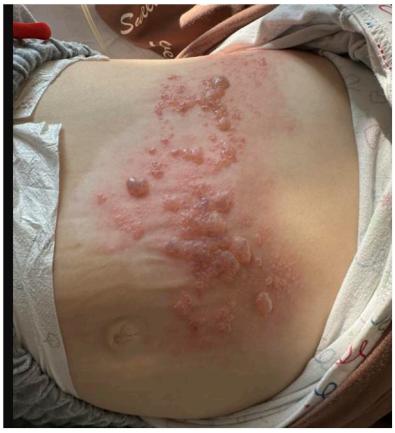

Figure 2. **Vesicular eruption of case 2.**

Discussion: TYK2 plays a crucial role in cytokine signaling pathways involved in both innate and adaptive immunity, including those for IL-12, IL-23, IFN-α/β, IL-6, and IL-10.
Conclusion: TYK2-deficient patients typically present with intracellular bacterial infections, particularly mycobacterial infections, as well as viral infections. Some patients may also experience fungal infections, allergic diseases, and adverse events following BCG vaccination.

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Unmasked by Pregnancy: A Case of Latent Hypogammaglobulinemia with a Familial Link to CVID

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Introduction: Hypogammaglobinemia in pregnancy can be an expected physiological change, resulting from hemodilution and active transfer of immunoglobulins to the fetus via the placenta. However, pregnancy can also reveal pathological causes of hypogammaglobinemia. Here, we present a case of a mother with normal prepregnancy IgG levels, whose predisposition for hypogammaglobulinemia was revealed only during pregnancy. This underlying genetic susceptibility for hypogammaglobulinemia is further suggested by her son's diagnosis of common variable immunodeficiency (CVID) requiring immunoglobulin replacement therapy (IgRT).
Case Description: A 30-year-old (G3P2) female, at 21 weeks of gestation, presents with low immunoglobulin levels. She was symptomatic during her pregnancy with recurrent sinusitis, Streptococcus pharyngitis, and several viral infections. Her IgG levels had decreased from a prepregnancy baseline of 849 mg/dL to 567 mg/dL. Her IgA and IgM similarly decreased from 58 and 146 mg/dL to 45 and 137 mg/dL, respectfully. She also showed evidence of specific antibody deficiency with poor durability of titers against tetanus, rubella, and pneumococcus, despite having been fully immunized to all of these microbes during childhood.

Her family history is significant for CVID in her son and a maternal cousin who passed away from an undefined immunodeficiency disorder. Her son's inborn error of immunity (IEI) genetic panel failed to identify the gene responsible for his CVID.

The patient was started on subcutaneous IgRT for the remainder of the pregnancy, which improved her IgG levels to 580–657 mg/dL. Three months post-partum, after discontinuing IgRT, her IgG level rebounded to 696 mg/dL, and ultimately to her prepregnancy IgG level. To prevent infectious complications in her subsequent pregnancies, she was preemptively started on IgRT at the end of the second trimester during each pregnancy.
Discussion: This case highlights a predisposition to hypogammaglobulinemia that was unmasked by the physiological stress of pregnancy in an otherwise asymptomatic woman. This patient's course suggests a transient, stress-induced manifestation of a yet-to-be-defined genetic condition. We hypothesize that the genetic defect in this family may be X-linked, as evidenced by a more severe humoral defect in her male offspring.

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Unmasking GATA2 Deficiency in an Adult with a Nocardia Brain Abscess

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We present the case of a 50-year-old man with a history of rheumatoid arthritis, chronic bronchitis, with a history of multiple lung infections, including *Mycobacterium avium* complex and *Aspergillus terreus* starting in his late 40s. He was hospitalized for seizures secondary to enlarging known cnetral nervous system (CNS) lesions with previously negative viral PCRs, bacterial, fungal, and Acid-Fast Bacillus (AFB) cultures from brain biopsy. He underwent craniotomy for resection of a right cerebral brain abscess, which grew *Nocardia abscessus*. Despite surgery and broad antimicrobial treatment, after initial improvement, the patient presented in status epilepticus and was found to have acute infarcts in bilateral basal ganglia and new pulmonary infiltrates. He passed shortly after secondary to hemodynamic collapse from septic shock.

Immunological workup revealed elevated IgG (2,572 mg/dL), reduced CD3 (460 cells/mm^3) and CD4 cells (257 cells/mm^3), and undetectable B and natural killer (NK) cells. He had adequate vaccine response to diphtheria and tetanus, but low *Streptococcus pneumoniae* IgG levels. His in vitro proliferation to tetanus and *Candida* antigens were negative. His dihydrorhodamine (DHR) was normal.

Genetic testing via a primary immune deficiency panel revealed a pathogenic variant in GATA2, which is associated with autosomal-dominant GATA2 deficiency. This missense variant, c. 1192C>T (p.Arg 398Trp) has been previously reported in two patients. The gene panel testing also indirectly revealed trisomy 8 in our patient (which is one of the most common duplications in GATA2 patients with myelodysplastic syndrome), as the report showed 3 copy numbers for 5 genes along the short and long arm of chromosome 8.

This case highlights the variability in presentation of GATA2 deficiency, as this is the first reported case of *Nocardia* brain abscess in GATA2 deficiency. It also emphasizes the importance of evaluating adults for immunodeficiency as soon as they develop recurrent, severe, or opportunistic infections. At the time of assessment, our patient was not a candidate for bone marrow transplantation due to his poor clinical status and low diffusion capacity on pulmonary function testing. This outcome may have been different if he had been diagnosed earlier in the course of recurrent lung infections.

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USIDNET Has Robust Longitudinal Data Across Multiple EMR Domains

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Introduction: The United States Immunodeficiency Network (USIDNET) collects de-identified patient data from hospitals across the country to study inborn errors of immunity (IEI). The registry contains records on >6,000 patients with IEI currently. The longitudinal data have been extracted back to 2018. This registry represents a critical resource for research on IEI. This study was done to evaluate the registry for its data quality.

Methods: PHIdentifier runs on a secure, high-performance computing (HPC) environment to efficiently process large volumes of text data to perform a multilayered de-identification process. The model's responses are combined with rule-based checks to ensure that only

sensitive information is replaced with placeholders, preserving all other clinical content. This has allowed a waiver of consent, which has facilitated enrollment. The current registry, as of January 2026, had field counts extracted for this study on data quality.

Results: The registry contains 6,272 patients. 45% are female. The predominant ethnicity was non-Latino, 4,143 (66%). The most frequently enrolled races reported were white (71%), other (8%), and black or African American (7%). Demographic data were found for 100% of enrollees. Social history was found for 88% of subjects, diagnosis for 77%, medications for 73%, immunizations for 69%, and allergies for 56%. The registry contains >1 million medications on 4,485 patients, >8,000 imaging reports on 2,793 patients, and >50,000 laboratory studies on 4,262 patients. These data represent a comprehensive landscape of 6,272 patients with IEI.

Conclusion: USIDNET is a very large registry of patients with robust longitudinal data of varying types, making it a valued resource for the community. Data requests are accepted on a rolling basis, and assistance is available for statistical support for those submitting queries producing large or complex data sets.

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Viral or Autoimmune? Acute Encephalitis in the Setting of Newly Diagnosed Primary Immunodeficiency

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Encephalitis in immunocompromised individuals presents a unique diagnostic and treatment challenge due to the interplay between infection and immune dysregulation.

A 48-year-old male with a history of recurrent sinusitis presented for seizure, agitation, rightward gaze, and fevers. He became obtunded and required intubation. Brain MRI showed three foci of acute-subacute infarcts in the left parietal and posterior temporal lobes. Chest X-ray revealed a right lower lobe infiltrate. Workup was positive for *Mycoplasma pneumonia* and *Bordetella bronchiseptica*. Cerebrospinal fluid (CSF) was positive for HSV-1 and undetectable IgG. Serum immunoglobulins were IgG <8, IgA <7, and IgM <5. B cell phenotyping revealed increased naive B cells and decreased memory cells and plasmablasts. Given that the radiological findings were not consistent with pure HSV encephalitis and an absence of blood in the CSF, there was concern for a parainfectious autoimmune encephalitis in the setting of newly diagnosed hypogammaglobulinemia. He received acyclovir, steroids, and high-dose intravenous immunoglobulins (IVIg) over 5 days. Repeat MRI showed worsening vasogenic edema. With concern for vasculitis, a brain biopsy was performed, which revealed a predominance of CD8+ T cells with no detectable B cells. HSV-1 was negative on biopsy; however, this was post-treatment. He improved in language function; however, he did not return to baseline and required further psychiatric hospitalization.

Monthly IVIg was continued.

This case is notable for CD8+ T cell predominance on brain biopsy with newly diagnosed hypogammaglobulinemia, suggesting possible T cell dysfunction leading to autoimmune encephalitis in the absence of immunoglobulins. Toll-like receptor and primary immunodeficiency genetic panel are pending. It highlights the importance of immunologic evaluation and a multidisciplinary approach to the diagnosis and treatment of patients with atypical encephalitis.

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VUS in Familial Novel COPA Variant: Two Related Cases with Cutaneous Manifestations

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Background: COPA syndrome is a rare autosomal-dominant immune dysregulation disorder caused by pathogenic variants in the COPA gene, typically presenting with autoimmunity, arthritis, and interstitial lung disease. However, genotype–phenotype correlations remain incomplete, and variants of uncertain significance (VUS) may contribute to atypical or partial clinical phenotypes.

Case Presentation: We report a family with a novel heterozygous COPA variant (c.2206G>A; p.Ala736Thr) identified through whole-exome sequencing in a father and his son. The son, a 20-year-old male, presented with recurrent soft-tissue abscesses (gluteal and thigh) and empyema requiring surgical intervention. He suffered from chronic psoriatic/eczema-like skin lesions for 5 years. Family history was remarkable for autoimmune diseases, including psoriasis/eczema in the father, paternal aunt, and cousins.

The father exhibited a long-standing chronic cutaneous condition initially labelled as atopic dermatitis, later reclassified as psoriasis, with suboptimal response to dupilumab and adalimumab therapy. Whole-exome sequencing of both individuals revealed the same heterozygous COPA variant, c.2206G>A (p.Ala736Thr), classified as a VUS. 13 out of 22 bioinformatic in silico programs predict a pathogenic effect for this variant. To the best of our knowledge, the variant has not been described in the literature so far. An allele frequency of this variant in the general population has not been documented (gnomAD v2.1.1 controls).

Conclusion: This report highlights a potentially novel COPA gene variant segregating within a family presenting inflammatory manifestations, including psoriasis and recurrent abscesses. While the clinical features diverge from classical COPA syndrome, the presence of immune dysregulation across generations suggests a possible contributory role of the p.Ala736Thr variant. Functional studies and further familial segregation analysis are warranted to clarify its pathogenicity and expand the phenotypic spectrum of COPA-associated disease.

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XIAP Deficiency Caused by a Deletion in the Noncoding Exon 1 Identified by Chromosomal Microarray

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X-linked inhibitor of apoptosis (XIAP) is essential for innate and adaptive immune responses, including programmed cell death inhibition, NFkB and MAPK activation, NLRP3 inflammasome activity regulation, and TNFR signaling (1, 2). XIAP deficiency is an immune dysregulation syndrome caused by hemizygous loss-of-function variants in XIAP, with prominent clinical features, including hemophagocytic lymphohistiocytosis, splenomegaly, and inflammatory bowel disease (IBD) (2, 3).

A 6-week-old previously healthy term male infant born to nonconsanguineous parents of West African heritage presented to the hospital with bloody diarrhea, hypoalbuminemia, anemia, elevated C-reactive protein (CRP), fever, and growth faltering. The family history was notable for a male sibling's death at 10 weeks from sepsis following a diarrheal illness.

A full septic workup was negative, and the child was empirically treated for culture-negative sepsis with minimal improvement. The working diagnosis was cow's milk protein-induced allergic proctocolitis, but his severe gastrointestinal symptoms persisted despite dietary modifications, including complete gut rest. Upper and lower endoscopy revealed flat ileal mucosa without villi, and edematous and friable colonic mucosa, while biopsies showed active duodenitis with villous blunting, and chronic active colitis.

Screening immune investigations, including neutrophil oxidative burst, were unremarkable. Whole-exome sequencing (WES) was reported as negative; however, chromosomal microarray (CMA) revealed a 5.7 Kb deletion in Xq25, encompassing the noncoding exon 1 of XIAP. Flow cytometry at Cincinnati Children's Hospital Diagnostic Immunology Lab showed absent XIAP expression in peripheral blood mononuclear cells. A functional defect in XIAP was demonstrated by absent production of TNF-alpha and IL-8 production by monocytes following stimulation with L18-MDP, with intact cytokine response to LPS stimulation.

