Meeting Abstracts

JHI Journal of Human Immunity

LASID Meeting 2025

October 15–18, 2025

Buenos Aires, Argentina

All abstracts were reviewed and approved by the LASID scientific committee, which held full responsibility for the abstract selections

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LASID MEETING ABSTRACTS 2025

https://doi.org/10.70962/LASID2025abstract.1
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.1

Patient with Common Variable Immunodeficiency Type 2 Due to a Likely Pathogenic Mutation in the TNFRSF13B Gene, Carrier Mother

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Introduction: Common variable immunodeficiencies (CVIDs) are the most frequent symptomatic primary immunodeficiencies, with an estimated frequency of 1:25,000. CVID type 2, linked to *TNFRSF13B* mutations (TACI), shows autosomal dominant or recessive inheritance, incomplete penetrance, and variable expressivity. The 2025 International Union of Immunological Societies update highlights its genetic complexity among 508 genes and 17 phenocopies.

Presentation of the Case: We present a 14-year-old male with chronic lung disease, including bronchiectasis and obliterative bronchiolitis, recurrent otitis media, and severe respiratory infections. He required intensive care unit admission and lobectomy. He is currently treated with subcutaneous immunoglobulin, bronchodilators, and leukotriene receptor antagonists. Whole exome sequencing revealed a likely pathogenic heterozygous frameshift variant in *TNFRSF13B* (c.49del; p.(Gln17ArgfsTer15)), inherited from his asymptomatic mother. This supports a diagnosis of CVID type 2 and demonstrates incomplete penetrance. Family history includes a healthy sister and a grandmother with asthma.

Discussion: This case highlights the importance of molecular diagnosis in CVID, particularly in patients with early-onset or atypical manifestations. A pathogenic *TNFRSF13B* variant (c.49del) was identified in both the patient and his asymptomatic mother, underscoring incomplete penetrance and phenotypic variability. This variant likely leads to a truncated, nonfunctional TACI receptor, impairing B cell signaling. Despite its classification as likely pathogenic by American College of Medical Genetics and Genomics criteria, expression may be modulated by genetic or epigenetic factors. These findings emphasize the need for long-term monitoring of carriers. Immunoglobulin therapy was effective, aligning with current CVID management recommendations.

Conclusion: The patient was diagnosed with CVID type 2 due to a likely pathogenic *TNFRSF13B* variant, also found in his asymptomatic mother. This highlights incomplete penetrance and phenotypic variability. Clinical and genetic correlation is essential for accurate diagnosis, long-term monitoring of carriers, personalized treatment, and appropriate genetic counseling within families.

https://doi.org/10.70962/LASID2025abstract.2
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.2

Artificial Intelligence Identification and Recruitment of Undiagnosed IEI Patients

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Introduction: Inborn errors of immunity (IEIs) often remain undiagnosed due to many factors including the fragmentation of care across subspecialties. The increasing complexity of these disorders poses a diagnostic challenge, even for immunologists. Artificial intelligence (AI) algorithms trained on electronic health records (EHRs) and expert knowledge can identify a broad range of IEI phenotypes. Clinical validation of these tools is needed to identify undiagnosed patients and impact care.

Objectives: We sought to describe patients with putative IEIs identified by an algorithm trained on EHR signatures.
Methods: We published an algorithm PheNet trained on EHR data of patients with IEIs [1]. PheNet identified suspected IEI patients across the University of California (UC) medical database. Algorithmically identified high-risk individuals were reviewed by clinicians and bioinformaticians; those of interest following chart review were recruited, consented, and underwent genetic and immune phenotyping.
Results: The top 500 cases identified via PheNet were subsequently reviewed by an immunologist. Each center found ~15 subjects that were considered suspicious for IEIs. Currently, there are 25 subjects who consented who have undergone sequencing and full immune workup. Immune phenotyping revealed T and B cell defects, while genetic testing has identified several actionable variants.
Conclusion: AI algorithms are useful in the identification of patients with IEI phenotypes, with meaningful clinical implications. By combining AI to identify subjects with concerning clinical phenotypes with in-person clinical examination and sequencing, we identified ~20 subjects who had remained undiagnosed despite receiving specialty care. One outcome of this effort will be to expand surveillance beyond simple "warning signs" to more sophisticated EHR signatures of IEIs.

Reference

1. Johnson, R., et al. 2024. *Sci. Transl. Med.* https://doi.org/10.1126/scitranslmed.ade4510

https://doi.org/10.70962/LASID2025abstract.3
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.3

From "Congenital Urticaria" to CAPS: An Atypical Presentation Within the NLRP3-AID Spectrum

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Introduction: Cryopyrin-associated periodic syndromes (CAPS) are rare, monogenic autoinflammatory diseases caused by gain-of-function variants in NLRP3. Traditionally classified into three phenotypes—familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome (CINCA/NOMID)—recent evidence supports a continuum of disease within the NLRP3-associated autoinflammatory disease (NLRP3-AID) spectrum.
Case Presentation: A 10-year-old girl presented with a lifelong history of daily urticarial rash since the first month of life. Lesions were spontaneous, painless, and non-pruritic. Symptoms worsened with cold exposure, temperature changes, and emotional stress, but also occurred spontaneously. She reported intermittent episodes (every 2–3 months) of self-limited low-grade fever, headache, abdominal pain, arthralgias, and non-purulent conjunctivitis lasting 2–3 days. At age 1, she was diagnosed with "congenital urticaria" based on skin biopsy (interstitial urticarial dermatitis without mast cell proliferation) and treated with H1-antihistamines, without improvement, severely impacting her quality of life. Repeated labs during asymptomatic periods showed persistent anemia, neutrophilic leukocytosis, elevated C-reactive protein/erythrocyte sedimentation rate, and increased IgG/IgD levels. No history of recurrent infections, autoimmunity, consanguinity, or similar family symptoms was reported. Examination revealed widespread urticarial lesions but no other abnormalities. A next-generation sequencing panel for inborn errors of immunity identified a heterozygous pathogenic NLRP3 variant (c.913G>A, p.Asp305Asn). A diagnosis of autosomal dominant NLRP3-AID was made. No neurologic, auditory, or joint damage was found. Colchicine was started while awaiting canakinumab approval. Interestingly, the Auto-Inflammatory Disease Activity Index (AIDAI) score improved from 51 to 39 points on colchicine.
Discussion: Despite cold sensitivity and a relatively mild course, this patient's persistent rash and systemic inflammation differ from classic FCAS, highlighting the relevance of adopting the broader NLRP3-AID term. In resource-limited settings, colchicine may offer temporary benefits while awaiting access to IL-1 inhibition targeted therapy.

https://doi.org/10.70962/LASID2025abstract.4
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.4

Report on the Latin American Hematopoietic Stem Cell Transplantation in Inborn Errors of Immunity Group's Activities: Bringing Us Together!

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Introduction: The Latin American Hematopoietic Stem Cell Transplantation (HSCT) in Inborn Errors of Immunity (IEIs) Group (GLATEII) was established at the 2023 Latin American Society for Immunodeficiencies (LASID) meeting in Mexico. Its goal is to unite Latin American immunologists and transplant specialists. We agreed to hold monthly meetings to discuss HSCT issues in IEIs, develop guidelines, and conduct multicenter reports on HSCT in IEIs. This report summarizes GLATEII's activities.

Results: To date, GLATEII has held 19 online meetings, one each month. Since February 2024, these meetings have been hosted and recorded by LASID. A total of 12 recordings are available up to April 2025, with an average of 23 participants per meeting (range 12–30). Attendees mainly include pediatric and adult immunologists and transplant specialists, along with infectologists and hematologists. Participants represent 38 institutions across 11 countries: Argentina, Brazil, Chile, Colombia, Costa Rica, Germany, Mexico, Paraguay, Peru, Uruguay, and the USA. Topics discussed include local experiences with HSCT for IEIs, case discussions, post-HSCT immune reconstitution, post-HSCT vaccination, and HSCT in specific IEIs. Regional concerns such as "transplante social," Bacillus Calmette–Guérin vaccination issues, IEI awareness gaps, financial shortages for treatments or studies, and access disparities have also been addressed. GLATEII has conducted multicenter reports on specific IEIs, one of which will be presented at LASID 2025.

Conclusion: GLATEII has successfully maintained monthly meetings focused on HSCT in IEIs from a Latin American perspective, highlighting regional similarities and differences. These gatherings promote advances in diagnosis, treatment, and transplant techniques while strengthening regional and international networks of healthcare professionals. We invite all LASID members to expand and continue these valuable activities.

https://doi.org/10.70962/LASID2025abstract.5
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.5

When Metabolism Meets Immunity: Inborn Errors of Metabolism Mimicking Primary Immunodeficiencies—A Case Series

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Several inborn errors of metabolism (IEMs) are known to affect immune function; the latter may arise from disruptions in metabolic pathways critical to immune cell development or from accumulation of toxic metabolites that impair immunity. This overlap can complicate diagnosis and management. We present seven patients with IEMs initially suspected of having inborn errors of immunity (IEIs) to highlight the phenotypic intersections between these disorders. All patients were referred for immunological evaluation due to recurrent infections, cytopenias, or abnormal immune profiles. Each was ultimately diagnosed with an IEM known to affect immune function.

Results:

- Purine nucleoside phosphorylase deficiency: A 4-year-old female with CMV infection, seizures, and lymphopenia was diagnosed with this T cell defect associated with purine metabolism. Good clinical response with intravenous immunoglobulin, oral prednisolone, folic acid, vitamin B, and antiviral.
- Propionic acidemia: Three patients presented with early-onset sepsis or viral infections. Immunologic findings included hypogammaglobulinemia, lymphopenia (particularly affecting B and natural killer cells), and neutropenia. Treated with carglumic acid, levocarnitine, protein-rich diet, and replacement immunoglobulin.
- Transcobalamin II deficiency: Two patients had recurrent infections, cytopenias, and global lymphopenia. One showed hypogammaglobulinemia. Good response with intramuscular B12 vitamin and folic acid.
- Thymidine phosphorylase deficiency: A 17-year-old male presented with ophthalmoparesis, severe abdominal pain, and angiographic images resembling vasculitis, with negative autoantibodies and poor response to immunosuppression. He died a few weeks after liver transplantation.

Conclusion: This series underscores the immunologic manifestations of IEMs, which can mimic IEIs and complicate diagnosis. Recognizing the bidirectional overlap is crucial: immune evaluation may uncover an underlying metabolic disorder, while persistent infections or immune alterations in IEMs warrant thorough immunological assessment. Immunologic interventions like immunoglobulins, antibiotic prophylaxis, vaccines, etc. may help to reduce the infectious burden in IEMs and improve quality of life. Timely diagnosis and comprehensive management are crucial for both groups of diseases.

https://doi.org/10.70962/LASID2025abstract.6
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.6

Chemotherapy-Induced Severe Immunodeficiency Mimicking Primary Immunodeficiency: A Diagnostic Challenge

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Introduction: Chemotherapy regimens, particularly BEP (bleomycin, etoposide, cisplatin), commonly cause transient immune dysfunction; however, profound and persistent lymphopenia resembling primary immunodeficiency (PID) is exceedingly rare. Such severe immune impairment post-chemotherapy, especially without identified genetic causes, presents critical diagnostic and management challenges.
Presentation of the Case: A male patient previously treated for metastatic testicular cancer with surgery, radiotherapy, and six cycles of BEP chemotherapy developed profound and persistent lymphopenia (CD3: 123/μL; CD4: 62/μL; CD8: 39/μL) and hypogammaglobulinemia (IgG levels persistently between 189–310 mg/dL). Extensive genetic evaluations, including whole-genome sequencing and multigene panel analysis, revealed no mutations associated with PID. Clinically significant was the occurrence of cryptococcal meningitis, successfully treated with prolonged fluconazole therapy. Monthly intravenous immunoglobulin therapy (IVIG, 0.53 g/kg) effectively maintains immunoglobulin levels and prevents further infections. Comprehensive interdisciplinary follow-up, including positron emission tomography–computed tomography imaging, excluded malignancy recurrence.
Discussion: This case highlights a clinically significant but under-recognized phenomenon—severe, persistent chemotherapy-induced immunodeficiency closely mimicking PID. Such phenocopies complicate clinical diagnostics, particularly when standard genetic analyses yield negative results. Recognition of this entity is crucial for improving patient management, emphasizing the importance of prolonged immunological monitoring and tailored prophylactic strategies following intensive chemotherapy regimens. Future studies should evaluate the incidence, mechanisms, and optimal management strategies for chemotherapy-induced severe immunodeficiency phenocopies.

https://doi.org/10.70962/LASID2025abstract.7
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.7

Longitudinal Outcomes in Adenosine Deaminase–Deficient SCID With Transplant: Case Series Highlighting Diverse Clinical Outcomes in a Child and Two Adults

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Introduction: Adenosine deaminase (ADA) deficiency is the second most common cause of severe combined immunodeficiency (SCID), leading to progressive T, B, and natural killer cell lymphopenia due to toxic metabolite accumulation. Early diagnosis, continuous monitoring, and timely intervention are critical to preventing irreversible complications, even in patients undergoing bone marrow transplantation (BMT).
Case Presentation: We present three patients with ADA-SCID managed with BMT and enzyme replacement therapy (ERT) post-transplant, demonstrating distinct therapeutic approaches and long-term outcomes. Patient 1, a 27-year-old female, underwent maternal HSCT at 1 month of age, achieving partial T cell engraftment but absent B cell recovery. Delayed initiation of ERT with elapegademase in adulthood improved biochemical markers but failed to prevent severe complications, including autoimmunity, neurocognitive decline, and adrenal insufficiency. Patient 2, a 26-year-old female, received multiple interventions including failed haploidentical HSCT and two autologous gene therapy infusions in early childhood. Due to limited engraftment, she required long-term ERT, transitioning from pegademase to elapegademase. Despite sustained deoxyadenosine nucleotide suppression, she developed chronic lung disease, metabolic dysfunction, and immune dysregulation. Patient 3, a 3-year-old female, was diagnosed through newborn screening and initiated on

pretransplant ERT before undergoing matched unrelated donor HSCT at 11 months. Despite early intervention, she experienced graft failure and is currently maintained on elapegademase.

Discussion: This series highlights the clinical heterogeneity of ADA-SCID and underscores the critical, long-term role of ERT, not only as a bridge to definitive therapy but also as an essential ongoing treatment in cases of incomplete or failed engraftment. While early HSCT or gene therapy offers curative potential, delays or failures can result in irreversible damage. These cases emphasize the importance of universal newborn screening and sustained access to ERT, particularly in resource-limited settings.

https://doi.org/10.70962/LASID2025abstract.8
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.8

A Patient Engagement Council to Support Inclusion and Engagement of the Low German Mennonite Community in Clinical Trial Research and Design

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Background: The Low German Mennonite (LGM) community originally migrated from Europe to Canada and now also has communities in Mexico and South America. Because of cultural isolation and practices of endogamy, there is known prevalence of specific genetic diseases in this population. One such disease is CD3δ severe combined immunodeficiency (SCID) caused by a founder C202T variant. Infants present with a complete lack of T cells and nonfunctional B cells, leading to early mortality if not treated with allogeneic hematopoietic cell transplant. Our research team is developing a gene editing clinical trial for CD3δ SCID. We have established an LGM Patient Engagement Council (PEC) to inform the design, development, and implementation of this trial to ensure results are more accessible and appropriate to the LGM community it aims to benefit.

Methods: After consulting with the Alberta SPOR SUPPORT Unit (AbSPORU) Patient Engagement Team, we connected with multiple groups working with the LGM and members of the community regarding participation in the PEC.

Results: The LGM PEC is a 12-member group comprised of community members, midwifery students, community health representatives/translators, and researchers. Terms of Reference were co-developed, online meetings are held once a month with additional opportunities for joining specific research training and working group opportunities, a presentation about LGM culture was shared through a teaching hospital, and focus groups in LGM language were held around Alberta. Compensation is offered to PEC members contributing lived experience.

Conclusion: The LGM PEC was successful in translating knowledge to the LGM community regarding research and consenting processes, creating trusting relationships, breaking down language barriers, and fostering mutual understanding. Future plans include the co-development of videos and podcasts in Low German to help further socialize health research engagement as well as co-development of an informed consent video for the upcoming CD3δ SCID gene therapy trial.

https://doi.org/10.70962/LASID2025abstract.9
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.9

Clinical and Genetic Insights into Partial RAG Deficiency in Adults: When to Consider Hematopoietic Stem Cell Transplantation?

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Introduction: Recombinase activating gene (RAG) deficiency is an inborn error of immunity (IEI) due to mutations in RAG1/2, impairing band T cell receptor repertoire diversity. While typically linked to severe combined immunodeficiency (SCID) in children, partial RAG deficiency (pRD) is increasingly identified in adults with milder phenotypes, leading to delayed diagnosis and treatment challenges. This study aimed to characterize the clinical and genetic profiles of adults with pRD and examine factors influencing hematopoietic stem cell transplantation (HSCT) decision.

Method: A retrospective multicenter analysis was conducted on 35 adults with pRD (27 RAG1, 7 RAG2, 1 both). Data included demographics, clinical severity, complications, laboratory results, transplant indication, and outcomes.

Results: Patients (age 17–74; median 37) exhibited diverse phenotypes: CID with granulomas/autoimmunity (49%), common variable immune deficiency or antibody deficiency (26%), classical CID (11%), and asymptomatic (14%). Molecular diagnosis occurred in adulthood, with infections starting between ages 3–35. Eight patients underwent HSCT at a mean age of 35.8 years (range 24-42), due to progressive disease, severe granulomatous inflammation, autoimmunity, and chronic pulmonary involvement. Survival was 50% among those transplanted, with transplant-related complications. The 27 non-transplanted patients displayed heterogeneous severity. Five asymptomatic individuals remained clinically stable during follow-up. At the time of analysis, 13 of the 35 patients (37%) had died (age range 28–74), mostly from infections, respiratory failure, or malignancy. Overall survival in the cohort was 63% (22/35) underscoring the high burden of morbidity and mortality in adult patients with partial RAG deficiency, regardless of phenotype.

Conclusions: pRD in adults is underdiagnosed and clinically variable. Genetic testing supports diagnosis, but HSCT timing remains uncertain. Findings highlight the need for prognostic markers and early genetic screening in adults with atypical antibody deficiencies or recurrent infections. Gene therapy could become a feasible alternative in carefully selected cases.

https://doi.org/10.70962/LASID2025abstract.10
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.10

Clinical Variance in an International Cohort of Families with Dominant-Negative FOXN1 Mutations

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Introduction: Transcription factor Forkhead box protein N1 (*FOXN1*) regulates thymic epithelial cell development. Bi-allelic and compound heterozygote loss-of-function mutations result in nude-severe combined immune deficiency with athymia, alopecia, and nail dystrophy requiring thymus transplantation. Dominant-negative heterozygous variants have incomplete and highly variable phenotypes. We 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 have access to 11 FOXN1 dominant-negative heterozygotes from 4 families with highly variable intrafamilial clinical courses and management. All variants locate near the C terminus, like variants in Rota et al. [1]. Immunological phenotype included 5/11 with Omenn syndrome (OS) early in life, otherwise presenting as asymptomatic (2/11) or with T cell lymphopenia (4/11), characterized by persistently low naïve T cells, and specific antibody deficiency (1/11) even in middle age. Alopecia and/or nail dystrophy was only noted in 1/11 patients. OS treatments ranged from conservative management (1/5), short-term steroids (1/5), long-term prednisolone alone (1/5), cyclosporine and prednisolone (1/5), and 1/5 OS patients received a bone marrow transplant prior to genetic diagnosis and later expired. (3/11) patients were placed on immunoglobulin replacement therapy. Only 3/11 patients experienced adverse outcomes, with 1/11 deaths. Other adverse outcomes include severe herpesviridae infections: *Varicella pneumonia* and CMV retinitis, respectively. 2/11 patients experienced EBV viremia and 2/11 with CMV viremia. 1/2 families tested were positive for anti-IFNα autoantibodies. Only one patient is being considered for thymic transplant.
Conclusions: This cohort demonstrates intrafamilial variability ranging from asymptomatic symptoms to OS, which has seldom been described in athymia patients. Heterogeneity indicates a need for distinct longitudinal treatment protocols for dominant negative FOXN1 patients, including lifelong protective immunoglobulin replacement therapy, and the possibility of thymic transplant for best outcomes, which has not been performed in FOXN1 heterozygotes before.

Reference

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https://doi.org/10.70962/LASID2025abstract.11
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.11

Mosaicism in IL2RG in an Adult With Combined Immunodeficiency: A Case Report

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Introduction: Combined immunodeficiencies in adulthood pose a diagnostic challenge. Mosaicism in genes classically associated with severe immunodeficiencies may underlie atypical phenotypes and complex clinical courses.
Case Presentation: A 47-year-old male with a history of chronic *Giardia lamblia* diarrhea since age 2, recurrent respiratory infections, and suppurative otitis was diagnosed in childhood with primary immunodeficiency characterized by functional antibody deficiency. He received intravenous immunoglobulin (IVIG) until the year 2000. In 2009, he resumed IVIG due to severe pneumonia, bronchiectasis, and chronic sinusitis. He experienced persistent respiratory infections, severe chronic obstructive pulmonary disease, and prolonged hospitalizations. In 2022, he developed bilateral pneumonia post-COVID-19 with esophageal candidiasis and extended hypoxemia. Additional findings included recurrent warts, cutaneous sarcoid granuloma, and chronic skin ulcers. Immunologic workup revealed hypogammaglobulinemia with undetectable IgA, marked B cell lymphopenia, and persistent CD4/CD8 inversion (70%). Secondary causes were excluded. Given the progressive clinical course, a next-generation sequencing panel for inborn errors of immunity identified mosaic mutation for a likely pathogenic IL2RG variant (c.924G>, p.Ser308=), a gene classically associated with X-linked severe combined immunodeficiency (SCID-X1).
Discussion: This case represents a milder form of X-linked combined immunodeficiency due to mosaicism in IL2RG. The presence of functional CD8+ T cells contributed to prolonged survival, albeit with ongoing infections and chronic pulmonary damage. The identification of mosaic variants in genes typically linked to severe phenotypes highlights the importance of advanced genetic testing in atypical presentations of primary immunodeficiency. This finding informs clinical follow-up, enables genetic counseling, and may guide personalized therapeutic approaches.

https://doi.org/10.70962/LASID2025abstract.12
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.12

Effective Management of Type III Hereditary Angioedema with Lanadelumab: A Case Report

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Introduction: Hereditary angioedema is a rare disorder characterized by recurrent episodes of edema in the skin and mucous membranes caused by a quantitative or qualitative defect in the C1 inhibitor, with a consequent exaggerated production of bradykinin. This clinical case presents the evolution and treatment of a patient with type III hereditary angioedema, initially diagnosed as type II.
Presentation of the Case: A 70-year-old patient with a history of hypertension, type II diabetes mellitus, and depression. She presented her first episode of angioedema in 1994 followed by multiple hospitalizations for facial angioedema and respiratory distress. Laboratory studies in 2017 revealed a C4 level of 3 mg/dl, normal C1q, and decreased functional C1 inhibitor (25%), leading to the diagnosis of hereditary angioedema type II. During a critical episode in 2020, orotracheal intubation (IOT) was required; endovenous C1 inhibitor had no effect, so icatibant was administered showing a good response. Upon further monitoring, C1 inhibitor and C4 values normalized, changing the diagnosis to hereditary angioedema type III, which made obtaining medication even more difficult. The patient continued to experience increasingly frequent angioedema attacks, requiring a large number of icatibant syringes. As of March 2025, prophylactic treatment with lanadelumab was initiated, resulting in the absence of angioedema crises up to date.
Discussion: This case highlights the importance of an accurate diagnosis in hereditary angioedema disorders, as effective treatment depends on it. The transition from type II to type III diagnosis highlights the need for ongoing evaluation in acquired or genetic undiagnosed cases. The introduction of lanadelumab has proven to be an effective therapeutic option, significantly improving the quality of life of a patient with type III hereditary angioedema.

https://doi.org/10.70962/LASID2025abstract.13
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.13

Dominant-Negative Ikaros: First Reported Case Associated with Adverse Reaction to Bacillus Calmette–Guérin Vaccination

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Introduction: IKAROS deficiency is caused by a mutation in the *IKZF1* gene, which plays a key role in the differentiation and development of lymphoid and myeloid cells, and negatively regulates cell proliferation. Mutations are classified according to protein expression as haploinsufficiency, dimerization defect, dominant-negative (DN), and gain-of-function; all are associated to varying degrees with susceptibility to infections, autoimmunity, allergy, and malignancy.
Presentation of the Case: Female infant received the Bacillus Calmette–Guérin (BCG) vaccine at 10 days of life. At 3 and 7 months of age, she presented with bronchiolitis and pneumonia, requiring hospitalization for 89 days, mechanical ventilation, broad-spectrum antibiotics, and treatment for severe viral, bacterial, and fungal infections. She developed swelling at the BCG injection site and ipsilateral axillary lymphadenopathy. Lymphocyte subpopulations showed B and T cell lymphopenia; CD20: 0.5%, hypogammaglobulinemia, normal dihydrorhodamine. Complete blood counts revealed monocytopenia, eosinopenia, and neutropenia. Genetic testing on 07/08/2024 revealed *IKZF1* c.476A>G (p.Asn159Ser). Currently 20 months old, she is undergoing hematopoietic stem cell transplant evaluation (father 50% HLA compatible); she is receiving maintenance-phase anti-tuberculosis therapy, prophylactic antibiotics, and intravenous immunoglobulin.
Discussion: This case involves a DN IKAROS mutation with an early-onset, severe, and fully penetrant phenotype. Of the nine cases reported worldwide, one-third received BCG vaccination without documented adverse reactions; these patients show increased susceptibility to malignancy, with no reported associations with autoimmunity or atopy. Definitive treatment is hematopoietic stem cell transplantation. IKAROS mutations are associated with a broad spectrum of immunological phenotypes; reporting of such cases contributes to timely recognition and treatment of these conditions.

https://doi.org/10.70962/LASID2025abstract.14
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.14

Roifman Syndrome: A Gene Within a Gene—First Report in Latin America

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Introduction: Roifman syndrome is a rare multisystemic disorder characterized by growth retardation, microcephaly, cognitive impairment, spondyloepiphyseal dysplasia, and immunodeficiency (classified as combined immunodeficiency with syndromic features). To date, only 31 cases have been described in the medical literature.
Case Presentation: We present the case of a 2-year-old female from a genetically isolated community, with no known consanguinity or relevant family history. She presented with three episodes of severe pneumonia (without microbiological isolates). Upon admission, she showed growth retardation, microcephaly, facial dysmorphism, short limbs, and hypotonia. Given the suspicion of an inborn error of immunity, workup revealed CD8+ and CD19+ lymphopenia, decreased IgM levels, and defective natural killer cell degranulation. Ultrasound imaging showed a hypoplastic thymus. A genetic panel identified a homozygous pathogenic variant in the *RNU4ATAC* gene: *n.16G>A*. The patient began replacement therapy with subcutaneous immunoglobulin, with favorable clinical evolution and no new infections to date. Extended immunophenotyping and parental segregation studies are currently being planned.
Discussion: The U12 spliceosome machinery plays a critical role in cell proliferation, differentiation, and growth. One of its essential components is the small nuclear RNA U4atac, encoded within the *CLASP1* gene. Mutations in *RNU4ATAC* are associated with Roifman syndrome. The *n.16G>A* variant has been rarely reported and, to our knowledge, never before in Latin America. Previous cases typically exhibit B cell and memory B cell lymphopenia—a finding shared with our patient. Notably, however, our case also demonstrated CD8+ lymphopenia and isolated low IgM, potentially suggesting a distinct immunologic phenotype associated with this specific variant.
Conclusions: Inborn errors of immunity present with a broad clinical spectrum. Syndromic immunodeficiencies should be considered in patients with multisystem involvement. A comprehensive diagnostic approach that includes genetic testing enables accurate phenotype characterization, improves clinical outcomes, and informs on familial recurrence risks.

https://doi.org/10.70962/LASID2025abstract.15
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.15

When ITP Isn't Just ITP: A Case of SOCS1 Haploinsufficiency with Bone Marrow Hypocellularity in a Pediatric Patient

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Background and Aims: Haploinsufficiency of suppressor of cytokine signaling 1 (SOCS1) is a recently identified autoinflammatory disorder characterized by significant rheumatologic, immunologic, and hematologic manifestations. We present a case of SOCS1 haploinsufficiency in a 4-year-old girl with bone marrow failure.
Methods: We collected data from clinical records, genetic testing, and functional immune assays.
Results: A 4-year-old female with no significant family history was referred to the immunology unit due to bone marrow aplasia. Her clinical course began at age 2 with immune thrombocytopenic purpura (ITP), which responded to intravenous immunoglobulin and corticosteroids. By age 3, she developed bone marrow aplasia, platelet refractoriness, recurrent fevers, gastrointestinal bleeding, and severe infections. Immunological workup revealed low IgM levels (-2 SD) prior to rituximab and normal lymphocyte subsets. Whole exome sequencing (WES) identified a heterozygous SOCS1 variant: NM_003745.2:c.295G>A, p.(Gly99Ser). Familial segregation analysis showed the mutation was de novo. A functional interferon (IFN) signature test revealed a markedly elevated IFN score of 64.5 (reference cutoff: 8.4, mean +2 SD). Based on these findings, treatment with the Janus kinase inhibitor (JAKi) ruxolitinib—targeting IFN-γ–mediated inflammation—was proposed.

