JHI Journal of Human Immunity

9th Scientific Meeting

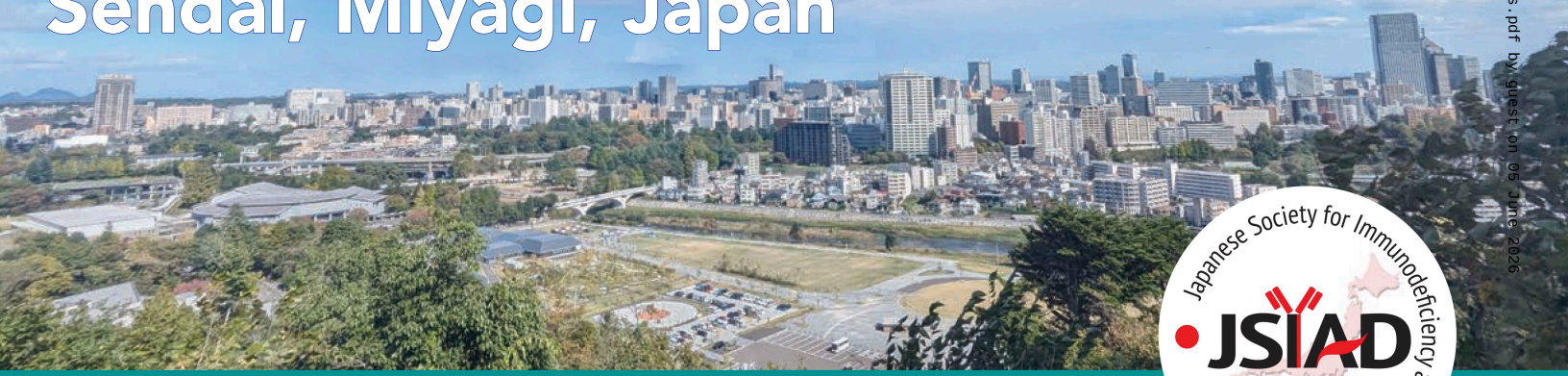
February 14–15, 2026

Sendai International Center
Exhibition Building

Chairperson
Yoji Sasahara
Department of Pediatrics,
Tohoku University
Graduate School of Medicine

Beyond the Boundaries of Immunology and Departments

Sendai, Miyagi, Japan



Japanese Society for Immunodeficiency and Autoinflammatory Diseases
JSIAD

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Meeting Abstracts

JHI Journal of Human Immunity

Abstracts from the 9th Scientific Meeting of the Japanese Society for Immunodeficiency and Autoinflammatory Diseases

February 14–15, 2026

Sendai, Miyagi, Japan

All abstracts were reviewed and approved by the
Japanese Society for Immunodeficiency and Autoinflammatory Diseases
Program Committee, which held full responsibility for the abstract selections

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JSIAD MEETING ABSTRACTS 2026

Plenary Lecture

https://doi.org/10.70962/JSIAD2026abstract.1
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.1

DOCK8 in Treg Cells Restrains Allergic Disease

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Dedicator of cytokinesis 8 (DOCK8)-deficient patients are highly susceptible to food allergy and have elevated serum mast cell (MC) tryptase levels. *Dock8*$^{-/-}$ mice have exaggerated IgE-mediated oral anaphylaxis, expansion of jejunal mucosal MCs (MMCs), and elevated serum levels of MMC-derived tryptase. This results in increased intestinal permeability, which promotes antigen absorption and thereby oral anaphylaxis. These events are driven by an intestinal cascade in which reduced interleukin (IL)-17 cytokines leads to dysbiosis, which drives IL-25 production. Increased IL-25 enhances T helper (Th)2 production of IL-4 that expands MMCs and exaggerates oral anaphylaxis. Failure of DOCK8-deficient T regulatory (Treg) cells to suppress intestinal IL-4 production and MC expansion leaves the exaggerated anaphylaxis unrestrained. Thus, multi-faceted coordination between the microbiome, mucosal T cells, and MCs to restrict oral anaphylaxis.

DOCK8-deficient patients have severe eczema, are highly colonized by *Staphylococcus aureus*, and have an intrinsically normal skin barrier. *Dock8*$^{-/-}$ mice develop exaggerated allergic skin inflammation following cutaneous exposure to *S. aureus* or antigen. Treg cells in their skin are diminished unstable and produce Th2 cytokines. Importantly, adoptive transfer of antigen-specific WT Treg cells dampens allergic skin inflammation in *Dock8*$^{-/-}$ mice and Treg-selective deletion of DOCK8 results in exaggerated allergic skin inflammation. Thus, Treg cell impairment underlies the severe eczema in DOCK8 deficiency.

The mechanism of impaired Treg cell dysfunction in DOCK8 deficiency involves impaired WASP-dependent F-actin polymerization, which is important for immune synapse formation, and Treg–target cell interaction, as well as WASP-independent impaired STAT5B tyrosine phosphorylation, which is important for induced Treg (iTreg) cell generation and stability. Disruption of both pathways in DOCK8 deficiency results in severely impaired Treg cell function and predisposition to allergic diseases.

Special Lecture

https://doi.org/10.70962/JSIAD2026abstract.2
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.2

Cell Biological Insights into the Pathogenesis of Autoinflammation

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Recent advances in microscopic observation technologies, typified by super-resolution microscopy, have enabled intracellular imaging with an xy-spatial resolution of less than 100 nm. By leveraging these technologies, it has become possible to precisely track the dynamics of innate immune-related molecules, including pattern recognition receptors. In this special lecture, focusing on our recent research achievements regarding STING (a molecule that induces type-I interferon and inflammatory responses in response to cytosolic double-stranded DNA), I will introduce how cell biological analyses, including microscopic observations, contribute to elucidating the mechanisms of autoinflammation. The importance of understanding intracellular trafficking pathways and organelle functions will be discussed.

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Congress Chairperson's Lecture

https://doi.org/10.70962/JSIAD2026abstract.3
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.3

From the Research of Wiskott-Aldrich Syndrome to the Pathogenesis of Related Pediatric Disorders

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Wiskott-Aldrich syndrome (WAS), an X-linked congenital immunodeficiency disorder, is characterized by three main symptoms—various immunodeficiencies, thrombocytopenia, and eczema—but it is also a diverse disease that can be complicated by autoimmune diseases, inflammatory bowel disease, and malignant tumors. Tohoku University Pediatrics has learned a lot from 13 WAS cases to date and has conducted basic research based on questions arising from clinical practice. We have also provided systemic management and hematopoietic stem cell transplant treatments in our own department, with long-term follow-up.