We describe a case of XIAP deficiency resulting from a copy number loss at Xq25 that was functionally supported by absent XIAP expression and NOD2-mediated cytokine production. This case highlights the phenotypic spectrum of XIAP deficiency, whereby IBD can present very early in life, and the importance of a prompt and thorough genetic evaluation for those with suspected monogenic inborn errors of immunity. Any patient suspected of having XIAP deficiency should have a CMA performed, as pathogenic deletions in the noncoding exon 1 of XIAP have been reported (4, 5), and may be missed on gene panels or WES.

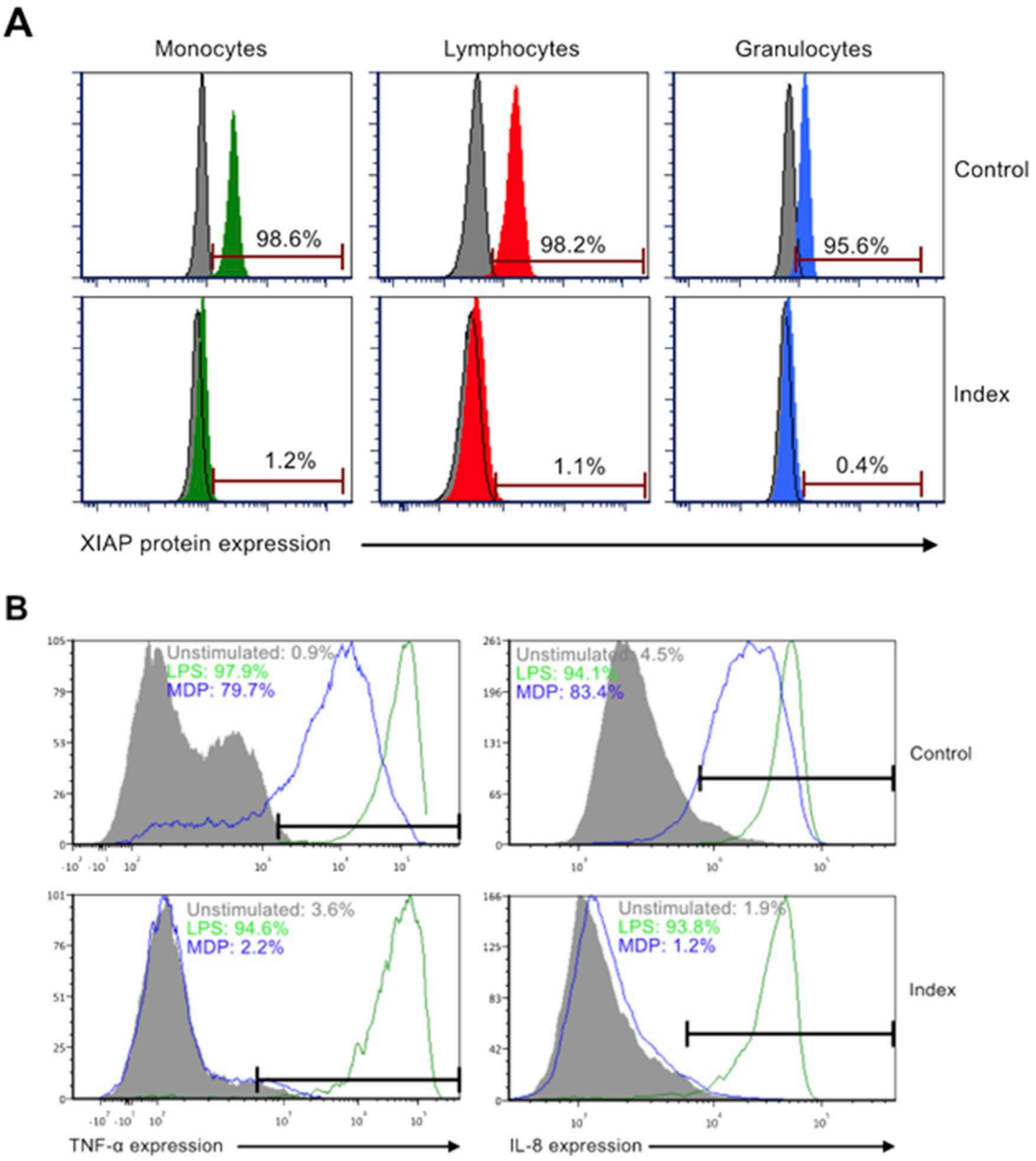

Figure 1. **A.** Whole blood from the index case and a healthy control were stained for intracellular XIAP protein and gated for monocytes, lymphocytes, and granulocytes. Histograms show the lack of XIAP protein staining in all leukocyte subsets. **B.** Isolated peripheral blood mononuclear cells were stimulated with either LPS as a positive control, L18-MDP as the experimental condition, or PBS as an unstimulated control. Gated monocytes from the control show upregulation of both TNF-a or IL-8 expression when stimulated with either LPS or muramyl dipeptide (MDP), but the patient did not show any upregulation with MDP stimulation. Normal responses noted with LPS indicating the patient's monocytes are viable and responsive.

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Poster Mania

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A Systems-Predicted Neutralizing Antibody Assay Identifies Compartment-Specific Features Correlating with Neutralization Breadth

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Quantifying neutralizing antibody levels across anatomical sites and understanding correlates of neutralization breadth is paramount for monoclonal antibody treatments and next-generation vaccination strategies. The systems serology platform allows for characterization of antibody responses at the isotype and subclass level to an array of analytes simultaneously, generating an antibody signature that can be correlated with an outcome. We sought to expand our platform through the development of a multiplexed neutralizing antibody quantitation assay that can be incorporated into our existing systems serology framework to identify antibody features that may be driving neutralization responses. We therefore developed a multiplex-based systems-predicted neutralizing antibody (SNAb) assay capable of quantifying antibody neutralization levels to dozens of targets simultaneously in a high-throughput manner. Through the incorporation of SNAb into our existing systems serology workflow, we have found that antibody signatures correlating with neutralization are highly influenced by preexisting immunity, anatomical compartment, and vaccination route. For H1-lineage human influenza virus and H5-lineage avian influenza virus, serum-circulating neutralizing antibodies generated through vaccination in nonhuman primates were strongly correlated with Fc-gamma receptor-binding antibodies, which have historically been linked with effector function. This is in contrast to mucosal-resident neutralization signatures that were largely driven by IgG and IgA binding antibodies. We further validated our system-based neutralization approach by correlating antibody features to other conventionally employed and regulatory-approved neutralization outputs, such as microneutralization (MN) and hemagglutination inhibition (HAI) assays.

These assays yielded almost identical antibody signatures correlating with neutralization compared to our SNAb assay, highlighting that none of these approaches imparts bias into predictive neutralization signatures. Collectively, we propose that neutralizing antibody titers can be quantified to an array of targets simultaneously and in distinct compartments for viruses such as influenza, SARS-CoV-2, and HIV-1 in a sample-sparing manner. Moreover, the antibody repertoire contributing to neutralization appears to be heavily influenced by the local immune milieu.

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Autopsies in Chronic Granulomatous Disease: A 35-Year Perspective

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[1]Laboratory of Clinical Immunology and Microbiology, NIAID; [2]Laboratory of Pathology, NCI, NIH

We performed a single-center retrospective analysis of chronic granulomatous disease (CGD) autopsy reports to better understand causes of death, end-organ damage, and disease pathophysiology. Forty-four autopsies of CGD patients, including one X-linked female carrier, were performed from February 1990 to June 2025. These cases represent approximately 60% of the CGD deaths over 35 years. There was an increase in age at death over this time, despite a heavy burden of infections. The immediate cause of death was infection n = 30 (68%); *Aspergillus* species (33%) was the most frequent pathogen. One death was associated with SARS-CoV-2. An aggressive new *Aspergillus* species, *Aspergillus tanneri*, and an unidentified *Burkholderia* species were identified in this cohort.

Noninfectious causes of death in 14 patients were associated to accident (1), respiratory failure (2), renal failure (2), surgical complications (1), post-transplant complications (2), cardiovascular complications (2), cerebral infarction (1), Transfusion-Related Acute Lung Injury (TRALI), a serious complication of blood transfusions where the recipient experiences acute lung injury in one case, and one death attributed to metastatic pancreatic ductal adenocarcinoma.

A substantial portion had characteristic pigmented-laden macrophages in multiple organs, with a high concentration in the brain parenchyma. Atherosclerotic manifestations were present in a third of the cases. One patient, p22phox, had minimal atherosclerosis manifestations early in life (19 yrs). Lungs and hearts were significantly heavier when compared to norms. Livers were not significantly larger, although there was evidence of underlying inflammatory disease. Periportal inflammation was noted in 19 patients (46%), and nodular regenerative hyperplasia (NRH) was found in 7 (16%). Kidneys were small overall (atrophic), which may be related to drug exposure, specifically amphotericin B. Glomerulosclerosis or chronic renal compromise was found in 17 patients (41%), two of whom were children. Among those with glomerulosclerosis, one had never received amphotericin B. This pathology review shows pigment-laden macrophages across multiple organs not previously recognized, including the brain parenchyma. This is the largest autopsy series known in this population, underscoring the increased survival over time. With fungal infections being the most common cause of death, this emphasizes the importance of antifungal development and definitive cure in this disease.

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CXCL13 as a Biomarker of Complex Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) is a group of heterogeneous disorders with common denominators of impaired antibody production and function and recurrent infections. Currently, prognostic biomarkers for CVID are limited. CXCL13 is a critical regulator of germinal center responses and antibody production, with T follicular helper (Tfh) cells as a major source, and acts as a potent B cell chemoattractant. Serum levels of CXCL13 are increased in chronic inflammatory conditions and malignancy. We aimed to explore whether serum CXCL13 levels are altered in CVID and whether they can categorize the patients based on their clinical and immune phenotype. We compared the serum levels of CXCL13 between CVID and healthy donors (HD) and associated them with the clinical and immune phenotype of the patients. The serum levels of CXCL13 were higher in CVID, especially in female patients, as compared to HD, and were positively correlated with the number of clinical complications in CVID and the total peripheral circulating Tfh cells (cTfh). CVID patients with higher levels of CXCL13 were more likely to have clinical complications and/or a high frequency of CD21low B cells or low frequency of switched memory B cells. CXCL13 can stratify heterogeneous patients with CVID and serve as a biomarker for complex disease.

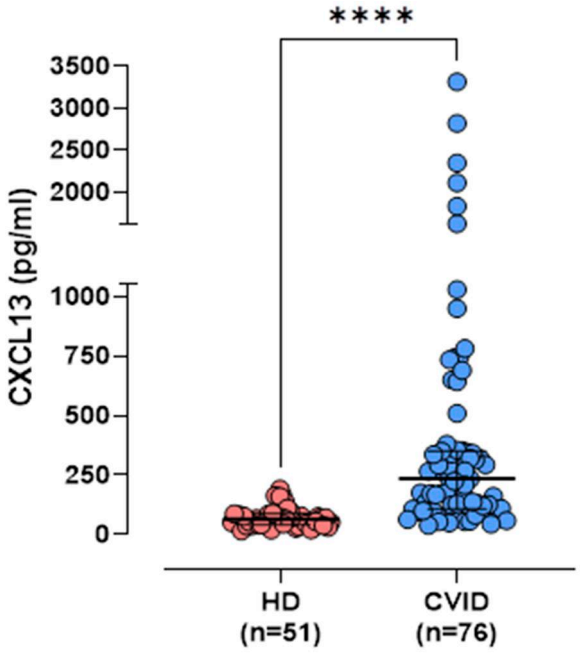

Figure 1.

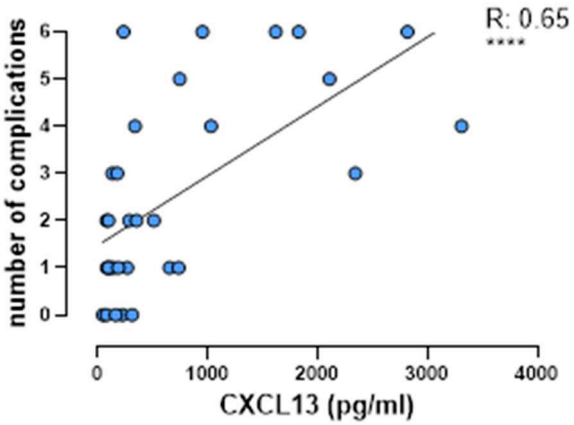

Figure 2.