Conclusions: This case underscores the importance of a multidisciplinary diagnostic approach and the role of comprehensive genetic evaluation in patients with atypical presentations of immune-mediated cytopenias. Early identification of monogenic immune disorders such as SOCS1 haploinsufficiency can guide targeted therapy and improve outcomes.

https://doi.org/10.70962/LASID2025abstract.16
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.16

A Novel Variant in the *NCF2* Gene Causing Autosomal Recessive Chronic Granulomatous Disease: Report of Two Unrelated Paraguayan Families

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Introduction: Chronic granulomatous disease (CGD) is an inborn error of immunity (IEI) characterized by severe and recurrent infections resulting from defects in the NADPH oxidase complex, which impairs neutrophil function. Mutations in *NCF2*, which encodes the cytosolic component p67-phox, lead to autosomal recessive (AR) CGD. We describe a novel *NCF2* variant identified in two unrelated patients with a clinical phenotype consistent with CGD.
Methods: As part of a national project to strengthen IEI diagnosis in Paraguay (2022–2024), we evaluated 115 children with recurrent infections. Forty-two patients with suggestive immunological findings underwent whole exome sequencing, supported by the Jeffrey Modell Foundation. In 17 cases, known pathogenic variants associated with IEI were identified. Additionally, a novel variant associated with AR-CGD was detected and confirmed by Sanger sequencing. Functional evaluation included in silico prediction tools and the dihydrorhodamine (DHR) assay.
Results: The patients—a 6-year-old girl and an 8-year-old boy—were born to non-consanguineous, unrelated parents. Both presented with recurrent pneumonia and lymphadenitis; the boy had prior pulmonary tuberculosis and the girl developed pulmonary sepsis and digital necrosis requiring amputation. Both were homozygous for the *NCF2* NM_000433.4:c.338G>A (p.Gly113Glu) variant. Their parents were heterozygous carriers. Although classified as a variant of uncertain significance (VUS) per American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria, in silico analyses predicted high pathogenicity. Routine immunological workups were normal; however, both patients had abnormal DHR test results (stimulation index 60).
Conclusion: Clinical, genetic, and functional evidence supports the diagnosis of AR-CGD caused by this novel *NCF2* variant. This finding expands the mutational spectrum of the NCF2 gene and underscores the importance of genetic analysis in diagnosing IEIs.

https://doi.org/10.70962/LASID2025abstract.17
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.17

Description of Invasive Aspergillosis in Mexican Patients with Chronic Granulomatous Disease

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Introduction: In chronic granulomatous disease (CGD), *Aspergillus* is the most common cause of invasive fungal infections and accounts for a high percentage of mortality.

Methods: The current study included 45 patients with a genetic diagnosis of CGD recruited between 2005 and 2024 from seven public hospitals in four Mexican cities.
Results: We recruited 45 patients of CGD with invasive aspergillosis (IA) events. The median age between the first CGD manifestation and first aspergillosis event was 65 months. Mortality rate was 57.7% for proven aspergillosis events, 23.1% for probable events, and 19.2% for possible events (p = 0.038). *Aspergillus fumigatus* was the most common species. Of the 45 patients, 26 (58%) had one IA event, nine (20%) had two, five (11%) had three, and five (11%) had four IA events. The median time between the first and second events was 35 months (15–65), between the second and third events was 26 months (17.5–32.5), and between the third and fourth events was 22 months (15.5–43.5). Of the 78 IA events, 43 (55%) were treated with monotherapy, 16 (20.5%) with dual therapy, 15 (19.2%) with triple therapy, three (3.8%) with quadruple therapy, and one (1.5%) with quintuple therapy. Twenty-six (58%) of the 45 patients died, out of which 18 (69%) had IA. The median age at death was 107.5 months (44.7–196). Overall survival of the 45 patients was 80.8% at 64 months.
Conclusions: The high mortality rate of IA in CGD patients could be reduced by early suspicion, initiating correct antifungal treatment over a long period, and considering the performance of hematopoietic stem cell transplantation.

https://doi.org/10.70962/LASID2025abstract.18
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.18

De Novo RHOG Variant in a Patient with Combined Immunodeficiency and Extensive Viral Infections: A Potential New Disease Mechanism

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Background: RHOG encodes a small GTPase involved in cytoskeletal dynamics, T cell activation, and immune synapse formation. Variants in RHOG have been implicated in combined immunodeficiencies affecting both cellular and humoral responses, although clinical reports remain scarce.
Case Presentation: We report a pediatric patient with a clinical diagnosis of common variable immunodeficiency (CVID), presenting with recurrent respiratory infections and widespread viral warts. Immunologic evaluation revealed combined immunodeficiency with defects in both T and B cell compartments. Exome sequencing identified a heterozygous missense variant in RHOG (c.34G>A; p.Gly12Arg), located within the conserved GTP-binding domain. The variant is absent from population databases including gnomAD and is predicted to be deleterious (Revel score: 0.906) (PM2_Supporting, PP3_Moderate). Parental and sibling testing confirmed that the variant arose de novo, supporting a causative role (PM6_Supporting).
Discussion: Based on American College of Medical Genetics and Genomics/ClinGen criteria, the variant meets multiple supporting and moderate-level criteria: PM6 (de novo in a patient with consistent phenotype), PM2 (absent from controls), and PP3 (multiple in silico tools predict damaging effect). This strengthens its classification as a variant of uncertain significance. The clinical phenotype is consistent with the emerging role of RHOG in human immunity.
Conclusion: This case adds new evidence supporting RHOG as a candidate gene for combined immunodeficiency with viral susceptibility. Functional validation is required to confirm the mechanism and establish RHOG deficiency as a distinct clinical entity.

https://doi.org/10.70962/LASID2025abstract.19
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.19

RNASEH2B at the Crossroads: From Aicardi–Goutières Syndrome to Monogenic Lupus

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Introduction: Biallelic mutations in *RNASEH2B* are classically associated with Aicardi–Goutières syndrome. However, heterozygous variants have recently been linked to monogenic systemic lupus erythematosus, expanding the clinical spectrum.

Case Reports: P1: A 29-year-old male. At age 18, developed chronic severe thrombocytopenia refractory to steroids and rituximab, with multiple hospitalizations for trauma-related bleeding. Later presented with hypothyroidism and chondritis. Labs showed normal immunoglobulins, positive antinuclear antibodies (1:160), low B (260/mm^3) and natural killer (NK) cells (58/mm^3), high double negative T (DNT) cells (9%), altered T and B subpopulations (high central memory T and DR+ T cells, low switched B cells, and high transitional B cells). Treated with sirolimus and hydroxychloroquine with mild response. With subcutaneous immunoglobulin, achieved platelet and DNT normalization.
P2: 14-year-old male. At age 4, presented with urticaria and angioedema on hands, ears, and face, worsened by sun exposure, unresponsive to antihistamines or steroids. Immunologic workup showed no cytopenia, normal acute-phase markers, low IgG (<1/2 SD), normal IgA/IgM, normal complement (C3/C4), negative autoantibodies, and normal lymphocyte subsets (CD3+, CD4+, CD8+, CD19+, CD56+).
P3: 27-year-old female. At age 25, presented two events of myopericarditis requiring hospitalization. Extensive cardiac workup confirmed elevated cardiac enzymes with normal imaging, and the patient responded to colchicine, nonsteroidal, anti-inflammatory drugs, and corticosteroids. Immunological studies showed normal immunoglobulins and complement, negative autoantibodies, and NK lymphopenia. All patients carried the heterozygous pathogenic variant *RNASEH2B* c.529G>A, p.(Ala177Thr). Interferon signature was performed in 2/3 patients and was markedly elevated in P1: 174.48 (cutoff 8.4) and IL-18 at 106.1 copies/ng (reference value <35); and P2: 28.2. P1 is currently on eltrombopag and in plan of starting baricitinib, P2 remains under expectant management, and P3 is receiving colchicine.
Discussion: These cases highlight that patients with heterozygous variants in *RNASEH2B* developed clinical symptoms. The elevated interferon signature supports type I interferonopathy as a shared pathophysiological mechanism in these patients. Early recognition is crucial to diagnose and guide targeted treatment.

https://doi.org/10.70962/LASID2025abstract.20
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.20

Canadian Inborn Errors of Immunity National Registry (CIEINR): A High-Quality Standardized Patient Data Platform to Support Patient Advocacy and Immune Deficiency Research

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Introduction: Inborn errors of immunity (IEIs) comprise a heterogeneous group of rare disorders, characterized by a wide spectrum of immunological alterations that influence the presentation and age at onset of disease. Approximately 30,000 Canadians suffer from primary immunodeficiency. Canada is home to several specific populations with a higher incidence of unique IEIs. Canada lacks a comprehensive database detailing the epidemiology, clinical and immunological phenotypes, and genotypes of patients with IEIs. We developed the novel and innovative Canadian Inborn Errors of Immunity National Registry (CIEINR), a machine-readable, high-quality dataset that promotes research through standardized data exchange and supports patient advocacy.
Methods: CIEINR was established by a national steering committee of 13 clinician scientists from 9 Canadian provinces, through monthly virtual meetings. Following a literature review of existing international IEI registries, the peer-reviewed study protocol, consent forms, and governance documents were developed. ImmUnity Canada, the national patient organization, was consulted to review the protocol. Ontology-based data collection forms were developed in collaboration with bioinformatics scientists to capture input data in a structured fashion. Regulatory documents and standardized data collection forms were harmonized with United States Immunodeficiency Network and European Society for Immunodeficiencies to support data sharing, methodological consistency, and interoperability. A continuous quality improvement framework aligns with the Canadian Drug Agency's Best Practices and Standards to Enhance the Quality of Rare Disease Registries in Canada.

Results: The CIEINR has been established and includes 25 centers across Canada. Electronic clinical research forms in the Research Electronic Data Capture (REDCap) platform were successfully piloted including the embedded analytic tools such as RareLink and Phenopackets on patients' data with variable forms of IEIs.
Conclusion: By collecting high-quality, precise, ontology-based patient data, the CIEINR will improve understanding of the Canadian IEI landscape, identify challenges and opportunities for patients and their healthcare providers, and support research and advocacy.

https://doi.org/10.70962/LASID2025abstract.21
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.21

Outcomes and Challenges of Hematopoietic Stem Cell Transplant in CD40L Deficiency

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Introduction: CD40 ligand (CD40L) deficiency is a rare X-linked primary immunodeficiency. Hematopoietic stem cell transplant (HSCT) is currently the only curative treatment. To date, regional studies have focused on reporting the clinical characteristics of this disease rather than transplant outcomes. This study aims to characterize pediatric patients with CD40L deficiency who have undergone HSCT in centers from Chile, Colombia, Brazil, Mexico, and Argentina. Objectives include describing clinical features, evaluating survival, identifying mortality-associated factors, and reporting major posttransplant complications.
Methods: We retrospectively reviewed pediatric patients with CD40L deficiency who underwent HSCT between January 2002 and December 2024. We analyzed clinical characteristics, survival outcomes, and complications. Descriptive statistics were used, and overall survival was estimated using Kaplan–Meier analysis. During this period, 27 patients with CD40L deficiency were included in the study. For one patient, data from a second HSCT were also collected.
Results: Twenty-seven pediatric patients with CD40L deficiency underwent HSCT, with a median age at transplant of 6 years (range 1–18). A confirmed genetic diagnosis was present in 96% of cases, and 12 patients (44%) had a positive family history. Pretransplant complications included pneumonia in 14 patients (52%), gastrointestinal symptoms in 15 patients (56%), neutropenia (26%), and cholangitis (11%). Infectious history included *Pneumocystis jirovecii* (22%), CMV (7%), *Cryptosporidium* (15%), and *Candida* (26%). Intravenous immunoglobulin (IVIG) supplementation was administered before transplant in 96% of patients, and 67% continued IVIG posttransplant. Cotrimoxazole prophylaxis was given prior to HSCT in 93% of cases. Unrelated donors were used in 70% of patients, and most received conditioning with treosulfan/busulfan plus fludarabine. Graft versus host disease (GVHD) prophylaxis included antithymocyte globulin (ATG) in 59% of patients and calcineurin inhibitors in 96%. Engraftment was achieved in 93% of patients, and 3 required a second transplant. Acute GVHD grade III–IV occurred in 30%, and chronic GVHD in 26%. CMV occurred in 10 patients, with one fatal case. A total of four deaths were reported—three were HSCT-related. Overall survival was 83.6% at 1 year, 78.7% at 3 years, and 78.7% at 5 years.
Conclusions: This multicenter retrospective study analyzed pediatric patients with CD40L deficiency who underwent HSCT. The cohort showed favorable 5-year overall survival. A genetic diagnosis was confirmed in 96% of patients, while one-third had a positive family history. Most patients experienced significant complications prior to transplant, and HSCT was delayed by a median of 5.5 years. Prophylaxis included IVIG in 96% of cases and cotrimoxazole in 93%. Most transplants used matched unrelated donors (MUD), with busulfan/fludarabine-based conditioning regimens. Conditioning approaches varied by center. Serotherapy (mainly ATG) was used in 70% of patients. Engraftment was successful in 93% of cases. Posttransplant complications were frequent. Acute GVHD occurred in 30% of patients, mostly in severe forms (grade III–IV), while 26% developed chronic GVHD. CMV reactivation was reported in 44%, and graft-related complications ("graft problems"), including secondary graft failure and mixed chimerism, were observed in 26% of cases.

https://doi.org/10.70962/LASID2025abstract.22
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.22

Outcomes Following Hematopoietic Cell Transplant in CD3δ SCID Patients in Canada

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Introduction: In the Low German Mennonite (LGM) population, CD3δ severe combined immunodeficiency (SCID) is the result of a homozygous c.202C>T; p.Arg68Ter pathogenic variant. The block in T cell development causes infant mortality without allogeneic hematopoietic cell transplantation (HCT). We evaluated outcomes following HCT in Canadian LGM infants from 2011-2023.
Methods: Data were collected and analyzed using descriptive statistics for 11 patients treated in Alberta and Manitoba in collaboration with the Primary Immune Deficiency Treatment Consortium.
Results: Trigger for diagnosis was newborn screening (NBS) in 4, family history in 1, infections prior to the implementation of NBS in 6. HCT donor and conditioning were as follows: matched related donor (MRD) (1): no conditioning; MRD (3), matched unrelated donor (2), and 9/10 mismatched unrelated donor (1): reduced intensity conditioning (RIC) alemtuzumab, treosulfan, and fludarabine; haploidentical TCRαβ/B cell deplete (3): myeloablative antithymocyte globulin, rituximab, treosulfan, and fludarabine; haploidentical with posttransplant cyclophosphamide (1): RIC with fludarabine and cyclophosphamide. Overall survival was 100%, with median follow-up of 3 years. Three patients developed grade I–II acute graft-versus-host disease (GVHD) and 2 chronic GVHD. By 12 months post-HCT, 7 patients achieved CD4 >500 × 10^6 cells/L. All but 1 patient had normal B cell numbers. Immunoglobulin was stopped by one year in all patients; one developed hypogammaglobulinemia 5 years post-HCT and restarted. All achieved full T cell chimerism (>95%); 4 had full chimerism in all cell lines. Myeloid and B cell chimerisms were <5% in 3 and mixed (5-95%) in 4.
Conclusion: Despite excellent survival, we observed incomplete T cell immune reconstitution, poor chimerism in myeloid and B cell lines, and GVHD. Further research is required to identify the optimal HCT approach and clinical significance of mixed chimerisms. Outcome data comprises the historical control for an upcoming clinical trial on base editing gene therapy for CD3δ SCID.

https://doi.org/10.70962/LASID2025abstract.23
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.23

Pulmonary Manifestations in Children with Predominantly Antibody Deficiencies: A Four-Year Cohort from a Referral Center in Bogotá Autores

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Introduction: Predominantly antibody deficiencies (PADs) are the most frequent group of inborn errors of immunity and commonly present with recurrent respiratory infections. Early recognition of pulmonary complications is essential to reduce long-term morbidity.
Methods: This descriptive retrospective cohort study aimed to characterize features of pediatric patients diagnosed with PADs, with a focus on pulmonary complications.
Results: We present a series of 72 pediatric patients diagnosed with PADs at a referral center in Bogota (June 2021 to June 2025). The most frequent diagnoses were specific antibody deficiency (SAD) (32 patients, 44.4%), selective IgA deficiency (12, 16.7%), common variable immunodeficiency (12, 16.7%), and X-linked agammaglobulinemia (XLA) (7, 9.7%). The median age at first infection was 7 months (interquartile range: 31.5), and the mean age at diagnosis was 70 months (SD: 44.7). Comorbid allergic diseases were highly prevalent (73.6%), particularly asthma (62.5%), allergic rhinitis (62.5%), and atopic dermatitis (34.7%). Pneumonia was observed in 60.9% of patients, otitis media in 37.7%, and sinusitis in 14.5%. Orotracheal intubation was required in 29.2% of patients, some on multiple occasions. Chest CT scans were performed in 32 patients; the most common findings were atelectasis (25%) and bronchiectasis (18.8%). Bronchiectasis was more frequent in those with XLA (3/7; 42.9%) and SAD (4/32; 12.5%). Lung function was abnormal in 80% of oscillometries (n = 20) and 42.1% of spirometries (n = 19). Bronchoalveolar lavage in 11 patients yielded three positive bacterial cultures. Immunoglobulin replacement was given to 65.3%; 25% received prophylactic azithromycin. One patient with an undiagnosed syndromic phenotype died.
Conclusion: This cohort highlights the high respiratory disease burden in children with PADs, including obstructive functional disorders, allergic comorbidities such as asthma and allergic rhinitis, and increased bronchiectasis in XLA.

https://doi.org/10.70962/LASID2025abstract.24
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.24

Genomic Diagnosis of Chronic Granulomatous Disease (CGD) in a Referral Hospital in Southern Brazil

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The objective of this study was to provide the first genomic diagnosis of chronic granulomatous disease (CGD) in a referral hospital in Southern Brazil, a rare and underdiagnosed disease with limited data in the country. Six male patients (P1-P6) were clinically and genetically analyzed, through medical reports review and massively parallel sequencing by a panel for the *CYBB*, *CYBA*, *NCF1*, *NCF2*, and *NCF4* genes and whole genome sequencing. The gene-scan technique was used to detect the Tyr26HisfsTer variant (ΔGT) in *NCF1* and to distinguish it of its pseudogenes (Ψ*NCF1*), which naturally have ΔGT. Variants were classified according to the American College of Medical Genetics and Genomics guidelines. Structural modelling was performed for missense variants using PyMOL and I-TASSER to verify their potential impact on the NADPH oxidase complex, which is defective in CGD. Among the clinical manifestations, the most commonly affected organs were the lungs, skin, and lymph nodes, with all patients presenting with recurrent infections and pneumonia. Adverse reactions to BCG vaccination were observed in two patients. Four patients carried variants in *CYBB*: (P1) p.Cys257Ser, a novel variant, and (P2) p.Cys257Arg, both classified as likely pathogenic and predicted to significantly affect the structure of NADPH oxidase, with Gibbs free energy values of 6.66 and 6.23 kcal/mol, respectively (reference value: >1.6 kcal/mol); p.Arg157Ter (P3), and p.Trp483Ter (P4), both classified as pathogenic and predicted to undergo nonsense-mediated mRNA decay. Gene-scan analysis revealed the ΔGT in two siblings: P5 (homozygous) and P6 (heterozygous). It was hypothesized that P6 may have an *NCF1*-related pseudogene lacking the ΔGT originated by unequal recombination with *NCF1*, resulting in the absence of functional alleles in P6. This study underscores the importance of genetic characterization for accurate diagnosis, reducing diagnosis odysseys and supporting the indication of bone marrow transplantation to prevent fatal outcomes, and reinforcing the contraindication of Bacillus Calmette–Guérin vaccination in patients with CGD.

https://doi.org/10.70962/LASID2025abstract.25
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.25

Clinical Picture of Post-Hematopoietic Cell Transplantation for Inborn Errors of Immunity: Single Center Experience

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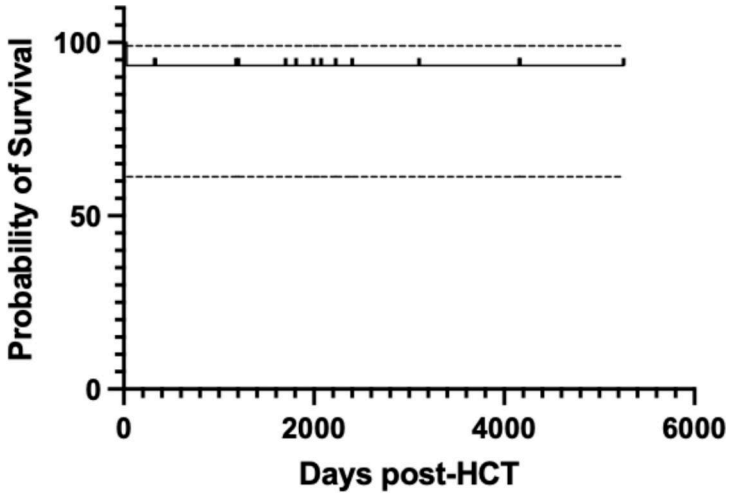
Background: Long-term follow-up for inborn errors of immunity (IEIs) after hematopoietic cell transplantation (HCT) remains poorly described. We report ≥5 years post-HCT.
Methods: Retrospective data collection from 16 clinical records.
Results: 12 males (75%) and 4 females (25%) with diagnosis of IEIs (1 severe combined immunodeficiency [SCID], 6 CID, 4 phagocyte defect, 3 immune dysregulation disease, and 2 bone marrow failure). Median follow-up 5.3 years [0-14] and median age at transplant 6.5 years [0-17]. Patients received bone marrow (n = 15) or peripheral blood stem cells (n = 1), from matched family (n = 1), matched (n = 11), or mismatched (n = 4) unrelated donors using (10, 62.5%) busulfan–fludarabine, (2, 12.5%) busulfan–cyclophosphamide, (2, 12.5%) melphalan–fludarabine, and (1, 6.3%) fludarabine–cyclophosphamide conditioning. 93.8% received serotherapy (antithymoglobulin). Tacrolimus and methotrexate as graft versus host disease (GvHD) prophylaxis in 10 patients (62.5%). 8 patients (50%) developed acute and 3 (18.8%) chronic GVHD. 4 (25%) had CMV, 3 (18.8%) EBV, and 1 (6.3%) adenovirus viremia. 1 patient (6.3%) developed severe veno-oclusive disease and died on day +30, and 1 (6.3%) had secondary graft failure. Post-HCT analysis was made in the 14 remaining patients. 7 (50%) improved growth, 4 (28.6%) had significant infections, and 4 (28.6%) improved or stabilized lung disease. 5 (35.7%) developed autoimmunity, most (4, 80%) were hematological (neutropenia, thrombocytopenia, or hemolytic anemia). 11 (78.6%) required immunoglobulin replacement after HCT, 8 (57.1%) suspended it with a median of 698 days [423-4,397]. 8 (57.1%) achieved GvHD prophylaxis suspension at 488 days [360-723]. 12 patients had whole blood chimerism performed >50% [50-100]. At last follow-up, 14 patients were alive and with good chimerism, resulting in a 16-year overall survival of 93%.
Conclusions: HCT for IEIs resulted in high long-term survival in our cohort. Most patients achieved good chimerism and showed improvement in clinical outcomes, despite significant posttransplant complications (infections, autoimmunity, GvHD). These findings highlight the effectiveness of HCT while underscoring the need for long-term follow-up.



https://doi.org/10.70962/LASID2025abstract.26
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.26

Clinical Heterogeneity in *NFKB1* Deficiency: Report of Two Cases

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Introduction: Heterozygous pathogenic variants in *NFKB1*, encoding the p105/p50 subunit of the NF-κB complex, are among the most frequent monogenic causes of combined immunodeficiency with immune dysregulation. Clinical manifestations are highly variable and may include autoimmunity, susceptibility to infections, autoinflammation, and even malignancy. Recent findings also suggest a role in hyperinflammatory responses due to impaired autophagy and enhanced type I interferon signaling.

Case Presentation:

Case 1: A 34-year-old male, previously healthy, presented at age 32 with genital verrucous lesions, dysphagia, weight loss, and oral candidiasis. He was diagnosed with HPV infection, ulcerative esophagitis, and later developed a Buschke–Löwenstein tumor and soft tissue infections. Laboratory findings showed IgG in 660 mg/dL, normal IgA and IgM, leukopenia, neutropenia, and lymphopenia. Genetic analysis revealed a heterozygous pathogenic variant in *NFKB1*: c.904dup (p.Ser302Phefs*7).

Case 2: A 21-year-old female began at age of 5 with idiopathic thrombocytopenic purpura, followed by autoimmune hemolytic anemia. She experienced recurrent pneumonias and an episode of septic shock. At her last admission, she had fungal otitis externa, lymphopenia, neutropenia, and hypogammaglobulinemia. Immunophenotyping showed reduced T (CD4+, CD8+), B (CD20+), and natural killer cell counts. She carried the heterozygous pathogenic variant in *NFKB1* c.909dup (p.Thr304Hisfs*5).

Discussion: These cases illustrate the broad clinical spectrum of *NFKB1* deficiency, from early-onset autoimmunity to severe infections. Both frameshift variants result in premature protein truncation and support a loss-of-function mechanism. Recognition of this heterogeneity is key for timely diagnosis. Genetic testing should be considered in patients with overlapping features of autoimmunity and immunodeficiency to guide appropriate management.

https://doi.org/10.70962/LASID2025abstract.27
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.27

Phenotypic Spectrum of Heterozygous NFKB1 Variants in Four Unrelated Families from Argentina

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Introduction: Nuclear factor-kappa B (NF-κB) is a pivotal transcription factor involved in immune regulation, inflammation, and cell survival. Initially identified as a key regulator in B cell development and function, mutations in NFKB1 have been increasingly recognized as a cause of inborn errors of immunity (IEIs), particularly common variable immunodeficiency (CVID). NF-κB also mediates inflammatory responses across various cell types, contributing to a wide array of clinical phenotypes. Variants in NFKB1 exhibit incomplete penetrance and variable expressivity, leading to diverse immunological and autoinflammatory conditions.

Objective: To characterize the clinical, immunological, and genetic features of patients harboring heterozygous NFKB1 variants from four unrelated Argentine families.

Methods: This retrospective study analyzed clinical data, laboratory results, and genetic findings from patients seen at the Bezrodnik Immunology Centre and Hospital El Cruce.

Results: A total of nine patients from four unrelated families carrying heterozygous NFKB1 variants were included. All variants were classified as likely pathogenic, according to the American College of Medical Genetics and Genomics/ClinGen guidelines. Two novel variants were identified: c.202G>A (p.Gly68Ser) and c.936_937del (p.Val313Fs). Sex distribution: four females and five males, median-age 26 years (range 6–75). Clinically, 55% experienced recurrent respiratory infections, 33% had lymphoproliferative features such as adenopathy and splenomegaly, and 22% presented with autoimmune cytopenias. Other manifestations: chronic diarrhea (11%) and onychomycosis (11%). Immunologically, hypogammaglobulinemia was observed in 66%, and reduced switched memory B cells in the same proportion. One exhibited CD21low 21%. Treatment approaches: 55% received immunoglobulin replacement therapy, three patients were on immunosuppressants (mycophenolate mofetil and systemic steroids), and one with rituximab. Interestingly, two asymptomatic carriers were identified, highlighting incomplete penetrance.

Conclusion: Heterozygous NFKB1 variants are associated with a broad spectrum of clinical phenotypes, including antibody deficiencies, lymphoproliferation, and autoinflammatory features. Further research into the mechanisms of phenotypic variability will enhance our understanding of NF-κB pathway disorders and inform future therapeutic approaches.

https://doi.org/10.70962/LASID2025abstract.28
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.28

Familial Novel NFKB1 Variant Associated with Common Variable Immunodeficiency and Chronic Fungal Infections

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Background: NF-κB1 is a key transcription factor involved in immune regulation, and pathogenic variants in this gene can lead to a spectrum of primary immunodeficiencies, including common variable immunodeficiency (CVID). We report a family with a novel heterozygous NFKB1 variant segregating across three generations with variable expressivity of immunodeficiency and chronic fungal infections.
Case Presentation: The index case is a 6.5-year-old girl who presented with severe hypogammaglobulinemia affecting all three immunoglobulin isotypes, impaired polysaccharide vaccine response, recurrent respiratory infections, chronic diarrhea, and candida onychomycosis. B cells were present but showed a disrupted maturation profile with reduced memory B cells and abnormal pre- and post-switched subsets. His 43-year-old father had recurrent infections, moderate hypogammaglobulinemia (IgG and IgM), facial fungal infections with hyaline branching hyphae on biopsy, chronic diarrhea, and severe intestinal polyposis. The 68-year-old grandmother also had a history of recurrent respiratory infections and hypogammaglobulinemia. Whole exome sequencing identified a novel heterozygous NFKB1 variant (c.202G>A, p.Gly68Ser) in the index case, which was confirmed in both the father and grandmother.
Discussion: The variant lies within the functional Rel homology DNA-binding domain (PM1_Moderate), a region enriched in known pathogenic variants. It is absent from population databases (PM2_Supporting), and in silico prediction using REVEL yields a high pathogenicity score (0.797; PP3_Moderate). The phenotype across three generations is consistent with reported clinical manifestations of NFKB1 haploinsufficiency, including CVID, impaired class-switch recombination, and chronic infections (PP4_Supporting). The variant cosegregates with the disease in the family (PP1_Supporting), supporting a pathogenic role. Based on the American College of Medical Genetics and Genomics/ClinGen guidelines, the variant is classified as a likely pathogenic variant.
Conclusion: We report a novel familial NFKB1 variant associated with a CVID-like phenotype and chronic fungal infections. Functional validation is needed to confirm pathogenicity and to guide targeted therapeutic approaches.

https://doi.org/10.70962/LASID2025abstract.29
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.29

A Lifelong Journey with Common Variable Immunodeficiency: Lessons from a Cohort Spanning Childhood to Old Age

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Introduction: Common variable immunodeficiency (CVID) is a highly heterogeneous immunodeficiency affecting individuals of all ages. We aim to characterize its clinical and immunological features throughout all stages of life.
Methods: We retrospectively reviewed patients with hypogammaglobulinemia evaluated at Hospital Italiano de Buenos Aires (2000–2025). After excluding secondary causes, only those fulfilling the 2019 European Society for Immunodeficiencies criteria for CVID were included and classified into three age-at-diagnosis groups: Group 1 (4–18 years), Group 2 (19–50 years), and Group 3 (51–80 years).
Results: Among 138 patients with hypogammaglobulinemia, 31 CVID patients from 30 families were included: 13 in Group 1, 11 in Group 2, and 7 in Group 3. The median follow-up was 8 years (interquartile range [IQR] 5–12). Group 2 had the longest diagnostic delay (median 6 years, IQR 4.5–19). Group 1 presented predominantly with infections and maintained this phenotype over a median of 14 years (IQR 4–22), except two patients with NFkB1 variants. Group 2 commonly exhibited combined infections and dysregulation, while Group 3 showed heterogeneous presentations. Bronchiectasis was diagnosed in three patients per group. Two patients developed lymphoma after age 40, and three in Group 3 developed solid tumors, all in remission.