The *WAS* gene product, WASP, is expressed in all hematopoietic cell lineages, including hematopoietic stem cells. It functions as a signaling molecule regulating the actin cytoskeleton in the cell membrane and cytoplasm, as a transcription factor regulating various gene expressions in the cell nucleus, and as a tumor suppressor gene. Our department has previously conducted research on rapid diagnostic systems using flow cytometry, the function of WASP in T cells and natural killer (NK) cells, which are the mainstay of immunodeficiency, and the regulation of gene expression in the cell nucleus. While studying in the United States, I had the opportunity to study WASP-interacting protein (WIP), revealing that WIP forms a complex with the N-terminus of WASP and plays an essential role in stabilizing the WASP protein, the formation of an immunological synapse via the TCR receptor signaling pathway, the mechanism of WASP proteolysis, and the reason why missense variants in the N-terminus of WASP are common in clinical cases of WAS. The discovery of WIP deficiency, an autosomal recessive inheritance pattern, provided insights that clearly explained its molecular mechanism. Subsequently, WAS has expanded to three disease types, including ARPC1B deficiency (autosomal recessive inheritance pattern), which binds to the C-terminus of WASP.

Thrombocytopenia in WAS is characterized by both suppressed production and increased destruction. To apply our WAS research platform to clarify the pathogenesis of related pediatric diseases, we collected cases of congenital thrombocytopenia, which is important for differentiating it from immune thrombocytopenia (ITP), from across Japan for genetic analysis. We reported various genetic variants and novel congenital thrombocytopenia cases. Because autoimmune diseases in patients with WAS are primarily characterized by abnormalities in the innate immune system and abnormal B cell differentiation, our department has reported cases in which rituximab was effective as an antibody therapy in situations where steroid use is difficult. Inflammatory bowel disease (IBD), associated with bloody stools as the first symptom in infancy with WAS, is primarily caused by abnormalities in regulatory T cells and the IL-10 signaling pathway. Hoping to find a solution for cases of very early-onset inflammatory bowel disease (VEO-IBD) that are difficult to treat, we began genetic analysis by collecting domestic cases. In recent years, domestic collaborative research has accumulated knowledge about IL-10 signaling abnormalities and other conditions. WAS is a disease that is prone to be complicated with malignant tumors such as malignant lymphoma in older children, and we have clarified its characteristics, such as decreased tumor immune surveillance function by T/NK cells, and additional genetic abnormalities in the tumor.

The concept of so-called X-linked thrombocytopenia (XLT) is disappearing from the analysis of long-term prognosis of cases. I would like to summarize the research themes that spontaneously emerged from the clinical perspective of WAS and the research results that have been applied to the clinical practice of pediatric diseases, transcending the boundaries of immunodeficiency disorders and other medical fields, and discuss future challenges.

Finally, I would like to express my deepest gratitude to the senior professors who have guided me along the way, my co-researchers, the colleagues and graduate students who have worked with me in this research, and everyone in this society for their guidance and cooperation.

Educational Lectures

https://doi.org/10.70962/JSIAD2026abstract.4
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.4

Genetic Testing in Inborn Errors of Immunity: Implications for Diagnosis and Research

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Advances in genomic analysis technologies have expanded the application of genetic testing in the diagnosis of rare diseases. Although genome analyses can identify nucleotide sequence variations, in Japan only licensed physicians are authorized to integrate these findings with clinical data and render diagnostic judgments. Commercial laboratories may provide analytical results but are not permitted to offer diagnostic interpretations.

Accurate diagnosis requires comprehensive expertise in gene structure analysis, human genetics, and disease-specific pathophysiology. However, genetic testing provides information primarily at the molecular level, and establishing causal relationships between genetic variants and clinical phenotypes remains challenging.

In this lecture, I will first outline the status and technical limitations of genetic testing and discuss the principles for interpreting standard genetic testing reports. I will then introduce currently available approaches for correlating structural genetic variants with clinical phenotypic manifestations.

In immunodeficiency disorders, including those with autoinflammatory features, genetic testing alone often fails to yield definitive diagnostic conclusions. These conditions involve complex and dynamic immune networks, which limit the utility of genetic testing as a standalone diagnostic tool. Consequently, definitive diagnosis frequently requires not only validated clinical laboratory assays but also complementary insights derived from research-based investigations.

Integration of routine clinical testing with emerging research findings is essential for improving diagnostic accuracy. This lecture aims to provide a framework for understanding the appropriate use and limitations of genetic testing, thereby contributing to more accurate and definitive diagnoses of immunodeficiency disorders.

https://doi.org/10.70962/JSIAD2026abstract.5
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.5

Diagnosis of Autoinflammatory Diseases

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In recent years, the proportion of infectious diseases and malignant tumors in cases of fever of unknown origin has decreased, while noninfectious inflammatory diseases and undiagnosed diseases have increased. Autoinflammatory diseases are included in noninfectious inflammatory diseases and undiagnosed diseases and are considered the fourth most common cause of fever of unknown origin, after infectious diseases, malignant tumors, and collagen diseases. When encountering a case of fever of unknown origin, the three major causes—infectious diseases, malignant tumors, and collagen diseases—should be checked. If these are ruled out, autoinflammatory diseases should also be considered in the differential diagnosis. Because the clinical symptoms of autoinflammatory diseases often include fever, joint pain, muscle pain, chest pain, abdominal pain, and skin rash, differentiating them from collagen diseases and related disorders, which have similar clinical symptoms, can be extremely difficult.

When there are characteristic clinical symptoms in periodic fevers, or when there is a family history of fever of unknown origin or a history of fever of unknown origin, autoinflammatory diseases should be considered, but the characteristic clinical presentation should be examined in detail. Furthermore, the presence or absence of disease gene mutations is important for diagnosis. Clinical symptoms differ for each disease, but fever is common. The pattern of fever can also help in infer the disease. In typical familial Mediterranean fever (FMF), the fever subsides within 3 days, but in TNF receptor-associated periodic syndromes (TRAPS), it often lasts for more than 3 days. However, this is not always the case in atypical FMF, and diagnosis is difficult based solely on the duration of fever. Diagnosis must be made in conjunction with other clinical symptoms.