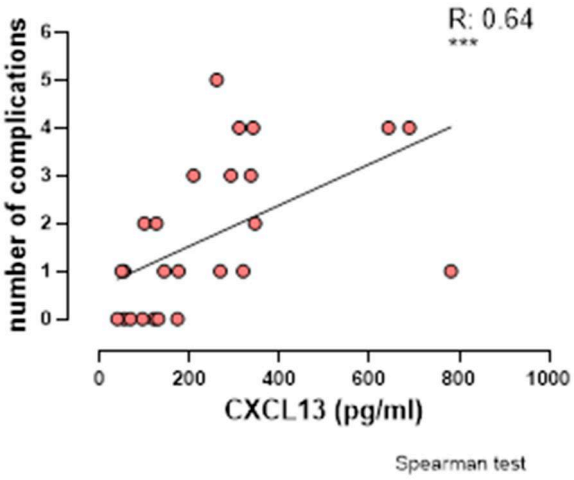

Figure 3.

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Determining the Risk of Developing Severe Sepsis Using Genetic Profiling of Innate Immunity Genes

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Background and Aims: The immune response to an infectious agent is regulated by a complex network of signaling pathways involving numerous genes encoding inflammatory mediators, proteins of the innate and adaptive immune systems, and cell surface receptors of the first line of immune defense (neutrophils, macrophages, dendritic cells, etc.) (e.g., Toll-like receptors [TLRs]). Polymorphisms in these genes can determine the genetic variability of the systemic immune response and, consequently, the variability of clinical manifestations and outcomes of sepsis.
Methods: We analyzed DNA samples (n = 154) of oncohematological patients of the anesthesiology and intensive care unit with severe sepsis. Polymorphisms of the TLR4: c.*1205G>A; TNF-α: -308G>A; HAVCR1: p.Leu179Pro; p.T207A; CD14: -159C>T; IL18: 137G>C; 607C>A; BCL2: -938 C>A was detected using capillary Sanger sequencing.

Results: The studies revealed the following: Polymorphism of the TLR4 gene: *1205G>A (odds ratio [OR] = 0.43 (0.2–0.9) (χ^2 = 5.7, p = 0.021)). HAVCR1:T207A (OR = 0.42 (0.2–0.86) (χ^2 = 5,8, p = 0.008)) increases the likelihood of developing septic shock. Polymorphism of the TNF-α:-308G>A (OR = 2.8(1.07–7.18)(χ^2 = 6.3,p = 0.012)); HAVCR1: T207A (OR = 0.28(0.1–0.8) (χ^2 = 7.6,p = 0.006)); BCL2: -938 C>A (OR = 0.4(0.18–0.9)(χ^2 = 5.0, p = 0.012)), the likelihood of developing sepsis-associated acute kidney injury with the need for renal replacement therapy increases. In the presence of polymorphisms IL18: -137G>C (OR = 2.8 (1.2–6.6) (χ^2 = 5.5, p = 0.009)); IL18: - 607C>A (OR = 0.34 (0.13–0.86) (χ^2 = 5.7, p = 0.006)), the probability of developing acute respiratory distress syndrome increases.

The absence of CD14 polymorphism: -159C>T (OR = 0.35 (0.16–0.78) (χ^2 = 6.9, p = 0.004)) is associated with an increased likelihood of a long (more than 14 days) stay in the intensive care unit and the development of a "chronic critical condition." Polymorphisms in the HAVCR1 gene: L179P (OR = 4.8 (1.37–16.6) (χ^2 = 7.1, p = 0.004)) are associated with the likelihood of developing an unfavorable outcome (28-day mortality) increases.

Conclusions: Based on the obtained results, the detection of polymorphisms in immune response genes and cytokines demonstrates high statistical significance, which may facilitate the identification of patients at risk for severe sepsis. For this category of patients, earlier transfer to the intensive care unit (ICU) is recommended to ensure timely initiation of risk-adapted, specialized, and high-tech care.

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Development of a Quantitative Measure of Lung Disease Severity in STAT3 Hyper-Ige Syndrome

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Introduction: Progressive lung disease remains the leading cause of morbidity and mortality in patients with STAT3 hyper-IgE syndrome (HIES), despite optimal supportive care. Forced expiratory volume in 1 second (FEV1) is a readily available quantitative measure of lung function that is known to predict survival across various lung diseases.

Methods: All FEV1 values (% predicted based on Global Lung Function Initiative equations) from STAT3 HIES patients enrolled in a natural history protocol (NCT00006150) were collected. Measurements were obtained prior to hematopoietic stem cell or lung transplantation, when applicable. A generalized additive model was used to plot the trajectory of FEV1 (% predicted) in the cohort. FEV1 (% predicted) at age 20 years was estimated using a Bayesian approach, and its association with time to death was analyzed using Cox proportional hazards models.

Results: A total of 1,056 FEV1 values (% predicted) were collected from 161 patients with STAT3 HIES. The longitudinal progression of FEV1 (% predicted) with age was modeled and adjusted for known factors affecting lung function, including scoliosis and lung surgery. For further analysis, we focused on patients with at least one FEV1 measurement between age 14 and 30 (n = 111), which enabled estimation of FEV1 (% predicted) at age 20, the physiological peak of lung function, across the cohort. We first showed a strong correlation between observed and estimated FEV1 (% predicted) at age 20 (Spearman's rho = 0.959, p < 0.001). We then demonstrated that the FEV1 (% predicted) at age 20 significantly correlated with time to death (hazards ratio = 0.962, p = 0.029).

Conclusion: In STAT3 HIES, estimated FEV1 (% predicted) at 20 years of age serves as a quantitative measure of lung disease severity and may facilitate identification of patients with extreme lung phenotype for further mechanistic investigation and therapeutic studies.

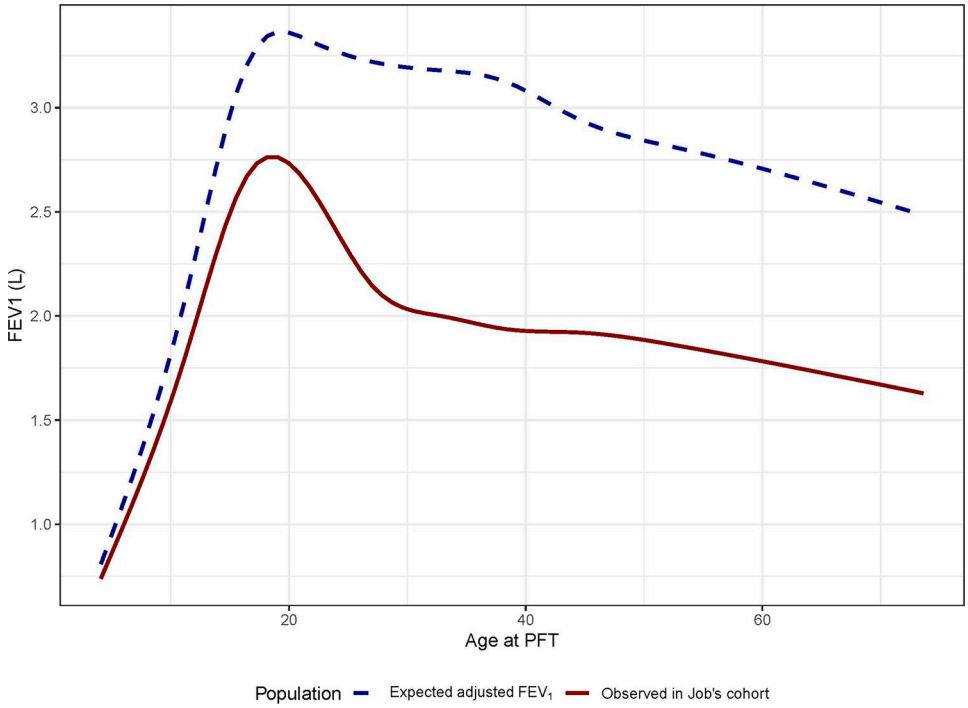

Figure 1. **Longitudinal changes in FEV1 with age among patients with STAT3 HIES.**

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Disease-Causing STAT3 Variants Can Be Discriminated by a Functional Flow Cytometry Test

Ana Esteve-Sole[1], Alexandra F. Freeman[2], Amy Hsu[2], Tiphanie P. Vogel[3], Lisa R. Forbes Satter[3], Jenna R.E. Bergerson[2], Taura Webb[2], Joseph Pechacek[2], Kristen McDaniels[4], Megan A. Cooper[4], Carolina Bouso[5], Matias Oleastro[5], Silvia Denielian[5], Luis Ignacio Gonzalez-Granado[6], Michail S. Lionakis[2], Steven M. Holland[2], Thomas A. Fleisher[1], HyeSun Kuehn[7], and Sergio Rosenzweig[7]

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Background: Heterozygous STAT3 protein variants acting by dominant-negative (DN), gain-of-function (GOF), or haploinsufficiency (HI) mechanisms have been associated with different clinical/immunological phenotypes. However, the biological impact of STAT3 protein variants is complex to determine, and it generally requires vector generation, transfection, and multiple iterations for definition.
Objective: To establish a single, reliable test to functionally characterize putative disease-causing STAT3 protein variants in patient primary cells.
Methods: We recruited patients carrying previously published/validated STAT3-DN (n = 13), STAT3-GOF (n = 4), and STAT3-HI (n = 5) variants. We functionally evaluated the IL-10-mediated/STAT3-dependent inhibition of LPS-induced TNF-a production by peripheral blood mononuclear cell (PBMC) monocytes using flow cytometry to assess the biological impact of STAT3 protein variants. Optimization and threshold definition were performed by bootstrapping and k-fold cross-validation of the receiver operating characteristic (ROC)-area under the curve (AUC).
Results: The inhibition ratio of TNF-a production was significantly diminished in STAT3-DN (-3.44-fold, $p < 0.0001$) and STAT3-HI patient samples (-2.28-fold, $p < 0.0001$), while significantly augmented in STAT3-GOF patient samples (+1.47-fold, $p = 0.002$) when compared to healthy controls (HC, n = 16). Optimization of the combinations of IL-10 concentrations discriminated between HC from

STAT3-DN (ROC-AUC = 1) and STAT3-GOF (ROC-AUC = 0.89). Further test optimization allowed discrimination of STAT3-HI variants when compared to HC (ROC-AUC = 1) and to STAT3-DN (ROC-AUC = 0.92).

Conclusion: Determination of the IL-10-mediated, STAT3-dependent TNF-α inhibition after LPS stimulation ratio in PBMC monocytes using flow cytometry is a sensitive and specific method to functionally assess and discriminate STAT3-DN, -GOF, and -HI variants. This test can be used in research and clinical laboratory settings.

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Elucidating the Pathogenesis of Chronic Norovirus in Inborn Errors of Immunity: Lessons from Single-Cell Transcriptomics of Biopsies and Patient-Derived Organoids

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Chronic norovirus infection (CNI) causes significant morbidity and mortality in immunocompromised patients, including those with inborn errors of immunity (IEI). Gastrointestinal samples from patients with CNI demonstrate mild histopathologic changes. No animal model for human norovirus infection is routinely accessible, and norovirus cannot be passaged in traditional cell culture.

In this study, we sought to identify the cell types permissive for human norovirus infection and to immunophenotype chronic norovirus-infected gastrointestinal tissue.

Two patients with CNI and immunodeficiency underwent traditional clinical immunophenotyping and gastrointestinal biopsies. Immunodeficiency diagnoses were Good's syndrome with severe T cell lymphopenia in patient 1 and NF-Kβ2 loss of function (LOF)/gain of function (GOF) disease in patient 2.

Single-cell RNA-seq (scRNA-seq) was performed on patient duodenal biopsies as well as patient-derived enteroids. Patient datasets were compared with healthy individuals or norovirus-negative patients with environmental enteropathy from public databases.

scRNA-seq of biopsy samples showed that late enterocytes contained the highest proportion of norovirus RNA; norovirus RNA was also present in M2 macrophages and enteroendocrine cells. Non-epithelial cells were present, including CD8, CD4, and γδ T cells, with a higher number of T cells bearing exhaustion markers, including CD160, TIGHT, and CXCL13, as compared to controls. Cells bearing B cell markers were absent in both patients. Furthermore, Rho GTPase, type I/II interferon, CXCL10, CXCL11, CXCL9, and PLA2G7 were all upregulated in patient samples. These tissue-based assays recapitulate findings from peripheral blood phenotyping, including absence of B cells and elevated systemic CXCL9 (range 5,088–6,987 pg/mL; upper limit of normal [ULN] 647 pg/mL). Additionally, CXCL9 staining was elevated in tissue via RNA-scope.

scRNA-seq of patient-derived duodenal enteroids also showed upregulation of type I and type II interferon, as well as multiple cytokines, including CXCL10, CXCL11, and CX3CL1, especially within late enterocytes. Within the enteroids, late enterocyte cells supported norovirus replication.