Notably, six patients in groups 2 and 3 had agammaglobulinemia with normal total B cells, of which two women (67 and 71 years) had no history of infections. Additionally, two female patients presented with hypogammaglobulinemia and absent B cells, with predominant multiorgan autoimmunity. No pediatric patients showed agammaglobulinemia at diagnosis. Genetic variants were identified in 3 of 10 tested patients: *NFκB1* (two siblings), *TRAF3*, and a heterozygous variant of uncertain significance in *DOCK8*. No genetic studies were performed in Group 3. All patients are on immunoglobulin replacement therapy. One patient (aged 68) died from COVID-19.

Conclusions: Most childhood-onset CVID cases preserved their initial phenotype. In adults, unexplained agammaglobulinemia or absent B cells warrant genetic evaluation. In elderly patients, findings suggest late-onset rather than delayed diagnosis.

	Group 1 (4-18 years)	**Group 2 (19-50 years)**	**Group 3 (51-80 years)**
	n = 13	**n = 11**	**n = 7**
Female sex*	6	6	5
Age at diagnosis	13 (6-16)	38 (33-40)	60 (58-69)
Current age	27 (18-28)	46 (39-49)	71 (67-75)
Follow-up	14 (4-22)	8 (5-10)	5 (4.5-12.5)
Diagnostic delay	1 (0-4)	6 (4.5-19)	2 (0-4)
Current phenotype*			
-Only infections	8	1	2
-Only dysregulation		2	2
-Both	3	8	3
-Asymptomatic	2		
Phenotype progression*			
-Only infections that adds dysregulation	1	3	3
-Dysregulation that adds infections	1	1	
Infections*	11	9	5
-Sinusitis	1	4	1
-Otitis	3	0	
-Pneumonia	9	6	4
-Gastrointestinal	1		
Bronchiectasis*	3	3	3
Autoimmunity*	3	8	5
-Cytopenias	2	2	3
-IBD	1	3	2
-Hepatitis		3	
-Alopecia areata	1	1	
Lymphoproliferation	2	9	2
-Splenomegaly	1	8	2
-Granulomatous and lymphocytic interstitial lung disease		2	
Neoplasia*			
-Lymphoma		1	1
-Lung cancer			2
-Prostate			1
-Pre-neoplastic lesions (cervical or vulvar intraepithelial neoplasm)		2	

Median (interquartile range 25-75).
*Absolute frequency.

https://doi.org/10.70962/LASID2025abstract.30
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.30

What We Have Learnt About Hematopoietic Cell Transplantation in Chronic Granulomatous Disease: A Single Pediatric Center Experience

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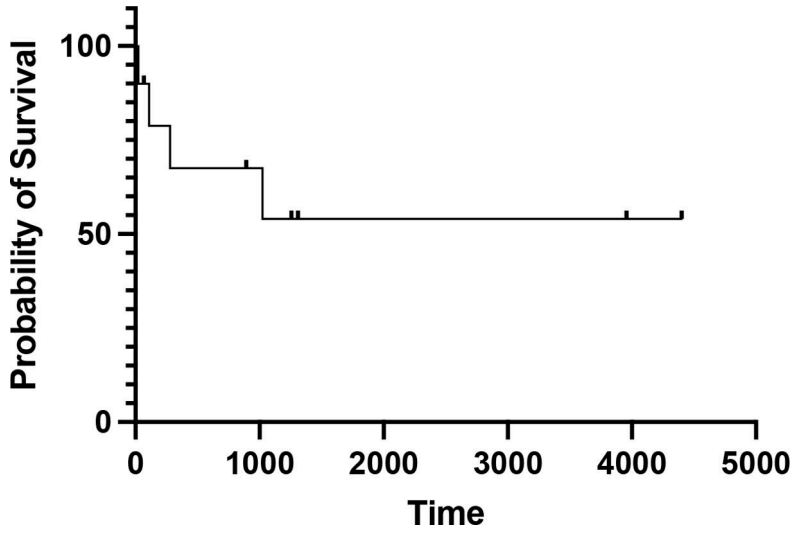
Introduction: Hematopoietic cell transplantation (HCT) is a curative treatment for chronic granulomatous disease (CGD). Post-HCT outcomes are poorly reported in Latin America. We describe the outcome of a CGD pediatric cohort.
Methods: Retrospective analysis from 11 clinical records. 1 patient excluded due to lack of enough information.
Results: 10 males, 9 X-linked CGD. Median follow-up 3.3 years (0-12), median age at transplant 6.9 years (range: 1-13). Pre-HCT patients had 10 severe infections, 10 growth failure, 9 lung disease, 8 CGD colitis, and 5 BCG complications. Patients received peripheral blood stem cells (n = 6), bone marrow (n = 3), or cord (n = 1) from matched (n = 3) or mismatched (n = 3) unrelated donors, haploidentical (n = 3) or matched sibling donor (n = 1) using (7, 70%) busulfan-fludarabine conditioning, (2, 20%) busulfan-cyclophosphamide, and (1, 10%) fludarabine-melphalan. Tacrolimus and mycophenolate as graft versus host disease (GvHD) prophylaxis in most patients (50%). 2 patients (20%) developed acute, and 2 (20%) chronic GvHD. 5 patients (50%) had CMV, 2 (20%) EBV, and 1 (10%) adenovirus viremia. 1 (10%) developed EBV posttransplant lymphoproliferative disease. At last follow-up, 6 patients were alive, resulting in a 12-year overall survival of 54%. Of the 4 patients that passed away, 2 had graft failure. During the follow-up: 5 patients (83.3%) stabilized lung disease, 5 (83.3%) resolved colitis, 3 (50%) had significant infections, and 3 (50%) improved growth. 4 patients had donor chimerism performed, being 100% with normal dihydrorhodamine (DHR). 6/11 patients had lab follow-up after day 360. 4 patients achieved T cell immune reconstitution (median CD4naive: 30.4%). At day 720, 1/5 showed normal B cell subsets with a median IgA 161 mg/dl and IgM 127 mg/dl (n = 5).
Conclusions: Most patients had multiple severe pre-HCT complications. Despite high mortality, HCT led to immune T reconstitution with improvement in lung disease and colitis. These results support HCT as a curative option for CGD and highlight the need for earlier referral and better transplant strategies.



https://doi.org/10.70962/LASID2025abstract.31
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.31

Novel Dominant-Acting IL2RB Splice Variant in a Patient with Severe Immune Dysregulation

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Background: The IL2RB gene encodes the beta subunit of the interleukin-2 (IL2) receptor, which transmits signals from the cytokines IL-2 and IL-15. IL2RB shows constitutive or induced expression on various types of immune cells, including CD4+ T regulatory cells, CD4+ and CD8+ T cells, B cells, and natural killer cells. *IL2RB* cytoplasmic domain is essential for JAK1/3 signaling. Biallelic loss-of-function variants typically cause autosomal recessive immunodeficiency. Here, we describe a patient with a novel heterozygous splice site variant and severe immune dysregulation.
Methods: Clinical evaluation and whole exome sequencing were performed. Variant classification followed the American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines. In silico predictions were used to assess the molecular consequences.
Results: A 4-year-old girl born to non-consanguineous parents presented with neonatal diabetes requiring insulin-pump therapy (anti-glutamic acid decarboxylase antibodies positive), autoimmune hypothyroidism (anti-thyroglobulin and anti-thyroperoxidase antibodies positive), autoimmune hemolytic anemia (direct Coombs positive), chronic diarrhea consistent with inflammatory bowel disease, and bullous pemphigoid (anti-bullous pemphigoid antibodies positive). This last manifestation was refractory to high-dose intravenous immunoglobulin, corticosteroids, dapsone, and rituximab, with only partial improvement; clinical stabilization was achieved after dupilumab plus palliative care. Whole exome sequencing identified a heterozygous IL2RB splice site variant (c.903+1G>T), absent from gnomAD and classified as likely pathogenic (PVS1, PM2). The variant disrupts the canonical donor site of intron 9, and in silico splicing predictors indicate activation of a cryptic donor site 26 nt upstream in exon 9, generating a frameshift and premature stop codon located within the last exon, thereby predicted to escape nonsense-mediated decay. The predicted truncated protein lacks most of the intracellular domain, likely compromising JAK1/3-mediated signaling.
Conclusion: This case raises the possibility of a dominant-negative or haploinsufficient mechanism of *IL2RB*-related disease. Functional studies are needed to confirm the impact on receptor signaling and clarify the inheritance pattern.

https://doi.org/10.70962/LASID2025abstract.32
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.32

First Case of Chronic Granulomatous Disease Due to NCF1 Mutation Successfully Treated with Pioglitazone

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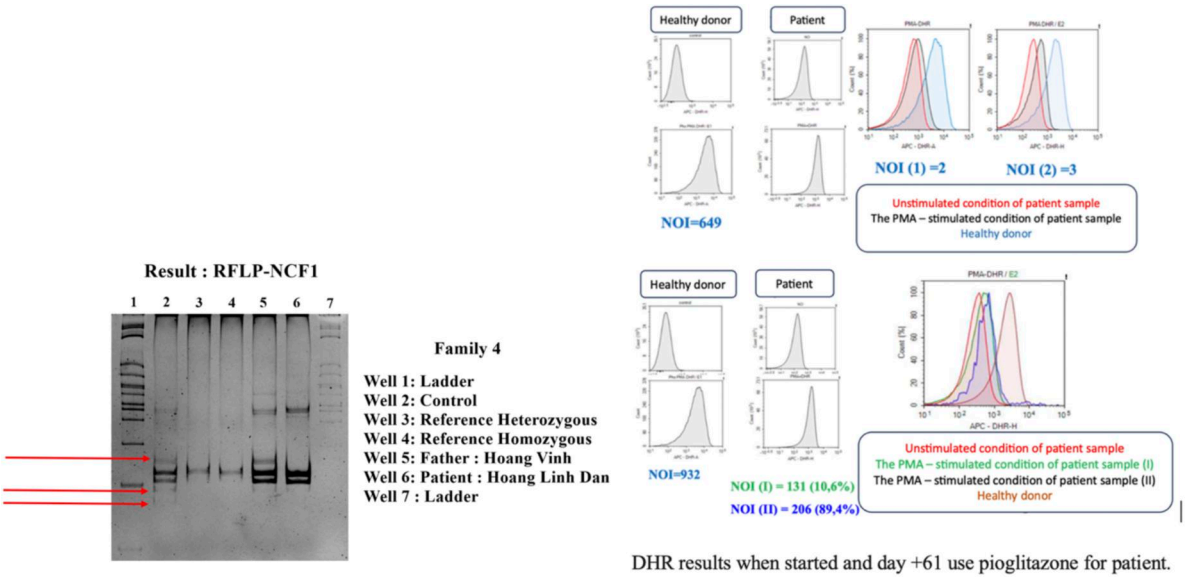
Introduction: Chronic granulomatous disease (CGD) is a rare genetic disorder resulting from mutations in the genes encoding subunits of the nicotinamide adenine dinucleotide phosphate oxidase complex. This condition leads to life-threatening infections and granuloma formation. Hematopoietic stem cell transplantation (HSCT) is a curative treatment for CGD but is complicated by the availability of matched donors and active infections. Recent studies suggest that pioglitazone, a peroxisome proliferator–activated receptor gamma agonist, may offer therapeutic potential in CGD. This report presents the first documented case of CGD due to an NCF1 mutation, treated successfully with pioglitazone.
Case Presentation: The patient is a 4-year-old girl from a non-consanguineous family with a history of recurrent infections, including necrotizing pneumonia, lymphadenitis, and sepsis, requiring multiple hospitalizations and broad-spectrum antibiotics. Despite multiple treatments, including anti-tuberculosis therapy, her condition persisted. A CT scan revealed poly-necrotizing pneumonia. Although laboratory findings, including complete blood count, immunoglobulin levels, and T cell markers, were normal, CGD was confirmed by a dihydrorhodamine (DHR) test showing absent right shift upon PMA stimulation. Whole exome sequencing (WES) failed to identify mutations due to NCF1 being a pseudogene. However, PCR–restriction fragment length polymorphism

(RFLP) analysis confirmed a homozygous mutation in NCF1. Given the absence of an HLA-matched donor, treatment with pioglitazone was initiated at 3 mg/kg/day. After two months, a significant improvement in DHR fluorescence was observed, indicating restored phagocytic function. The patient showed rapid clinical improvement, with a reduction in hospitalization frequency and no severe infections for six months.

Conclusions: This case demonstrates the effectiveness of pioglitazone in treating CGD due to NCF1 mutation, particularly in patients lacking suitable donors or facing delays in HSCT. The use of pioglitazone may represent a promising alternative treatment strategy for CGD, especially in resource-limited settings.



DHR results when started and day +61 use pioglitazone for patient.

https://doi.org/10.70962/LASID2025abstract.33
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.33

Hematopoietic Stem Cell Transplantation in ADA-SCID: A Multicenter and Multinational Latin American Report

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Introduction: Adenosine deaminase (ADA) deficiency accounts for 10-15% of severe combined immunodeficiency cases. Treatment options include enzyme replacement therapy (ERT), gene therapy, and hematopoietic stem cell transplantation (HSCT). We report a multicenter case series of Latin American patients with ADA-SCID treated with HSCT.

Methods: Participants of the monthly online Latin American Society for Immunodeficiencies HSCT meetings reported data from eleven patients who underwent HSCT between 2013 and 2023.

Results: Six patients were female. Median age at diagnosis was 5.1 months (range: 0.9–50.0). Presentations included severe bacterial infections (5/11), viral pneumonia (5/11), diarrhea (2/11), pneumocystis pneumonia (2/11), oral candidiasis (2/11), and family history (1/11). Diagnosis was confirmed by genetic testing (7/11), enzyme assay (2/11), or immunophenotype and clinical features (2/11). Ten patients received Bacillus Calmette–Guérin vaccination; seven developed complications (three local, four disseminated). ERT was used in three

cases. Median age at HSCT was 9.7 months (range: 3.7–54.4). Donors included matched family (3), unrelated adults (5), unrelated cord blood (2), and one haploidentical donor. Conditioning regimens varied; three patients received no conditioning. Graft versus host disease (GVHD) prophylaxis included a calcineurine inhibitor (10/11), antithymocyte globulin (7/11), antimetabolites (5/11), and posttransplant cyclophosphamide (2/9). Three patients died after transplant due to multiorgan failure, acute respiratory distress syndrome, and pneumonia. Median follow-up is 3.6 years (range: 0.1–10.7); overall survival is 72.7%. Acute GVHD occurred in 7/10 evaluable patients (3 with grade III–IV). Complications among 8 long-term survivors included EBV reactivation (6/8), invasive aspergillosis (2/8), neurological disabilities (7/8), hypothyroidism (2/8), and dermatofibrosarcoma protuberans (1/8). All patients engrafted; three have mixed chimerism. All are off intravenous immunoglobulins and 6/7 have normal lymphocyte subsets.

Conclusion: HSCT for ADA-SCID is feasible in resource-limited settings. This report shows encouraging outcomes despite significant clinical challenges.

https://doi.org/10.70962/LASID2025abstract.34
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.34

Novel RELA Mutation Associated with Macrophage Activation Syndrome and Familial Lupus: Linking NF-κB to Monogenic SLE

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Introduction: RELA encodes the p65 subunit of NF-κB, a transcription factor involved in cell survival, inflammation, and immune regulation. Heterozygous RELA variants have been linked to inborn errors of immunity (IEIs) presenting with early-onset systemic lupus erythematosus (SLE), mucocutaneous ulcers, Behçet-like features, autoimmune lymphoproliferative syndrome–like symptoms and variable infectious susceptibility [1].

Clinical Case: We report a 9-year-old girl with a history of recurrent infections. At age 8, she was admitted with septic shock due to necrotizing pneumococcal pneumonia. During that hospitalization, she developed Raynaud's phenomenon, hip synovitis, pancytopenia, and SLE-associated autoantibodies (antinuclear antibody 1/640, anti–double-stranded DNA antibody, anti-Ro/La) with low C3/C4 levels, leading to a diagnosis of SLE. She received steroids, hydroxychloroquine, and mycophenolate. At age 9, she developed spontaneous pneumococcal peritonitis, which triggered macrophage activation syndrome (MAS) (hyperferritinemia >8,000 ng/mL, IL-6 >5,000 pg/mL, hypo-fibrinogenemia, cytopenias, and elevated liver enzymes and triglycerides). Despite intensive immunosuppressive therapy (steroids, cyclosporine, intravenous immunoglobulin, and cyclophosphamide), she died of multiorgan failure. Immunologic workup revealed global lymphopenia, IgG2/IgG4 subclass deficiency, and hypocomplementemia. Genetic testing identified a heterozygous RELA variant (c.1502C>G; p.T501S, variant of uncertain significance [VUS]), also found in her father, who had adult-onset SLE with nephritis and severe infections (pneumococcal sepsis, herpes zoster meningoencephalitis). Interferon signature testing is pending.

Discussion: This case shows the overlap between monogenic autoimmunity and IEIs. RELA mutations may exert dominant-negative or gain-of-function effects, impairing NF-κB signaling and enhancing type I interferon signature. The severity/familial segregation support a possible pathogenic role of the VUS, though functional validation is needed. Recurrent infections raise the possibility that RELA may play a role in infectious immunity, particularly in mucosas. TNF agents have shown benefit in some patients; JAKinhibs are a promising option for refractory cases.

Conclusion: IEIs should be suspected in children with early-onset SLE and severe infections. Functional studies are essential to determine variant pathogenicity and guide-targeted interventions.

Reference

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https://doi.org/10.70962/LASID2025abstract.35
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.35

A Novel Heterozygous OAS1 Variant in a Child with Systemic Inflammation, Epilepsy, and Urticaria: Expanding the Spectrum of Type I Interferonopathies

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Background: Variants in genes involved in the type I interferon pathway, such as OAS1, can lead to autoinflammatory disorders with neurological and systemic manifestations. We report a pediatric patient with a novel heterozygous OAS1 variant and a complex clinical phenotype.
Case Presentation: We report the case of a 1-year-8-month-old female, born to non-consanguineous parents, who presented with failure to thrive, gastrointestinal symptoms characterized by alternating constipation and diarrhea associated to food allergies refractory to dietary restrictions. She had a prior diagnosis of epilepsy and showed signs of global developmental delay and sensorineural hearing loss. Dermatologic examination revealed livedo reticularis. Laboratory evaluation revealed normal immunoglobulin levels but reduced post-switched memory B cells. However, interferon-related biomarkers were elevated: the IFN score was 9.81 (mean control 6.8), and IL-18 mRNA expression was 52.2 copies/ng (mean control 35). During follow-up, she developed recurrent febrile episodes accompanied by systemic inflammation and exacerbations of chronic urticaria. Exome sequencing identified a heterozygous OAS1 variant (c.199G>A, p.Gly67Ser), classified as a variant of uncertain significance due to its absence from population databases and location in a conserved region involved in double-stranded RNA sensing.
Discussion: Although the IFN signature was elevated, it did not reach the diagnostic range for monogenic interferonopathies. The clinical features and molecular data suggest a possible dysregulation of the interferon response. The variant has not been functionally validated, and parental segregation is pending. Based on clinical severity and molecular findings, empirical treatment with JAK inhibitors is being considered.
Conclusion: This case supports the involvement of OAS1 variants in early-onset inflammatory syndromes with neurologic and cutaneous features. Functional studies are required to confirm pathogenicity and elucidate the mechanism of disease.

https://doi.org/10.70962/LASID2025abstract.36
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.36

Homozygous ISG15 Deletion in a Patient with Recurrent Encephalitis, BCGitis, and Severe Infections

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Introduction: ISG15 encodes an interferon-stimulated ubiquitin-like modifier essential for the type I interferon signaling pathway. Biallelic ISG15 mutations have been associated with susceptibility to mycobacterial infections, as well as autoinflammatory manifestations.
Case Presentation: We describe a 23-year-old woman who has presented with BCGitis following routine neonatal vaccination. Throughout childhood, she experienced recurrent episodes of life-threatening infections and two episodes of encephalitis of unknown etiology, both requiring intensive care admission. At age 22, she developed severe COVID-19 pneumonia. Additional clinical features included seizures and persistent leukopenia. Immunological assessment included lymphopenia, low serum IgM, and reduced circulating memory B cells. Despite intensive care, the patient died from severe neurological complications. Whole exome sequencing identified a likely pathogenic homozygous deletion in ISG15 (c.299_312delTGACGCAGACCGTG; p.Leu100fs), predicted to disrupt protein stability and ISGylation function. Segregation analysis is currently underway.

Discussion: This case expands the clinical spectrum of ISG15 deficiency, illustrating its association with severe viral infections, BCGitis, and fatal neurological involvement. Although ISG15 is not a classical considered antiviral effector, it plays a pivotal role in modulating type I interferon responses. The patient's recurrent encephalitis and severe COVID-19 pneumonia likely reflect an exaggerated type I IFN-mediated inflammatory response.
Conclusion: Homozygous ISG15 mutations should be considered in patients with Bacillus Calmette–Guérin (BCG)-related complications, recurrent infections, and unexplained central nervous system inflammation. Early genetic diagnosis may facilitate prompt consideration of IFN-targeted therapies such as JAK inhibitors.

https://doi.org/10.70962/LASID2025abstract.37
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.37

Compound Heterozygous NFATC2 Variants in Adult Patients with Severe Atopy, Immune Dysregulation, and Recurrent Infection

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Introduction: NFATC2 encodes the nuclear factor of activated T cells 2, a transcription factor essential for T cell activation, cytokine gene expression, and the maintenance of immune tolerance. Germline variants in NFATC2 have recently been implicated in a spectrum of inborn error of immunity (IEI) marked by combined immunodeficiency and immune dysregulation.
Case Presentations: We report two unrelated patients with recurrent and severe infections, atopy, and autoimmunity.
Patient 1: A 21-year-old female presented with a history of viral meningitis, severe atopic dermatitis, asthma, and multiple recurrent infections. Immunological workup revealed markedly elevated serum IgE levels (5,780 IU/mL) and a reduced circulating Th17 cells. Genetic testing identified compound heterozygous variants in NFATC2 : c.677T>A (p.Leu226His) and c.1952G>A (p.Arg651His), affecting conserved regions involved in DNA binding and transcriptional activity.
Patient 2: A 62-year-old woman with a history of recurrent otitis media and cutaneous abscesses since childhood, as well as bone marrow dysplasia and autoimmune hypothyroidism. Immunological evaluation revealed persistently elevated serum IgM levels, decreased naïve B cell counts, and the presence of antineutrophil cytoplasmic antibodies (ANCA). Genetic analysis revealed compound heterozygous variants c.1282G>C (p.Gly428Arg) and c.2462G>A (p.Arg821His), also located in functional domains of NFATC2.
Discussion: Both cases demonstrate overlapping features with immune dysregulation and susceptibility to infections, consistent with impaired NFATC2 function. The identified compound heterozygous variants in NFATC2 affect highly conserved residues located within functional domains involved in DNA binding and transcriptional activation, and are predicted to impair protein function. Although functional validation is pending, the consistency between the immunophenotypes and the known biology of NFATC2 strongly supports their pathogenicity.
Conclusion: Compound heterozygous NFATC2 variants may underlie a distinct IEI phenotype. Early recognition is essential to guide immunologic assessment, genetic counseling, and consideration of targeted therapies.

https://doi.org/10.70962/LASID2025abstract.38
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.38

First Steps with Facilitated Subcutaneous Immunoglobulin (fSCIg) Therapy: A Single Center Experience

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Introduction: Several studies have shown that facilitated subcutaneous immunoglobulin (fSCIg) is as good as intravenous (IVIg) and conventional subcutaneous immunoglobulin (cSCIg) preventing infections in innate errors of immunity (IEIs).
Presentation: The objective is to describe the follow-up of 29 patients with fSCIg treatment in the last 3 years in a single center in Argentina (April 2022 – June 2025). 29 patients (p) were included who diagnosed with (15p) common variable immunodeficiency, (5p)

specific antibody deficiency with normal Ig levels and normal B cells, (2p) hypogammaglobulinemia and specific antibody deficiency, (2p) primary hypogammaglobulinemia, (1p) x-linked agammaglobulinemia, (1p) specific antibody deficiency with IgA deficiency, (1p) specific antibody deficiency and familial Mediterranean fever, (1p) LRBA deficiency, and (1p) autoimmune lymphoproliferative syndrome and IgA deficiency. Mean time of follow-up with fSCIg was 20 months [1.1 – 38.6]. Mean dose was 560 mg/kg/month [345 – 1,360]. 76% received fSCIg every 4 weeks, the others more frequently. Mean serum IgG level was 1,274 mg/dl [range 615 – 3,014]. Annual rate of infection was 0.27 infections/year of follow-up. 8/29p suffered 13 cases of bacterial infections: 3 pneumonia, 3 bronchitis, 2 acute media otitis, 1 giardiasis, 1 adenitis, 1 bacterial parotitis, 1 pharyngitis, and 1 tracheitis. One patient with low adherence to treatment required two hospitalizations (pneumonia, adenitis).

Tolerance: 9p (31%) reported local symptoms: erythema (5p), swelling (4p), pain (2p), and pruritus (2p); most of them lasted less than 24 hours; only 3p reported erythema (1p) and swelling (2p) of 4-5 days of duration; none of the local symptoms required treatment. 4p reported systemic adverse reactions (headache and/or fever) during the first infusions.

Discussion: fSCIg therapy is safe and effective for replacement treatment in patients with IEIs. Further systemic clinical studies are needed to better define optimal dosage and application intervals.

https://doi.org/10.70962/LASID2025abstract.39
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.39

Patient with Severe Congenital Neutropenia Associated with ELANE Gene Mutation: c.684C>G, p.Tyr228Ter*

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Introduction: Severe congenital neutropenia type 1 (SCN1) is a rare hereditary disorder caused by a maturation arrest in granulocyte development, most frequently associated with mutations in the *ELANE* gene, which encodes neutrophil elastase.

Case Presentation: Female patient, 3 years and 5 months old, with a history of recurrent perianal infections and necrotizing fasciitis secondary to complicated appendicitis with septic shock. She required laparotomy, appendectomy, ileostomy, debridement, and vasopressor support. During hospitalization, persistent severe neutropenia, lymphopenia, and eosinophilia were identified. Bone marrow aspiration showed a maturation arrest in the myeloid lineage with absence of neutrophils. Infectious isolates included *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and rhinovirus/enterovirus. Absolute neutrophil counts remained persistently low (100–530/µL), with a response to the administration of G-CSF (granulocyte colony stimulating factor: 5 mcg/kg/dose). Genetic sequencing revealed a heterozygous nonsense mutation in *ELANE* (c.684C>G, p.Tyr228Ter).

Discussion: The diagnosis of SCN1 was clinically supported by severe infections, persistent neutropenia, absence of mature granulocytes in the bone marrow, and genetic confirmation. This mutation generates a premature stop codon. Other relevant variants include *GFI1*, *HAX1*, *VPS45*, *JAGN1*, *CSF3R*, and *WAS*.

Conclusion: SCN1 should be suspected in pediatric patients with recurrent severe infections and persistent neutropenia. Early identification and treatment with G-CSF may improve clinical outcomes and reduce infectious complications.

https://doi.org/10.70962/LASID2025abstract.40
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.40

Neurodegenerative Complications in XLA

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Introduction: X-linked agammaglobulinemia (XLA) is commonly associated to central nervous system (CNS) infections; however, the incidence of neurodegenerative disease without a known pathogen remains unknown, with only 15 cases reported to date.

Presentation: A male patient was diagnosed with XLA at the age of 4 after having pneumonia and meningitis and was started on immunoglobulin therapy (IVIG). At 17, he received anti-tuberculosis therapy for lung tuberculosis. At 25, he developed gait instability and

hearing loss. MRI revealed extensive cerebellar atrophy resembling multisystem atrophy type C. Infectious causes were ruled out through comprehensive cerebrospinal fluid (CSF) and blood analysis. He was started on a high-dose IVIG (1 g/kg every 2 weeks) alongside selegiline, amantadine sulphate, pregabalin, vitamin E, B3, and zinc. Over the next 4 years, there was mild neurocognitive improvement, with stable MRI findings. IVIG was reduced to 0.6 g/kg every 3 weeks. Several months after, a slight neuropsychological deterioration was observed but was attributed to psychological trauma of losing a family member. A year later, regardless of high trough IgG levels (12.7 g/L), he was hospitalized due to bilateral pneumonia caused by *Haemophilus influenzae* and was treated with ceftriaxone and azithromycin with a favorable effect. IVIG was again increased to 1 g/kg every 2 weeks, resulting in clinical stability, no severe infections, and stable MRI findings during the next 2-year period in now a 32-year-old patient, although slight neurocognitive and motor decline persisted.
Discussion: This case highlights the complexity of managing neurodegenerative complications in XLA, a rare and poorly understood manifestation with no established treatment protocol. High-dose IVIG provided some improvement, but progressive neurocognitive decline appears to be inevitable.

https://doi.org/10.70962/LASID2025abstract.41
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.41

Variable Clinical Presentation in Complement Deficiency Disorders: Single-Center Experience

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Introduction: Complement deficiency disorders, characterized by autoimmunity and recurrent bacterial infections, are diagnosed through complement pathway testing and genetic analysis, with management involving antibiotics, vaccination, and treating autoimmune manifestations.
Presentation: This case series outlines six patients with diverse presentations. First 3 patients had recurrent meningococcal infections: a 25-year-old male had meningococcal meningitis at the age of 15 and 22; a 30-year-old female had meningococcal sepsis at 10 and 19; and a 30-year-old female had meningococcal meningitis at 15 and sepsis at 22. In all three patients, terminal complement pathway deficiency was confirmed, where the first patient is homozygous for a C8B deficiency and heterozygous for C9. The second and third patients are also homozygous for C8B deficiency.