Currently, many genetic tests for autoinflammatory diseases are covered by insurance in Japan. Diagnosing autoinflammatory diseases requires a combination of genetic testing and clinical symptoms.

Symposium

https://doi.org/10.70962/JSIAD2026abstract.6
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.6

Inborn Errors of Immunity and Endocrine Disorders

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Inborn errors of immunity (IEI) represent a rapidly expanding group of disorders characterized not only by susceptibility to infection but also by profound immune dysregulation affecting multiple organs. Among these manifestations, autoimmune endocrine diseases provide one of the most visible clinical consequences of failed immune tolerance. In many patients, endocrine abnormalities constitute an early and sometimes defining clue to an underlying IEI. The reported prevalence of endocrine involvement among IEI varies across cohorts but is estimated to range from approximately 5% to nearly 30%.

The association between immune dysfunction and endocrine disease has been recognized for nearly a century. Early descriptions of chronic mucocutaneous candidiasis accompanied by endocrine failure ultimately led to the concept of autoimmune polyendocrine syndromes. Identification of the *AIRE* gene subsequently established the molecular basis of autoimmune polyendocrine syndrome type 1 (APS-1), highlighting the central role of immune tolerance in endocrine homeostasis. Advances in human genetics have since revealed that many IEI affecting immune regulatory pathways frequently present with endocrine autoimmunity. Disorders characterized by regulatory T cell dysfunction—collectively termed Tregopathies—including IPEX syndrome, CTLA-4 haploinsufficiency, and LRBA deficiency, show particularly strong associations with endocrine diseases such as early-onset type 1 diabetes and autoimmune thyroiditis. In addition, dysregulation of key immune signaling pathways, including NF-κB signaling (e.g., A20 haploinsufficiency) and interferon signaling (e.g., STAT1 gain-of-function), further broadens the spectrum of IEI presenting with endocrine pathology. Despite their diverse genetic origins, emerging evidence suggests that many of these disorders may converge on shared immune effector mechanisms, particularly interferon-γ–dominant inflammatory responses contributing to organ-specific autoimmune damage in endocrine tissues.

Collectively, these observations highlight endocrine autoimmunity as a key clinical interface between immunology and endocrinology. Recognition of endocrine manifestations as potential indicators of IEI may facilitate earlier diagnosis and enable the application of emerging immunologically targeted therapies. Ultimately, these observations suggest that diverse IEI may converge on shared immune effector pathways contributing to endocrine autoimmunity, highlighting endocrine disease as a window into immune tolerance breakdown.

https://doi.org/10.70962/JSIAD2026abstract.7
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.7

Neurological Manifestations of Inborn Errors of Immunity

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Inborn errors of immunity (IEI) are increasingly recognized not only as disorders of infection susceptibility but also as systemic diseases with diverse manifestations across multiple organs. The central nervous system (CNS) is a major site of involvement, and neurological manifestations in IEI may arise through a variety of mechanisms, including infection, autoinflammation, immune dysregulation, vasculopathy, and lymphoproliferative disease.

Among infection-related complications, bacterial meningitis associated with MYD88 or IRAK4 deficiency represents a classic example. In autoinflammatory disorders, including NLRP3-associated disease, a broad spectrum of CNS inflammation has been described, such as

aseptic meningitis and white matter lesions. In ADA2 deficiency, vasculopathy-related cerebral infarction is a characteristic neurological manifestation.

Familial hemophagocytic lymphohistiocytosis (FHL) provides another important example of CNS involvement in IEI. Neurological manifestations in FHL3 have long been recognized. More recently, patients with FHL2 carrying PRF1 missense variants have been reported to develop slowly progressive CNS lesions during adolescence or adulthood, in some cases preceding the onset of hemophagocytic lymphohistiocytosis (HLH). In addition, several patients showing pontine punctate and curvilinear contrast enhancement characteristic of CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) have been found to carry a hypomorphic variant in one UNC13D allele, without necessarily developing overt HLH. These observations suggest a potentially novel phenotype linking partial impairment of lymphocyte cytotoxicity to CNS-restricted inflammation.

In this seminar, I will review the neurological spectrum of IEI as a manifestation of systemic immune dysfunction and highlight recent advances that are reshaping our understanding of CNS pathology in these disorders.

https://doi.org/10.70962/JSIAD2026abstract.8
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.8

Inborn Errors of Immunity and Very Early-Onset Inflammatory Bowel Disease (VEO-IBD): Advances in Diagnosis and Research Based on Monogenic Disorders

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Inborn errors of immunity (IEI) are systemic disorders that can affect multiple organs, with gastrointestinal manifestations often representing the initial presentation and serving as a critical clue for early diagnosis. In this lecture, I will provide an overview of the relationship between IEI and gastrointestinal diseases, with a particular focus on very early-onset inflammatory bowel disease (VEO-IBD) and monogenic IBD.

VEO-IBD is defined as IBD with onset before 6 years of age, and its incidence has been increasing worldwide, including in both Western and Asian populations. Among these patients, especially those with infantile onset, a substantial proportion is attributed to monogenic IBD caused by single-gene defects involving approximately 75–80 genes. These conditions often exhibit distinct clinical phenotypes and treatment responses compared to conventional ulcerative colitis and Crohn's disease. Clinically, they are characterized by severe enterocolitis, refractory perianal disease, early onset, recurrent infections, and autoimmune manifestations, all of which should prompt strong suspicion of an underlying genetic disorder.

In this lecture, I will present representative cases of monogenic IBD with severe enterocolitis, including endoscopic findings, inflammatory features, and clinical courses achieving remission following hematopoietic stem cell transplantation (HSCT), accompanied by illustrative images. I will also discuss the clinical aspects of intestinal inflammation in IEI.