M2 macrophages differentiated from healthy donor peripheral blood mononuclear cells (PBMCs) incorporated viral particles, initiated viral replication and capsid protein synthesis, and released new viral RNAs/virions in vitro, suggesting an important role for tissue-based macrophages.

Understanding the tissue-based immune dysregulation induced by chronic norovirus infection may help identify novel treatment strategies as well as tissue-based diagnostic targets and immunophenotyping.

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Enhanced Diagnosis of Primary Immunodeficiencies, Including Bronchiectasis Cases, Using Transcriptomic Artificial Intelligence

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This study presents PrimDx, a diagnostic test that applies machine learning (ML) to whole blood transcriptomic data to improve early detection and diagnosis of primary immunodeficiency (PID). Delays in PID diagnosis are common and contribute to preventable complications and morbidity, highlighting the critical need for accurate, accessible, and timely early-stage testing.

To demonstrate utility for PrimDx in a clinical setting, this study incorporated participants with bronchiectasis, a presentation common for PID patients.

Whole blood RNA sequencing was performed on samples collected from 66 individuals (aged 2–67) with antibody deficiencies and 89 controls. Both groups included participants with non-cystic fibrosis bronchiectasis (NCFB; 7 PID, and 15 controls). Over 15,000 genes were quantified per sample, providing a comprehensive transcriptional profile. The data underwent systematic preprocessing and feature selection using Least Absolute Shrinkage and Selection Operator (LASSO) to extract key predictive markers. Many of these markers are not well characterized and appear to be predominantly expressed in lymphocytes.

Multiple ML models were built and assessed using a structured pipeline that applied class balancing, feature scaling, and 5-fold cross-validated grid-search tuning. Models were trained on 80% of the dataset and evaluated on a blinded 20% holdout set. Among the models, a Feature Subspace Ensemble method with logistic regression achieved the strongest performance, with 90% accuracy, 93% F1-score, 95% receiver operating characteristic (ROC)-area under the curve (AUC), and 95% average precision, including robust performance across previously unseen datasets with batch variability. Among participants with NCFB, the model identified antibody deficiency with 93% accuracy.

These findings demonstrate the feasibility and potential clinical utility of integrating RNA sequencing with calibrated ML models to support earlier, more accurate PID diagnosis, including in NCFB patients, potentially enabling timelier treatment and improved patient outcomes. Ongoing work aims to expand the transcriptomic reference library to improve diagnostic accuracy for common PID presentations and enhance clinical applicability.

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Enrichment of Variants of Known and Unknown Significance in Specific Inborn Error of Immunity Categories in Children with Autoimmune Cytopenia

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Autoimmune cytopenias (AIC) are characterized by immune-mediated destruction of platelets (immune thrombocytopenia [ITP]), red blood cells (autoimmune hemolytic anemia [AIHA]), neutrophils (autoimmune neutropenia [AIN]), or multiple lineages (Evans Syndrome [ES]). Although AIC are a common first presentation for IEI, the majority of patients with AIC remain without a genetic diagnosis. Utilization of clinical genetic testing is increasing in the evaluation of patients with AIC, but it is challenging to assess the contribution of certain variants, particularly variants of unknown significance (VUS) and monoallelic variants in recessive genes, to AIC development. Even if these variants do not lead to an IEI diagnosis, their role in the development of an AIC remains unclear. To investigate this question, we aimed to assess whether variants in specific IEI categories were more frequent in patients with AIC than the expected occurrence. In collaboration with Labcorp (formerly Invitae), we obtained results of clinical genetic testing in children under 21 years with AIC who had sequencing with one of six available IEI next-generation sequencing panels. We included 912 patients (ITP, n = 430; AIHA, n = 119; AIN, n = 197; and ES, n = 166). In these patients, there were a total of 2,953 variants identified, including 2,459 VUS. We analyzed the enrichment in specific IEI categories based on the International Union of Immunological Societies (IUIS) classification by comparing the proportion of variants found in each category to the number of genes within this category. We found that three categories were overrepresented:

complement deficiency, immune dysregulation, and phagocyte defects (Figure 1 A). The direction of enrichment remained the same whether we considered only VUS, only likely pathogenic/pathogenic variants, or both. In the phagocyte subcategory, we found a significant enrichment in respiratory burst defect genes, both for VUS and likely pathogenic/pathogenic variants (Figure 1 B). No subcategory of immune dysregulation was significantly overrepresented (Figure 1 C), and there are no complement deficiency subcategories in the IUIS classification. Our data suggest that variants in specific IEI categories are overrepresented in patients with AIC and that VUS may contribute to AIC occurrence, specifically those in respiratory burst genes.

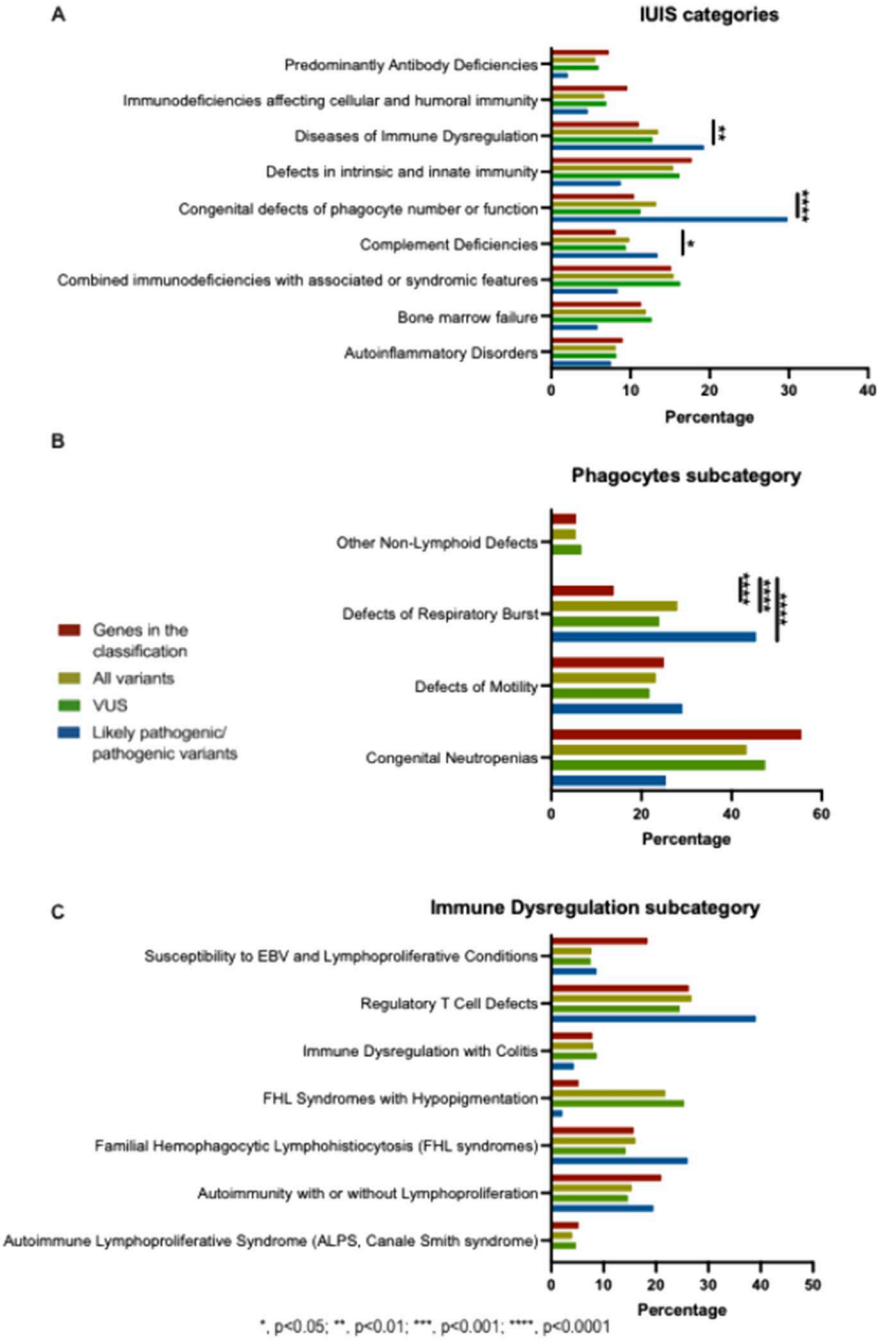

Figure 1.

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Genetic Spectrum of ATM Founder Mutations and Malignancy in Ataxia-Telangiectasia

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Background: Ataxia-telangiectasia (A-T) is a rare autosomal recessive disorder caused by pathogenic variants in the ATM gene and characterized by genomic instability, immunodeficiency, and a markedly increased risk of cancer. In Costa Rica, a strong founder effect has been described, with four recurrent ATM mutations accounting for most cases.
Methods: A retrospective observational study was conducted using the molecular registry of the National Children's Hospital in Costa Rica. Patients with a clinical diagnosis of A-T and molecular confirmation of biallelic ATM mutations were included. Genetic data were analyzed to determine allele frequencies, homozygosity, and associations with consanguinity. Cancer occurrence in patients and family history of malignancy were systematically recorded.
Results: Forty-two patients with confirmed A-T were analyzed, corresponding to 84 ATM alleles. Founder mutations predominated, with CRAT-A being the most frequent allele (51.2%), followed by CRAT-D (23.8%) and CRAT-C (11.9%); CRAT-B was rare (1.2%). Over 60% of patients carried at least one CRAT-A allele, and approximately one third were homozygous for a founder mutation. Parental consanguinity, documented in 11.9% of cases, was significantly associated with homozygosity (odds ratio [OR] 8.39; p = 0.013), supporting a shared ancestral origin of these variants.

Cancer was diagnosed in 14% of patients, and all malignancies were B cell lymphomas. No statistically significant association was identified between specific founder mutations and cancer development.

However, a family history of cancer was present in 33% of patients, most commonly breast and gastric cancer. Mothers and maternal aunts were the most frequently affected relatives, consistent with the increased cancer risk reported in heterozygous ATM carriers.
Conclusions: This study confirms a strong ATM founder effect in Costa Rica, with CRAT-A as the predominant allele, and demonstrates a significant association between consanguinity and homozygosity. Although cancer occurrence in patients with A-T was not linked to specific founder mutations, the high frequency of lymphoid malignancies and the substantial burden of familial cancer highlight the need for structured oncologic surveillance and targeted genetic counseling for affected families. These findings support population-specific diagnostic strategies and long-term cancer risk assessment in both patients with A-T and heterozygous ATM carriers.

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Haploinsufficiency for Human ABCF1 Underlies Gastrointestinal Autoimmunity

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While studying familial celiac disease, we identified four individuals with a rare heterozygous loss-of-function variant in the highly conserved, early-evolved ABCF1 gene. In addition, the 246 individuals heterozygous for ABCF1 loss-of-function variants in the All of Us, UK Biobank, and BioMe cohorts had a higher risk of autoimmune diseases, including 10% with inflammatory bowel disease. Peripheral blood mononuclear cells (PBMC) from ABCF1-deficient patients had high levels of constitutive interferon-stimulated gene expression and enhanced cellular responses to type I interferon and cytokines. We show here that ABCF1 plays an essential role in regulating the JAK–STAT pathway in humans and mice. ABCF1 binds to ribosomal proteins and is involved in liquid–liquid phase separation via its low-complexity domain.

Activation of the stress responses can lead to the trafficking of both STAT1 and ABCF1 into stress granules, and this sequestration eventually inhibits STAT1 phosphorylation. Finally, Abcf1-deficient mice displayed more severe inflammatory responses and tissue damage in response to dextran sulfate sodium challenge. Gastrointestinal inflammation in Abcf1-deficient mice is driven primarily by increased infiltration of myeloid cells, which can be treated with tofacitinib, a JAK kinase inhibitor. We have, thus, discovered a new genetic etiology of autoimmunity and gastrointestinal inflammation, and suggest a targeted treatment for individuals with ABCF1 haploinsufficiency and chronic inflammation.