Two other patients had a more complicated infectious diathesis: a 48-year-old male had pneumonia at 10, followed by sepsis at 19 and meningococcal meningitis at 47; a 53-year-old female had an episode of meningitis at the age of 1, followed by recurrent pneumonias since childhood and the development of emphysema and pulmonary arterial hypertension leading to lung transplantation. Functional analysis in the male patient showed a deficiency in all three complement pathways, but the terminal complex activity was elevated (genetic testing is pending), whereas in the female patient, a terminal complement pathway deficiency was confirmed with a homozygous variant in C2 gene.

One patient had predominantly autoimmune manifestations: a 58-year-old female with systemic lupus erythematosus and thrombocytopenia. A severely reduced classical and lectin pathway was found, with low C4, C1 inhibitor, and factor B and I. Genetic testing is pending.
Discussion: The cases illustrate heterogeneity in complement deficiency presentations, leading to delayed diagnosis. Genetic testing remained incomplete in some patients. Early diagnosis and vigilant monitoring are crucial to reduce infection recurrence and autoimmune progression.

https://doi.org/10.70962/LASID2025abstract.42
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.42

Molecular and Clinical Profiling of Patients with Suspected Inborn Errors of Immunity at a Rare Disease Center in Southern Brazil: First-Year Preliminary Data

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Introduction: Inborn errors of immunity (IEIs) are rare genetic disorders caused by pathogenic germline variants affecting immune function. They lead to increased susceptibility to infections, autoimmunity, autoinflammatory syndromes, bone marrow failure, and malignancies. Over 500 IEI types are known, and their clinical and molecular heterogeneity poses major diagnostic challenges, often delaying diagnosis and treatment.
Methods: This study was conducted at a Rare Disease Reference Center in Southern Brazil, combining retrospective and prospective data collection from 2023 to 2025, through a medical records review and informed consent sign. To date, 77 patients with suspected IEIs have been enrolled, and recruitment of new participants remains ongoing, following informed consent. Genetic analyses were performed in a research setting, using exome sequencing, gene panels, or single-gene analysis, according to clinical indication and test availability.
Results: Among the patients, 70% (n = 54) were male, with a median age at symptom onset of 36 months (range: 0–915). IEI-related symptoms occurred in 46% within the first two years of life. However, the median age at genetic investigation was 10.4 years, highlighting a diagnostic delay of 7–8 years. Exome sequencing was performed in 57%, gene panels in 35%, and single-gene testing in 2.6%. Genetic results were available for 36% (n = 28/54), with a diagnostic yield of 50% (n = 14/28). Among positive findings, the most common category was congenital phagocyte defects (36%), followed by combined cellular and humoral immunodeficiencies (28%), syndromic combined immunodeficiencies (21%), intrinsic/innate immunity defects (7%), and immune dysregulation disorders (7%).
Conclusions: Despite early symptom onset, genetic testing was delayed, highlighting a significant diagnostic gap. Contributing factors include low medical awareness, challenges in referral to specialized centers, and limited test access. Establishing specialized IEI clinics is essential for early diagnosis, improved care, family support, and ultimately improve clinical outcomes and quality of life.

https://doi.org/10.70962/LASID2025abstract.43
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.43

Dominant-Negative IL10RA Variant in a Family with Variable Autoimmune Manifestations: Expanding the Spectrum of IL10R-Associated Immune Dysregulation

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Background: Interleukin-10 receptor (IL10R) plays a critical role in immune regulation by mediating anti-inflammatory effects of IL-10 through STAT3 phosphorylation and downstream signaling. While biallelic mutations in *IL10RA* are well established as causative of very early onset inflammatory bowel disease (VEO-IBD) and severe immune dysregulation, the clinical relevance and functional consequences of heterozygous variants remain poorly defined.
Case Presentation: We report a multi-generational Argentinean family with three affected individuals—two males and one female—from distinct branches, all carrying a heterozygous nonsense variant in *IL10RA* (c.787C>T; p.Arg263*). Clinical phenotypes ranged from VEO-IBD to common variable immunodeficiency with autoimmunity. In contrast, heterozygous relatives without overt disease showed either normal immune profiles or mild immunological alterations.
Functional Studies: The p.Arg263* variant introduces a premature stop codon in the penultimate exon, within 50 bp of the exon–exon junction, and is predicted to escape nonsense-mediated decay. Consistently, Western blot analysis of peripheral blood mononuclear cells demonstrated expression of a truncated IL10Rα protein in both patients and asymptomatic mothers, with higher protein levels in symptomatic individuals, supporting a dose-dependent dominant-negative effect. Patient-derived peripheral blood mononuclear cells (PBMCs) showed diminished STAT3 phosphorylation upon IL-10 stimulation. Furthermore, LPS stimulation induced elevated secretion of pro-inflammatory cytokines (IL-6, TNF-α) in both patients and healthy donors; however, only in healthy controls did IL-10 co-stimulation effectively suppress cytokine production. This regulatory effect was absent in patient cells, suggesting a defect in IL-10–mediated immune suppression. In vitro reporter assays using HEK293T cells co-transfected with wild-type or mutant *IL10RA* constructs demonstrated reduced STAT3-GFP activation in the presence of the mutant receptor, consistent with a dominant-interfering mechanism.
Conclusion: These findings support a dominant-negative effect of the IL10RA p.Arg263* variant. This case expands the spectrum of IL-10R–associated immune dysregulation and suggests that heterozygous truncating variants may underlie dominant inheritance patterns. Functional testing is essential for variant interpretation and patient care.

https://doi.org/10.70962/LASID2025abstract.44
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.44

Functional Characterization of STAT1 and STAT3 Variants in Pediatric Patients with Immune Dysregulation

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Background: STAT1 and STAT3 are transcription factors activated by cytokines such as IFN-γ and IL-6, respectively. Germline variants in these genes are associated with distinct immune dysregulation syndromes, and functional validation is essential for variant interpretation.
Case Presentation: We report two Argentinean pediatric patients with novel variants in STAT1 and STAT3. Patient 1, a 10-year-old male with chronic mucocutaneous candidiasis, persistent diarrhea, eczema, recurrent respiratory infections, failure to thrive, and oral candidiasis, carried a heterozygous STAT1 variant c.874G>A(p.Asp292Asn). Patient 2, a 12-year-old male, presented with splenomegaly, multiple adenopathies, leukopenia, thrombocytopenia, eosinophilia, hypogammaglobulinemia, and bone marrow hypoplasia. A lymph node biopsy showed reactive follicular hyperplasia. Genetic analysis revealed a heterozygous STAT3 variant c.1044A>C (p.Lys348Asn). Both variants arose de novo as confirmed by parental testing.
Methods: We used site-directed mutagenesis to introduce novel variants into FLAG-tagged STAT1 and STAT3 expression plasmids. HEK293T cells were transfected with WT or mutant constructs. STAT1 activity was assessed using a luciferase reporter activated by IFN-γ and STAT3 activity was measured via a STAT3-responsive GFP reporter upon IL-6 stimulation. Additionally, STAT1 phosphorylation levels upon IFN-γ stimulation were assessed on monocytes by flow cytometry.
Results: The *STAT1* p.Asp292Asn variant phosphorylation in patient monocytes was increased to approximately twice the level observed in healthy controls, confirming a gain-of-function (GOF) effect. The STAT3 p.Lys348Asn variant showed increased GFP reporter activity following IL-6 stimulation, suggesting a GOF effect. These functional hyperactivations were compatible with immune dysregulation phenotypes.
Conclusion: Our findings highlight the pathogenic role of the STAT1 and STAT3 variants in immune dysregulation syndromes. We were able to establish that both variants confer a GOF effect. Functional assays are critical for interpreting variants of uncertain significance and contribute to precise diagnosis and tailored therapeutic strategies in patients with suspected monogenic immune diseases.

https://doi.org/10.70962/LASID2025abstract.45
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.45

Novel PTPN2 Variants in Pediatric Patients with Autoimmune and Immunodeficiency Phenotypes: Functional Impact on STAT Signaling

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Background: Protein tyrosine phosphatase non-receptor type 2 (PTPN2) is a key negative regulator of the JAK/STAT pathway and is essential for immune homeostasis. Loss-of-function variants in PTPN2 have been implicated in monogenic autoimmunity.
Case Series: We identified novel heterozygous PTPN2 variants in three unrelated Argentinean pediatric patients presenting immune dysregulation. A patient with polyautoimmunity and polyinflammation was found to carry compound heterozygous variants c.515T>C (p.Ile172Thr) and c.865T>C (p.Trp289Arg), inherited from healthy heterozygous parents. In a second case, a child with Evans syndrome harbored the c.515T>C (p.Ile172Thr) variant. The third case involved a girl evaluated for recurrent bronchitis and diagnosed with an inborn error of immunity (IEI), carrying the c.865T>C (p.Trp289Arg) variant. Notably, her mother had previously been diagnosed with common variable immunodeficiency and died of gastric cancer.
Methods: To assess the functional consequences of these variants, we cloned wild-type (WT) PTPN2 cDNA into a mammalian expression plasmid with an HA-tag and introduced the two mutations via site-directed mutagenesis. HEK293T cells were transfected with

WT/mutant PTPN2 constructs. Protein expression was evaluated by Western blot. Functional assays included co-transfection of PTPN2-HA constructs, WT-STAT3, and a STAT3-responsive GFP reporter, followed by IL-6 stimulation. Additionally, STAT1 activity was assessed using a STAT1-luciferase reporter system after IFN-γ stimulation.

Results: Mutant PTPN2 proteins were expressed at levels comparable to WT, suggesting preserved protein stability. However, cells expressing both PTPN2 variants (compound heterozygous state) showed significantly enhanced STAT3 activity upon IL-6 stimulation. STAT1 pathway analysis revealed altered luciferase activity in response to IFN-γ in cells transfected with each or both mutant constructs, suggesting broader dysregulation of JAK/STAT signaling.

Conclusion: These novel PTPN2 variants may contribute to immune dysregulation by enhancing STAT signaling. Functional evidence supports a pathogenic role consistent with the observed clinical phenotypes. Further studies are needed to define their contribution to autoimmunity and IEIs, and to explore therapeutic implications.

https://doi.org/10.70962/LASID2025abstract.46
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.46

NADPH Oxidase Subunits by Flow Cytometry in Recessive Chronic Granulomatosis Disease

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Introduction: Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by impaired phagocytic function due to mutations in the five NADPH oxidase subunits and two other genes that are not part of this complex (gp91phox, p22phox, p47phox, p67phox, p40phox, EROS, and Rac1/2 GTP binding protein), leading to severe, recurrent bacterial and fungal infections with granuloma formation and inflammatory bowel disease-like colitis. Almost 30% of CGD result from recessive mutations.

Aim: Describe the utility of the quantification of NADPH oxidase subunits by flow cytometry in CGD.

Case Presentation: A 9-year-old girl born from non-consanguineous parents, admitted for prolonged febrile syndrome and abscessed pneumonia unresponsive to antibiotics, referred from the Hospital of Catamarca. Disseminated coccidioidomycosis was diagnosed, also based on central nervous system involvement, along with a positive PCR for coccidioidomycosis in bronchoalveolar lavage and lung biopsy. Her medical history includes hospitalizations for bilateral pneumonia due to SARS-CoV-2 and multisystem inflammatory syndrome in children with mild pericarditis at 6 years old. No family history of an inborn error of immunity. Currently waiting for hematopoietic stem cell transplantation plan. First immunology evaluation showed hypergammaglobulinemia (IgG, A, M) with normal protein response, positive autoantibodies. Normal lymphocyte subpopulations (T lymphocyte, B lymphocyte, natural killer) with high activation markers in T cells compartments (CD4+/CD8+). Increased frequencies of switched memory B lymphocyte and plasma cells. Normal lymphocyte proliferation assay with adequate TNFa production in monocytes after Bacillus Calmette–Guérin and IFNg stimulus. Normal IL-12RB1 and IFNg receptors. Complete deficiency of dihydrorhodamine oxidation with normal result for the mother. NADPH oxidase subunits by flow cytometry showed a marked decrease in gp91phox and gp67phox with normal expression of gp47phox and gp22phox. Molecular study confirmed absence of NCF2 gene transcripts. Further studies are ongoing to characterize this variant.

Discussion: Flow cytometry–based evaluation of NADPH oxidase components is a surrogate marker for identifying the genetic defect in CGD. This is a rapid assay for neutrophils that can be tested in any clinical laboratory.

https://doi.org/10.70962/LASID2025abstract.47
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.47

XMEN: Not Always an EBV-Related Inborn Error of Immunity

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Introduction: X-linked immunodeficiency with magnesium defect, Epstein–Barr virus infection, and neoplasia (XMEN) syndrome is an inborn error of immunity caused by loss-of-function (LOF) mutations in the magnesium transporter gene (*MAGT1*).

Aim: To describe clinical and laboratory findings of 2 siblings (P) with XMEN syndrome and no chronic EBV infection.

Case Presentation: Two males, P1 (19 years old) and P2 (17 years old). Maternal uncle with common variable immunodeficiency (CVID) at 21 years who died of diffuse large B cell lymphoma. P1: Follow-up since 3 years old for recurrent wheezing, respiratory infections, and regular weight/height progression. P2: Previously healthy, consulted at 16 years due to 3-month-term fever, bilateral cervical lymphadenopathy, weight loss, and asthenia. Biopsy confirmed classical Hodgkin lymphoma. Positive blood EBV IgG and negative EBV PCR in blood and lymph nodes biopsy. Immunological evaluation showed panhypogammaglobulinemia in P1. Impaired protein/pneumococcal response, increased frequency of CD4+ central memory T cells with high activation markers, severe impairment of B cell compartment, and high transitional B cells with decreased total memory B cell (IgM and switched memory B lymphocyte) in both patients. While P1 was diagnosed with CVID and started monthly intravenous immunoglobulin (IVIG), P2 began chemotherapy and IVIG treatment. No variants in *SH2D1A* gene. Almost absent NKG2D in CD8+ and natural killer cells in both patients. Molecular study identified absence of *MAGT1* gene transcripts and confirmed a hemizygous deletion encompassing exons 9 and 10 in both patients and the mother as a heterozygous carrier. Follow-up: P1 presented chronic onychomycosis and respiratory infections. P2 presented a relapse of his lymphoma and received haploidentical hematopoietic stem cell transplantation with his mother.
Discussion: XMEN disease should be considered as a differential diagnosis in male patients presenting with a CVID-like phenotype and malignancy, even in the absence of chronic EBV infection, due to its heterogeneous clinical presentation and significant impact on immune function.

https://doi.org/10.70962/LASID2025abstract.48
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.48

CARD8: An Emerging Genetic Cause of Autoinflammatory and CVID-Like Syndromes?

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Introduction: CARD8 encodes the caspase recruitment domain-containing protein 8, a negative regulator of the NLRP3 inflammasome and a modulator of innate immune signaling. Although not yet formally classified among inborn errors of immunity (IEIs), emerging evidence suggests a potential role of *CARD8* variants in autoinflammatory syndromes and immune dysregulation.
Case Presentations: We describe three unrelated patients from different families with variable phenotypes involving autoinflammation and immune dysregulation.

Patient 1: A 15-year-old female with an IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)-like phenotype, including alopecia universalis, growth retardation, pubertal delay, and elevated serum IL-18 levels. A heterozygous frameshift variant in *CARD8* (c.40delG, p.Glu14fs) was identified.

Patient 2: A 3-year-old male presenting with neonatal lupus-like rash, severe atopic dermatitis, refractory autoimmune cytopenias, persistent hepatitis, and total villous atrophy on intestinal biopsy (Marsh 3b). A heterozygous frameshift variant (c.68dupG, p.Ser24fs) was detected.

Patient 3: A 42-year-old female with adult-onset CVID (common variable immunodeficiency)-like phenotype, including recurrent pneumonia, chronic diarrhea, and persistent hypogammaglobulinemia requiring immunoglobulin replacement. A heterozygous missense variant (c.1093A>C, p.Met365Leu) was identified.

Discussion: These cases illustrate the broad clinical spectrum associated with *CARD8* variants, ranging from severe early-onset autoinflammatory disease to adult-onset humoral immunodeficiency. The presence of elevated IL-18 and multi-organ involvement supports dysregulated inflammasome activation as a key pathogenic mechanism. Importantly, heterozygous variants may result in incomplete penetrance and variable expressivity, complicating diagnosis and counseling.
Conclusion: *CARD8* mutations should be considered in patients presenting with unexplained autoinflammation, immune dysregulation, or CVID-like phenotypes. Recognition of this spectrum may facilitate earlier diagnosis, appropriate therapeutic interventions targeting IL-1/IL-18 pathways, and genetic counseling for affected families.

https://doi.org/10.70962/LASID2025abstract.49
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.49

Monogenic Inflammasomopathies in Pediatric Patients: Insights from a Rheumatology Unit in Argentina

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Introduction: Monogenic systemic autoinflammatory diseases (SAIDs) are driven by innate immune dysregulation, often due to aberrant inflammasome activation. Inflammasomopathies, those involving NLRP3, MEFV, MVK, and TNFRSF1A mutations, constitute a subgroup marked by sterile inflammation and overlapping symptoms like fever, serositis, rash, and arthritis. However, diagnostic complexity from phenotypic variability and incomplete penetrance makes genetic and immunological confirmation essential. This study aimed to characterize the clinical, biochemical, immunological, and genetic profiles of pediatric patients with confirmed or suspected inflammasomopathies at a tertiary care center.

Methods: Data were obtained from a monogenic SAID registry. Genetic analysis was performed using panel-based exome sequencing, and inflammatory biomarkers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], MRP8/14) were evaluated.

Results: Over a 10-year period, 36 patients were assessed, of whom 13 (36%) had definitive diagnoses. Median age at symptom onset was 18 months, while diagnosis occurred at a mean age of 99 months, highlighting diagnostic delay. Predominant symptoms included fever (25%), ocular inflammation (12.5%), rash, arthritis, and aphthous ulcers (9% each). Despite identical NLRP3 mutations, phenotypic variation suggested roles for modifier genes or environmental factors. All patients showed laboratory signs of systemic inflammation—elevated ESR, CRP, MRP8/14, leukocytosis, and thrombocytosis—with absence of autoantibodies, consistent with autoinflammatory etiology. Overall variants were classified according to the ACMG (American College of Medical Genetics and Genomics) in inflammasome-related genes. Tailored to treatment strategies included IL-1 and TNF inhibitors.

Conclusions: This cohort reinforces the pivotal role of the inflammasome in monogenic autoinflammatory diseases. Clinical heterogeneity, even among patients with identical mutations, underscores the need for individualized evaluation. Early integration of clinical, immunological, and genetic data guiding targeted cytokine therapies that can mitigate innate immune dysregulation improving outcomes in children.

https://doi.org/10.70962/LASID2025abstract.50
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.50

Homozygous RFX5 Frameshift Variant in a Patient with Syndromic Combined Immunodeficiency and Cancer Predisposition

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Introduction: *RFX5* encodes regulatory factor X 5, a transcription factor essential for MHC class II gene expression and proper antigen presentation. Homozygous mutations cause Bare Lymphocyte Syndrome type II (BLS II), a form of combined immunodeficiency with variable clinical severity.

Case Presentation: We report a 50-year-old female patient presenting with a syndromic combined immunodeficiency. Since childhood, she exhibited recurrent respiratory tract infections, persistent mucocutaneous candidiasis, and severe viral infections, including herpesvirus reactivations. Clinical features included proportionate short stature, facial dysmorphism (flattened midface, hypertelorism), and mild developmental delay. Immunological workup revealed hypogammaglobulinemia with low switched memory B cells, CD4+ lymphopenia, with decreased effector CD4+ cells and absent DR expression, reduced antigen-specific proliferative responses. Over an eight-year follow-up period, the patient received intravenous immunoglobulin replacement therapy, experiencing a fair quality of life. She presented with recurrent respiratory infections necessitating multiple hospitalizations, with *Aspergillus flavus*, *Aspergillus fumigatus*, and *Nocardia cyriacigeorgica* isolated from cultures. She developed an invasive vulvar squamous cell carcinoma. Due to the extensive nature of the lesion, the surgery was planned in two stages. Surgical treatment was incomplete due to her physical condition. The patient died due to septic shock. Genetic testing identified a homozygous frameshift variant in RFX5: c.857_858+19delAGGTAAGGAAGTCAGTGGCCC (p.Gln286fs), predicted to disrupt DNA binding and abolish MHC class II expression.

Discussion: This case illustrates a severe form of RFX5-related combined immunodeficiency with syndromic features, opportunistic infections, and malignancy, likely reflecting profound antigen presentation impairment. The development of early-onset cancer underscores the broader oncogenic risk associated with chronic immune dysregulation in MHC class II deficiency.

Conclusion: Homozygous RFX5 mutations should be considered in patients with combined immunodeficiency and syndromic features. MHC class II expression testing remains critical in the diagnostic approach to such patients. Early genetic diagnosis is critical for anticipatory management and considering different therapeutic options.

https://doi.org/10.70962/LASID2025abstract.51
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.51

Atopy Beyond the Skin: CARMIL2 Deficiency

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Introduction: Primary atopic disorders (PADs) are a group of inborn errors of immunity characterized by severe eczema, elevated IgE, eosinophilia, and recurrent infections. Among them, CARMIL2 deficiency is a rare combined immunodeficiency with prominent skin manifestations and dysregulated T cell function.
Clinical Case: We present a case of a 47-year-old male with a lifelong history of refractory atopic dermatitis, dependent on high-dose systemic corticosteroids, leading to significant sequelae such as tooth loss and osteoporosis. He had recurrent bacterial, fungal, and viral infections, including pneumonia, otitis media with hearing loss, histoplasmosis, molluscum contagiosum, herpes zoster, and chronic skin and nail infections. Over time, he developed chronic diarrhea and was diagnosed with ALK-negative anaplastic large-cell T cell lymphoma (ALCL). Immunological evaluation revealed normal immunoglobulin levels with elevated IgE, eosinophilia, impaired vaccine responses, global lymphopenia, with reduced naive T cells, B-switched and memory impairment. Next-generation sequencing identified two heterozygous variants in CARMIL2 (one likely pathogenic, one of uncertain significance). The patient was put into immunoglobulin replacement and dupilumab, which initially improved his dermatitis. After that, he began chemotherapy (brentuximab, cyclophosphamide, doxorubicin, and corticosteroids) with initial clinical improvement. However, he relapsed with central nervous system involvement and died despite further treatment.
Discussion: This case illustrates the diagnostic challenge of adult-onset primary immunodeficiencies with predominant atopic features. CARMIL2 deficiency affects actin polymerization and T cell signaling, impairing immune regulation and barrier function. The temporal association between dupilumab use and lymphoma onset raises concern about biologic therapy in immune-dysregulated hosts. While ALCL has not been previously reported in CARMIL2 deficiency, this case suggests potential associations worth further investigation. Whether allogeneic hematopoietic stem cell transplantation should be considered in such cases remains an open question.

https://doi.org/10.70962/LASID2025abstract.52
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.52

Clinical Report of X-linked Agammaglobulinemia Patients in a Single Center in Argentina

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Background: X-linked agammaglobulinemia (XLA), caused by mutations in btk gene, is characterized by low or absent B cells and reduced levels of immunoglobulins. Immunoglobulin replacement therapy (IgRT) is its primary treatment that allows to reach adequate levels of IgG serum and reduce rates of invasive infection, improving life expectancy. However, patients continue to experience significant infectious and noninfectious complications.
Results: Retrospective analysis of clinical evolution in 13 XLA patients (pt). The median age at diagnosis was 2.05 years with a median follow-up of 10.8 years; 3 pt discontinued follow-up controls. All patients are receiving IgRT: 6 pt intravenous immunoglobulin (IVIG), 3 pt conventional subcutaneous immunoglobulin, and 1 pt receives facilitated subcutaneous immunoglobulin. All patients were able to reach adequate levels of IgG and reduce severe and invasive infections; however, they continue suffering from respiratory tract infections needing oral antibiotics. 1 pt had evidence of bronchiectasis and was hospitalized because of infection (acute respiratory disease due to SARS-CoV-2).

Despite receiving adequate treatment, patients have developed noninfectious complications. 6/10 pt present allergic rhinitis, needing specific treatment to avoid secondary infections. 1 pt presented in his evolution recurrent abdominal pain with nausea and weight loss. Colonoscopy showed moderately active chronic gastritis caused by *Helicobacter pylori*, chronic duodenitis (Marsh 1), and chronic colitis with intense activity. He developed inflammatory bowel disease and low IgG serum levels despite having adequate treatment. He started

with esomeprazole and metronidazole treatment for *Helicobacter pylori* and began gluten-free diet and mesalazine 3 g/day and high doses of IVIG (1g/k every 21 days), achieving very good recovery.

Discussion: XLA patients experience complications despite optimal therapy; therefore, they require close monitoring with particular attention for gastrointestinal manifestations. Current therapies for XLA patients reduce early mortality, but patients continue to experience complications that impact organ function.

https://doi.org/10.70962/LASID2025abstract.53
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.53

Heterozygous IRF2BP2 Variant Associated with Immune Dysregulation and Recurrent Infections

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Introduction: IRF2BP2 encodes interferon regulatory factor 2 binding protein 2, a transcriptional co-repressor involved in modulating multiple immune pathways and maintenance of immune tolerance. Heterozygous IRF2BP2 variants have been linked to immune dysregulation, autoimmunity, and susceptibility to infections.

Case Presentation: We evaluated a family in which the index case, an adult, presented a benign lesion in the floor of the cavernous sinus showing lymphocytosis. He also suffered recurrent respiratory infections, chronic active hepatitis, and febrile episodes without infectious triggers. Immunological workup: hypergammaglobulinemia with elevated IgG and IgA, normal IgM levels, and persistent lymphocytosis characterized by an expansion of double-negative T cells. His 55-year-old sister presents arthritis, sicca, and Raynaud with altered capiloroscopy and C3 consumption, atopy, and lymphoproliferation. Whole exome sequencing (WES) identified a heterozygous missense variant in IRF2BP2 (c.1502G>T, p.Ser501Ile), located within a conserved domain critical for its repressor function. The same variant was confirmed by Sanger sequencing in his symptomatic sister. Sanger sequencing is pending in another sister who has severe arthritis and his niece, with recurrent *Staphylococcus* infections and prominent lymphadenopathy, and other family members with autoimmunity. Type I interferon-stimulated gene (ISG) profiling showed an elevated interferon signature in the proband and his sister. These findings are consistent with a possible autosomal dominant inheritance pattern with full penetrance but variable expressivity.

Discussion: Functional impairment of IRF2BP2 likely disrupts immune homeostasis by altering the transcriptional repression of pro-inflammatory pathways and regulatory T cell function, contributing to the development of autoimmunity and recurrent infections. Lymphoproliferation, including the expansion of unconventional T cell subsets, supports the presence of immune dysregulation.

Conclusion: IRF2BP2 variants should be considered in patients with unexplained immune dysregulation, overlapping features of autoimmunity, lymphoproliferation, and recurrent infections. Genetic testing facilitates early diagnosis and supports targeted management strategies, including immunosuppressive therapy and family counseling.

https://doi.org/10.70962/LASID2025abstract.54
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.54

Digenic Heterozygosity for a Cis Double-Hit in RECQL4 and a FASLG p.Arg198Gln Variant in a Patient with Recurrent Infections, Hypogammaglobulinemia, and Primary Sclerosing Cholangitis

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Background: Pathogenic biallelic variants in RECQL4 underlie autosomal-recessive disorders such as Rothmund–Thomson, RAPADILINO, and Baller–Gerold syndromes. Heterozygous carriers are usually asymptomatic, but isolated reports suggest immune or malignancy phenotypes in some. Likewise, FASLG loss of function is classically recessive, yet heterozygous dominant-

negative effects have been reported in autoimmune lymphoproliferative syndrome (ALPS). Emerging evidence indicates that pathogenicity can arise from digenic heterozygosity, where variants in two genes that converge on related pathways together produce disease.

Case Presentation: We describe a patient who is heterozygous for two RECQL4 variants that lie on the same allele (cis configuration)—a rare missense change c.1568G>C (p.Ser523Thr) and a truncating frameshift c.1574_1578del (p.Cys525Serfs*11) predicted to undergo nonsense-mediated decay. In addition, the patient carries a heterozygous FASLG variant c.593G>A (p.Arg198Gln), classified as a variant of uncertain significance. Clinical features include childhood-onset recurrent sinopulmonary infections and two episodes of *Campylobacter* bacteremia; progressive hypogammaglobulinemia requiring immunoglobulin replacement; primary sclerosing cholangitis with portal hypertension, esophageal varices, and inflammatory colitis; marked splenomegaly and a prior diagnosis of non-Hodgkin lymphoma; and absence of poikiloderma, skeletal anomalies, or other classical RECQL4 dysmorphisms.