Furthermore, I will outline current diagnostic strategies, ranging from targeted gene panels for IEI and monogenic IBD to comprehensive approaches such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), highlighting practical considerations in clinical settings. Finally, I will introduce recent advances in research, including multi-omics approaches such as epigenetic analysis, microbiome profiling, and single-cell and spatial transcriptomics. Drawing on my research experience in Germany, I will discuss future perspectives for elucidating the molecular pathogenesis of monogenic IBD.

https://doi.org/10.70962/JSIAD2026abstract.9
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.9

Skin Diseases Due to Inborn Errors of Immunity

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Inborn errors of immunity (IEI) include various primary immunodeficiency disorders and hereditary autoinflammatory diseases, many of which present with skin symptoms. "Ten signs to suspect primary immunodeficiency" include skin infections such as

cellulitis, subcutaneous abscesses, persistent cutaneous mycoses, and severe, widespread verrucae. However, atopic dermatitis-like dermatitis is also common, as seen in hyper-IgE syndrome, Wiskott-Aldrich syndrome, and Netherton syndrome due to skin barrier disruption. On the other hand, hereditary autoinflammatory diseases present with characteristic skin lesions depending on the disease, ranging from erysipelas-like erythema in familial Mediterranean fever to urticarial erythema in cryopyrin-associated periodic fever syndromes, lichenoid papules in Blau syndrome, pyoderma gangrenosum in pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, lipoatrophy in Nakajo-Nishimura syndrome, and chilblain-like rashes in Aicardi-Goutières syndrome.

In this lecture, I will provide an overview of skin eruptions that characterize each disease and that serve suspicion and clues for diagnosis of the diseases.

https://doi.org/10.70962/JSIAD2026abstract.10
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.10

Inborn Errors of Immunity Manifesting as Refractory Allergic Diseases

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Allergic diseases have long been considered multifactorial disorders arising from the complex interplay of multiple genetic susceptibilities and environmental factors. However, accumulating evidence has shown that, in a subset of patients with severe or treatment-refractory disease, single-gene mutations may underlie the pathogenesis. In 2022, we identified gain-of-function (GoF) mutations in *STAT6* as the cause of a patient who exhibited severe atopic dermatitis, eosinophilic gastrointestinal disease characterized by lymphoid follicular hyperplasia in the stomach and duodenum, elevated serum IgE levels, and eosinophilia. Within just a few years, more cases of severe allergic disease caused by *STAT6*-GoF have been reported worldwide, revealing a broad and heterogeneous clinical spectrum, with marked interindividual differences in disease severity and organ involvement. *STAT6*-GoF is now becoming established as a distinct form of IEI predominantly characterized by allergic phenotypes. In addition, patients with GoF mutations in *JAK1* have also been identified. These patients likewise show diverse clinical manifestations, including refractory atopic dermatitis accompanied by autoimmune disorders. At the same time, both the shared and distinct features among cases, as well as phenotypic differences related to the location of each mutation and the degree of pathway activation, are gradually becoming clearer. In this lecture, I will provide an overview of the clinical characteristics, immunological background, and pathogenic mechanisms of refractory allergic diseases caused by monogenic variants, with a particular focus on *STAT6*-GoF and *JAK1*-GoF.

https://doi.org/10.70962/JSIAD2026abstract.11
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.11

Review of Recently Identified Inborn Errors of Immunity

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Inborn errors of immunity (IEI) comprise a heterogeneous group of disorders. The number of disorders classified as IEI has rapidly increased in recent years, driven by the expansion of the disease concept beyond susceptibility to infections and advances in genetic analysis technologies. Given that approximately 2,000 genes are involved in human immunity, additional disorders are expected to be identified in the future. To systematically organize these disorders, the International Union of Immunological Societies (IUIS) has established a classification system for IEI. In the latest IUIS classification (2024 update), 508 causative genes, 559 diseases, and 17 phenocopies are listed. Compared with the previous 2022 classification, 67 diseases and 2 phenocopies have been newly added.

The identification of new IEIs contributes not only to an increase in the number of rare diseases but also to a better understanding of the roles of these genes in human immunity. Novel insights have been revealed that could not be obtained from animal models, further deepening our understanding of human immune systems.

In this presentation, although it is not feasible to cover all newly identified disorders due to time constraints, I will provide an overview of selected IEIs that are particularly intriguing from a pathophysiological perspective, as well as those reported from Japan (including disorders likely to be identified in Japan in the future).

https://doi.org/10.70962/JSIAD2026abstract.12
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.12

Integrative Multi-Omics Approaches to Improve Genetic Diagnostic Yield in Inborn Errors of Immunity: Lessons from Our Cohort

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Inborn errors of immunity (IEI) are a heterogeneous group of disorders caused by monogenic defects and encompassing more than 500 disease-causing genes, as catalogued in the International Union of Immunological Societies (IUIS) 2024 classification. Genetic diagnosis is essential for understanding disease pathophysiology and guiding therapeutic decision-making; however, a substantial proportion of patients remain undiagnosed even after comprehensive genomic analyses, including targeted gene panel testing and whole-exome sequencing. The functional interpretation of variants of uncertain significance (VUS) represents a major unresolved challenge in this field. To address this, we implemented an integrative multi-omics approach combining targeted RNA sequencing (RNA-seq) and liquid chromatography-mass spectrometry (LC-MS)-based proteomics and applied this strategy to cases that had not achieved a diagnosis through conventional genomic analysis. This workflow enabled cross-platform evaluation of aberrant gene expression, splicing dysregulation, and protein-level alterations, thereby providing functional evidence to support VUS reclassification. As a result, we achieved an incremental diagnostic yield of 6% (4 of 70 cases). In this presentation, we describe our implementation strategy and outcomes and discuss the clinical impact of multi-omics approaches and future perspectives for their broader application in IEI diagnostics.

https://doi.org/10.70962/JSIAD2026abstract.13
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.13

The Forefront of Hematopoietic Stem Cell Transplantation: Focus on Inborn Errors of Immunity

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Approximately 100 allogeneic hematopoietic stem cell transplantation (HSCT) procedures are performed for nonmalignant diseases in Japan annually. Inborn errors of immunity (IEIs) account for approximately one-third of patients with nonmalignant diseases (NMDs), which mainly comprises chronic granulomatous disease, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and hyper IgM syndrome.

Unlike hematological malignancies, no tumor cells do exist to be elucidated in the setting of allogeneic hematopoietic cell transplantation (HCT) for IEIs; therefore, intensive conditioning regimens, or rapid reduction or discontinuation of immunosuppressive agents to enhance alloreactive anti-tumor effect, is not required. However, because these patients do not generally receive pre-HCT chemotherapy, they can occasionally show sufficient immune response to reject donor cells, leading to higher risks of graft failure or mixed chimerism. Furthermore, patients with preexisting infection and organ failure due to the underlying disease itself or long-term use of immunosuppressive agents have a higher risk of severe early transplant-related adverse effects. These fundamental differences might affect the development of original transplant strategy for IEIs.