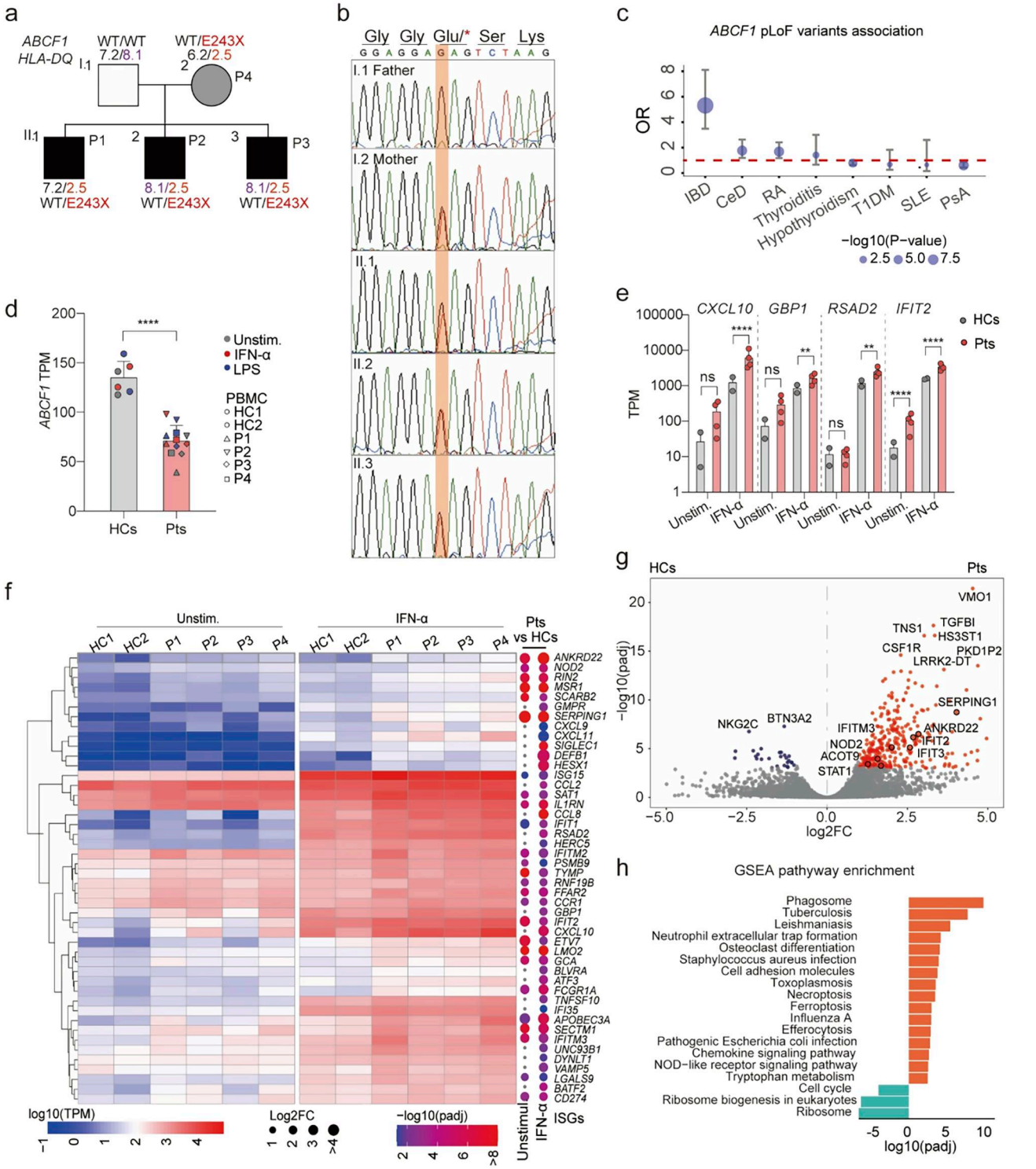

Figure 1. **A rare pLoF variant of *ABCF1* disrupts cellular responses to IFN-α and multiple pathways in a family including multiple individuals with celiac disease. a.** Pedigree of a family containing three patients (P1, P2, and P3) diagnosed with CeD in childhood. The three patients were found to be heterozygous for an *ABCF1* mutation (E243X). The mother is also a carrier but has a mild phenotype. HLA-DQ genotype is indicated. **b.** Sanger sequencing electropherogram. **c.** A phenotype-association study was performed on 246 individuals heterozygous for an *ABCF1* pLoF variant found in the UK Biobank, All of Us, and BioMe databases. Results of RNA sequencing on PBMCs from two wild-type healthy controls (HCs) and four patients (Pts) (d–h). **d.** *ABCF1* mRNA level. **e.** Constitutive and IFN-α-stimulated mRNA levels for *CXCL10*, *GBP1*, *RSAD2*, and *IFIT2*. **f.** Heatmap of ISGs differentially expressed in the presence and absence of IFN-α stimulation. In the bubble plot on the right, circle size indicates the fold-change difference, and colors indicate the adjusted *p*-value. **g.** Volcano plot of genes displaying differential constitutive expression between patients and controls. **h.** Gene set enrichment analysis (GSEA) of genes displaying differential constitutive expression (at least a two-fold change and adjusted *p* value < 0.001). Unstim.: unstimulated; IFN-α: 40 ng/mL interferon-alpha; LPS: 1 µg/mL

lipopolysaccharide. TPM: Transcripts per million. Log_2FC: log_2 fold-change, padj: *p*-values adjusted by the false discovery rate (FDR) procedure. *P* values were calculated in unpaired one-tailed Student's *t* tests (d and e). ns, not significant; $^{**}p < 0.01$; and $^{****}p < 0.0001$.

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Immune Diagnoses and Infection Burden in Down Syndrome: A Nationwide Epic Cosmos Analysis (2015–2024)

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Introduction: Down syndrome (DS) is associated with increased infections and immune dysregulation, yet contemporary large-scale United States (U.S.) data quantifying immune diagnoses, infection burden, and immunoglobulin (IgG) use are limited. We aimed to characterize these patterns using the Epic Cosmos nationwide dataset.
Methods: We performed a retrospective cross-sectional analysis of individuals with DS (ICD-10 Q90*) in Epic Cosmos (2015–2024). Immune diagnoses, infection codes, and IgG administration encounters were extracted and summarized descriptively.
Results: We identified 209,751 individuals with DS and U.S. residence. Sex distribution was 50.5% males and 49.5% females. Age groups included 20.1% <10 years, 22.3% 10–19 years, and 57.6% ≥20 years. Race/ethnicity was predominantly White (72.0%) and Black (13.4%), with 18.2% Hispanic/Latino. Humoral immune diagnoses included hypogammaglobulinemia in 1,323 patients (0.63%), common variable immunodeficiency in 456 (0.22%), and selective IgA deficiency in 232 (0.11%); hemophagocytic lymphohistiocytosis was identified in 155 (0.07%).

The infectious burden was substantial. Respiratory infections included acute upper respiratory infections in 25.2% (62,010 encounters), pneumonia in 21.1% (103,338 encounters), otitis media in 14.2% (77,950 encounters), and sinusitis in 10.5% (48,886 encounters). Skin and mucocutaneous infections were also frequent, including cellulitis (11.3%; 33,929 encounters), abscess (9.3%; 32,316 encounters), and candidiasis (9.0%; 31,541 encounters). Serious infections included bacterial sepsis (2.7%), osteomyelitis (0.26%), endocarditis (0.10%), and bacterial meningitis (0.09%). IgG replacement was recorded for 2,296 patients (1.1%), primarily through intravenous administration.
Discussion: Although formal humoral immune diagnoses were found in fewer than 1% of individuals with DS, these codes still represented more than 1,300 patients nationwide, suggesting a meaningful subgroup with immune dysfunction. Infection burden was strikingly high, with many infections occurring repeatedly, as reflected by encounter counts exceeding patient counts two- to threefold. Despite this, only 1.1% received IgG replacement therapy. These findings suggest substantial under-recognition or under-treatment of immune dysfunction in DS and highlight the need for standardized approaches to immune evaluation and infection management in this population.

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Immunogenetic Screening Reveals Hidden Inborn Errors of Immunity in Pediatric Lymphoproliferative Disorders

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Background and Aims: Pediatric lymphoproliferative disorders (LPD), both malignant and nonmalignant, may conceal underlying inborn errors of immunity (IEI), yet systematic screening is rarely performed. We hypothesized that comprehensive immunogenetic

evaluation would reveal a high prevalence of IEI in children with persistent LPD, providing actionable targets for precision therapy and surveillance.

Methods: We prospectively enrolled 38 patients (age <20 years) with polyclonal LPD (PL, n = 21) or malignant lymphoma (ML, n = 17) persisting >6 months off therapy. All underwent extended flow cytometry immunophenotyping and genomic analysis via panel/whole-exome sequencing filtered for International Union of Immunological Societies (IUIS) 2024 IEI genes. An IEI diagnosis required pathogenic variants and/or European Society for Immunodeficiencies (ESID) clinical criteria. Results were compared with age-matched healthy controls.

Results: We identified confirmed IEI in 42% of patients (16/38): 57% in PL and 24% in ML. Pathogenic variants included FAS, PIK3CD, STAT3, NFKB1/2, PRKCD, IKZF1, SH2D1A, and TACI. An additional 34% harbored variants of uncertain significance in IEI or lymphoma-associated genes (CTLA4, STAT5A, and ATM), yielding a total diagnostic yield of 66%. Remarkably, most patients lacked classic infection-related immunodeficiency signs. Immunophenotyping revealed distinctive IEI signatures: significantly elevated double-negative T cells (DNT; $CD3^+CD4^-CD8^-TCR\alpha\beta^+$, >2% of $CD3^+$) and unswitched memory B cells ($CD27^+IgD^+IgM^+$) compared to both non-IEI patients and controls ($p < 0.01$, $p < 0.001$). These patterns persisted across multiple IEI subtypes, suggesting potential screening biomarkers preceding genetic confirmation. Strikingly, all confirmed IEI in ML occurred exclusively in B cell lymphomas (Burkitt, diffuse large B cell lymphoma [DLBCL], and Hodgkin), reinforcing the critical role of B cell immune dysregulation in lymphomagenesis.

Conclusions: Over 60% of pediatric LPD patients harbor IEI-associated variants, even without classical immunodeficiency presentation. Our findings establish elevated DNT cells and altered B cell memory compartments as accessible screening biomarkers that could trigger genetic workup. This high diagnostic yield supports integrating routine immunogenetic screening into pediatric LPD diagnostic pathways, enabling gene-targeted interventions (sirolimus, abatacept), personalized surveillance protocols, and improved long-term outcomes. These data advocate for a paradigm shift toward precision immunology in pediatric oncohematology.

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Integrating Functional, Structural, and Predictive Data in the Analysis of the Recombination Activating Gene (RAG) Genomic Variants

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The RAG1 and RAG2 genes encode proteins essential for initiating V(D)J recombination in T cell receptor and immunoglobulin gene loci. Biallelic pathogenic variants in these genes are implicated in a spectrum of immunodeficiency disorders, characterized by clinical heterogeneity. Previous studies from our laboratory have demonstrated that the severity of both clinical and immunological manifestations correlates with the residual recombination activity of the mutant RAG proteins, as assessed by an in vitro functional recombination assay.

In this study, we tested the recombination activity of 58 RAG1 and RAG2 variants whose functional activity had never been previously reported. Subsequently, we compiled a list of almost 250 RAG1 and RAG2 missense variants that had been functionally tested in our laboratory throughout the years. We confirmed that in RAG1, the most severe variants (<10% of residual activity) predominantly localize at the catalytic core, especially at the nonamer-binding domain (NBD), responsible for DNA recognition and binding. In RAG2, the most severe variants cluster within the catalytic beta-propeller domain. We then compared the functional data to the in silico AlphaMissense predicted pathogenicity score to evaluate how this tool correlates with the empirical values. Predictions for both RAG1 and RAG2 variants were concordant with our functional assay in more than 80% of the cases to define likely pathogenic variants. However, AlphaMissense predicted only around 67% of the functional variants as benign, reflecting a lower negative predictive value. Interestingly, the variants whose activity was discordant between the two methods do not seem to be clustered in specific domains. To address these discrepancies, we performed computational modelling to predict variant residual activity using models based on different RAG1/RAG2 complex functional states. The predicted recombinase activity scores leveraging computational structural genomic measures correlated very well with our laboratory measures ($r = 0.93$, $p < 1 \times 10–16$).

Overall, with this work, we aim to elucidate how specific RAG gene variants impact protein structure and recombination, and how this correlates with the clinical phenotypes. The final goal is to help to predict the severity of these mutations and to contribute to the interpretation of variants of uncertain significance (VUS).

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Interim Safety and Efficacy Outcomes of an Open-Label Long-Term Extension Study of Treatment with PI3Kδ Inhibitor Leniolisib in Pediatric Patients Aged 4-11 Years with Activated PI3Kδ Syndrome (APDS)

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Leniolisib, a selective PI3Kδ inhibitor, is a Food and Drug Administration (FDA)-approved treatment for activated PI3Kδ syndrome (APDS) in patients ≥12 years weighing ≥45 kg. To determine its impact on children, patients aged 4-11 years with APDS were enrolled in a two-part, prospective, open-label, single-arm, international study to evaluate its safety and efficacy (NCT05438407). Results of 12-week treatment (part 1) were previously reported.