Discussion: The genotype represents digenic heterozygosity affecting two genes implicated in lymphocyte survival: RECQL4 haploinsufficiency may impair DNA-damage repair during lymphocyte proliferation, predisposing to immunodeficiency and cancer. FASLG p.Arg198Gln, located in the extracellular TNF-homology domain, could weaken Fas-FasL–mediated activation-induced cell death, a mechanism central to immune homeostasis. Although each variant alone may be insufficient for disease, their combined impact on apoptotic regulation and genome stability offers a plausible explanation for the complex phenotype—reminiscent of reports of FAS + CASP10 or PIK3CD + PIK3R1 digenic interactions.

Conclusion: This case broadens the spectrum of RECQL4- and FASLG-associated disorders by highlighting a putative digenic mechanism arising from heterozygous variants in both genes. Recognizing such interactions will refine variant interpretation, guide functional testing, and improve diagnostic accuracy in atypical immune-dysregulation phenotypes.

https://doi.org/10.70962/LASID2025abstract.55
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.55

Functional Consequences of IRF2BP2 Variants in Patients with Isolated Immune Dysregulation

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Introduction: IRF2BP2 was originally identified as a co-repressor of IRF2 in the JAK–STAT signaling pathway. Upon stimulation with type I or type II interferons (IFNs), STAT1 levels increase. STAT1 then forms either the ISGF3 complex (STAT1/STAT2/IRF9) or GAF (STAT1 homodimers), which translocate to the nucleus and bind ISRE or GAS sequences, respectively, to induce transcription of interferon-stimulated genes (ISGs). STAT1 also regulates IRF1 expression. IRF1 and IRF2 compete for the same ISRE regulatory elements but have opposing effects: IRF1 activates ISGs, while IRF2 represses them. Germline variants in IRF2BP2 have been linked to common variable immunodeficiency (CVID) and immune dysregulation.

Results: We functionally analyzed four novel heterozygous IRF2BP2 variants of uncertain significance, identified by whole exome sequencing in five patients presenting with isolated immune dysregulation, and one CVID patient with autoimmunity (P6, p.Glu253fs). P1 (p.Val7_Aladup) and P2 (p.Met192Ile) developed hemophagocytic lymphohistiocytosis. Inflammatory symptoms included skin and gastrointestinal involvement. P3, P4, and P5 (p.Ser501Ile) belong to the same family, all with arthritis and lymphoproliferation. To assess the functional impact of these variants, we examined IFN–JAK–STAT pathway activation in patient samples using droplet digital PCR. Our results revealed upregulation of STAT1 mRNA in all patients except P6. IRF1, a GAS-responsive ISG mainly induced by IFN-γ, was also elevated in most cases. Given IRF1's role in amplifying ISG expression via ISRE binding, we measured expression of ISGs linked to type I (MX1, ISG15, IFIT1, RSAD2) and type II IFN signatures (IRF1, IRF8, GBP1, ICAM1). P6, the only patient without inflammation, showed normal signatures. In contrast, 4/5 patients with inflammatory symptoms had elevated IFN-α signatures, and all patients had increased IFN-γ signatures.

Conclusion: Our data reveal consistent hyperactivation of the IFN–JAK–STAT1 axis in IRF2BP2-deficient patients associated with inflammation. This aligns with IRF2BP2 loss-of-function variants lacking suppression of STAT1–IRF1 activity, suggesting dysregulated type I/II IFN signaling. JAK inhibitors may offer an effective therapeutic strategy.

https://doi.org/10.70962/LASID2025abstract.56
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.56

Improving Diagnosis and Treatment in Inborn Errors of Immunity Patients After the Implementation of Systematized Interventions: A Chilean Single-Center Experience

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Introduction: Inborn errors of immunity (IEIs) are a heterogeneous group of primarily genetic disorders affecting the immune system, whose diagnosis can be challenging.
Objective: To describe the characteristics of a pediatric IEI cohort at a single tertiary center in Santiago, Chile, and to evaluate the impact of a set of systematized interventions (SIs) on diagnosis and management.
Methods: We analyzed patients with active follow-up for IEIs as of July 2025. Patients were grouped according to whether they were diagnosed before or after the implementation of the SIs (06/24): inclusion of an immunologist in daily clinical rounds; educational seminars on IEI for healthcare personnel; systematic review of medical records to identify suggestive clinical features; training of primary care centers for timely referral; use of the Jeffrey Modell Foundation (JMF) warning signs.
Results: Eleven patients were included. The mean age at diagnosis was 6.48 years (range: 0.19–15.44 years). Table 1 describes the characteristics of the cohort. After implementing the SIs, there was a tendency to reduce the time from first medical contact to diagnosis (18.61 vs. 0.02 months). Additionally, the overall time from first medical contact to treatment was shortened (22.03 vs. 1.71 months). One asymptomatic case was also identified. Compared to a similar period prior to the implementation of SIs (06/24 to 07/25 vs. 04/23 to 05/24), there was a significant increase in the number of diagnoses (6 vs. 1), including more family member screenings (3 vs. 0) and outpatient diagnoses (4 vs. 1).
Conclusion: This is the first report from our tertiary center in Chile on IEI. These disorders are rare and frequently underdiagnosed; the implementation of a simple set of SIs had a significant impact on improving diagnosis and treatment.

Table 1. **Demographic, genetic, and clinical information**

Patient	Family	Gender	Family history	Deceased relatives from IEI	Consanguinity	Diagnosis	Genetic variant	IUIS group	Initial manifestation	Age at Dx (years)	Outpatient Dx	FMC to Dx (months)	FMC to Tx (months)	IRT	Abx prophylaxis	Other Tx	Outcome
Before systematized interventions																	
P1	1	M	No	No	No	CD40L deficiency	*CD40LG* :c.598A>T; p.Arg200*	I	Infection and failure to thrive	3.07	No	0.03	0.20	Yes	Yes		Alive
P2	2	M	Yes	Yes	No	STAT3-HIES	*STAT3* :c.1144C>T; p.Arg382Trp	II	Infection and failure to thrive	6.25	No	74.63	74.70	No	Yes		Alive
P3	3	M	No	No	No	XLA	*BTK* :c.1558C>T; p.R520X	III	Infection	4.35	No	18.20	18.20	Yes	Yes		Alive
P4	4	M	No	No	No	XLA	*BTK* :c.894+2dup(splice site)	III	Infection and neutropenia	0.99	No	0.20	0.57	Yes	No		Alive
P5	5	F	Yes	Yes	No	HAE type 1	Not assessed	VIII	Angioedema	7.32	Yes	0.00	16.50	No	No	On-demand	Alive
After systematized interventions																	
P6	6	F	No	No	No	FHL2	*PRF1* :c.445G>A; p.Gly149Ser c.50del; p.Leu17Argfs*34	IV	HLH	0.19	No	0.00	0.00	No	Yes	CyA pre HSCT	Alive
P7	7	M	Yes	No	No	HAE type 2	Not assessed	VIII	Angioedema	15.44	Yes	0.00	3.57	No	No	On-demand	Alive
P8	4	M	Yes	No	No	XLA	*BTK* :c.894+2dup(splice site)	III	Asymptomatic	0.33	Yes	0.00	0.47	Yes	No		Alive

Table 1. **Demographic, genetic, and clinical information (*Continued*)**

Patient	Family	Gender	Family history	Deceased relatives from IEI	Consanguinity	Diagnosis	Genetic variant	IUIS group	Initial manifestation	Age at Dx (years)	Outpatient Dx	FMC to Dx (months)	FMC to Tx (months)	IRT	Abx prophylaxis	Other Tx	Outcome
P9	5	F	Yes	Yes	No	HAE type 1	Not assessed	VIII	Recurrent abdominal attacks	8.50	Yes	0.00	2.17	No	No	On-demand	Alive
P10	5	M	Yes	Yes	No	HAE type 1	Not assessed	VIII	Angioedema	14.48	Yes	0.00	2.17	No	No	On-demand	Alive
P11	8	F	Yes	Yes	No	SLE and SAD	In progress	Not classified yet	Infection	10.35	No	0.10	1.87	No	Yes	Steroids, Aza, HCQ	Alive

Abx: antibiotic; Aza: azathioprine; CyA: cyclosporine; Dx: diagnosis; F: female; FLH2: familial hemophagocytic lymphohistiocytosis type 2; FMC: first medical contact; HAE: hereditary angioedema; HCQ: hydroxychloroquine; HLH: hemophagocytic lymphohistiocytosis; HSCT: hematopoietic stem cell transplantation; IEI: inborn errors of immunity; IRT: immunoglobulin replacement therapy; IUIS: International Union of Immunological Societies; M: male; SAD: specific antibody deficiency; SLE: systemic lupus erythematosus; STAT3-HIES: STAT3 hyper-IgE syndrome; Tx: treatment; XLA: X-linked agammaglobulinemia.

https://doi.org/10.70962/LASID2025abstract.57
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.57

Recurrent Homozygous DOCK8 Microdeletion Suggests a Founder Mutation in Two Unrelated Kaingang Children

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Introduction: Indigenous Kaingang communities of southern Brazil display a high burden of recessive disorders attributable to long-standing demographic isolation and high rate of consanguinity. We describe the clinical, immunological, and molecular profile of two unrelated Kaingang children with autosomal-recessive DOCK8 deficiency, a rare autosomal-recessive combined immunodeficiency in the general population.
Methods: A retrospective case review extracted clinical data, laboratory results, and genetic analyses from medical records.
Results: Case 1: Male, 5 years and 4 months, experienced recurrent cutaneous and fungal respiratory infections, severe atopic dermatitis, hepatosplenic involvement, microcytic anemia, and marked eosinophilia. Total IgE reached 19,391 IU/mL; CD4 counts were intermittently low and the dihydrorhodamine assay was abnormal. A multigene panel revealed a homozygous 299-bp deletion at 9p24.3 (g.334 155_334 454del), resulting in the loss of at least exon 11 of the DOCK8 gene. Case 2: Female, 5 years old, presented at 2 months of age with widespread eczematous lesions, multiple food and drug allergies, hyper-IgE, and persistent eosinophilia. A homozygous 1.5-kb deletion at 9p24.3 (g.333421_334903del) was identified by whole genome sequencing, resulting in the exon 11 loss in DOCK8 gene. She underwent allogeneic hematopoietic stem cell transplantation from a heterozygous sibling donor, achieving full donor chimerism and marked dermatological improvement, although IgE and eosinophilia remained elevated. The two deletions overlap by more than 90% and were found in children from neighboring, geographically isolated villages, strongly indicating a single ancestral breakpoint and a potential founder effect for DOCK8 deficiency in the Kaingang population.
Conclusions: The recurrence of an almost identical homozygous DOCK8 microdeletion in two indigenous Kaingang children from unrelated families points to a likely founder mutation in this ethnicity and could guide targeted carrier screening, genetic counseling, and early intervention strategies in this population.

https://doi.org/10.70962/LASID2025abstract.58
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.58

Wiskott–Aldrich Syndrome: Clinical and Immunological Diagnosis Despite Negative Genetic Testing

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Introduction: X-linked thrombocytopenia (XLT) is a milder variant within the Wiskott–Aldrich syndrome (WAS) spectrum, an immunodeficiency characterized by thrombocytopenia with small platelets, eczema, and recurrent infections. Unlike classic WAS, XLT predominantly presents with hematologic symptoms and less immunological involvement. Diagnosis can be challenging, especially in early stages or when genetic tests are inconclusive.
Case Report: An 8-month-old male infant with a family history of a maternal uncle who died from an unspecified hematologic disease presented with bicytopenia at 2 months of age that did not improve despite iron supplementation and transfusions. Bone marrow aspirate revealed primary thrombocytopenia with suspected immune etiology. Steroid treatment was initiated, resulting in partial improvement. By 6 months, the patient developed eczema and diaper area dermatitis without severe infections. Laboratory studies showed low platelet volume, anemia, decreased IgM, and poor isohemagglutinin response. Prophylaxis was started and breastfeeding was discontinued. Whole exome sequencing revealed no pathogenic variants. Due to refractory thrombocytopenia, flow cytometry was performed, demonstrating decreased expression of WAS protein (WASp) in CD3+ T lymphocytes, supporting the diagnosis. The patient remains stable and is currently enrolled in a hematopoietic stem cell transplant protocol.
Discussion: Functional assays such as protein expression analysis are essential to establish diagnosis, even when exome sequencing is negative. Clinical and functional findings guide diagnosis, management, and prognosis.

https://doi.org/10.70962/LASID2025abstract.59
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.59

Chronicle of a Gene Foretold: A Family Case Report

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Introduction: Gata2 deficiency is an autosomal dominant inborn error of immunity due to mutations in this transcription factor involved in hematopoiesis. It has a variety of clinical symptoms ranging from recurrent infections to myeloid malignancy and immunodeficiency.
Clinical Case: The index case (IC) is the first daughter of non-consanguineous parents. Personal history: hypothyroidism, hysterectomy with right oophorectomy secondary to a uterine cancer, nephrectomy secondary to abscess, lower respiratory tract infections, chronic galactophoritis, and HPV conization. Family background: Her mother passed away from mediastinal cancer at the age of 50 years old, and two brothers died at the age of 29 and 36, one with systemic lupus erythematosus with warts and infections and the other with myelodysplastic syndrome (MDS). She also has a 24-year-old daughter who was transplanted due to MDS. The IC, at the age of 44, was referred to a regional hospital with febrile neutropenia. Multiple cultures were done, showing isolation of *Histoplasma capsulatum* in the bone marrow aspiration, and was referred for an immunology evaluation. Laboratory tests revealed leukopenia with normal immunoglobulin levels. Lymphocyte population: T, B, and natural killer lymphopenia, T lymphocyte subset with low naive T cells, and increased levels of central and effector memory in both profiles. With all her background, a whole exome sequence was performed, showing a c.351C>G pathogenic variant in GATA2 gene. She underwent an unrelated bone marrow transplant. The familiar segregation was

performed, showing 3 affected nephews, all of them with abnormal immunological evaluations. At the time of evaluation, one of them presented with warts and HPV conization. Months later, she developed an acute myeloid leukemia currently in treatment.
Discussion: In this report, we describe a familiar case of a GATA2 deficiency. This case highlights the importance of medical records, interdisciplinary working, molecular diagnosis, and familial segregation for diagnosis and treatment.

https://doi.org/10.70962/LASID2025abstract.60
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.60

Chronic Granulomatous Disease: A Case Series

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Introduction: Chronic granulomatous disease (CGD) presents with life-threatening infections caused by a hereditary defect in forming reactive oxygen. A retrospective case review conducted at the Instituto Nacional de Salud del Niño (INSN), Breña, over the last 10 years allows us to understand the demographic, laboratory, and clinical characteristics of affected patients within a Peruvian pediatric population.
Objective: To describe clinical manifestations and laboratory findings of eight children with CGD.
Results:

Table 1. **Demographic characteristics**

Patients	Sex	Symptom onset (months)	Age at diagnosis	Current age
P1	Male	6	2 years	-
P2	Male	2	6 months	-
P3	Male	5	12 months	-
P4	Male	2	4 years	-
P5	Female	11	11 years	19 years
P6	Male	4	5 months	-
P7	Male	8	2 years	2 years 5 months
P8	Male	1	3 months	6 months

Table 2. **Infectious agents and clinical manifestations**

Patients	Infectious agents	Viral serology	Clinical manifestations	Vital status	Treatment
P1	*Staphylococcus haemolyticus, Pseudomonas, Aspergillus*	Not detected	Skin lesion, granuloma, pneumonia	Deceased	
P2	*Serratia marcescens*	EBV IgM/IgG, CMV IgG	Pneumonia, abscesses, anemia	Deceased	
P3	*Salmonella sp.*	CMV IgG	Abscesses, diarrhea, fever, anemia	Deceased	
P4	*Pseudomonas, Klebsiella, Candida*	CMV IgG	Abscesses, diarrhea, fever, vomiting, pneumonia	Deceased	
P5	*Mycobacterium tuberculosis, Aspergillus*	EBV IgG	Pneumonia, abscesses	Alive	ATB+ATF+Cortocoid
P6	*E. coli*	CMV IgG, EBV IgG	Abscess, fever, diarrhea	Deceased	
P7	*Staphylococcus aureus*	CMV IgG	Fever, cervical and axillary lymphadenopathy	Alive	TMP/SMX
P8	No report	CMV IgM	Abscesses, pneumonia	Alive	TMP/SMX

ATB = antibiotics, ATF = antifungals, TMP/SMX = trimethoprim/sulfamethoxazole, CST= corticosteroid treatment.

Table 3. **Laboratory findings**

Patients	NBT[1]	DHR[2] SI[3]	TB-PCR	BCG-itis	Affected gene
P1	5	Not done	Not done	No	CYBB
P2	5	1	Not done	No	Not done
P3	Not done	2.4	Not done	No	Not done
P4	Not done	2	Not done	No	Not done
P5	Not done	1.5	Positive	No	NCF2
P6	Not done	1.2	Not done	No	Not done
P7	Not done	1.1	Negative	Yes	Not done
P8	Not done	0.9	Not done	Yes	Not done

[1]NBT: nitroblue tetrazolium.
[2]DHR: 123 Dihydrorhodamine,
[3]SI: stimulation index.

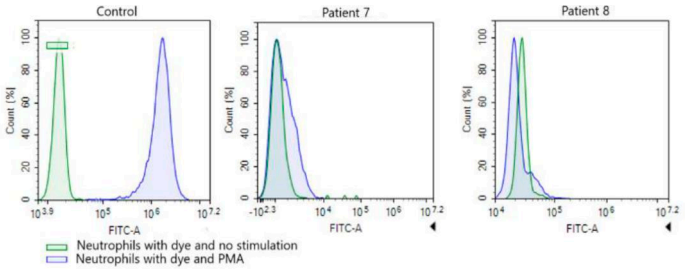

Figure 1. Dihydrorhodamine (DHR) test in patient 7, patient 8, and a healthy control.

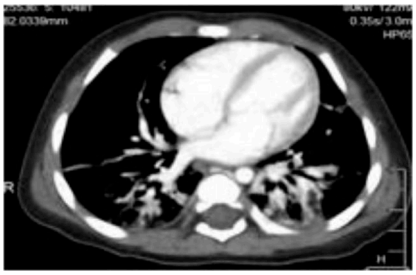

Figure 2. Chest CT of patient 7.

Discussion: The average age of diagnosis was 5 years. The mean diagnostic delay was 2 years and 5 months. *Staphylococcus aureus*, *Pseudomonas spp.*, *Aspergillus spp.*, and *Salmonella spp.* were the most frequently identified pathogens. The most common clinical manifestations were abscesses, pneumonia, and persistent fever. Less findings included skin involvement, lymphadenopathy, and gastrointestinal symptoms such as diarrhea and vomiting. Severe complications following Bacillus Calmette–Guérin vaccination occurred in two children.

https://doi.org/10.70962/LASID2025abstract.61
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.61

Use of Abatacept for Refractory Colitis in an APDS1 Patient: A Case Report

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PI3Kδ syndrome (APDS) manifests as immunodeficiency and immunodysregulation, including inflammatory bowel disease (IBD). We report a case of a 12-year-old female with APDS1 (heterozygous *PIK3CD* p.Glu1021Lys variant), with a familial background—mother with APDS1 diagnosis with adolescent-onset symptoms—and personal history of recurrent respiratory infections, bronchiectasis, failure to thrive, and developmental delay since age three. She exhibits a combined immunodeficiency with a HyperIgM phenotype, chronic EBV/CMV viremia, and autoimmune cytopenias. Persistent lymphoproliferation in cervical, axillary, and abdominal lymph nodes, along with chronic splenomegaly, is present. Intravenous immunoglobulin and cotrimoxazole prophylaxis is required.

At age 10, abdominal CT showed cecal wall thickening and increased size of intra-abdominal lymph nodes, though she remained asymptomatic. Malignancy and infections were ruled out, and sirolimus was initiated. At age 11, she developed chronic bloody diarrhea, intermittent fever, weight loss, elevated liver enzymes, and high inflammatory markers (erythrocyte sedimentation rate 75 mm/h, C-reactive protein 7 mg/L, calprotectin 287 ug). Endoscopy revealed upper gastrointestinal tract with edema, erythema, and mild colitis in the sigmoid and rectum. Biopsies: colitis with minimal chronic features. Meprednisone (1 mg/kg/day) led to clinical improvement, but symptoms recurred during tapering despite therapeutic sirolimus levels. After 6 months, a repeat endoscopy showed moderate colitis and severe rectal ulcerations. Biopsy revealed malakoplakia and marked T cell infiltration (images available). She was considered refractory to corticosteroids and sirolimus. Due to lack of access to leniolisib in Argentina and the complexities surrounding hematopoietic stem cell transplantation in APDS, abatacept was initiated as a targeted therapy for T cell–mediated dysregulation plus a long course of oral ciprofloxacin (1 g/daily). After three monthly IV doses (500 mg), she achieved complete clinical and laboratory remission—including autoimmune cytopenias, transaminitis, and inflammation markers. Treatment continued for six months; follow-up endoscopic results are pending but remain asymptomatic.

Immunodysregulation in APDS is a challenge and tailored therapies like abatacept could be considered as an alternative treatment.

https://doi.org/10.70962/LASID2025abstract.62
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.62

Tracking Secondary Immune Deficiencies in Pediatric BCP-ALL Patients: A Prospective Study from Single Center

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Introduction: Leukemias are the most common pediatric neoplastic diseases, with approximately 80% classified as B cell precursor acute lymphoblastic leukemia (BCP-ALL). Its treatment often leads to secondary immunodeficiency. The LLA-GATLA-ALLIC2022 protocol includes assessment of the impact of immunotherapy targeting CD20 in patients with CD20+ blast at day (D)15. We describe the immune status of pediatric BCP-ALL patients throughout the course of their treatment.
Methods: Prospective study of 35 BCP-ALL patients [1-14 years] were evaluated, intra-induction/pre-rituximab (D22), preconsolidation (D78), and intra-maintenance (D360). Patients (p) were classified into two groups based on their randomization to receive rituximab (G1) (n = 5) or not (G2) (n = 30). Serum immunoglobulin levels, complete blood count, and lymphocyte subset counts were evaluated. ANOVA test was performed.
Results: At diagnosis, none of the patients exhibited hypogammaglobulinemia of any isotype. During treatment, both groups experienced reduction in IgG and IgM levels; however, patients in G1 showed significantly lower IgG and IgM levels at D78 ($p < 0.001$). At D22, 24/35p (69%) developed neutropenia ($p < 0.001$); G2, 0.04% ($p < 0.001$). G2 maintained a significant reduction in B lymphocyte (mean: 2.7%, $p < 0.001$) at D360. Natural killer cell mean counts (%) (D78: G1: 3.4; G2: 7.9, D360: G1: 7.8; G2: 6.5) remained low throughout the first year of treatment compared to D22.
Conclusion: This study serves as a crucial starting point, providing guidance for a wider patient cohort and establishing follow-up protocols to assess the immune status during BCP-ALL treatment. This will allow earlier detection of secondary deficiencies and the implementation of prophylaxis and specific treatments.

https://doi.org/10.70962/LASID2025abstract.63
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.63

Understanding Haploinsufficiency of A20: From Clinical Presentation to Functional Tests

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Introduction: A20 is a protein encoded by TNFAIP3 gene and acts as a critical negative regulator of inflammation by inhibition of both nuclear factor k light-chain enhancer of activated B cells (NF-kB) and interferon (IFN) signaling pathways. Loss-of-function mutation in TNFAIP3 gene leads to haploinsufficiency of A20 (HA20). We report a patient with HA20: clinical manifestations, laboratory, genetic, and functional tests.
Clinical Presentation: Female patient presented in her first year of life with recurrent episodes of orogenital aphthosis and perianal ulcers, abdominal pain, and fever. Initially, frequency was biannual, but episodes increased, reaching 3-4 per month by the age of 3 years. Her mother and maternal grandmother had orogenital aphthosis since childhood.
Physical Examination: Cutaneous-mucous pallor, oral mucosa with 2 ulcers. Weight: 14.4 kg (p10-25). Height: 94 cm (p10). Cardio-pulmonary, abdominal, joint, and neurological examination and complementary tests showed no abnormalities.
Laboratories: Hypochromic microcytic anemia, elevated acute phase reactants and MRP8/14, polyclonal hypergammaglobulinemia. Negative ANA (antinuclear factor), ANCA (antineutrophil cytoplasmic antibody), RF (rheumatoid factor), and anti-thyroid antibodies. Negative stool calprotectin.
Genetic Analysis: Whole exome sequencing revealed a heterozygous stop codon variant in TNFAIP3 gene, NM_001270507.1:c.547C>T p.(Arg183*), classified as pathogenic (Infevers, ClinVar).
Functional Tests (under basal conditions)
Flow Cytometry: Inflammasome activity showed a marked increase in our patient (9%) vs. healthy control (0.6%).
Digital PCR: Interferon signature (MX1, ISG15, IFIT1, RSAD2) was significantly increased compared to normal controls (169 vs. 8.4, $p<0.0001$). NLRP3 and IL-18 RNA levels were significantly increased compared to normal controls (NLRP3: 302 vs. 54, IL-18: 117 vs. 19, $p<<0.0001$).
Conclusion: HA20 is a relatively new autoinflammatory disease with incomplete understanding of its pathogenesis. Heterogeneous characteristics make clinical diagnosis a challenge. Genetic and functional tests on inflammasome activity help us in understanding it. The ability of reporting clinical differences allows us to broaden the range of suspicion of disease.

https://doi.org/10.70962/LASID2025abstract.65
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.65

XLA in Adults With Severe Gastrointestinal Disease and Opportunistic Coinfection

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Introduction: X-linked agammaglobulinemia (XLA) is caused by mutations in the BTK gene, leading to an arrest in B cell maturation and profound hypogammaglobulinemia. Although immunoglobulin replacement therapy significantly improves survival, adults with XLA may develop complications beyond recurrent bacterial infections, including autoimmunity, bronchiectasis, gastrointestinal inflammation, and, more rarely, opportunistic infections. Despite therapeutic advances, recent data suggest a 5-year survival rate of 75%, with a median age at death of 21 years. Long-term follow-up of adult XLA patients remains critical to anticipate and manage noninfectious and atypical complications.
Aim: To report the case of a 40-year-old male with a history of XLA who developed severe diarrhea and cytomegalovirus (CMV) infection.
Case Presentation: A 40-year-old man with genetically confirmed XLA (BTK exon 14 deletion, CCTG1335) was referred in January 2025 due to severe, chronic diarrhea and progressive weight loss. His medical history included recurrent infections since childhood, idiopathic juvenile arthritis, and bronchiectasis diagnosed at age 10. He had been receiving regular IgG replacement since then. At presentation, he had lost 10 kg, with >10 bowel movements per day. Endoscopy and capsule studies revealed diffuse villous atrophy, jejunitis, and an ulcerated lesion. Upon admission, he developed anasarca and respiratory failure requiring mechanical ventilation. Bronchoalveolar lavage was positive for CMV by PCR. Ganciclovir was initiated. Despite treatment, the patient experienced multiple complications: catheter-related sepsis, hepatotoxicity, electrolyte imbalances, and persistent diarrhea. Immunoglobulin dosing was intensified to maintain protective levels. Repeat endoscopic biopsies confirmed disseminated CMV enterocolitis. The patient died 44 days after admission.
Conclusion: This case illustrates the potential severity of gastrointestinal and opportunistic complications in adult XLA patients. Chronic diarrhea warrants thorough investigation, including viral studies. CMV reactivation, although rare, can be life-threatening. Multidisciplinary management and vigilant long-term monitoring are crucial for improving outcomes in adults with XLA.

https://doi.org/10.70962/LASID2025abstract.66
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.66

Assessment of Immune Reconstitution After Hematopoietic Cell Transplantation in Pediatric Patients with Inborn Errors of Immunity

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Introduction: Hematopoietic cell transplantation (HCT) offers a curative treatment for many inborn errors of immunity. Immune reconstitution (IR) of different cellular subsets occurs at variable time points (days, D) and may differ in completeness and functional capacity. We aim to summarize laboratory findings in patients post-HCT.
Methods: Retrospective analysis of laboratory data collected of 21 post-HCT patients (p) diagnosed with Wiskott–Aldrich syndrome (7p), chronic granulomatous disease (8p), severe combined inmunodefiency (2p), CD40L (3p), and XIAP (1p) deficiency. We evaluated lymphocyte subsets, T/B cell compartments, immunoglobulin levels, and proliferative assay. Spearman correlation was performed.
Results: 21p (20 male), median age at HCT 3 years [0.5-11]. 1 died before D+90 post-HCT. By D+360, immune monitoring showed the following median values across lymphocyte subsets: CD3+CD4+ (23%), CD3+CD8+ (39%), CD16+CD56+ (8.5%), and CD19+ (19%) with a persisted inverted CD4/CD8 ratio. CD4+ lymphocytes (mm^3) gradually increased by D+180, D+360, D+540, and D+720 (median [mm^3]: 378, 618, 809, and 1,211). 13/17p achieved adequate T cell IR, defined as CD4+ naive T cell >20% (median: 35%) and good proliferative response to PHA after D+360. Furthermore, CD4+ naive count correlated inversely with HLA-DR expression (r:0,4926 p:0.022), suggesting reduced T cell activation as IR progressed. According to humoral reconstitution at different points (D+60, D+120, D+180, D+360, D+720), median levels of IgA (mg/dl) (8, 47, 76, 90, 161) and IgM (mg/dl) (33, 38, 73, 75, 94) display an increase over time. 5/13p showed a normal B cell subset after D+540.
Conclusion: As reported in the literature, T cell reconstitution occurs first, while B cell compartment reconstitution tends to take much longer. Standardizing immune monitoring post-HCT could improve the assessment of immune recovery and optimize patient management.

https://doi.org/10.70962/LASID2025abstract.67
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.67

Retrospective Genetic Molecular Diagnosis for Inborn Errors of Immunity in Patients with Autoimmunity: Experience from a Single Center

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Adults diagnosed with inborn errors of immunity (IEI) frequently lack a history of recurrent infections, but often present a myriad of autoimmune or inflammatory manifestations. Suspicion for an underlying IEI in patients with autoimmunity should be accounted for those patients with poly-autoimmunity (endocrinal or systemic or both), atypical course of disease, refractory immune cytopenias, and concurrent neoplasia or history of it. A recent work from Riviere et al. tested retrospectively a scoring system for diagnosis of IEI in a cohort of pediatric and adult patients. The most frequent warning sign among adults identified as high risk was bronchiectasia in the absence of cystic fibrosis, followed by systemic and endocrine autoimmune diseases, cytopenias, and more than 3 pneumonias.
Case Patients: Here, we present a case series of seven patients that were selected for molecular genetic testing. Among these patients, poly-autoimmunity, recalcitrant eczema, autoinflammatory clinical traits, immune cytopenias, atypical course and refractory disease were the main criteria for testing (Sanger, next-generation sequencing, whole exome sequencing).
Results: All seven patients presented IEI genetic variants of genes congruent with their disease profile. Patient characteristics and genetic results are depicted in Tables 1, 2. The most frequently diagnosed defect was common variable immune deficiency and immune dysregulation and autoinflammatory syndromes. Most of the variants found were not previously reported, of uncertain significance, and autosomal dominant in heritance. One patient had compound heterozygous likely pathogenic variants of AIRE gene, and one patient had a pathogenic variant of NOD2 gene. No patient had a history of recurrent infections.