Recent rapid advancements in transplant strategy have a great impact on allogeneic HSCT. Particularly, introduction of novel graft versus host disease (GVHD) prophylaxis, such as post-transplant cyclophosphamide and anti-CD52 antibody alemtuzumab, has enabled safe allogeneic HSCTs from alternative donors. Due to relatively higher post-transplant survival rates, it is essential to transplantation methods that ensure high survival rates while reducing the risk of early and late post-transplant complications. Therefore, there is a need for a scoring system for defining conditioning intensity and comprehensive assessments of late complications.

In this session, I will provide an overview of the current status and future challenges of allogeneic HSCT for IEI, mainly based on the results of retrospective studies using a nationwide database established by the Japanese Data Center for Hematopoietic Cell Transplantation.

https://doi.org/10.70962/JSIAD2026abstract.14
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.14

Current Situation and Future Perspective of the Validation Project for Newborn Screening of Severe Primary Immunodeficiency Diseases by the Children and Families Agency

Kohsuke Imai

Department of Pediatrics, National Defense Medical College

Primary immunodeficiency diseases (PIDs) are a group of disorders caused by abnormalities in a single gene that result in immune dysfunction, with over 500 distinct subtypes. For severe combined immunodeficiency (SCID) caused by T cell deficiency and agammaglobulinemia caused by B cell deficiency (BCD)—the most severe forms of PID—we have developed a newborn screening (NBS) method using T cell receptor excision circles (TREC) and immunoglobulin kappa-deleting recombination excision circles (KREC) quantitative PCR (qPCR) and have been working to implement it nationwide.

In particular, through a Japan Agency for Medical Research and Development (AMED) research group established in fiscal year 2019, we developed a domestically produced qPCR assay kit that also includes the *SMN1* gene, whose abnormality causes spinal muscular atrophy (SMA). Although currently offered as an optional test, the release of kits by other companies has made PID-NBS testing available nationwide. Furthermore, under the Children and Families Agency's fiscal year (FY)2023 supplementary budget, SCID and SMA were selected as target diseases for a demonstration project. In the first year, 13 prefectures were selected; in FY2024, 27 prefectures; and in FY2025, 38 prefectures. As a result, approximately 700,000 newborns per year can now undergo PID-NBS at public expense. This demonstration project requires us to "demonstrate" the utility of PID screening, particularly for SCID, and surveys and analyses are being conducted primarily by the Technical Committee of the Japanese Society for Mass Screening and the Newborn Screening Working Group of the Japanese Society for Immunodeficiency and Autoinflammatory Diseases (JSIAD). Through this demonstration project, the full public funding of SCID-NBS means that a future is just around the corner where infants with SCID in Japan can be safely and completely cured through hematopoietic cell transplantation without suffering infections.

In this talk, I will provide an overview of the current status and future prospects of the Children and Families Agency Newborn Screening Demonstration Project for primary immunodeficiencies.

https://doi.org/10.70962/JSIAD2026abstract.15
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.15

Impact of Primary Immunodeficiency Screening on Preterm Infants in the NICU

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Background: The implementation of newborn screening (NBS) for primary immunodeficiency (PID) has led to an increasing frequency of low T cell receptor excision circle (TREC) results among preterm infants in Neonatal Intensive Care Units (NICUs). However, the diagnostic process poses significant challenges: confirmatory testing requires substantial blood volumes and notifying parents of a potential immune deficiency significantly exacerbates the anxiety of those already dealing with their infant's fragility. These issues raise critical questions regarding the clinical benefit of early diagnosis in preterm infants and whether these dilemmas are shared across institutions.
Methods: We conducted a survey among members of the Japanese Neonatologist Association to investigate current management strategies and clinical responses to low TREC levels in preterm infants.
Results: The survey results highlighted widespread clinical uncertainty. Respondents emphasized the urgent need for preterm-specific cutoff values, optimization of blood sampling timing, the option to defer testing during acute phases, and a deeper understanding of preterm-specific pathophysiology among clinical immunologists.
Discussion: Neonatal care must account for the physiological immaturity of the immune system. While the NICU provides stringent infection control, the absence of fever does not necessarily indicate immunocompetence. Furthermore, preterm management involves unique constraints, such as limited blood volume and the frequent necessity of blood transfusions, which can complicate the interpretation of TREC results. Clinical dilemmas also extend to essential care: breastfeeding is vital for neurodevelopment and the prevention of complications like necrotizing enterocolitis, and family contact is regarded as a critical medical intervention for psychological support

and parent-infant bonding. However, these may be restricted if PID is suspected. Furthermore, the timeline for clinical decision-making is tight, as the first live vaccines are typically administered around 2–3 months of corrected age.

Conclusion: From the perspective of neonatal medicine, we aim to advocate for a balanced screening framework that ensures the reliable detection of PID while safeguarding the specialized care and well-being of preterm infants.

https://doi.org/10.70962/JSIAD2026abstract.16
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.16

Transition of IEI Care from Pediatric to Adult Services: The Role of Pediatricians

Toshinao Kawai

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Inborn errors of immunity (IEI) most commonly present during childhood, including infancy. However, advances in early diagnosis through newborn screening, improved monitoring and management of complications, and progress in therapeutic approaches such as hematopoietic cell transplantation have led to an increasing number of patients surviving into adulthood. As most IEIs require ongoing specialized medical care beyond childhood, and patients may additionally develop common age-related comorbidities in adulthood, it is considered difficult to provide optimal long-term care within pediatric services alone. Therefore, many patients with IEI require transition to adult healthcare services. In Japan, the Transition Working Group of the Japan Pediatric Society (JPS-TWG) published recommendations on transitional care for patients with childhood-onset diseases in 2014. Subsequently, in 2023, the TWG further clarified the definitions of transitional care, transition, and transfer to adult healthcare services.