We report safety and efficacy outcomes of the 1-year extension study. Twenty of 21 patients enrolled in part 1 transitioned to the extension. Leniolisib was administered orally twice daily with dosing based on weight at study visit, ranging from 20–70 mg. The primary endpoint was safety. Additional efficacy outcomes included change from part 1 baseline (CFB) at day (D) 252 in log10-transformed sum of product of diameters (SPD) of index lymph nodes, spleen volume, and naïve B cells. No formal statistical hypotheses were tested.

Median treatment exposure was 51 weeks (range, 18–64 weeks). Median treatment compliance was 98.7% (range, 26-100%), with 2 patients ≤80%. Leniolisib was well tolerated (supplemental table). Seventeen patients had 68 adverse events (AEs). The only grade 3 AE was a femur fracture; the rest were grade 1 or 2. Two serious AEs deemed unrelated to leniolisib were reported by 1 patient each: femur fracture and lymphoid tissue operation. Six patients had 7 treatment-related AEs. No AEs led to leniolisib discontinuation. Efficacy outcomes improved at D252 of treatment. Mean CFB in log10-transformed SPD was -0.267 (SD, 0.191; n = 18; 897.1 mm2 to 487.3 mm2), corresponding to -41%. Mean CFB in spleen volume was -66.0 cm3 (SD, 56; n = 20; 242.3 cm3 to 176.3 cm3), corresponding to -25%. Mean CFB in naïve B cells (CD19+CD20+CD27-IgD+) out of total B cells was 9.7% (SD, 9.5; n = 10; 78.6% to 89.7%), corresponding to 27.0% (SD, 26.21; n = 10; 24.9% to 51.9%) in calculated naïve B cells (naïve–transitional B cells) and 25.6% (SD, 19.7; n = 8; 30.6% to 56.2%) in mature naïve B cells.

Body weight–adjusted doses of leniolisib were well tolerated and maintained durable outcomes with long-term exposure in patients aged 4-11 years with APDS. Data are consistent with prior studies in adolescents and adults.

Tabular data are included as downloadable supplement files.

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Introducing the MIRACLE Task Force: Maternal Immunity, Reproduction, and Inborn Errors of Immunity Collaboration

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Introduction: The MIRACLE Task Force is a multidisciplinary, multi-institutional work group comprising immunology, genetics, obstetrics/gynecology, and maternal fetal medicine providers dedicated to understanding reproductive and pregnancy outcomes in individuals with inborn errors of immunity (IEIs).

Methods: The first study is a retrospective cohort analysis using data from the National Inpatient Sample (2016–2022), a database capturing approximately 20% of hospital discharges in the United States. Delivery admissions, comorbidities, severe maternal morbidity (SMM), and IEI diagnoses were identified through ICD-10 codes. A multivariable binary logistic regression was used to assess the impact of IEI on SMM, while controlling for comorbidities. The second study involved qualitative interviews with individuals with IEIs who had been cared for during pregnancy in a single health system to capture reproductive experiences.

Results: For study #1, a total of 5,026,871 delivery hospitalizations were identified. Diagnosis of IEI was found in 931 admissions. The most common IEIs represented included primary antibody deficiencies (30%) and DiGeorge syndrome (10%). Obstetrical comorbidities were more common among patients with IEI vs. without, notably asthma (21.0 vs. 5.7%), major mental health disorders (22.0 vs. 8.9%), anemia (21.0 vs. 14.0%), gastrointestinal disease (19.0 vs. 5.9%), and bleeding disorders (11.0 vs. 2.3%). SMM occurred in 7.4% of patients with IEI versus 1.6% without, mostly driven by immune-related comorbidities. In the logistic regression model, IEI was associated with SMM even after controlling for the number of comorbidities (odds ratio [OR] 2.66, 95% confidence interval [CI] 2.04–3.42, $p < 0.001$). For study #2, 5 females with CVID, 3 primigravida, and 2 multigravidas were included. All individuals were concerned about passing their immune disease onto their offspring, and all had undergone preconception genetic testing. During pregnancy, 4 out of the 5 felt their OBGYN team disregarded how their IEI affected their health, particularly regarding the treatment of infections. Complications arose during birth and postpartum in 4 participants, including cytopenias and infections. All participants endorsed the need for better knowledge of IEI by the OBGYN team.

Conclusions: These two reports demonstrate that IEI is associated with severe maternal morbidity, and better communication between immunology and OBGYN is critical in the care of pregnant IEI patients.

Tabular data are included as downloadable supplement files.

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Investigating Hidden Drivers of Progressive Multifocal Leukoencephalopathy in the NIH Natural History Cohort

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Background: Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic brain infection caused by the JC virus, and idiopathic PML is increasingly recognized. Deeper profiling of such patients often reveals occult immune deficiency. We describe a cohort within the National Institutes of Health (NIH) PML Natural History Study with known or suspected inborn errors of immunity (IEIs), aiming to gain insight into PML susceptibility.

Methods: The NIH PML Natural History Study (NCT01730131) has enrolled 150 participants to date. Enrollees undergo standardized assessments to characterize immune profiles and disease course. Whole-exome or -genome sequencing (WES, WGS) is conducted in idiopathic cases, with additional targeted deep sequencing of somatic variants and anti-cytokine autoantibody testing in a subset.

Results: Forty-one patients (27%) are included in this cohort. Median age was 55 years, and 56% were male. At enrollment, 9 had a diagnosis of IEI, including CD40LG deficiency, DOCK8 deficiency, STAT1 GOF, FOXN1, and X-SCID. Thirty-two patients had idiopathic PML. Among these, 19 patients had CD4 lymphopenia (median 162 cells/μL) and 14 had CD19 lymphopenia (median 26 cells/μL). Genetic sequencing identified three previously undiagnosed pathogenic variants in RELB, SASH3, and CARMIL2. One patient had previously unrecognized thymoma and Good's syndrome; one had previously unrecognized T cell lymphoma. Anti-cytokine antibodies, assessed in 16 patients without a genetic diagnosis, revealed only one patient with a suspicious type I IFN autoantibody. Four patients underwent targeted deep sequencing after WES/WGS was nondiagnostic; no pathogenic somatic variants were found. Notably, 13 patients (32%) had spontaneous recovery of PML, 24 (59%) received experimental immunotherapy, and 4 with IEI (10%) underwent hematopoietic stem cell

transplantation (CD40LG deficiency, DOCK8 deficiency, and X-SCID). Overall survival was 61%, although four have had <6 months of follow-up to date.

Conclusions: IEIs are an important risk factor for PML. Among patients with idiopathic disease, comprehensive immunologic evaluation can yield definitive diagnoses. It is notable that a substantial fraction of this cohort achieved spontaneous recovery of PML. Understanding the immune pathways involved may guide future therapeutic strategies and improve outcomes.

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IRF4 p.T95R Combined Immunodeficiency: Clinical Features and Transplant Outcomes

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Introduction: Inborn errors of interferon response factors (IRFs) are a subset of monogenic inborn errors of immunity, occurring as a result of damaging variants in the IRF genes. Of these diseases, IRF4 deficiencies are associated with the broadest range of phenotypes, each of which is highly genotype dependent. In 2023, our consortium characterized seven patients carrying the IRF4 p.T95R variant, which was demonstrated to be damaging through various models. The clinical profile of these patients has not been described in detail.

Methods: This study summarizes our understanding of IRF4 p.T95R in all nine known patients, including two patients new to this report. Key features were extracted from clinical records, publications, and follow-up with clinicians, with a focus on pretransplant infectious susceptibility and treatment outcomes, particularly following hematopoietic stem cell transplant (HSCT).

Results: 7/9 patients are male, with ages ranging from 6.5 to 31 years at last update. All had opportunistic infections before 1.5 years of age. Notable pretransplant opportunistic infections included *Pneumocystis jirovecii* (8/9), cytomegalovirus (CMV) (3/9), onychomycosis (3/9), and weakly virulent mycobacteria (2/9). 5/9 patients also had gastrointenstinal (GI) manifestations, including colitis, proctocolitis, and mucosal eosinophilia. All had combined immunodeficiency with notable defects in B cell development and antibody production (9/9 hypo/agammaglobulinemia). All patients received immunoglobulin replacement therapy and antimicrobial prophylaxis. 4/9 patients received HSCT. Of those transplanted, one had good outcomes (i.e., resolution of enteropathy and protection from infections), 2/4 died (pre-transplant CMV and cryptosporidium), and 1/4 lost their graft. In those managed without transplant, 2/9 have reached adulthood (20 and 31 years at last update).

Conclusion: This cohort of 9 patients with combined immunodeficiency due to heterozygosity for IRF4 p.T95R experienced a spectrum of outcomes. IRF4 p.T95R patients all have profound combined immunodeficiency, characterized by classic opportunistic infections early in life. HSCT is potentially curative (n = 1). Active infection at the time of transplant was associated with poor outcomes, further emphasizing the value of early recognition and intervention. The phenotype of IRF4 p.T95R is uniquely severe when compared to the growing list of IEIs affecting IRF4, emphasizing the critical need to consider IRF4 genotype-specific effects in IEI patients.

A

IRF4 p.T95R Cohort							
Family	Patient	Age (at last update, years)	Status	Sex	Inheritance	Transplanted	Onset <1 year
F1	P1	16	Alive	Male	*de novo*	Yes	Yes
F2	P2	Dead (3)	Dead	Male	*de novo*	Yes	Yes
F3	P3	Dead (13)	Dead	Male	*de novo*	Yes	Yes
F4	P4	8	Alive	Male	*de novo*	Yes	Yes
F5	P5	20	Alive	Male	*de novo*	No	Yes
F6	P6	13	Alive	Female	mosaic mother	No	Yes
	P7	7.5	Alive	Male	mosaic mother	No	Yes
F7	P8	31	Alive	Male	*de novo*	No	Yes
F8	P9	6.5	Alive	Female	*de novo*	No*	Yes

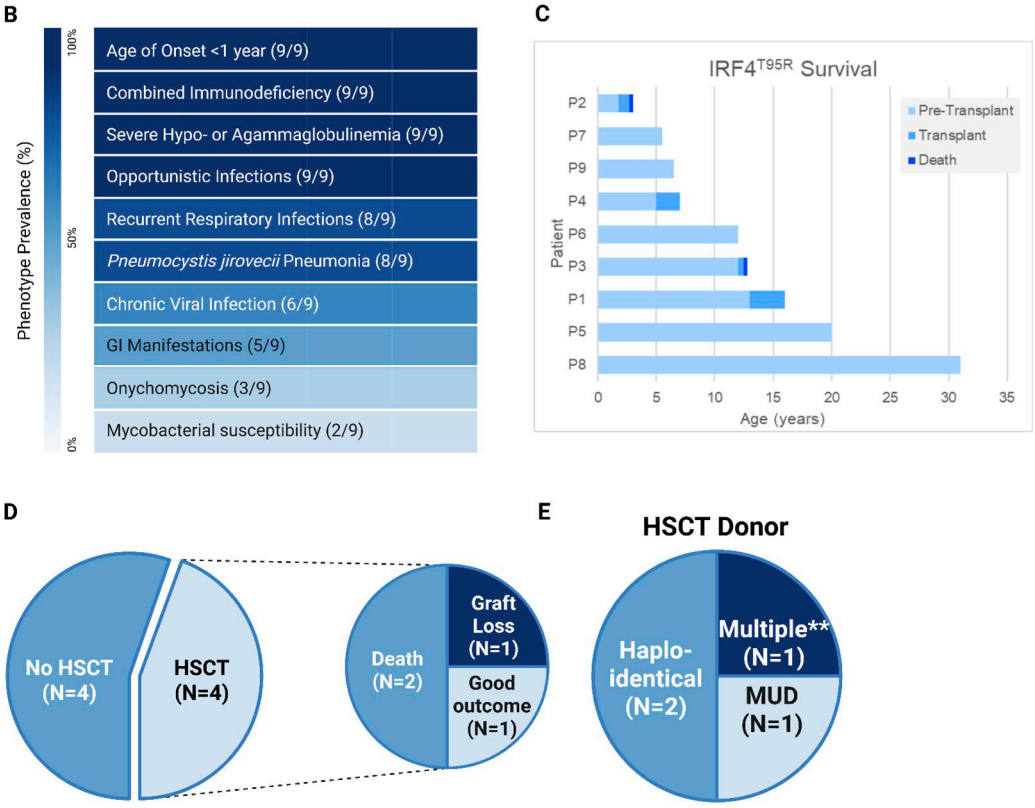

Figure 1. **Clinical features and transplant outcomes of IRF4 p.T95R patients. (A)** IRF4 p.T95R cohort. *Awaiting first transplant. **(B)** Phenotypes of IRF4 p.T95R patients. **(C)** Survival timelines for IRF4 p.T95R patients. **(D)** Transplant outcomes for IRF4 p.T95R patients. **(E)** HSCT donor types. MUD, matched unrelated donor. **Patient received multiple grafts, including grafts from haploidentical and MUD.