Table 1. **Genetic testing of the seven patients.**

Patient	Gene	Variant (cDNA)	Effect	Zygocity	Variant type	Methodology	Reported	ACMG classification
1	*AIRE*	1. c.1095+6G>A	1. -	Compound heterozygous	Germinal	Sanger	1. Yes	1. LP
		2. c.834C>G	2. p.S278_R				2. No	2. VUS
2	1. ***CR2***	1. c763C>T	1. p.Arg255Trp	Heterozygous	Germinal	Targeted NGS	1. No	1. VUS
	2. ***JAK3***	2. c478G>T	2. Gli160cis				2. No	2. VUS
3	1. ***NOD2***	1. C.2104C>T	1. p.Arg702Trp	Heterozygous	Germinal	Targeted NGS	1. Yes	1. P
	2. *IL6ST*	2. c.371-3T>A	2. Intrónica	Heterozygous			2. No	2. VUS
	3. *MSN*	3. c.1304G>C	3. p.Arg435Pro	Heterozygous			3. No	3. VUS
	4. *PRKDC*	4. c9071C>T	4. p.Pro3024Leu	Heterozygous			4. No	4. VUS
4	***CASP10***	c.738C>A	p.Asp246Glu	Heterozygous	Germinal	Targeted NGS	No	VUS
5	***NCKAP1L***	c.2189C>T	p.Thr730Met	Heterozygous	Germinal	Targeted NGS	No	VUS
6	1. *ATP6AP1*	1. c1219GzA	1. p.Val407Ile	Heterozygous	Germinal	Targeted NGS	1. No	1. VUS
	2. *LYST*	2. c4313C>G	2. p.Ala1438Gly	Heterozygous	Germinal	Targeted NGS	2. No	2. VUS
	3. **TRFC**	3. c.1575C>G	3. p.Asp525Glu	Heterozygous	Germinal	Targeted NGS	3. No	3. VUS
	4. **IKZF3**	4. c.707C>T	4. p.Thr236Ile	Heterozygous	Germinal	Whole exome sequencing	4. No	4. VUS
7	***PIK3CD***	c.707C>T	p.Pro236Leu	Heterozygous	Germinal	Whole exome sequencing	No	VUS

In bold, the genes mainly related to the patient's phenotype. NGS: next-generation sequencing; LP: likely pathogenic; VUS: variant of uncertain significance; P: pathogenic.

Table 2. **Genetic, clinical, and phenotypical characteristics of the tested patients.**

Patient	Sex	Age	Gene	Zygocity	Heritance	Family affected	Clinical phenotype	T-B lymphocytes phenotype	IEI phenotype
1	F	60	*AIRE*	Compound heterozygous	AR	No	Polyendocrinopathy + autoimmune hepatitis + celiac disease + undifferentiated spondyloarthropathy.	CD4 - CD8 naive lymphopenia. B1a lymphopenia.	Atypical autoimmune polyglandular syndrome
2	F	62	1. ***CR2***	Heterozygous	AD	No	Lung granulomas. Bronchiectasia.	CD4 - CD8 naive lymphopenia. NK deficit.	CVID
			2. ***JAK3***	Heterozygous					
3	F	21	1. ***NOD2***	Heterozygous	AD	No	Recurrent fever. Lymphoproliferation. Rash.	Normal.	Yao Syndrome
			2. IL6ST	Heterozygous	AD				
			3. MSN	Heterozygous	LX				
			4. PRKDC	Heterozygous	AR				
4	M	30	***CASP10***	Heterozygous	AD	No	ALPS + psoriasis.	CD4 - CD8 naive lymphopenia. CD8 early effectors elevated. B naive -pre-switch memory lymphopenia.	ALPS

Table 2. **Genetic, clinical, and phenotypical characteristics of the tested patients. (*Continued*)**

Patient	Sex	Age	Gene	Zygocity	Heritance	Family affected	Clinical phenotype	T-B lymphocytes phenotype	IEI phenotype
5	F	65	***NCKAP1L***	Heterozygous	AR?	No	Autoimmune hepatitis + Sjögren's syndrome.	CD4 - CD8 naive lymphopenia. NK deficit. B lymphopenia: transitional, pre-post switch memory.	CVID
6	F	56	***IKZF3***	Heterozygous	AD	Yes (daughter)	Panuveitis + IgA nephropathy.	CD4 - CD8 naive lymphopenia. NK deficit. B lymphopenia: transitional.	AIOLOS haploinsufficiency
7	M	48	***PIK3CD***	Heterozygous	Variable	No	Behcet's disease (skin, oral, neurological). Anti-phospholipid syndrome atypical epilepsy.	Normal.	Activated PIK3CD syndrome

In bold, the genes mainly related to the patient's phenotype. F: female; M: male; AR: autosomal recessive; AD: autosomal dominant; ALPS: autoimmune lymphoproliferative syndrome; CVID: common variable immune deficiency.

Conclusion: Testing for IEI should be taken into account in patients with poly-autoimmunity, atypical manifestations, or refractory disease. A proper diagnosis of underlying IEI in this group could facilitate management and result in less morbidity for these patients.

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https://doi.org/10.70962/LASID2025abstract.68
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.68

MLPA+Ddpcr: Dual Molecular Strategy to Detect Copy Number Variations (CNVs) in Inborn Error of Immunity (IEI) Genes: A Case Study of the WAS Gene

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Introduction: IEIs are a heterogeneous group of primarily inherited genetic disorders characterized by impaired immune system function. While most genetic alterations are single nucleotide variants (SNVs), some cases are caused by larger genomic changes such as insertions or deletions that lead to copy number variations (CNVs). To identify potential large deletions in the WAS gene, we developed a molecular strategy combining a novel own design multiplex ligation-dependent probe amplification (MLPA) assay specific to WAS with a droplet digital PCR (ddPCR) assay.

Methods: Three patients with suspected Wiskott–Aldrich syndrome (WAS) were studied. Initial analysis involved Sanger sequencing. When a CNV was suspected, additional methodologies were incorporated: a WAS-specific MLPA test (covering exons 1, 2, 3, 4, 5, 6, and 8) designed according to the manufacturer's recommendations and a ddPCR assay targeting designed exons 7, 8, 9, and 12.

Results: None of the patients showed amplification of individual WAS exons by PCR. MLPA analysis revealed a complete absence of all exons in two patients, while the third patient showed absence of exon 8 by MLPA and absence of exons 7, 8, 9, and 12 by ddPCR. Both

methodologies allowed for the analysis of women carriers of this X-linked hereditary pathology, leading to the identification of a carrier.

Conclusions: These patients clearly demonstrate the importance of having more than one screening strategy for efficient diagnosis and family genetic counseling, mostly in cases where the clinical suspicion is very strong but conventional diagnostic strategies yield negative results. In many IEIs, bioinformatic algorithms in next-generation sequencing studies detect potential CNVs that need to be confirmed. Both MLPA and ddPCR are complementary techniques that would allow for a definitive diagnosis in these cases.

https://doi.org/10.70962/LASID2025abstract.69
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.69

A Tale of Two Hits: Compound Heterozygous NFATC2 Variants Unravel a Complex Primary Immunodeficiency with Severe Lung and Gastrointestinal Disease

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Background: Nuclear factor of activated T cells 2 (NFATC2), also known as NFAT1, is a critical calcium/calcineurin-dependent transcription factor essential for immune homeostasis. Human inborn errors of immunity (IEIs) due to biallelic *NFATC2* mutations are exceedingly rare, with only two distinct phenotypes previously described a syndromic disorder of joint contractures, osteochondromas, and B cell malignancy (JCOSL) from a homozygous C-terminal frameshift mutation, and a severe immunodeficiency with EBV-associated lymphoproliferation from a homozygous N-terminal deletion. The full spectrum of disease remains to be defined.

Case Presentation: We report a 12-year-old female with a severe, early-onset immunodeficiency characterized by recurrent sinopulmonary infections, bloody diarrhea, chronic lung disease, and profound failure to thrive (body mass index 12). Immunological workup revealed anemia and thrombocytosis, as well as pan-hypogammaglobulinemia, with reduced CD4+ and CD8+ T cells. Whole exome sequencing identified two novel, ultra-rare, highly conserved heterozygous missense variants in *NFATC2*, located in exons 3 and 8 (Gly408Arg/Arg646Gln).

Discussion: The clinical and immunological phenotype of our patient closely resembles the previously reported case with a homozygous N-terminal deletion, but contrasts sharply with the JCOSL phenotype. The variants in our patient are predicted to affect two critical functional domains: the N-terminal regulatory NFAT homology region (NHR) and the C-terminal DNA-binding REL homology region (RHR). The combined impact of these two mutations may result in a profound loss of NFATC2 function, disrupting T cell and B cell development and homeostasis, leading to a combined immunodeficiency. Chronic lung and gastrointestinal diseases are likely a consequence of both impaired pathogen clearance and underlying immune dysregulation. This case of compound heterozygous NFATC2 deficiency expands the genetic and clinical spectrum of a rare IEI, reinforcing the emerging genotype–phenotype correlation: variants affecting the N-terminal and DNA-binding domains result in severe immunodeficiency. It highlights the necessity of considering NFATC2 in the differential diagnosis of complex CVID-like presentations with multi-organ involvement.

All authors declare no potential conflicts of interest to disclose.

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https://doi.org/10.70962/LASID2025abstract.70
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.70

Late-Onset X-Linked Lymphoproliferative Disease Type 1 (XLP-1): A Mild Phenotype Possibly Explained by Somatic Reversion in SH2D1A

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Introduction: X-linked lymphoproliferative disease type 1 (XLP-1) is caused by pathogenic variants in the *SH2D1A* gene, which encodes the SLAM-associated protein (SAP). Patients develop hypo-gammaglobulinemia and are highly susceptibility to EBV infection. Somatic reversion of inherited variants may lead to mosaicism and milder clinical phenotypes.
Presentation of the Case: We report a 46-year-old male with a diagnosis of common variable immunodeficiency (CVID) at age 34, who presented with two episodes of meningococcal meningitis within 8 months, both requiring hospitalization. Since childhood, he had chronic sinusitis and recurrent pneumonia, several of which also required hospitalization. Notably, there was no clinical or serological evidence of previous Epstein–Barr virus (EBV) infection. At diagnosis, laboratory studies revealed hypogammaglobulinemia affecting all isotypes and a reduced memory B cell compartment genetic testing through whole exome sequencing identified a hemizygous pathogenic variant in *SH2D1A* (c.251T>C). Natural killer T cells were present (0.08%) but TCRVb11 and TCRVa24 expressed with a lower intensity compared to normal. SAP expression in CD3+T cells by flow cytometry revealed a bimodal pattern with 97% of cells negative and 3% showing a normal SAP expression. Cell sorting followed by Sanger sequencing demonstrated absence of the pathogenic variant in the SAP-positive population and presence of the variant in SAP-deficient cells, consistent with somatic reversion.
Conclusion: This case highlights an atypical, late-onset and relatively mild presentation of XLP-1, likely influenced by the presence of a small reverted T cell population. Although detected late in life, these reverting cells may have contributed to a less severe disease course.

https://doi.org/10.70962/LASID2025abstract.71
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.71

Central Nervous System (CNS) Manifestations in Chronic Granolomatous Disease (CGD): Single Pediatric Center Experience

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CNS involvement in CGD reflects a complex aspect of the disorder. We retrospectively reviewed 70 pediatric CGD patients (<18 years) diagnosed between 1987 and 2024 in our institutional database. Eight male patients (11.4%)—seven with X-linked CGD (*CYBB*) and one with autosomal recessive CGD (*NFC2*)—presented with CNS manifestations, identified through ICD-10 codes (G00–G09) with a documented follow-up at our center.

The median time from CGD diagnosis to CNS involvement was 3 years. Notably, in three patients, neurologic symptoms preceded CGD diagnosis by 1–5 years, and these patients had substantial residual oxidative burst activity on dihydrorhodamine testing.

In contrast, those who developed CNS manifestations after CGD diagnosis were already under antimicrobial prophylaxis and/or treatment for systemic or concurrent infections.

CNS presentations included status epilepticus (n = 3), lower limb spastic diplegia with paresthesia (n = 1), chronic progressive demyelinating disease (n = 2; siblings), and incidental asymptomatic neuroimaging findings (n = 2). MRI revealed intracranial abscess (n = 1), spinal/paravertebral lesions (n = 1), nodular inflammatory/infectious lesions (n = 4), and demyelinating processes (n = 2). Abnormal EEGs were observed in three patients. CSF microbiology analyses were uniformly negative. CNS biopsies (n = 5; 2 patients) identified *Aspergillus fumigatus* in one case. Additional fungal pathogens (*Scedosporium apiospermum* and *Aspergillus fumigatus*) were isolated from non-CNS tissues (n = 2) and unknown etiology remained in two others.

Antifungal therapy was administered in four patients, with voriconazole resistance reported in two; long-term posaconazole was the preferred alternative. Corticosteroids and granulocyte transfusions were used selectively. Clinical outcomes ranged from full recovery to persistent neurological deficits; no deaths related to CNS complications were observed.

CNS involvement in CGD, while uncommon, was linked to active systemic infections in 62.5% of cases—mostly fungal—and likely driven by a hyperinflammatory process in the remaining 37.5% (patients with residual oxidative burst activity). Early diagnosis and personalized multidisciplinary management are critical.

Limitations: Data affected by underreporting and transition to digital records after 2014.

https://doi.org/10.70962/LASID2025abstract.72
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.72

Health Care Utilization and Morbidity in Patients with Genetically Confirmed Primary Immune Regulatory Disorders

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Primary immune regulatory disorders (PIRDs) are inborn errors of immunity that result in a wide spectrum of immune dysregulation. PIRD can manifest as autoimmunity, hyperinflammation, lymphoproliferation, malignancy, and severe atopy. Genetic diagnosis in PIRD patients is usually translated to precision therapies which have the advantage of fewer global immunosuppressive effects and increased survival rates. The objective of this study was to describe and compare the clinical manifestations and healthcare resource utilization (HCRU) of patients with PIRD diagnosis.

This retrospective chart review assessed the burden of HCRU for PIRD patients followed at Texas Children's Hospital over a period of ten years. One-year pre- and post-diagnosis data were collected and compared for each patient with genetically confirmed PIRD. The data included clinical manifestations such as infectious and noninfectious manifestations (NIMs) of the disease and HCRU such as outpatient clinic and emergency care visits, inpatient admissions, procedures, imaging studies, medical technology use, and medication use.

A total of 25 patients met chart review criteria. The comparison of 1-year pre- versus 1-year post-PIRD diagnosis revealed some positive clinical and economic results. Clinically, an overall decrease in infections was observed in the post-diagnosis period, especially for sinopulmonary infections. Cytopenias, lymphoproliferation, and inflammatory end organ manifestations, all decreased, including a statically significant decrease in patients who received hematopoietic stem cell transplantation. Regarding HCRU, a significant decrease in emergency care visits was noted, while increments in medication use and outpatient clinic visits were observed.

This research confirms the improvement in clinical manifestations in patients with a genetically confirmed PIRD diagnosis. Furthermore, it also provides the first comprehensive assessment of HCRU in this population. Although there were no significant reductions in overall HCRU in the first 12 months post-diagnosis, the observed changes suggest improved patient care, potentially leading to better outcomes and reduced HCRU over time.

https://doi.org/10.70962/LASID2025abstract.73
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.73

Smoldering Inside: Clinical Presentation and Genetics of Autoinflammatory Disorders: Case Series of 15 Patients

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Introduction: Autoinflammatory diseases are inborn errors of immunity caused by dysregulation of the innate immune system. Despite increasing recognition of genetically defined disorders, reports from Mexico remain limited. We describe fifteen Mexican patients with monogenic autoinflammatory diseases, summarizing their clinical, genetic, and therapeutic features to expand phenotypic understanding.

Presentation: Among the fifteen patients, 66% were female, with a median symptom onset age of 2.5 years (range 0.2–16 years). According to the inflammatory pathways, patients were categorized as: inflammosomopathies (20%; *NLRP12*, *NLRC4*, *MVK*), type I interferonopathy (26.7%; *TREX1*, *TMEM173*, *PSMB8*, *POMP*), cell death–driven mechanism (26.7%; *TNFAIP3*,*RELA*, *RNF31*, *RIPK1*), and uncategorized monogenic autoinflamatory disease (26.6%; *NOD2* [two cases], *IL1RN*, *PLCG2*). Common clinical features included recurrent fever (20%), oral ulcers (20%), cutaneous involvement (60%), arthritis (26.7%), hemophagocytic lymphohistiocytosis (HLH) (20%), uveitis (20%), vasculitis (20%), hepatosplenomegaly (33%), lymphadenopathy (33%), central nervous system involvement (33%), and serositis (6.6%). Laboratory findings revealed anemia (66%), leukocytosis (60%), thrombocytosis (40%), autoantibody positivity (40%), dysgammaglobulinemia (46%), elevated erythrocyte sedimentation rate/PCR (73%), and hyperferritinemia (20%). Biologic or immunosuppressors included anti-CD20 (n = 3), anti-TNF (n = 5), IL-6 blockers (n = 4), JAK inhibitor (n = 1), colchicine (n = 5), conventional synthetic disease-modifying antirheumatic drugs (n = 14), and intravenous immunoglobulin (n = 10). At last follow-up, outcomes among living patients (n = 13) were remission in 30.8% (n = 4), minimal activity in 23% (n = 3), and moderate activity in 46% (n = 6). Two patients (13%) died.

Conclusion: This first large Mexican cohort from a single referral center highlights the clinical and genetic heterogeneity of monogenic autoinflammatory diseases. Cutaneous manifestations were the most frequent, followed by joint involvement and HLH. Universal genetic confirmation enabled targeted therapies; however, 69% of patients remain with minimal or moderate activity, reflecting challenges in early diagnosis and access to precision treatments, which are essential for optimal outcomes in these patients.

https://doi.org/10.70962/LASID2025abstract.74
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.74

Time to Think About Anti-Cytokine Autoantibodies

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Introduction: Recently, neutralizing autoantibodies against different cytokines have been found to explain susceptibility to infections. Because the clinical pictures mimic innate immune disorders (IIDs), they have been defined as phenocopies of IIDs. Autoantibodies against GM-CSF have recently been associated with disseminated cryptococcosis and alveolar proteinosis.

Clinical Case: The patient was a 17-year-old female with no family or personal history of disease. She presented with clinical symptoms for one year, characterized by fainting episodes, headaches, and vomiting. She underwent multiple medical evaluations, but no diagnostic conclusions were reached. Over time, the headache intensity increased and was associated with fever, asthenia, refusal of food, and subcutaneous lesions on the abdomen and chest that appeared to be lipomas. Ultimately, her condition was associated with mastitis, a solid nodule, and inflamed lymph nodes in the axillary regions. The biopsy revealed chronic granulomatous mastitis with Langhans giant cells and structures consistent with *Cryptococcus spp*. The cytochemical study of the cerebrospinal fluid showed hyperproteinorrhea and hypoglycorrhachia. The brain MRI revealed a lesion in the right basal ganglia related to cryptococcosis. Disseminated cryptococcosis was confirmed, and she completed six weeks of amphotericin B. It was suspended due to kidney damage and changed to fluconazole, which remains on to date. The immunological approach included a complete blood count, immunoglobulins, and lymphocyte subpopulations with normal values for her age. The autoimmunity approach and HIV test were negative. Antibodies against cytokines were requested, with identification of anti–GM-CSF autoantibodies.

Discussion: In all patients with disseminated cryptococcosis, we must look for immunological abnormalities. If no monogenic defects are found, we must look for autoantibodies against GM-CSF. In Mexico, we have implemented this search in the immunodeficiency laboratory. Patients may develop alveolar proteinosis, so they should be followed up by a pneumologist. Autoantibodies are compatible with autoimmunity, so treatment is immunosuppressive and immunomodulatory.

https://doi.org/10.70962/LASID2025abstract.75
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.75

Establishing the Brazilian National Center for Inborn Errors of Immunity and Immunedysregulation (CNE3i): A Multicenter Study

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Introduction: Inborn errors of immunity (IEIs) comprise a group of heterogeneous diseases with a strong genetic background and a clear clinical predisposition to recurrent infections, multiple autoimmune conditions, hyperinflammation, severe/recalcitrant allergies, and a predisposition to neoplasms. Over the past 10 years, advances in genetic sequencing have allowed the recognized number of IEIs to expand to 565 in the latest International Union of Immunological Societies classification [1]. Epidemiological data from USIDNET in the USA found that 6 in 10,000 individuals may have an IEI with a frequency similar to that of rare diseases [2]. However, data from the LASID registry in Brazil estimated the frequency at 1 in 100,000 individuals [3]. Therefore, there is a need to improve the recognition and diagnosis of IEIs in our country. Moreover, there are several peculiarities in the genetic background of the Brazilian population, where unique findings are highly probable.

Aim/Objective:

1. To establish a national multicenter study to conduct genetic sequencing for the diagnosis of IEIs in Brazil.
2. To extract robust clinical and epidemiological data on pediatric and adult IEIs in Brazil, in order to support public policies for this group of not-so-rare diseases.
3. To improve disease awareness and guarantee continual medical education by conducting periodic "active medical education" sessions with clinical case discussions and itinerant medical symposia in all five Brazilian macro regions.
4. To validate novel causative mutations using ex vivo and in vitro immunological functional assays for lymphocytes and phagocytes.
5. To guarantee adequate training for medical and other health professionals in the proper diagnosis and treatment of IEI patients and their families.

Methods: A novel and innovative Brazilian multicenter study is being conducted since November 2024 using the COBEII (National Network for Reference Centers for IEI) in Brazil. Clinical and laboratory data of patients with suspected IEIs of any age and gender have been included in an in-house platform for rare diseases registry (www.doencasraras.org). Genomic DNA was extracted from peripheral blood and sent to the central hub of the network located at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. The whole exome sequencing was performed using Illumina NovaSEQX and the analysis was done using the Emedgene Illumina.

Results: As shown in Figure 1, at least 53 reference centers from across Brazil joined the project so far. Most of these centers are located in the southeast, south, and northeast regions. As expected, there are no specialized centers in the northern and central regions of Brazil. Up to the last visit, 1,221 patient samples were sent to our center for genetic sequencing, and almost half of these have been entered into the online registry (n = 577). There were no gender discrepancies, with 43% (n = 253) of patients being male. The same pattern of patient frequency and geographical distribution was observed in Brazil (see Figure 1). Similar age distribution (< and > 16 years old) could be observed among the first individuals sequenced (n = 231; 41%). Sequencing and analysis started in July 2025 after the NovaSeq X was installed. At least 214 cases have already been sequenced, of which 50 have been analyzed. A definitive/conclusive diagnosis (genotype-related pathogenic/likely pathogenic variants) was found in 38% (n = 19) of cases, most of them were biallelic (recessive fashion), followed by X-linked, as observed in Figure 2. At least four (n = 4; 0,03%) of those analyzed died, all of them children under the age of 6. No novel mutation/gene was yet validated. Disease awareness and continuous medical education was conducted monthly by the CoBEII online meetings and by the Itinerant Symposium in Federal universities of Paraíba, Rio Grande do Norte, Santa Maria, Fronteira Sul, and São Carlos.

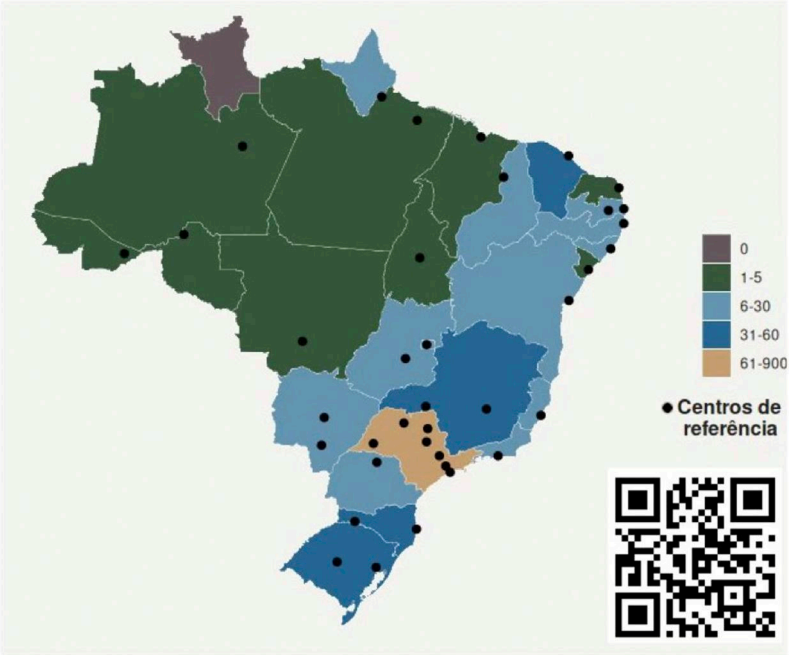

Figure 1. Geographical distribution of reference centers and patients with IEIs in Brazil. The black dots indicate the number of centers registered per state, as well as the frequency with which patients are sent for sequencing by state. The scale of individual distribution is on the right and only one state had more than 60 patients (orange: São Paulo). The QR code lists all the centers marked on the map.

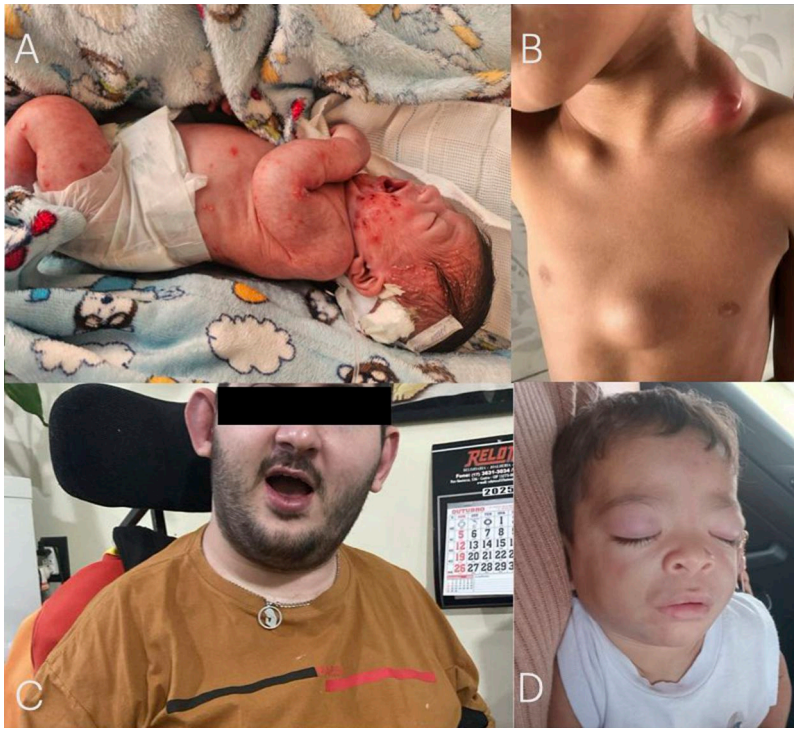

Figure 2. Remarkable diagnosis established by the initial analysis of the CNE3i project. A: Diffuse cutaneous pustulosis affecting a DIRA patient carrying the known homozygous c.213_227del; p.Asp72_Ile76del variant in the IL1RN gene. B: Diffuse and generalized paracoccidioidomycosis lymphadenopathy in a patient with a novel compound heterozygous variant in the *DOCK8* gene (c.3209A>G; p.Asn1070Ser and c.2554G>A; p.Val852Met). C: An adult patient with a 24-year history of unexplained fever and severe neurological impairment, who carries a homozygous variant in the *RNASEH2B* gene (c.529G>A; p.Ala177Thr). D: Erythematous eyelash nodules in a patient with CANDLE syndrome harboring a novel homozygous mutation affecting the *PSMB8* gene (c.280G>C; p.Ala94Pro).

Conclusions: This work reports the initial findings resulting from a FINEP-funded project to construct a national center for inborn errors of immunity and immunodysregulation (CNE3i) in Brazil, which is open to the public. Although preliminary, the findings already demonstrate the project's significant impact on all regions of Brazil, with a representative number of individuals from across the country undergoing sequencing. Furthermore, we confirm the genetic variability of the Brazilian population due to the novel mutations identified in Figure 2. Finally, we identified another deficiency of the natural antagonist of interleukin-1 antagonist (DIRA) patient harboring the same mutation previously described by our group, suggesting that this variant may have a founder effect for DIRA patients in Brazil. There is a need for continuous medical education and disease awareness for IEIs in Brazil.