The Transition Working Group of the Japanese Society for Immunodeficiency and Autoinflammatory Diseases (JSIAD-TWG) conducted questionnaire surveys of JSIAD physician members in 2023 and 2025 regarding their current practices in transition support. This study reports the current status of adult patient care within pediatric settings, the progress of transition, specific transition support initiatives, and changes observed over the two-year period. As no nationwide survey targeting experts has previously been conducted in Japan regarding transitional care and transfer to adult services in IEI, the present findings provide a basis for discussing future perspectives on transitional care required for this rare group of disorders.

https://doi.org/10.70962/JSIAD2026abstract.17
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.17

How to Promote Transitional Care, from Adult Healthcare Clinicians

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In transitional care for patients with primary immunodeficiency diseases (PID) within inborn errors of immunity (IEI), the adult specialty responsible for accepting patients differs depending on the underlying pathology. In general, rheumatology departments, which manage immune dysregulation and infectious diseases, most commonly assume responsibility. However, pulmonology departments often manage patients with recurrent respiratory infections, while hematology departments frequently take care of patients with hematologic abnormalities or those who have undergone hematopoietic stem cell transplantation. In some institutions, infectious disease or general internal medicine departments are responsible for their care, although identifying an appropriate adult department for transition can sometimes be challenging.

At Institute of Science Tokyo Hospital, the departments of pediatrics and rheumatology have long collaborated closely in both outpatient and inpatient settings to manage patients with rheumatic diseases and IEI. Since 2020, a transitional care clinic has been established in our department, and we have actively accepted not only patients with rheumatic diseases but also those with IEI.

Many patients with PID have an uncomplicated clinical course with appropriate infection control and continued immunoglobulin replacement therapy. However, autoimmune and inflammatory complications are not uncommon, and the use of immunosuppressive therapy increases the risk of opportunistic infections. In both IEI and rheumatic disease patients, treatment is continued with modifications or additions of medications according to the patient's life stage.

Genetic testing plays a key role in the diagnosis of IEI, and in recent years, the number of patients diagnosed in adulthood has increased. In our institution, diagnostic evaluation is conducted in collaboration with the departments of pediatrics and clinical genetics. In this symposium, we will present the current status and challenges of transitional care for patients with IEI, as well as our institutional experience.

Regular Abstracts

https://doi.org/10.70962/JSIAD2026abstract.18
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.18

Nationwide Registry Study of VEXAS Syndrome in Japan: One-Year Follow-Up Results

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Background: VEXAS syndrome is an autoinflammatory disease of older adults caused by acquired mutations in the ubiquitin-activating enzyme UBA1. Standard treatment has not been established, and the prognosis is poor. Therefore, it is important to clarify the clinical characteristics, prognosis, and treatment status of patients in Japan and to develop prognostic factors and biomarkers. Since 2023, we have been conducting a nationwide prospective registry study supported by the Japan Agency for Medical Research and Development (AMED).
Objective: To investigate the 1-year outcomes after enrollment in the registry and to clarify the current clinical management of VEXAS syndrome in Japan.
Methods: From May 2023 to September 2025, patients suspected of having VEXAS syndrome were enrolled at participating institutions. Peripheral blood samples from all patients were sent to the Kazusa DNA Research Institute, where all exons of UBA1 were analyzed by next-generation sequencing. In patients diagnosed with VEXAS syndrome, clinical manifestations, UBA1 genotypes, treatments, disease activity assessed by the VEXAS Current Activity Form (VEXASCAF), C-reactive protein (CRP) levels, survival, and adverse events were prospectively evaluated every 3 months for 1 year. For patients followed for more than 1 year, the date of final observation was also recorded. In patients without UBA1 mutations, survival status at the final observation date was investigated.
Results: As of September 2025, 130 patients with suspected disease had been enrolled from 36 institutions across Japan, and 66 of them were found to carry UBA1 mutations and were diagnosed with VEXAS syndrome. The median age was 74.0 years (range, 55-89), and all patients were male. The genotypes consisted of 27 Thr, 23 Leu, 11 Val, 4 splice variants, and 1 noncanonical variant. The median variant allele frequency (VAF) was 56.0%. As previously reported, the Leu genotype had a significantly higher VAF than the Val genotype. The median observation period was 343.0 days. By the final observation date, eight patients had died, and five had become transfusion dependent. Although VEXASCAF and CRP levels significantly decreased from baseline, no substantial change was observed from week 12 to week 48. Eleven patients (19%) fulfilled the complete remission criteria proposed by the French National VEXAS study group (FRENVEX) during follow-up. Glucocorticoid dose did not change from baseline to week 48. A total of 59 adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher were observed, affecting 50% of patients. After adjustment for the observation period from symptom onset, overall survival was better in patients with the Leu genotype than in those with other genotypes, consistent with previous overseas reports. Patients without UBA1 mutations had significantly worse survival than those with VEXAS syndrome.
Conclusion: This study clarified the current clinical characteristics and outcomes of patients with VEXAS syndrome in Japan.

https://doi.org/10.70962/JSIAD2026abstract.19
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.19

Clinical Overview of 100 Patients with Inborn Errors of Immunity at National Defense Medical College

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Background: Inborn errors of immunity (IEI) are rare disorders; characterizing their clinical features and underlying genetic causes is essential for both clinical practice and research. Despite advances, causative genes remain unidentified in many patients. Clarifying the genetic basis of IEI is crucial to deepening our understanding of its pathophysiology and improving patient management.
Methods: We retrospectively analyzed 100 patients with IEI followed up at National Defense Medical College Hospital between April 2014 and September 2025. Evaluated variables included age, sex, diagnostic category, registration status in the Primary Immunodeficiency Database in Japan version 2 (PIDJ2), use of immunoglobulin replacement therapy (IGRT), and the identification of causative genes.
Results: Patients ranged in age from 0 to 68 years (median: 19.5 years); 65 were male, and 35 were female. Based on the International Union of Immunological Societies (IUIS) classification, the diagnostic categories were predominantly antibody deficiencies (n = 57), combined immunodeficiencies with associated or syndromic features (n = 12), immunodeficiencies affecting cellular and humoral immunity (n = 10), diseases of immune dysregulation (n = 8), congenital defects of phagocyte number or function (n = 4), autoinflammatory diseases (n = 4), defects in intrinsic and innate immunity (n = 2), phenocopies of inborn errors of immunity (n = 2), and complement deficiencies (n = 1). Forty-seven patients were registered in PIDJ2. IGRT was administered to 43 patients (intravenous: 12; subcutaneous: 31). Causative genes were identified in 51 patients. Among the 41 patients who remained without an identified causative gene (excluding those who had completed follow-up), the most common categories were predominantly antibody deficiencies (n = 25, including 15 with common variable immunodeficiency [CVID]) and immunodeficiencies affecting cellular and humoral immunity (n = 6, including 5 with late-onset combined immunodeficiency).
Conclusion: This single-center analysis provides a comprehensive overview of the clinical and genetic characteristics of IEI and highlights that many cases, particularly CVID, still lack an identified genetic cause. Expanding PIDJ2 registration and participating in multicenter collaborative studies may facilitate a more comprehensive understanding of IEI pathophysiology.