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Metabolic Stress Caused by Inadequate Glutamine Uptake in Activated T Cells Can Drive Th2 Cytokine Production in NRF2-Dependent Fashion

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Genome-wide association studies have identified members of the CARD11/MALT1/BCL10 (CBM) complex as susceptibility loci for common allergic disorders, while carriers with rare loss-of-function (LOF) variants in MALT1 or CARD11 can develop severe atopy and elevated T cell Th2 cytokine production, in addition to other immunopathology. Loss of CBM complex function impairs lymphocyte receptor–mediated activation of

NFκB as well as glutamine uptake—thereby selectively reducing signaling in mTORC1, but not mTORC2. In tumor models, glutamine starvation results in mTORC2-dependent activation of NRF2—a known transcriptional inducer of Th2 cytokines. Because patients with NFkB deficiency do not develop significant Th2 phenotypes, while those with gain-of-function mutations in the PI3K/AKT/mTORC2 pathway can, we therefore investigated how glutamine deprivation and mTORC1/mTORC2 dysregulation might lead to Th2-associated allergic predisposition.

CARD11 LOF mutations were introduced or corrected via CRISPR-Cas9 base editing of primary CD4⁺ T cells or studied in a CARD11 LOF mouse model. Cytokine production, glutamine uptake, reactive oxygen species (ROS), and NRF2 expression were measured by flow cytometry. Transcriptomics were measured via bulk RNA sequencing.

We observed reduced glutamine uptake and reduced mTORC1 but not mTORC2 signaling upon TCR stimulation in primary patient CD4⁺ T cells, base-edited CD4⁺ T cells expressing patient mutations, or the addition of bioorthogonal glutamine competitors. These conditions, as well as glutamine starvation of dividing WT CD4⁺ T cells, resulted in increased Th2 phenotypes, while base editing of patient CD4⁺ T cells to WT or glutamine supplementation decreased Th2 phenotypes. Increased ROS production was detected in glutamine-deprived WT CD4⁺ T cells and in human and mouse CARD11 LOF CD4⁺ T cells, which was associated with higher NRF2 protein expression. Finally, small molecule inhibition or genetic knockdown of NRF2 or antioxidant treatment suppressed the elevated Th2 cytokine production in the CARD11 LOF and glutamine-deprived WT CD4⁺ T cells.

Decreased CBM function or glutamine uptake may promote Th2 differentiation and cytokine production by triggering a stress response characterized by ROS production and NRF2 activation, which can drive Th2 phenotypes. Strategies to mitigate these processes may be helpful in treating CBM-associated disease and other forms of Th2-driven disease.

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NFKB1 Truncating Variants Associated with Significant Autoimmunity and Lymphoproliferation in Common Variable Immunodeficiency

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Heterozygous NFKB1 variants have been increasingly identified in patients with common variable immunodeficiency. These patients, however, often experience substantial immune dysregulation beyond humoral deficiency. NFKB1 encodes p105, which undergoes proteolytic cleavage to release p50, the transcriptionally active subunit of canonical NF-κB. While several in vitro transfection systems have demonstrated loss-of-function of these variants regarding canonical NF-κB reporter activity, the immune-related phenotypes of these patients differ from those with well-characterized defects leading to impaired canonical NF-κB activation (i.e., IKBKG or NFKBIA variants). Notably, the C-terminal part of p105 contains ankyrin repeats, which can repress downstream signaling by retaining NF-κB dimers in the cytosol. We therefore hypothesize that loss of p105 inhibitory function may contribute to the immune dysregulation observed in some affected patients.

In this study, we evaluated 8 patients from 8 unrelated kindreds presenting with early-onset common variable immunodeficiency, complicated by diverse and severe immune dysregulations, including multiple autoimmunity and lymphoproliferation (NCT00001355). In addition to immunoglobulin replacement therapy for hypogammaglobulinemia, all required multiple immunomodulatory therapies. One patient ultimately underwent allogeneic hematopoietic stem cell transplantation for disease control.

All patients harbored private germline heterozygous NFKB1 truncating variants (nonsense, n = 2; frameshift, n = 5; splice, n = 1) located in the N-terminal p50 part of the protein, prior to the ankyrin repeats. Beyond the well-recognized B cell failure in these patients, peripheral blood mononuclear cells showed lower basal IκBα level and enhanced IκBα degradation following ex vitro stimulation, indicating activation of canonical NF-κB signaling. Their T cells showed increased phospho-AKT upon stimulation. Together, these findings suggest a potential loss of p105 inhibitory function in these patients. Further elucidation of the mechanisms underlying profound immune dysregulation is crucial because these patients may benefit from the PI3Kδ inhibitor leniolisib, given the observed PI3K signaling activation. A prospective clinical trial is currently recruiting such participants to investigate this targeted therapy (NCT06549114).

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Novel Senolytic Clinical Trial in CVID with GLILD

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Background: Granulomatous-lymphocytic interstitial lung disease (GLILD) is a major cause of morbidity and mortality in common variable immunodeficiency (CVID), yet its pathophysiology remains incompletely understood, and no Food and Drug Administration (FDA)-approved therapies exist. Cellular senescence, a state associated with inflammation and fibrosis, has been implicated in chronic lung diseases, including idiopathic pulmonary fibrosis, where senolytic therapies have shown benefit. Cellular senescence has also been described in some cases of GLILD.

Objective: To evaluate the efficacy of fisetin, a senolytic flavonoid, compared with placebo in adults with CVID-associated GLILD.

Methods: We conducted a randomized, double-blind, placebo-controlled pilot trial in 10 adults with GLILD (Figure 1). Participants received fisetin 20 mg/kg or placebo on days 0–1 and 28–29, with follow-up over 180 days. Assessments included pulmonary function testing (PFT) and Short Form Health Survey (SF-36).

Results: Fisetin was well tolerated, with no adverse events. SF-36 Mental Health scores were numerically higher in fisetin participants (day 28: −0.28; day 180: 0.00) than placebo (day 28: −0.56; day 180: −0.28).

Mental Component Summary scores remained stable in the fisetin group (−0.65 to −0.70) but declined in the placebo group (−1.09 to −1.94). All other SF-36 domains were comparable between groups.

Mean spirometry measures were stable in both groups. With fisetin, lung volumes increased over time, with increases in mean total lung capacity (5.46 to 5.76 L), residual volume (1.69 to 2.09 L), and residual volume (RV)/total lung capacity (TLC) (0.31 to 0.37). In contrast, the placebo group demonstrated decreases in total lung capacity (4.72 to 4.62 L), residual volume (1.89 to 1.72 L), and RV/TLC (0.41 to 0.38). Diffusion capacity corrected increased from baseline to day 90 in the fisetin group (13.9 to 15.9) and remained stable at day 180, whereas it declined in the placebo group by day 180 (19.1 to 17.6).

Discussion: In this randomized pilot study, fisetin was well tolerated and showed benefit in diffusion capacity, lung volumes, and mental health–related outcomes compared to placebo in GLILD. The temporal pattern of changes suggests that alternative dosing strategies may warrant further evaluation, in addition to potentially larger future studies.

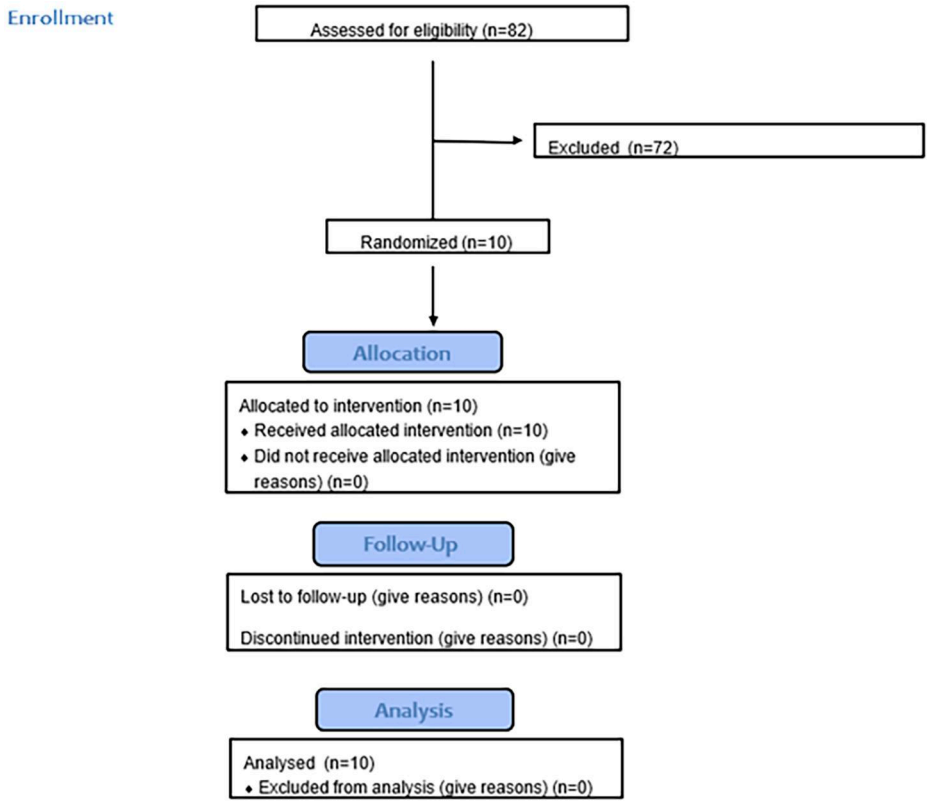

Figure 1. **CONSORT flow diagram.**

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Prospective Clinical Trial of Mycophenolate Mofetil (MMF) Duration De-Escalation in Allogeneic Hematopoietic Cell Transplantation (HCT) for Inborn Errors of Immunity: Is MMF Dispensable After Reduced Intensity Conditioning, Posttransplantation Cyclophosphamide(Ptcy)-Based HCT?

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Hematopoietic cell transplantation (HCT) offers curative potential for inborn errors of immunity (IEI) patients, who often enter HCT with significant comorbidities and disease sequelae, active infections, and/or limited donor options. Strategies to enhance engraftment must be balanced against graft-versus-host disease (GVHD) risk and the need for prompt immune reconstitution.

Recipients of T cell-replete HLA-matched (related or unrelated) or HLA-haploidentical grafts (n = 44) received serotherapy-free, radiation-free reduced-intensity conditioning (pentostatin/cyclophosphamide/2 days busulfan), with PTCy, sirolimus, plus/minus mycophenolate mofetil (MMF) as GVHD prophylaxis. Given promising outcomes with very low GVHD incidence in 20 patients who received MMF on post-HCT days 5–35 (MMF35) (1), MMF duration was reduced (MMF18) and/or omitted (MMF0) via a duration de-escalation schema for the subsequent 24 patients (supplemental table).

Overall and graft-failure-free survival, along with engraftment kinetics, were largely unaffected by MMF duration, but patients who received MMF18 or MMF0 attained full donor T cell chimerism earlier (Figure 1) and required fewer unplanned donor cell infusions. Lymphocyte reconstitution differed in the T cell, but not natural killer (NK) cell, compartment at days 28 and 42, with higher T cell counts in the MMF18 and MMF0 groups even accounting for graft type, but the effect disappeared by day 60 (Figure 2). Viral complications, including BK-associated cystitis incidence and duration, were similar across cohorts (supplemental table, Figure 2).