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https://doi.org/10.70962/LASID2025abstract.76
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.76

ERBIN Variant in a Patient with Atopic Dermatitis, Hyper-IgE Phenotype, and Recurrent Respiratory Infections

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Introduction: ERBIN (ERBB2-interacting protein), encoded by ERBB2IP, is a scaffolding protein involved in TGF-β signaling, epithelial cell polarity, and immune regulation. Disruption of ERBIN function has been implicated in atopic disorders and may overlap with hyper-IgE syndromes (HIES) due to impaired regulation of Th17 and Th2 pathways.
Case Presentation: We report a patient with a clinical phenotype characterized by markedly elevated serum IgE levels (>5,000 IU/mL), recurrent pneumonias, recurrent bronchitis, atopic dermatitis since infancy, and allergic rhinitis. He also presented with a peculiar facial appearance but no skeletal abnormalities. The HIES score was 30, supporting a HIES-like phenotype. Family history is positive for moderate allergic rhinitis. Genetic testing through targeted next-generation sequencing revealed a heterozygous missense variant in ERBIN: c.4178T>C (p.Ile1393Thr), located in the leucine-rich repeat (LRR) domain, which is critical for protein–protein interactions. According to the American College of Medical Genetics and Genomics criteria, this variant is classified as a "variant of uncertain significance" supported by PM1 and PM2. Further functional studies are required to determine the pathogenicity of this variant.
Discussion: The identified ERBIN variant may alter its scaffolding function, leading to dysregulated TGF-β signaling, impaired Treg function, and enhanced Th2 responses. This immune imbalance likely contributes to severe atopy, impaired defense against respiratory pathogens, and susceptibility to infections. The reduction in Th17 cells may further compromise mucosal immunity, a feature overlapping with STAT3-HIES but without the full syndromic spectrum.
Conclusion: This case adds to the emerging role of ERBIN mutations in Hyper-IgE-like disorders, underscoring the need to consider ERBIN variants in patients with severe atopic dermatitis, elevated IgE, and recurrent infections. Genetic testing may facilitate accurate diagnosis and guide personalized treatment approaches.

https://doi.org/10.70962/LASID2025abstract.77
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.77

Loeys–Dietz Syndrome and Its Connection to Allergies and Hyper-IgE

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Introduction: Loeys–Dietz syndrome is a genetic disorder caused by mutations in TGFBR1 and TGFBR2, inherited in an autosomal dominant pattern, primarily affecting connective tissue. It is characterized by the development of aneurysms, cleft palate or bifid uvula, and long extremities. It has also been associated with a higher predisposition to allergic diseases and inflammatory gastrointestinal disorders.

Case Presentation: A 5-year-old male preschool patient. Notable history includes threatened miscarriage at the third month of gestation and lack of progress during delivery. He was diagnosed with Loeys–Dietz syndrome by the genetics department, with a pathogenic heterozygous variant in TGFBR2 c.1610G>C (p.Arg537Pro). He was referred to our clinic due to multiple episodes of sinusitis treated by ENT without full improvement. Laboratory tests showed blood eosinophils at 530 cells/μL, nasal mucus eosinophils at 40%, and total IgE of 322 IU/mL. Skin prick testing was positive for *Fraxinus*, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus*. Treatment was initiated with specific immunotherapy, antihistamines, and antileukotrienes. The patient experienced a 90% improvement with specific immunotherapy and has not had further infections.

Discussion: Loeys–Dietz syndrome is a genetic disorder affecting the TGF-β receptor. The literature reports an up to 30% higher prevalence of allergic diseases compared to general population, along with allergic gastrointestinal inflammation, including eosinophilic esophagitis and inflammatory bowel disease.

Conclusion: This is a condition in which certain symptoms may go unnoticed or undervalued; however, these patients can progress to asthma, exhibit hyper-IgE syndrome symptoms, and even develop inflammatory bowel disease in adulthood. Therefore, proper follow-up and timely treatment are essential.

https://doi.org/10.70962/LASID2025abstract.78
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.78

The Usefulness of Inborn Errors of Immunity IUIS Categories for Designing Targeted NGS Diagnostic Panels: Experience as an Argentinian Public Referral Center for Molecular Diagnosis

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Inborn errors of immunity (IEIs) are a heterogeneous group of disorders, genetically diverse but phenotypically overlapping. Over 500 IEI-related genes have been identified. Next generation sequencing (NGS) enables the simultaneous evaluation of a large number of genes in multiple patients in parallel.

Since 2017, in our setting, custom IEI panels have been useful mainly for patients displaying clinical phenotypes of immune dysregulation and autoinflammatory disorders. Our aim is to evaluate the performance of targeted NGS panels based on International Union of Immunological Societies (IUIS) gene categories by examining how many patients achieved a conclusive diagnosis.

A retrospective analysis was performed on 361 index cases submitted to four chronologically successive targeted NGS custom panels. The first panel included 124 IUIS genes, most of them related to autoimmune and immune dysregulation disease categories. The second panel contained 143 IUIS genes, including defects of innate immunity. The third and fourth, large panels covering 314 and 325 IUIS genes, respectively, included/comprised the majority of IUIS disease categories, with focus on autoinflammatory, immune dysregulation, and intrinsic immunity disease categories.

From a total of 361 samples studied, 264 were referred due to clinical suspicion of immune dysregulation, autoinflammatory disease, or defects in innate immunity. Twenty-three percent of them (61/264) achieved a confirmed or highly probable genetic etiology. According to the main IEI IUIS disease categories included in targeted panels, immune dysregulation represented 26% (32/123) of these diagnoses, autoinflammatory disorders 21% (18/85), and defects in innate immunity 19% (11/56). In the remaining patients studied, 42% (41/97) of them achieved a conclusive diagnosis in others IEI IUIS disease categories.

The NGS approach demonstrated the expected IEI diagnostic rate. The strategy of designing panels oriented toward IEI disease categories that present the greatest variability in clinical presentations with overlapping phenotypes proved to be effective regarding achievement of conclusive diagnoses in our cohort.

https://doi.org/10.70962/LASID2025abstract.79
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.79

Beyond Genetics: Immunological Approach to a Suspected Case of Autoimmune Lymphoproliferative Syndrome (ALPS)

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Introduction: Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of immune dysregulation caused by defects in the extrinsic apoptotic pathway. It is characterized by nonmalignant lymphoproliferation, autoimmune cytopenias, and expansion of αβ+ $CD4^-$ $CD8^-$ double-negative T cells (DNT). Current diagnostic criteria combine clinical features with laboratory markers such as DNT, vitamin B12, and soluble FAS ligand (sFASL) [1].
Case Presentation: An 8-year-old male was referred for persistent splenomegaly, multiple lymphadenopathies since infancy, and recurrent idiopathic thrombocytopenic purpura treated at age 5 with corticosteroids and intravenous immunoglobulin. Infectious, onco-hematologic, and storage diseases were ruled out.
Laboratory Findings: IgG: 1,214 mg/dL; IgA: 168 mg/dL; IgM: 84 mg/dL; serum protein electrophoresis: polyclonal hypergammaglobulinemia; IgG subclasses, anti-pneumococcal, and tetanus toxoid antibodies: within normal limits; vitamin B12: 1,687 pg/mL; sFASL: >1,000 pg/mL; DNT: 8.5% (128 cells/μL); next-generation sequencing panel of 513 genes for inborn errors of immunity (including FAS, FASLG, CASP10, CASP8, NRAS, PRKCD, CTLA4, LRBA): no pathogenic or likely pathogenic variants detected. Reopening of the genetic panel in process: NKT is yet to be performed; functional apoptosis assay is yet to be performed. The patient meets the two required criteria (lymphoproliferation and elevated DNT) and three of the secondary accessory criteria (autoimmune cytopenias, hypergammaglobulinemia, and elevated biomarkers), supporting a probable diagnosis of ALPS. Treatment with rapamycin and eltrombopag was initiated, with clinical stability achieved.
Discussion: Robust clinical and immunophenotypic evidence enabled timely initiation of immunomodulatory therapy in this case, having probable diagnosis without genetic confirmation. This case highlights the critical role of mid-complexity laboratories in the identification of IEIs and underscores the need to expand access to molecular and/or functional testing to achieve definitive diagnoses and ensure diagnostic and therapeutic equity.

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https://doi.org/10.70962/LASID2025abstract.80
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.80

Chronic Granulomatous Disease: A Case Series of Intrafamilial Phenotypic Variability with a New CYBB Variant

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Chronic granulomatous disease (CGD) is an inborn error of immunity that causes impaired phagocyte function, generating an inflammatory phenotype and recurrent fungal and bacterial infections. Although there is a classic CGD phenotype, a variability of symptoms is observed between cases. In this study, we report the case of a family with 8 children diagnosed with CGD who, despite sharing the same variant, present heterogeneous symptoms and severity.

P1 (index case) presented at two months of age with severe gastrointestinal infection requiring intensive care unit admission, followed by bronchiolitis and late-onset BCGitis. Immunological investigation revealed an abnormal dihydrorhodamine test and a CYBB mutation (c.T769A:p.C257S). This missense variant has not been previously reported in population databases such as gnomAD, ClinVar, or dbSNP. Family screening of 22 relatives identified 5 female carriers and 7 additional affected boys. Clinical features among the other CGD patients

ranged from recurrent respiratory and gastrointestinal infections (P2, P3), to Behçet-like symptoms (P4, P5), and atypical manifestations including allergic features, blepharitis, and skin desquamation (P6–P8). Notably, some cases were initially misdiagnosed or under-recognized due to milder or nonspecific symptoms.

With this study, we can learn more about CGD's phenotypic heterogeneity, emphasizing the importance of family genetic screening, even in less severe cases. What is crucial is to reduce diagnostic delay and prevent complications. Our findings reaffirm the need for attention among clinicians of the potential phenotypic diversity of CGD, even within the same family.

https://doi.org/10.70962/LASID2025abstract.81
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.81

Agammaglobulinemia Associated with a Mutation in the TCF3 Gene with Initial Autoimmune Manifestation

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Introduction: Agammaglobulinemia is an innate immune deficiency (IID) characterized by an alteration in B lymphocyte maturation due to genetic defects. One of the less common causes of this condition is a mutation in the TCF3 gene, which can be transmitted through autosomal dominant or recessive inheritance. This mutation affects the expression of transcription factors essential for B cell development, causing a decrease in peripheral blood and, consequently, severe hypogammaglobulinemia.
Case Report: An 8-year-old female patient with a history of juvenile idiopathic arthritis diagnosed at age 6 and a history of recurrent respiratory infections since the first year of life, including multiple episodes of pneumonia. In the immunological evaluation, immunoglobulin dosage revealed markedly decreased levels: IgG at 287 mg/dL, IgM <20 mg/dL, and IgA <10 mg/dL. Analysis of lymphocyte subpopulations showed an isolated decrease in B lymphocytes, representing only 1.3% of the total (68 cells/mm^3). Genetic testing by sequencing identified a pathogenic variant in the TCF3 gene. Given these findings, treatment with intravenous human immunoglobulin was initiated every three weeks, accompanied by antibiotic prophylaxis.
Discussion: The TCF3 gene mutation is an IEI of the antibody deficiency group, which is rare, with few cases reported worldwide. It is characterized by recurrent infections during childhood, agammaglobulinemia, growth failure, and in some cases is associated with neoplastic diseases. However, our patient presents with systemic joint disease as the initial presenting symptom accompanying recurrent infections. Due to its varied phenotypic expression, it requires multidisciplinary management for diagnosis and treatment.

https://doi.org/10.70962/LASID2025abstract.82
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.82

A Mild Pediatric Phenotype of PAMI/PAPA Syndrome Associated with PSTPIP1 Variant

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Pathogenic variants in *PSTPIP1* enhance pyrin inflammasome activation, leading to overproduction of interleukin-1 (IL-1). These variants are associated with autoinflammatory syndromes such as PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) and PAMI (PSTPIP1-associated myeloid-related proteinemia inflammatory) syndrome. We report a pediatric case presenting an oligosymptomatic and previously under-recognized phenotype.

The patient is the first child of a non-consanguineous couple. His father has a history of childhood-onset neutropenia and chronic treatment-refractory acne. At 7 months of age, the child developed a lesion at the Bacillus Calmette–Guérin (BCG) vaccination site, treated empirically with isoniazid despite lack of microbiological confirmation. Initial immunologic evaluations—including immunoglobulins, lymphocyte subsets, and dihydrorhodamine—were normal.

At age 6, he presented with transient synovitis, intermittent fever, recurrent adenitis, hepatosplenomegaly, and myalgia. After age 10, he developed reactivation of the BCG site (deltoid cellulitis), persistent hepatosplenomegaly, and bicytopenia (iron-refractory anemia and

neutropenia). Elevated acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate) were noted, while immunologic workup—including IL-12/IFN-γ receptor expression—was normal. Bone marrow aspirate showed no abnormalities.

Due to persistent inflammation, whole exome sequencing was performed at age 13, revealing a *PSTPIP1* variant (c.748G>A, autosomal dominant), previously associated with PAMI syndrome and classified as likely pathogenic. Markedly elevated MRP8/14 levels (>25,000 ng/mL) supported this diagnosis. Plasma zinc results are pending.

Currently, the patient experiences moderate myalgias (with normal CPK [creatine phosphokinase]) and mild persistent neutropenia. Functional assays assessing inflammasome activation and interferon signatures are underway to guide personalized treatment.

This case broadens the clinical spectrum of *PSTPIP1*-associated autoinflammatory diseases, suggesting that PAMI syndrome may manifest with mild or oligosymptomatic phenotypes in childhood. Early genetic and functional investigations may help avoid diagnostic delay and inform targeted therapy strategies.

https://doi.org/10.70962/LASID2025abstract.83
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.83

CARD11 Deficiency: Heterogeneity of Phenotypes Related to Autosomal Dominant Inheritance with Loss-of-Function Variant

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CARD11 is a component of the CBM complex, which plays a critical role in the antigen-dependent activation of B and T lymphocytes via the NF-κB. Mutations in CARD11 have been associated with three distinct inborn errors of immunity. One of these forms is caused by dominant-negative loss-of-function mutations, characterized by atopy, hyper-IgE, and hypogammaglobulinemia. However, clinical presentations could be heterogeneous, as reported in the literature. We describe the case of a female patient, born to non-consanguineous parents, who presented with early-onset severe atopic dermatitis occasionally associated with secondary bacterial skin infections beginning at two months of age. Laboratory evaluation revealed hyper-IgE syndrome and hypogammaglobulinemia, with reduced levels of IgM and IgG. Immunoglobulin replacement was initiated at 10 months of age. By this time, she had also been diagnosed with food allergy. Within one year, the patient underwent two procedures for the removal of disseminated molluscum contagiosum lesions, with one curettage involving more than 300 lesions. Despite no evidence of lymphopenia in blood count, immunophenotyping revealed mildly reduced levels of natural killer cells. Four months later, a primary immunodeficiency orientation tube (PIDOT) analysis identified lymphopenia in both naive and post-germinal center B cell, with or without rearrangement. Whole exome sequencing revealed a heterozygous loss-of-function variant in CARD11:c.C119A/p.A40D. This variant was classified as likely pathogenic following functional assay, in accordance with the American College of Medical Genetics and Genomics guidelines. Family segregation analysis showed that the patient's mother also carries the same variant. She presented with a milder phenotype, including psoriasis, skin allergic manifestations, and asthma particularly during childhood. This family case highlights the phenotypic variability associated with loss-of-function dominant-negative CARD11 mutations. While the proband exhibited a severe atopic and infectious phenotype requiring early intervention, her mother displayed only mild symptoms.

https://doi.org/10.70962/LASID2025abstract.84
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.84

Immunodeficiency and Autoimmunity: Immune Dysfunction in Chromosome 18q Deletion Syndrome – A Case Report

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Chromosome 18q deletion syndrome is characterized by multiple comorbidities, some of which are defined by immune dysfunction, which will encompass the scope of the case discussion presented. The patient is a 12-year-old male, an only child of non-consanguineous parents. His prenatal care was uneventful, and his mother had a second miscarriage. He was born at term by

cesarean section, weighing 3,530 g. At birth, he had a cleft lip and palate, congenital clubfoot, congenital heart disease, and global developmental delay. In his early years of life, he was frequently hospitalized for fevers of unknown origin and infections, with his first hospitalization at 3 months of age. At the age of 1 year and 5 months, a reduction in lymphocytes and immunoglobulins was observed: IgG 483.65 (<p3), IgM 33.43 (<p3), CD3 575 (<p10), CD4 386 (<p10), CD8 153 (<p10), followed by changes in thyroid hormones, indicating secondary hypothyroidism at 2 years and 5 months (thyroid-stimulating hormone 8.45 T4L 0.77). Since the diagnosis, he has been on monthly IV immunoglobulin replacement, prophylactic antibiotic therapy, and levothyroxine, showing clinical and laboratory improvement to date. Chromosome analysis of lymphocytes using the G-banding technique revealed 46 XY, der(18)t(8;18) (q24.1;q21) of paternal origin, which confers partial deletion of the long arm of chromosome 18 and partial duplication of the long arm of chromosome 8.

Chromosome 18q deletion sndrome associates the deletion of certain gene loci with the prevalence of immunodeficiency and autoimmunity. In patients with a distal 18q deletion (18q21–q23), as mentioned above, hypogammaglobulinemia, defects in B cell maturation, antibody production, lymphocyte survival, cytokine signaling, and regulatory T cell homeostasis are predominant. Consequently, there is a predisposition to immunodysfunction, leading to recurrent infections characteristic of immunodeficiency and autoimmune diseases, requiring appropriate therapeutic intervention and multidisciplinary monitoring.

https://doi.org/10.70962/LASID2025abstract.85
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.85

Severe Opportunistic Infections Without a Monogenic Defect: Clues to a Phenocopy?

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Background: Diagnosing phenocopies of inborn errors of immunity is challenging due to broad and nonspecific clinical presentations. Patients exhibit severe, recurrent, or opportunistic infections that mimic monogenic immune defects but lack identifiable genetic variants. Therefore, diagnosis may be delayed or missed altogether. Here, we describe an adult case of progressive immunodeficiency features without known monogenic cause, raising suspicion for an acquired etiology, including anti–interferon-gamma autoantibodies.

Case Presentation: A 31-year-old Brazilian male, HIV-negative, was first admitted with fatigue, weight loss, dyspnea, and fever. X-ray showed an important lung lesion, and pulmonary cryptococcosis with central nervous system dissemination was diagnosed. During hospitalization, the patient presented COVID-19, which evolved with multiple complications, namely, secondary sclerosing cholangitis, stroke, peripheral polyneuropathy, and renal failure requiring hemodialysis. He was hospitalized for 7 months and also developed herpes zoster and a sacral ulcer complicated with osteomyelitis (due to *K. pneumoniae*). Afterwards, he was periodically hospitalized to treat urinary and bronchopulmonary infections with IV antibiotics. Eight months after discharge, he presented hemoptysis and was diagnosed with bacilliferous pulmonary tuberculosis. Dihydrorhodamine (normal) and immunoglobulin testing (IgA 113; IgM 55; IgG 1,246; IgE 373) were performed. Immunophenotyping of peripheral blood: CD3 658 (83.7%); CD4 432 (54.9%); CD8 179 (22.8%); CD4-/CD8- 6%; lymph B: CD19 63 (8%); natural killer lymph [CD56+/CD3-]: 65 (8%). No family history of immune diseases was reported. Exome sequencing was negative for pathogenic variants that would justify phenotype.

Discussion: Given the patient's atypical infectious profile, absence of pathogenic variants on exome sequencing, and preserved basic immune parameters, a nongenetic immune dysregulation is suspected. We plan to investigate anti–IFN-γ autoantibodies, which could confirm a phenocopy of Mendelian susceptibility to mycobacterial disease. This case underscores the importance of considering phenocopies in the differential diagnosis of adult-onset infectious syndromes with no identifiable monogenic defect.

https://doi.org/10.70962/LASID2025abstract.86
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.86

Phenotype Compatible with Late-Onset, Nonclassical Combined Immunodeficiency (CDI)

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Introduction: Inborn errors of immunity (IEIs) with cytopenias and immunodysregulation can mimic hematological malignancies, making timely diagnosis difficult. The identification of mutations associated with inborn errors of immunity allows for clarification of their nature. **Case Presentation:** A 16-year-old female (Cajamarca, Peru) with a history of multiple early maternal deaths. Since the age of 13, she has presented with recurrent respiratory and gastrointestinal infections, with a partial response to antimicrobials. She presented with persistent fever, epistaxis, lymphadenopathy, polyserositis, hepatosplenomegaly, and chronic diarrhea. Blood tests showed persistent pancytopenia with marked lymphopenia, microcytosis, schistocytes, and dacryocytes in peripheral blood smears. Bone marrow aspirate and biopsy revealed mild dysplastic changes, without leukemic clonality; a second study ruled out myelodysplasia. Immune competence study showed severe hypogammaglobulinemia with vaccine failure (hepatitis B and pneumococcus).

CD3+ T (cells/µL)	CD4+ T (cells/µL)	CD8+ T (cells/µL)	CD19 (cells/µL)	NK (cells/µL)
779 (<p10)	429 (<p10)	208 (p<10)	10 (p<10)	109 (p<10)

Flow cytometry (PIDOT) showed profound B and T lymphopenia, with natural killer (NK) cells at the lower limit. Genetic testing using a panel of inborn errors of immunity (Invitae, 2025) identified four heterozygous variants of uncertain significance (VUS) in the genes RTEL1, POLD2, and TMEM173, involved in telomere maintenance, DNA repair, and type I interferon activation, respectively.

Gene	Variant
POLD2	c.1471G>A (p.Gly491Arg)
RTEL1	c.2299A>G (p.Ser767Gly)
TMEM173	c.228-3C>T (Intronic)
TMEM173	c.751G>A (p.Gly251Arg)

Discussion: The triad of B-T-NK lymphopenia, mild bone marrow dysplasia, and vaccine failure suggests combined immunodeficiency with hematopoietic compromise. Variants in POLD2 (DNA replication and repair) and TMEM173 (SAVI-like interferonopathy) could explain the cytopenia, inflammation, and polyserositis. Functional studies (polymerase deficiencies or repair defects, interferon score) and family genetic evaluation are required to confirm the diagnosis and to consider hematopoietic transplantation as a possible definitive treatment.

https://doi.org/10.70962/LASID2025abstract.87
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.87

WHIM Syndrome: Long-Term Evolution of an Adult Patient

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Introduction: WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis) is an inborn error of immunity, caused by a heterozygous gain-of-function mutation in the CXCR4 gene. Therapeutic options aim to overcome the main causes of mortality (infections and HPV-associated neoplasms). These are granulocyte colony-stimulating factors (G-CSF), antibiotic prophylaxis, IgG replacement therapy (IgGRT), bone marrow transplantation (BMT), and, lately, CXCR4-specific nanobodies and CXCR4 antagonists.

Presentation of the Case: A 30-year-old female patient presented during her childhood leukopenia, chronic neutropenia, recurrent infections, bronchiectasis, splenomegaly, and two bone marrow biopsies with myeloid hyperplasia. At age 14, she started IgGRT due to hypogammaglobulinemia. At age 20, warts were found on hands, knees, abdomen, and face. Direct sequencing of the CXCR4 gene reported a heterozygous p.Arg334STOP mutation. The patient evolved favorably maintaining treatment with G-CSF, antibiotic prophylaxis, and IgGRT and HPV vaccination. Three years ago, she abandoned treatment, presenting pneumonia, upper airway, and skin and soft tissue infections. Laboratories showed hypogammaglobulinemia, 296 neutrophils, and 846 lymphocytes. Clinically, there was no progression of skin warts, with stable splenomegaly and normal respiratory functional test. It was indicated to restart treatment.
Discussion: Treatments in WHIM syndrome aim to correct neutropenia and hypogammaglobulinemia, avoiding associated infections, including those due to HPV that could progress to neoplasia. The most commonly used are G-CSF, IgGRT, and antibiotic prophylaxis. The few reports of BMT show humoral immunity reconstitution and increase of peripheral white blood cells, low mortality, but limited experience in adult patients. CXCR4-specific nanobodies have limited clinical validation. CXCR4 antagonists decrease the frequency of infections and extension of warts; however, these are short-term studies involving small populations. Although our patient presented infections associated with treatment discontinuation, no significant organ involvement nor progression of wart lesions were observed. Under this scenario, therapeutic decisions, such as BMT or CXCR4 antagonists, are questionable given an adult, clinically stable patient.

https://doi.org/10.70962/LASID2025abstract.88
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.88

Haploidentical Stem Cell Transplantation for Severe Combined Immunodeficiency (SCID): Experience from Latin America

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Introduction: Severe combined immunodeficiencies (SCIDs) lead to early death from overwhelming infection, usually in the first year of life. Haploidentical transplantation should be considered when there are no matched related donors for its immediate donor availability and when any delays may lead to catastrophic results.
Method: Retrospective study including patients with SCID receiving their first hematopoietic cell transplantation (HCT) using a haploidentical donor in 6 Latin American transplant centers.
Results: At a median age of 9.3 months, 52 SCID patients were transplanted between 04/2011 and 06/2024. Bone marrow was the stem cell source in 86% and the father was the donor in 76% of all transplants. A total of 49 patients received a conditioning regimen, the majority being busulfan-based (81%). The 1-year and 2-year overall survival (OS) were 70% and 64.2%, respectively. At 100 days, cumulative incidence (CI) of acute graft versus host disease (GVHD) was 19.2% and, at 2 years, CI of chronic GVHD was 8.3%. The CI of CMV reactivation was 35.4% at a median of 25 days after transplant. Severe hepatic sinusoidal obstruction syndrome (SOS) was observed in one quarter of the cases (27%), all in the busulfan group. Twenty-one patients died, with 8 very early deaths (before day +28), seven due to infection and one due to SOS. In the conditioned group, there were 4 graft failures (1 primary and 3 secondary), 2 successfully rescued with a second procedure, and 2 deaths related to CMV infection. Mixed chimerism was frequent (46%) and led to an inability to stay off intravenous immunoglobulin (IGIV) after transplant in 30% of patients. One patient was later found to be FOXN1 mutated, currently expecting a thymus transplantation.
Conclusions: Haploidentical transplants are feasible and, considering the late diagnosis and active infection on admission, our OS was good. Earlier diagnosis through newborn screening and intensive infection prevention/treatment may allow for better outcomes in the future.

https://doi.org/10.70962/LASID2025abstract.89
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.89

NEMO Syndrome (EDA-ID): Possible First Reported Case in Peru and South America With a VUS in IKBKG

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Introduction: Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) is an X-linked inborn error of immunity caused by hypomorphic mutations in the *IKBKG* gene, disrupting NF-κB signaling. Its clinical presentation is heterogeneous and includes severe bacterial, mycobacterial, viral, and fungal infections, along with classic ectodermal features such as hypohidrosis, hypotrichosis, and hypodontia.
Case Presentation: We report a 1-year-4-month-old Peruvian male with recurrent severe infections since the first month of life, including oral candidiasis, complicated pneumonia, central nervous system tuberculous granuloma, sepsis, and cytomegalovirus viremia. Physical examination revealed facial dysmorphism, sparse hair, xerosis, hypohidrosis, and conical teeth. Immunological evaluation showed hypogammaglobulinemia (IgG 435 mg/dL) with normal IgA and IgM levels, and unremarkable T, B, and natural killer cell subsets. Monthly intravenous immunoglobulin therapy and antimicrobial prophylaxis were initiated. A primary immunodeficiency gene panel revealed only variants of uncertain significance (VUS), and exome sequencing failed to identify a candidate gene. Ultimately, targeted Sanger sequencing identified a VUS in *IKBKG* [c.522_527dup; p.R175_A176dup], located in a functionally critical region of the NEMO protein.
Discussion: The clinical phenotype and genetic findings support a presumptive diagnosis of EDA-ID. The localization of the VUS suggests a potential structural disruption, impairing IKK complex oligomerization and NF-κB activation, affecting both innate and adaptive immunity. This may represent the first clinically well-documented suspected case of EDA-ID in Peru and South America. The case underscores the importance of early clinical recognition and stepwise molecular diagnostics in immunodeficiencies and highlights the regional need for functional and familial studies to confirm the pathogenicity of *IKBKG* variants and improve diagnosis.

https://doi.org/10.70962/LASID2025abstract.90
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.90

APECED: JAK Inhibition in an Adult Case with Long-Term Follow-up

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Introduction: APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), also known as APS-1, is a rare monogenic autoimmune disease caused by loss-of-function mutations in the AIRE gene. This impairs central immune tolerance, leading to autoreactive T lymphocytes and autoantibodies against various organs. It typically presents with chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency, plus other diverse manifestations. Novel therapeutic strategies, such as Janus kinase (JAK) inhibitors, are crucial for improving clinical management.
Case Presentation: We present the case of a 37-year-old female patient with a molecularly confirmed diagnosis of APECED. Her comprehensive clinical history includes severe recurrent hypocalcemia due to hypoparathyroidism, adrenal insufficiency, universal alopecia areata, chronic mucocutaneous candidiasis (onicomycosis, oral candidiasis), multiple verrucae, chronic diarrhea, hypogonadism, dry eye with corneal erosions, dyslipidemia, renal lithiasis, bilateral cataracts, and an epileptic syndrome. Parental consanguinity was identified; her older brother, also diagnosed with APECED, passed away in his third decade of life from complications of his disease. Genetic analysis revealed a pathogenic variant, c.232T>C (p.W78R) in homozygosity in the AIRE gene, consistent with autosomal recessive inheritance. This variant is classified as pathogenic in ClinVar (ID. 189060) and Human Genome Mutation Database (CM012586) and has a population frequency (minor allele frequency: 0.000007970, gnomAD). Current treatment includes symptomatic and hormone replacement therapies. Ruxolitinib was initiated in May 2024. By April 2025, (approximately 11 months of treatment), the patient demonstrated significant improvement, including hair regrowth, resolution of plantar verruca, and partial improvement of onychodystrophy. This case is notable due to the patient's adult age, contrasting with the predominantly adolescent or young adult cases typically reported.
Discussion: This case highlights APECED's marked complexity and multisystemic nature. The favorable clinical response to ruxolitinib in multiple manifestations underscores the significant potential of targeted immunomodulatory therapies. These findings suggest JAK/STAT pathways are involved in APECED pathogenesis and that JAK inhibitors can improve patient quality of life.