https://doi.org/10.70962/JSIAD2026abstract.20
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.20

A Hypomorphic *UNC13D* Variant Causes Pancytopenia in a 12-Year-Old Girl Without Systemic Inflammation

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Background: Familial hemophagocytic lymphohistiocytosis (FHL) is an immune dysregulation disorder in which most patients develop hemophagocytic lymphohistiocytosis (HLH) within the first year of life. Recently, an increasing number of patients with hypomorphic variants in FHL-related genes presenting with atypical features in late childhood or adulthood have been reported.
Case: A previously healthy 12-year-old girl presented with painful erythema at age 10. Laboratory tests revealed pancytopenia, and she was referred to our department. Although the erythema resolved spontaneously, splenomegaly was noted. Bone marrow examination showed hypocellularity without dysplasia or malignancy. Flow cytometry demonstrated TCRαβ$^+$ double-negative T cells (DNTs) accounting for 2.5% of lymphocytes (3.3% of T cells). Cytokine analysis revealed markedly elevated IL-18 (5,804 pg/mL) and CXCL9 (8,688 pg/mL), while IL-6 was <3 pg/mL, and soluble TNF receptor II was 5,390 pg/mL. Based on these findings, an immune dysregulation disorder such as autoimmune lymphoproliferative syndrome (ALPS) was suspected. Genetic testing revealed compound heterozygous variants in *UNC13D* (c.2588G>A and c.1596+1G>C). Functional analysis showed mildly reduced Munc13-4 expression in platelets and impaired degranulation function in natural killer cells and cytotoxic T lymphocytes.
Discussion: Previous reports have described late-onset FHL and CLIPPERS syndrome in patients with missense variants in *UNC13D* or *PRF1*, most of which suggested these are hypomorphic variants. Variants in FHL-related genes can produce a broad clinical spectrum ranging from early-onset FHL to late-onset or atypical inflammatory phenotypes, depending on the degree of residual cytotoxic function.
Conclusion: We report a case of atypical cytopenia associated with hypomorphic *UNC13D* variants. Currently, pancytopenia is the only clinical manifestation, and the patient is receiving prophylactic trimethoprim–sulfamethoxazole. However, considering the risk of neurological sequelae with central nervous system involvement, hematopoietic stem cell transplantation is being considered.

https://doi.org/10.70962/JSIAD2026abstract.21
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.21

Novel Single-Nucleotide Variant of SAMHD1 and Somatic Large Deletion in Chromosome 20 Identified in a Case of Late-Onset Chilblain Lupus

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Introduction: Genetic mutations in *SAMHD1* (*SAM domain- and HD domain-containing protein 1*) are responsible for two types of autoinflammatory interferonopathies: autosomal dominant familial chilblain lupus and recessive Aicardi-Goutières syndrome. Somatic mutations in various genes cause adult-onset autoinflammatory diseases, but none involving *SAMHD1* have been reported. Here, we report a sporadic case of late-onset chilblain lupus with a novel single-nucleotide variant of *SAMHD1* and a somatic large deletion in chromosome 20.

Case Presentation: A 76-year-old man presented with widespread erythema and deforming ulcers of the fingers and auricles, starting at age 70 and worsening in winter. Negative autoantibodies and an elevated interferon score suggested autoinflammatory interferonopathy. Targeted sequencing identified a novel single-nucleotide variant (SNV) in *SAMHD1* (PolyPhen-2 score: 1.000) with a variant allele frequency of 60%, along with a reduced read depth in *SAMHD1* (75%) in blood, suggesting a somatic deletion. Whole-genome sequencing identified a large deletion in chr20, including *SAMHD1* on the SNV-free allele, which was absent in oral mucosa. The deletion rates in monocytes, neutrophils, B cells, and T cells were 81%, 54%, 53%, and 0%, respectively. Given its frequent occurrence in myeloid malignancies, del(20q) likely contributed to clonal expansion. These results suggest that the late-onset chilblain lupus can result from biallelic loss-of-function mutations in *SAMHD1* in leukocytes.

Discussion: We detected a novel *SAMHD1* SNV and a somatic large deletion in leukocytes in a case of late-onset chilblain lupus. Although functional analyses are ongoing, these findings suggest that leukocyte dysfunction alone may be sufficient to trigger chilblain lupus. Furthermore, this case suggests the importance of analyzing somatic mutations in late-onset chilblain lupus or lupus erythematosus.

https://doi.org/10.70962/JSIAD2026abstract.22
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.22

A Case of ROSAH Syndrome Diagnosed Following Unexplained Splenomegaly and Thrombocytopenia in Early Childhood

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Introduction: ROSAH (Retinal dystrophy, Optic nerve edema, Splenomegaly, Anhidrosis, Headache) syndrome is caused by a gain-of-function mutation in the *ALPK1* gene and is classified as a systemic autoinflammatory disease due to constitutive activation of the NF-κB pathway. Ocular symptoms are the most frequent initial presentation; however, splenomegaly in early childhood rarely leads to a diagnosis.

Case Presentation: A 4-year-old boy was diagnosed with splenomegaly at a local hospital and referred to our department at the age of 5 years. At 9 years of age, he developed recurrent fever; at 10 years of age, thrombocytopenia and bilateral abducens nerve palsy appeared; and at 12 years of age, papilledema and retinal degeneration were observed. At 14 years of age, he developed macular edema and uveitis. Prednisolone was administered; however, it was ineffective. Whole-exome analysis performed at 15 years of age in 2017 failed to identify a disease-associated gene, as the causative gene for ROSAH syndrome was discovered in 2019. At 20 years of age, comprehensive genetic analysis identified a heterozygous *ALPK1* c.710C>T (p.Thr237Met) variant, confirming the diagnosis of ROSAH syndrome. At 23 years of age, anemia and positive fecal occult blood were observed, and both upper and lower gastrointestinal endoscopies were performed; however, no signs of inflammatory bowel disease were found. Currently, he continues to experience periodic fever of 38–39°C with

associated elevation of C-reactive protein (CRP), recurring almost every 7 days, and his visual impairment is progressing. In addition, during the course of his illness, he exhibited general fatigue, loss of appetite, decreased sweating, reduced saliva secretion, dental caries, odontoma, hyperuricemia, thoracic vertebral malformation, and conjunctival dermoid. He did not experience headache or joint pain.