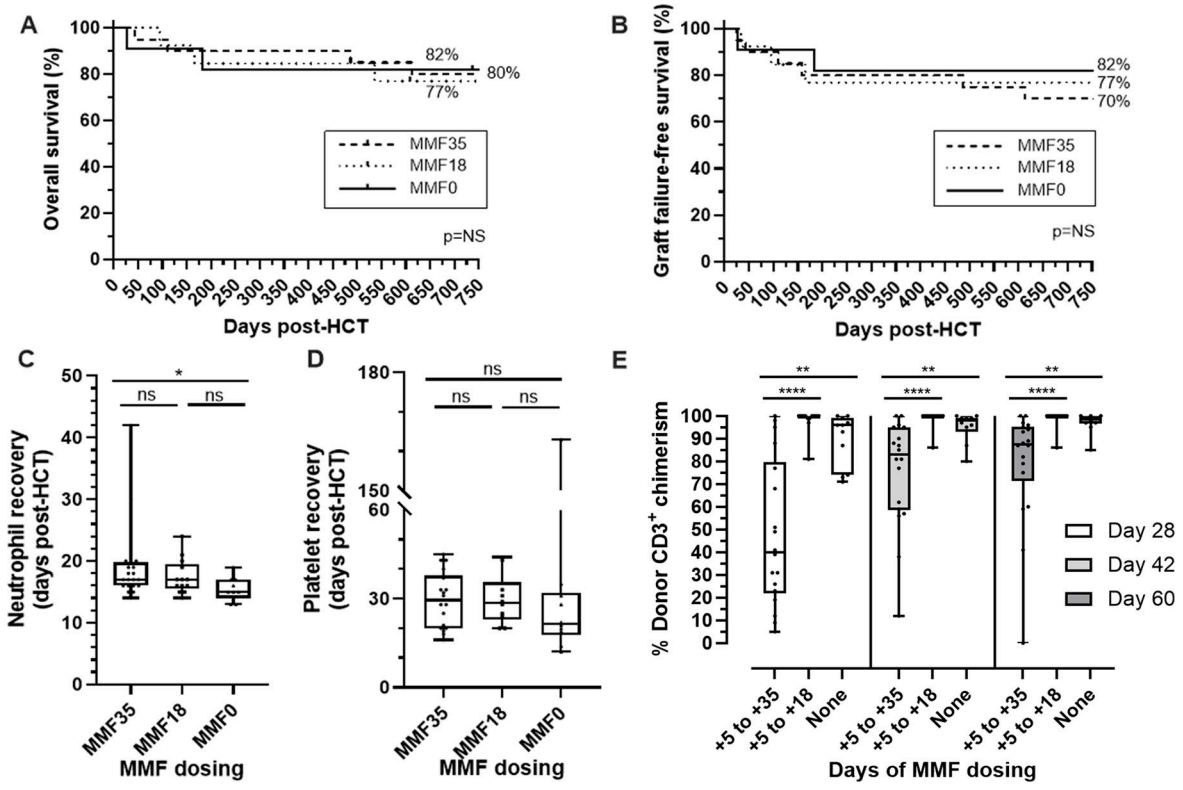

Figure 1. **Engraftment and survival by mycophenolate mofetil (MMF) exposure.** Overall survival (A), graft failure-free survival (B), neutrophil recovery (defined as >500 neutrophils/uL on 3 consecutive days post-HCT) (C), and platelet recovery (defined as >20,000 platelets/uL on 3 consecutive days post-HCT

without transfusion in preceding 7 days) (D) do not vary with MMF exposure, except for neutrophil recovery, where the effect disappeared when only marrow grafts were analyzed. Donor CD3+ chimerism at days 28, 42, and 60 is significantly higher in patients with reduced MMF exposure, even accounting for graft type (E). Statistical significance depicted as: ns (p > 0.05), *, (p < 0.05), ** (p < 0.001), *** (p < 0.001), and **** (p < 0.0001).

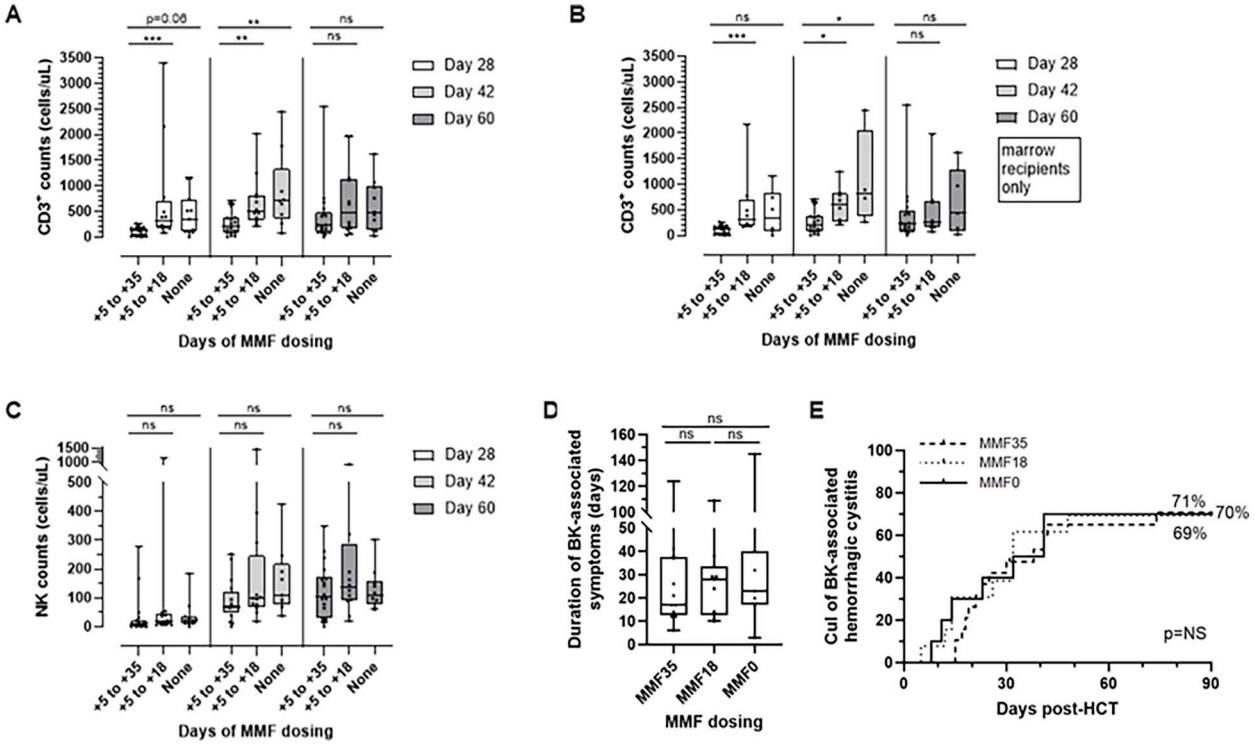

Figure 2. **Lymphocyte reconstitution and viral complications by mycophenolate mofetil (MMF) exposure.** CD3+ counts are significantly greater at days 28 and 42, but not day 60, post-HCT with reduced MMF exposure (A), and this trend persists if peripheral blood stem cell recipients are excluded (B). NK counts do not vary with MMF exposure (C). Duration of BK-associated symptoms (D) and cumulative incidence (Cul) of BK-associated hemorrhagic cystitis (E) do not vary with MMF exposure. Statistical significance depicted as: ns for p > 0.05, *, p < 0.05, ** for p < 0.01, *** for p < 0.001, and **** for p > 0.0001.

Importantly, there was only 1 infection-related death in the MMF18 and MMF0 cohorts (4%), as compared to 3 in the MMF35 cohort (15%). Among 7 haploidentical HCTs using MMF18, 1 patient experienced engraftment syndrome, later dying of chemotherapy-associated lung toxicity, while another died of GVHD complications and idiopathic pneumonia syndrome; both had received peripheral blood stem cell (PBSC) grafts.

Overall, steroid-refractory acute GVHD occurred only in 2 recipients, both with haploidentical HCTs at MMF18, compared to none in the original MMF35 cohort. Of note, chronic GVHD, mostly mild, occurred only in PBSC recipients.

Reduced MMF duration/omission in our platform is associated with excellent outcomes for matched HCTs. Mismatched HCT outcomes and the role of PBSC vs. marrow graft receipt require further study with larger patient numbers. Across patients, reducing MMF exposure is associated with earlier donor T cell reconstitution and no adverse effect on survival or engraftment.

Tabular data are included as downloadable supplement files.

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The CARD11–BCL10–MALT1 (CBM) Complex Regulates Nutrient Transport and mTORC1 Activation to Shape CD4+ T Cell Differentiation

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Introduction: The precise mechanisms linking TCR-dependent nutrient import and metabolic reprogramming to CD4+ T helper (Th) fate and function remain elusive. Here, we show that the CARD11–BCL10–MALT1 (CBM) complex facilitates activation-induced expression of the glutamine transporter ASCT2 and the glucose transporter GLUT1 on human CD4+ T cells. Notably, patient T cells carrying deleterious dominant-negative (DN) CARD11 mutations exhibit impaired activation-induced upregulation of both transporters, which we hypothesize contributes to the abnormal Th2 skewing and severe atopy observed in this cohort.
Methods: To test if observed phenotypes resulted from decreased CBM-dependent nutrient transport, we employed siRNA-mediated knockdown and pharmacological inhibition of CBM components, ASCT2 and GLUT1, in primary human T cells. Nutrient uptake and mTORC1 function were quantified in healthy and CARD11 DN samples using QUAS-R/2-NBDG import assays, flow cytometry, and immunoblotting. Th differentiation was assessed by spectral flow cytometry and high-sensitivity electrochemiluminescent immunoassays.
Results: We found that knockdown of any CBM component, or inhibition of MALT1 protease activity, markedly reduced TCR/CD28-dependent cell surface expression of ASCT2 and GLUT1, concomitant with impaired glutamine-dependent mTORC1 activation. While activation-induced ASCT2 transcription was repressed in CBM knockdown cells, GLUT1 upregulation was controlled by a CBM-dependent post-transcriptional mechanism. Similarly, ASCT2 and GLUT1 induction was significantly reduced in CARD11 DN patient T cells. Targeted disruption of ASCT2 and GLUT1 themselves reduced glutamine and glucose import, respectively, and decreased mTORC1 activity, including protein translation. Consequently, we observed reduced production of IFNy and augmented secretion of Th2 (IL-4) and Tfh (IL-21) cytokines. These results were consistent with nutrient-dependent shifts in lineage-defining transcription factors, mirroring programs observed in CARD11 DN patient cells. Supplementing CARD11 DN T cells in vitro with glutamine and/or glucose boosted mTORC1 activity and yielded rebalanced differentiation toward a Th1 phenotype.
Conclusions: Collectively, our results show that the CBM signalosome governs nutrient transport and mTORC1 activation to support Th1 differentiation of human T cells. Enhancing ASCT2/GLUT1 expression and/or nutrient import may represent a viable therapeutic strategy for treating patients with CARD11 DN mutations and other Th2-driven pathologies.

Late-Breaking Abstract

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The Hao-Fountain Syndrome Gene USP7 Restricts Neurotropic Orthoflavivirus Entry via Intrinsic Antiviral Activity

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Inborn errors of immunity (IEI) can manifest with neurological disorders, indicating genetic overlap between immune and nervous system diseases. However, neurological disorder genes are rarely screened systematically for immune or antiviral functions. To address this, we performed arrayed RNA interference screens targeting neurodevelopmental disorder genes whose functions overlap with steps of the neurotropic flavivirus Zika virus (ZIKV) life cycle. From infected cells, we quantified viral replication and innate immune/inflammatory gene induction using quantitative RT-PCR (RT-qPCR). These screens identified ubiquitin-specific protease 7 (USP7) as a potent intrinsic inhibitor of multiple neurotropic orthoflaviviruses.

Monogenic mutations in USP7 cause Hao-Fountain syndrome (HAFOUS), a rare autosomal-dominant disorder leading to developmental delay, autism spectrum disorders, and intellectual disabilities.

In human cell lines, we found that USP7 potently restricted flavivirus infection independently of innate immune activation, as treatment with pan-JAK and TBK1 inhibitors did not abrogate this restriction.

Using CRISPR/Cas9 base editing, we validated that introducing loss-of-function mutations in USP7's catalytic core diminishes its antiviral activity. Virus internalization assays showed that USP7 primarily limits ZIKV entry into cells. As ZIKV enters via endocytosis, this restriction is reminiscent of USP7's function in endosomal trafficking, which is disrupted in HAFOUS. USP7 stabilizes the E3 ligase TRIM27, and together they regulate WASH ubiquitination to promote endosomal tubulation and recycling.

Because TRIM27 also inhibited flavivirus entry, we hypothesized that impaired endosomal recycling flux promotes viral infection. Consistently, silencing core recycling regulators, including Rab11 and Rab35 GTPases, increased flavivirus infection. Identified in 2015, initial HAFOUS phenotyping studies did not describe immune dysregulation. However, patient record review identified previously undescribed rhinovirus and respiratory syncytial virus (RSV) infections requiring hospitalization and IgA deficiency among HAFOUS individuals. Ongoing investigations are exploring whether USP7 pathogenic mutations contribute to higher viral loads in patient primary cells and viral pathogenesis in vivo.

This discovery aligns with recent virology studies showing that certain endosomal recycling pathways restrict viral entry by preventing access to downstream organelles. As endosomal recycling defects feature in multiple neurodevelopmental and neurodegenerative diseases, characterizing this intrinsic antiviral defense is particularly important for patients with such comorbidities.