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https://doi.org/10.70962/LASID2025abstract.91
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.91

Immune Cytopenia as the Initial Presentation of an X-Linked Lymphoproliferative Syndrome

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Introduction: Inborn errors of immunity (IEIs) can present atypically, including with autoimmune cytopenias or persistent viral infections. X-linked lymphoproliferative syndrome type 1 (XLP-1) is a rare primary immunodeficiency caused by mutations in the *SH2D1A* gene, characterized by hypogammaglobulinemia, Epstein–Barr virus (EBV) susceptibility, and risk of hemophagocytic lymphohistiocytosis (HLH).
Case Presentation: A previously healthy 3-year-old boy initially presented with immune thrombocytopenic purpura at 1 year and 11 months, with good response to dexamethasone and intravenous immunoglobulin. Months later, he developed signs of lymphoproliferation, including generalized lymphadenopathy and hepatosplenomegaly. Persistent hypogammaglobulinemia and EBV infection were subsequently documented. Lymphocyte subset analysis was within normal ranges and bone marrow aspiration showed no pathological infiltration. Genetic analysis revealed a pathogenic mutation in *SH2D1A*, confirming the diagnosis of XLP-1. The patient was started on immunoglobulin replacement therapy and antivirals, with hematopoietic stem cell transplantation under consideration as definitive treatment.
Discussion: This case highlights the need to suspect primary immunodeficiencies in pediatric patients with autoimmune cytopenias and recurrent viral infections. Early identification of XLP-1 enables targeted therapeutic interventions that significantly improve outcomes. The integration of clinical, immunological, and genetic findings was critical for diagnosis.

https://doi.org/10.70962/LASID2025abstract.92
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.92

Disseminated BCG Infection Revealing Mendelian Susceptibility to Mycobacterial Disease in an Infant with IFNGR1 Deficiency

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Introduction: Mendelian susceptibility to mycobacterial disease (MSMD) is a group of immune disorders causing increased risk of mycobacterial and other intracellular infections, with mutations in the interferon-γ receptor 1 (IFN-γR1) among the first described causes.
Case Report: A 6-month-old girl, second child of consanguineous parents from rural Mexico, had a sibling who died at 4 months from ganglionar tuberculosis and disseminated mycobacteriosis linked to a confirmed IFNGR1 mutation. She received BCG (vaccine stands for Bacillus Calmette–Guérin) at birth. At 4 months, she developed right axillary lymphadenopathy that partially improved; at 5 months, it recurred with inflammation, respiratory symptoms, pancytopenia, and an erythematous, scaly rash. A biopsy drained pus and cultured positive for mycobacteria; she was treated with a cephalosporin, metronidazole, and anti-tuberculous therapy. Referred to tertiary care for respiratory instability, she presented mild malnutrition, microcephaly, holosystolic murmur, ascites, hepatomegaly (4 cm), splenomegaly (7 cm), severe diaper dermatitis, and an axillary mass. Disseminated BCG disease was diagnosed; treatment continued with anti-tuberculous drugs, steroids, human immunoglobulin therapy, and prophylaxis with trimethoprim/sulfamethoxazole and fluconazole. Labs showed normocytic anemia, anisocytosis, thrombocytopenia, hypoalbuminemia, direct hyperbilirubinemia, and severe hypoglycemia. Ultrasound showed hepatosplenomegaly, portal hypertension, and bilateral cervical lymphadenopathy; bone marrow was normal. Gastric bacilloscopy, HIV, and viral PCR were negative except for *Acinetobacter baumannii* in a respiratory panel. She developed sepsis-related cholestasis, coagulopathy, factor XII deficiency, colitis, catheter-related infection, suspected fungal infection, and ventilator-associated pneumonia due to *A. baumannii*, treated with broad-spectrum antibiotics. Given the family history, IFNGR1 sequencing confirmed a pathogenic homozygous nonsense mutation c.672G>A (p.Trp224*); both parents were heterozygous carriers.

Discussion: In countries with routine BCG vaccination, recognizing possible inborn errors of immunity and assessing family history support early diagnosis and appropriate treatment.

https://doi.org/10.70962/LASID2025abstract.93
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.93

Tracking NK and Memory T Cell Dynamics in Children Affected by Multisystem Inflammatory Syndrome (MIS-C)

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Background: Multisystem inflammatory syndrome in children (MIS-C) is a severe condition that arises 4–6 weeks after SARS-CoV-2 exposure, marked by persistent fever, mucocutaneous symptoms, cardiac involvement, and shock. Natural killer (NK) cells are thought to contribute during the acute phase due to their antiviral and immunoregulatory roles, but their phenotype during recovery is not well defined. An expansion of TCR Vβ21.3+ T cells has been observed during acute MIS-C, though their long-term presence and significance remain unclear.
Methods: Peripheral blood mononuclear cells (PBMCs) were collected from 4 healthy pediatric controls, 4 febrile (non-COVID) controls, 4 children with acute COVID-19, 9 with acute MIS-C, 8 MIS-C convalescents (6–12 months), and 6 long-term MIS-C convalescents (4 years). TCR Vβ21.3 expression was analyzed using a T cell panel (CD3, CD4, CD8, CD27, CD45RA, TCR Vβ21.3). NK cell phenotype was assessed after co-culture with K562 cells using markers including CD56, CD3, CD16, CXCR6, Ki67, NKG2D, NKG2C, and CD158.
Results: NK cells from acute MIS-C patients showed decreased CD57, CD158, and CD107a, along with increased NKG2D expression. Clustering analysis revealed a unique NK cell population exclusive to acute MIS-C, defined by absent CD107a and elevated CXCR6 and Ki67. Most alterations resolved within 6–12 months, except CD158, which remained low even after 4 years. TCR Vβ21.3+ T cells persisted for up to a year but were undetectable at 4 years.
Conclusions: MIS-C triggers a transient NK phenotype marked by reduced cytotoxicity and increased activation, suggesting a hyper-activated or dysregulated immune profile. Persistent downregulation of the inhibitory receptor CD158 may indicate prolonged NK activation. TCR Vβ21.3+ T cells appear to be short lived. Further long-term studies with larger cohorts are needed to validate these findings.

https://doi.org/10.70962/LASID2025abstract.94
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.94

Unexpected High Frequency of *Pneumocystis jirovecii* Pneumonia at SCID Diagnosis

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Patients with severe combined immunodeficiency (SCID) have a predisposition to opportunistic infections, including *Pneumocystis jirovecii*. Previous reports based on traditional microscopy and culture estimate the prevalence of *Pneumocystis jirovecii* pneumonia (PJP) at diagnosis of SCID around 20%. Polymerase chain reaction (PCR) for the diagnosis of PJP in bronchoalveolar lavage (BAL) demonstrates high sensitivity when compared to traditional culture methods.

We present three cases of SCID who underwent routinely *Pneumocystis jirovecii* PCR at the time of SCID diagnosis in the past year, during which PCR testing for *Pneumocystis jirovecii* became routinely available at our institution. All patients underwent a chest computed

tomography (CT) at the time of diagnosis. Imaging findings included ground-glass opacities in two patients, consolidation in two patients, and atelectasis in two patients.

One patient had no respiratory symptoms, oxygen requirement, or clinical evidence of pulmonary involvement prior to the CT scan. However, imaging revealed ground-glass opacities and consolidation. During the BAL procedure, the patient experienced clinical deterioration, including a respiratory arrest, and required mechanical ventilation.

All three SCID patients tested positive for *Pneumocystis jirovecii* by PCR at the time of diagnosis. Each received empirical treatment with co-trimoxazole prior to the availability of PCR results. Only qualitative PCR was available, which may lead to some false-positive results. However, in the context of SCID patients with consistent clinical or radiological findings, infection was presumed.

With the advent of more sensitive and specific diagnostic tools such as PCR for *Pneumocystis jirovecii*, the true incidence of this infection at the time of SCID diagnosis may be higher than previously recognized, even among asymptomatic patients. We recommend routine PCR-based screening for *Pneumocystis jirovecii* in all newly diagnosed SCID patients, when available.

https://doi.org/10.70962/LASID2025abstract.95
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.95

Characterizing SCID in Bogota: A Single-Center Experience

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Severe combined immunodeficiency (SCID) is a group of inborn errors of immunity that severely impair the immune system and lead to high susceptibility to infections. We present the cases of nine patients with SCID diagnosed at a pediatric referral center in Bogotá.

Of the nine patients, seven (78%) were female and two (22%) were migrants. Consanguinity was reported in two cases, and one involved endogamy. The median age at diagnosis was 4 months and the median age at first infection was 2 months.

Bacterial infections were documented in five patients, mostly due to Gram-negative organisms. Seven patients (78%) had BCGitis, three progressed to BCGosis. IgA and IgM levels were decreased in seven patients; total IgE was <15 IU/mL in all. IgG levels were low in all but one patient, reflecting maternal antibodies.

Lymphoproliferative responses were severely decreased when tested. Seven cases were classified as "classical" SCID: five due to defects in IL2RG, IL7R, RAG1, RAG2, DCLRE1C, and ADA; two due to compound heterozygosity in RAG2 (one of whom presented with maternal T cell engraftment); and one secondary to a complete 22q11.2 deletion with athymia. There was one patient with leaky SCID secondary to ORAI1 mutations.

All patients received immunoglobulin replacement, trimethoprim/sulfamethoxazole, fluconazole, and four-drug therapy for BCG (Bacillus Calmette–Guerin)-related disease. Acyclovir and palivizumab prophylaxis were given to 56% of patients. Two patients died before hematopoietic stem cell transplantation (HSCT) due to severe infections and one patient with 22q11.2 deletion was not a HSCT candidate.

Colombia currently lacks a newborn screening program for SCID, leading to delayed diagnoses typically after severe infections during early infancy, frequently with organ involvement that negatively impacts survival. This case series highlights the clinical complexity and diagnostic challenges of SCID in a resource-limited setting, emphasizing the urgent need to guide public health policies for early detection and other strategies.

https://doi.org/10.70962/LASID2025abstract.96
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.96

Case of Autoinflammatory Syndrome with Mutation in NLRP1

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Introduction: Autoinflammatory syndromes are inherited disorders where the body's innate immune system becomes abnormally activated, leading to episodes of spontaneous inflammation and fever. These conditions are often characterized by recurrent fevers, rashes, joint pain, and inflammation in other organs.
Presentation of the Case: A 4-year-old male who has had recurrent periods of fever, abdominal pain, diarrhea, and arthralgia since the age of 2. Extensive microbiological investigations were negative. High-dose oral prednisone was started, leading to partial clinical improvement, because immunosuppression with methotrexate was started, with marked improvement. A genetic panel was performed, where a variant of uncertain significance was reported in the NLRP1 gene, variant c.392G>A. 6 months later, intestinal bleeding was added; mesalazine and enteral budesonide were added with improvement.
Discussion: Our case is relevant because although a variant of uncertain significance was reported, the clinical correlation with the reported mutation helped us provide early treatment, as the patient presented with fever, arthritis, abdominal pain, and intestinal bleeding.

https://doi.org/10.70962/LASID2025abstract.97
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.97

Immunophenotyping in Adult Patients with Common Variable Immunodeficiency

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Introduction: Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by low antibody levels. Immunophenotyping is crucial for classifying CVID patients and predicting severe complications by analyzing lymphocyte subsets.
Methods: Retrospective cohort of patients who fulfilled the 2019 European Society for Immunodeficiencies criteria for CVID and had performed a flow cytometry immunophenotype treated at a referral center in Buenos Aires.
Results: We analyzed 19 patients, of whom 10 were male and 9 female with a mean age of 51 years (20-66 years). The median follow-up was 12 years (6-35 years). Key findings included profoundly low CD19+ B cells (84.2%), decreased natural killer cells (68.4%), and inverted CD4/CD8 ratio (73.7%). T cell subpopulations showed a decrease in naive CD4+ T cells in 15 patients (78.9%); T helper (Th) profiles demonstrated skewing toward a Th1 profile in 12/13 patients (92.3%), accompanied by a decrease in Th2 and Th17 populations. Naive CD8+ T lymphocytes were decreased in 15/18 patients (83.3%) and increased in 3/18 (16.7%); effector memory cells were decreased in 2 (11.1%) and increased in 3 (16.7%). Terminal effector cells were decreased in 9 patients (50%) and increased in 9 patients (50%). Immune dysregulation (autoimmune cytopenias, granulomatous-lymphocytic interstitial lung disease, enteropathy) affected 52.6% of patients, 9/10 showed increased transitional B cells, 8/10 increased CD21low B cells, 8/10 a skewing to a Th1 profile, and 7/10 had an inverted CD4/CD8 ratio. 6/10 had decreased regulatory T cells (Tregs). Lymphoproliferation was present in 57.9%. Notably, 15.8% of the total cohort developed non-Hodgkin's lymphoma. 10/10 showed increased transitional B cells, 8/10 increased CD21low B cells, 9/9 presented a skewing to a Th1 profile, and 9/10 had an inverted CD4/CD8 ratio.
Conclusion: Immunophenotyping including T cell subsets may be useful to characterize CVID patients at risk of complex noninfectious complications.

https://doi.org/10.70962/LASID2025abstract.98
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.98

From Genetic Dysregulation to Targeted Therapy: Managing Autoimmunity in Down Syndrome with JAK Inhibitors

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Introduction: Chromosome 21 encodes multiple interferons and their receptors. Under normal conditions (disomy 21), interferon binding activates the kinases JAK1 and TYK2, leading to STAT1 phosphorylation and transcription of interferon-stimulated genes (ISGs). In trisomy 21, overexpression of these receptors results in dysregulated, chronic activation of this pathway, causing baseline inflammation, tissue damage, and increased susceptibility to autoimmunity.

Case Report: We present a 9-year-old male from Guanajuato, Mexico, with karyotype-confirmed trisomy 21. During infancy, he was diagnosed with patent ductus arteriosus and autoimmune thyroiditis, managed with levothyroxine. At age 2, he developed alopecia areata treated with topical steroids and minoxidil. One year later, he exhibited vitiligo vulgaris, partially responsive to topical tacrolimus and corticosteroids. Inflammatory bowel disease was ruled out despite chronic diarrhea. Immunological assessment revealed positive antinuclear antibodies (ANAs) and antiphospholipid profile, persistent lymphopenia affecting CD3+, CD4+, and CD19 populations, with preserved humoral response to polysaccharide antigens. Due to refractory autoimmune manifestations and evidence of chronic interferon–JAK/STAT pathway activation, treatment with ruxolitinib, a selective JAK1/2 inhibitor, was initiated, resulting in progressive clinical improvement and immunological stabilization.
Discussion: This case exemplifies the immune dysregulation in trisomy 21, where hyperactivation of interferon–JAK/STAT signaling contributes to a complex autoimmune phenotype. The coexistence of polyglandular autoimmunity, vitiligo, and autoantibodies reflects this dysregulation. Although increased type I interferon sensitivity in trisomy 21 is established, recent transcriptomic, proteomic, and functional studies have further elucidated its role in shaping the altered immune profile. The positive response to ruxolitinib underscores the potential of JAK inhibitors as targeted therapies for refractory autoimmunity in this population. Further studies are warranted to confirm their safety and efficacy in individuals with Down syndrome.

https://doi.org/10.70962/LASID2025abstract.99
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.99

22q11.2 Deletion Syndrome and Immune Dysregulation: A Case Report

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Introduction: The 22q11.2 deletion syndrome is a multisystemic genetic disorder characterized by a broad spectrum of clinical manifestations, including congenital heart defects, palatal anomalies, neurodevelopmental disorders, and immunodeficiencies. In rare cases, it may be associated with immune dysregulation, including autoimmunity and lymphoproliferation, which, combined with immunodeficiency, predispose patients to severe infections and poor response to treatment.
Case: We report a 4-year-old female with a history of surgical closure of a patent ductus arteriosus at 1 year, psychomotor developmental delay, and viral pneumonia requiring mechanical ventilation. At 2 years, she developed bicytopenia (hemoglobin 8.7 g/dL, platelets 6 × 10^3/μL), a positive direct Coombs test, and splenomegaly. Leukemia was excluded by bone marrow aspirate and molecular studies. Flow cytometry revealed marked reductions in $CD4^+$ naïve (76/μL), $CD8^+$ naïve (70/μL), and $TCR\gamma\delta^+$ $CD4^-CD8^-$ cells (8/μL). Immunological studies showed IgG 1,264 mg/dL, IgM 314 mg/dL, IgA 86 mg/dL, C3 73 mg/dL, and C4 11 mg/dL. Genetic testing identified a 22q11.2 deletion and a variant of uncertain significance in the TLR8 gene. She was started on prednisone and mycophenolate, achieving partial response. At 4 years, she was readmitted with pancytopenia (leukocytes 3.94 × 10^3/μL, hemoglobin 3.1 g/dL, platelets 47 × 10^3/μL) and septic shock secondary to bacterial pneumonia, requiring intensive care unit admission, broad-spectrum antibiotics, vasopressors, and intravenous immunoglobulin. Imaging revealed multiple cervical and peritoneal lymphadenopathies and hepatosplenomegaly. Additionally, positive antiplatelet antibodies were detected. Despite immunosuppressive therapy, she exhibited persistent cytopenias and incomplete hematologic response to date.
Discussion: This case illustrates a severe and atypical presentation of immune dysregulation in 22q11.2 deletion syndrome, manifesting as immunodeficiency, autoimmune cytopenias, and lymphoproliferation. The findings underscore the importance of early immunological and genetic evaluation in patients with refractory cytopenias and recurrent severe infections. Conventional immunosuppressive therapy may be insufficient, requiring tailored strategies in complex cases.

https://doi.org/10.70962/LASID2025abstract.100
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.100

From Prenatal Diagnosis to Transplant Indication: A Case Series on the Variable Immune Phenotypes of Cartilage-Hair Hypoplasia Syndrome

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Introduction: Cartilage-hair hypoplasia syndrome (CHHS) is a rare autosomal recessive metaphyseal chondrodysplasia caused by mutations in the RMRP gene (chromosome 9p13). It features short-limbed dwarfism, sparse hair, and variable immune dysfunction, ranging from selective T cell lymphopenia to combined immunodeficiency, often with autoimmune phenomena and increased susceptibility to severe infections. The immune phenotype varies from leaky SCID to late-onset cytopenias and persistent viral infections. Hematopoietic stem cell transplantation (HSCT) is the curative option, though multisystem involvement complicates management.

Case Series: Case 1: A prematurely born girl to non-consanguineous parents was hospitalized at 9 months with anemia and positive CMV IgM. During hospitalization, she developed pancytopenia with autoimmune hemolytic anemia confirmed by positive Coombs tests. Corticosteroids had limited effect. She had recurrent infections and hemolysis, requiring antibiotics, steroids, and immunoglobulin replacement. Persistent lymphopenia and refractory CMV viremia persisted despite ganciclovir. Immunophenotyping revealed total lymphocytes of 1,324/μL, with CD3 602/μL, CD4 190/μL (14 naïve cells [NC]), CD8 154/μL (3 NC), CD19 375/μL, and natural killer (NK) cells 104/μL. Genetic testing confirmed pathogenic RMRP variants (NR_003051.3:n.-24_-10dup / NR_003051.3)n.6C>T)). Currently, at 2 years old, CMV remains uncontrolled, and she awaits HSCT.

Case 2: Diagnosed prenatally with compound heterozygous RMRP variants (NR_003051.3:n.1_2insAGGACGTG / NR_003051.3:n.73A>G), newborn screening revealed very low T cell receptor excision circles (1), prompting early immunologic evaluation. Immunophenotyping showed moderate T cell lymphopenia (CD4: 607/μL, 265 NC) with preserved B and NK cells. She is asymptomatic on sulfamethoxazole–trimethoprim prophylaxis without infections. Both share phenotypic features: proportionate short stature, fine light-red hair, and metaphyseal dysplasia.

Discussion: Despite overlapping clinical features and immunologic dysfunction, the early diagnosis in case 2—prior to the onset of infections or hematologic complications—may lead to a more favorable clinical trajectory, although long-term follow-up remains essential. In contrast, case 1 already presents a clear indication for HSCT due to progressive immune failure and viral persistence.

https://doi.org/10.70962/LASID2025abstract.101
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.101

Immune Chaos in a Child with Takenouchi–Kosaki Syndrome: A Case of Dual Dysregulation and Multisystem Involvement

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Introduction: Takenouchi–Kosaki syndrome (TKS) is a rare multisystem disorder caused by a heterozygous mutation in the CDC42 gene, often presenting with immune dysregulation, developmental anomalies, and inflammatory features. We report a complex case of TKS manifesting with combined immunodeficiency and autoinflammatory symptoms.

Case Report: Brazilian female, born to non-consanguineous parents, presented at birth with multiple congenital anomalies, including a single umbilical artery, hypoplasia of the corpus callosum, and congenital heart disease. At 4 months of age, she was hospitalized due to a severe systemic infection and hemolytic anemia. Immunophenotyping revealed CD3 1,969 cells/μL, CD4 275 cells/μL (83 naïve), and CD8 1,500 cells/μL (144 naïve), with a markedly inverted CD4/CD8 ratio of 0.2.

During her hospitalization, she experienced recurrent infections, most notably a persistent cytomegalovirus (CMV) infection with high and refractory viral load. She also exhibited fever, diarrhea, and seizure episodes. At one year of age, hypogammaglobulinemia was confirmed (IgA 1 mg/dL, IgM 27.8 mg/dL, IgG 379 mg/dL), along with a pericardial effusion unresponsive to high-dose intravenous immunoglobulin (IVIG). Genetic analysis identified a heterozygous mutation in CDC42 (specific variant: c.242G>T;p.(Cys81Phe).

Now two years old, the patient is maintained on immunoglobulin replacement therapy and prophylactic antibiotics. Her CMV load remains controlled under valganciclovir therapy. For autoimmune cytopenias, she is being treated with sirolimus and erythropoietin, with partial hematologic improvement. She continues to experience systemic inflammatory flares resembling sepsis, and her chronic pericardial effusion is currently managed with colchicine.

Discussion: This case illustrates an early-onset, non-SCID (severe combined immunodeficiency) lymphopenia with pronounced autoinflammatory features, reflecting the dual immune dysfunction characteristic of TKS. The underlying CDC42 mutation leads to impaired lymphocyte development and antibody production, alongside constitutive NF-κB pathway activation, contributing to the inflammatory phenotype. Management remains complex and largely supportive; however, emerging data suggest that anti–IL-1 therapy may offer clinical benefit in patients with similar presentations.

https://doi.org/10.70962/LASID2025abstract.102
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.102

An Autoinflammatory Syndrome Caused by PSMB9 Deficiency: The Power of Functional Testing to Guide Therapy

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Introduction: Proteasome-associated autoinflammatory syndromes (PRAAS) are monogenic systemic autoinflammatory diseases (SAIDs) caused by proteasome mutations. PSMB9 deficiency is classified as an autoinflammatory disease in the IUIS2024. They show a strong type I interferon response, which can be modulated by JAK inhibitors.

Case: A 9-year-old girl, born to non-consanguineous parents, with no relevant family history. Healthy until age 8, when she developed fever, bicytopenia, hyperferritinemia (20,000 ng/mL), and bone marrow hemophagocytosis; diagnosed with partial hemophagocytic lymphohistiocytosis (HLH), which improved with corticosteroids. After tapering steroids, she had recurrent episodes of systemic hyperinflammation with fever, arthralgias, and shock, requiring ICU admission. Labs showed leukocytosis with neutrophilia, thrombocytosis, anemia, hyperfibrinogenemia, hyperferritinemia, elevated erythrocyte sedimentation rate and C-reactive protein, and high IL-6 (1,336 pg/mL). Immunological tests (CD3, CD4, CD8, CD19, and immunoglobulins) were normal. Symptoms were partially controlled with corticosteroids. She was refractory to cyclosporine after 6 months. No infection, autoimmunity, malignancy, or rheumatologic disease was found.

To investigate the disease mechanism, we analyzed the interferon (IFN) pathway in patient cells using droplet digital PCR. Our results showed overexpression of type I (MX1, ISG15, IFIT1, RSAD2) and type II (GBP1, IRF1, IRF8, ICAM1) IFN-inducible genes. IFN-α signature: 19.8 (cutoff: 8.4); IFN-γ signature: 14.6 (cutoff: 3.6). IFN-γ mRNA also elevated. Due to dysregulated type I/II IFN signaling, ruxolitinib (2.5 mg twice a day) was started, leading to clinical/lab improvement after 3 months. Subsequently, gene panel (371 genes) found novel variant of uncertain significance (VUS) heterozygous PSMB9 variant (c.88G>A, p.G30R).

Discussion: IFN pathway testing guided JAK inhibitor use in suspected monogenic SAID unresponsive to steroids with clinical improvement. Later genetic testing identified a VUS in the PSMB9 gene, which was reclassified to probably pathogenic through functional studies. Together, functional and genetic approaches led to the patient's definitive diagnosis.

https://doi.org/10.70962/LASID2025abstract.103
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.103

ORAI1: An Unusual Cause of Combined Immunodeficiency

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Introduction: Loss-of-function mutations in *ORAI1* cause a rare autosomal recessive disorder with an estimated prevalence of <1 in 1,000,000, characterized by multisystemic involvement secondary to impaired intracellular calcium influx.

Case Presentation: A 3-month-old female born to consanguineous parents, with a family history notable for a sister who died at 2 months of age from respiratory syncytial virus pneumonia and an unexplained fetal loss at 5 months of gestation. She was hospitalized due to respiratory failure. Physical examination revealed moderate protein-caloric malnutrition, anhidrosis, and global hypotonia. Cultures identified *Pseudomonas aeruginosa* in tracheal secretions; blood cultures grew *Candida tropicalis* and *Klebsiella pneumoniae*. Bronchoalveolar lavage revealed a positive PCR for *Pneumocystis jirovecii*. Immunological evaluation showed normal lymphocyte counts and age-appropriate immunoglobulin levels (IgG, IgA, IgM, and IgE). Lymphoproliferation assay with PHA demonstrated reduced proliferation percentage and division index. Genetic panel revealed a homozygous variant in *ORAI1* (c.365T>G, p.Leu122Arg). Treatment included

intravenous immunoglobulin every 21 days, antibiotic prophylaxis, and nocturnal noninvasive mechanical ventilation due to severe hypotonia. The patient subsequently underwent hematopoietic stem cell transplantation (HSCT) from a matched sibling donor.
Discussion: Calcium plays a pivotal role in regulating numerous metabolic processes, signaling pathways, and cellular functions. *ORAI1* deficiency severely disrupts calcium influx into cells, leading to multisystemic dysfunction. The condition is characterized by combined immunodeficiency, hypotonia, and ectodermal dysplasia with anhidrosis. HSCT can correct the immunological defect; however, it does not resolve extramedullary manifestations, necessitating long-term multidisciplinary follow-up for affected individuals.

https://doi.org/10.70962/LASID2025abstract.104
J. Hum. Immun. (2025) 1 (LASID2025): eLASID2025abstract.104

Myelodysplastic Syndrome and Hypogammaglobulinemia Associated with a *SAMD9L* Mutation and Monosomy 7: A Case Report

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Introduction: The *SAMD9L* gene regulates proteins involved in the cell cycle and DNA damage repair. Mutations in the SAMD9L protein have been associated with monosomy 7 in myelodysplastic syndrome, leukemia, ataxia-pancytopenia syndrome, and immunodeficiency.
Case Presentation: A 10-year-old female presented with anemia, neutropenia, and thrombocytopenia since 2 years and invasive infections (pneumonia) at 6 years. Her brother died at 18 months of age due to pancytopenia. Immunological assessment revealed hypogammaglobulinemia (IgG: 247 mg/dL), $CD20^+$ lymphopenia (73 cells/mm^3), decreased pre-switch memory B cells (2%), increased transitional B cells (12.5%), and reduced natural killer cells (24 cells/mm^3). Bone marrow biopsy showed myelodysplastic changes and cytogenetic analysis identified monosomy 7 in 8 metaphases (45,XX,-7), for a total of 20 metaphases analyzed. Whole exome sequencing (WES) identified a heterozygous variant in the *SAMD9L*: c.4469A>C (p.Lys1490Thr), classified as a variant of uncertain significance (VUS). Additionally, two heterozygous VUS were identified in the *TCN2* gene (c.940+delT and c.940+25delGCCCAACTTTTTGTGGAAGCAC), which were excluded due to normal vitamin B12, folic acid, and homocysteine levels. Sanger sequencing confirmed the presence of the *SAMD9L* variant in the patient's mother; father and brother tested negative. Immunoglobulin replacement therapy was initiated with good evolution and she remained asymptomatic. At 9 years, cytopenias had resolved. Serial bone marrow examinations showed persistent monosomy 7, although with a reduced number of metaphase abnormalities in cytogenetic analyses (two metaphases with 45,XX,-7). She is currently a candidate for hematopoietic stem cell transplantation (HSCT).
Discussion: Mutations in *SAMD9L* can present with variable clinical expressivity; therefore, evaluation of family members is recommended. Somatic inactivating mutations in the bone marrow have been reported; however, there is currently no consensus regarding the use of HSCT in patients with mild phenotypes or spontaneous reversion of monosomy 7. Long-term monitoring of bone marrow abnormalities is essential to guide therapeutic decision-making.