Discussion: ROSAH syndrome should be considered in the differential diagnosis of unexplained splenomegaly and thrombocytopenia in early childhood. Multifaceted evaluations, including ophthalmological findings, inflammatory markers, abnormal sweating, dental caries, and genetic testing, are useful for early diagnosis. Although some studies have reported the effectiveness of treatments such as tocilizumab, they are generally insufficient to prevent the progression of visual impairment, highlighting the need for the development of new treatment options.

https://doi.org/10.70962/JSIAD2026abstract.23
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.23

Secondary Use of Unanalyzed Next-Generation Sequencing Data to Improve Diagnostic Yield in Inborn Errors of Immunity

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Inborn errors of immunity (IEI) are monogenic disorders characterized by considerable phenotypic variability and genetic heterogeneity, for which genetic confirmation is essential to establish an accurate diagnosis and guide appropriate treatment. In Japan, genetic testing for IEI is covered by the national health insurance system. As of October 2025, clinicians select the most appropriate panel from among 32 available gene panels (comprising a total of 312 genes) based on the clinical diagnosis. However, owing to the broad phenotypic spectrum of IEI—wherein identical gene variants can manifest as distinct clinical presentations, and conversely, similar clinical features may result from mutations in different genes—selecting the optimal panel is inherently challenging, and the current insurance-covered testing system has recognized limitations. Against this background, a pilot study on the secondary use of unanalyzed next-generation sequencing (NGS) data generated as a by-product of insurance-covered testing was launched in 2023 at nine principal institutions across Japan, including the Department of Pediatrics at Hiroshima University. This initiative enabled a comprehensive evaluation of more than 242 IEI-associated genes. In the pilot study, 160 patients with undiagnosed IEI were analyzed, and a definitive genetic diagnosis was established in 15 cases (9.4%). Building on these results, the program was expanded in February 2025 under the auspices of the Japanese Society for Immunodeficiencies and Autoinflammatory Diseases (JSIAD), with 91 institutions across Japan enrolled as collaborative sites.

In this presentation, we report the current progress of the JSIAD-led secondary analysis program for unanalyzed NGS data. For cases in which a definitive genetic diagnosis was established, we cross-reference the findings with the originally selected insurance-covered gene panel and correlate discrepancies with the clinical phenotype, thereby identifying limitations of the current testing framework. Furthermore, drawing on the cumulative findings of this research, we discuss future directions for genetic testing strategies in IEI.

https://doi.org/10.70962/JSIAD2026abstract.24
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.24

Rapid Flow Cytometric Diagnosis of XIAP Deficiency

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Introduction: X-linked inhibitor of apoptosis protein (XIAP) deficiency is an inborn error of immunity caused by pathogenic variants in *XIAP*. It presents with a wide range of symptoms, including recurrent hemophagocytic lymphohistiocytosis and inflammatory bowel disease. Previous reports investigated the intracellular tumor necrosis factor-alpha (TNF-α) production capacity following stimulation with muramyl dipeptide (MDP)—a specific agonist of nucleotide-binding and oligomerization domains 2 (NOD2), a specific agonist of XIAP. However, obtaining the analysis results required two days, making it a time-consuming test.
Method: We established a method to measure the downregulation of L-selectin (CD62L) on the cell surface following MDP stimulation in monocytes and neutrophils from patients with XIAP deficiency using flow cytometry, with the entire process taking a total of 4 hours. Additionally, we measured TNF-α and CD62L levels following MDP stimulation in patients with XIAP deficiency after allogeneic hematopoietic cell transplantation (HCT) to evaluate the utility of this method for functional analysis.
Results: We analyzed 6 patients with XIAP deficiency. We evaluated the percentage of inhibition (%Inhibition) of the mean CD62L expression levels in monocytes and neutrophils, respectively. The inhibition rates of CD62L expression in patients' monocytes and neutrophils were 8.5% and 11.3%, respectively, on average, and were significantly lower compared to healthy controls (monocytes: 85.4%, neutrophils: 85.4%). Furthermore, in 3 patients with XIAP deficiency following HCT, we measured TNF-α and CD62L levels after MDP stimulation post-HCT and confirmed that these parameters improved in accordance with donor chimerism.
Conclusion: In XIAP deficiency, measuring cell surface CD62L following MDP stimulation enabled more rapid functional analysis. Additionally, these analyses proved useful for functional assessment following HCT.

https://doi.org/10.70962/JSIAD2026abstract.25
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.25

A Family with a Novel Heterozygous Loss-of-Function Variant in the N-Terminal Domain of *STAT1* Showing Variable Clinical Phenotypes

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Introduction: Autosomal dominant (AD) loss-of-function (LOF) variants in STAT1 are a known cause of Mendelian susceptibility to mycobacterial disease (MSMD); however, the clinical phenotype is highly heterogeneous.
Case Presentation: We report three individuals from a single family harboring a novel heterozygous STAT1 variant (p.D92A).
Case 1: A 4-year-old boy born to non-consanguineous parents with no history of recurrent infections or early neonatal deaths presented at 1 year and 10 months of age with a right mandibular mass and gait disturbance. Contrast-enhanced computed tomography revealed destructive mass lesions involving the right mandible and the vertebral bodies (Th1 and Th11). Biopsy of the Th11 lesion demonstrated CD1a-negative, CD68-positive, and factor XIIIa-positive histiocytes, but a definitive diagnosis was not established. Based on the clinical findings, systemic juvenile xanthogranuloma was suspected, and chemotherapy was initiated; however, the disease relapsed repeatedly. Subsequent genetic reevaluation identified the STAT1 p.D92A variant. Functional analyses demonstrated reduced STAT1 tyrosine phosphorylation following IFN-γ stimulation compared with wild type, and luciferase assays confirmed significantly decreased transcriptional activity, consistent with an LOF effect. Although *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) was not definitively detected in biopsy specimens, BCG osteomyelitis associated with MSMD was suspected. The patient achieved and maintained remission with anti-mycobacterial therapy.
Case 2: The younger sister of Case 1, currently 2 years old, was identified to carry the same variant through family screening at 1 month of age, and BCG vaccination was withheld. At 2 years of age, she presented with erythema and swelling of the right ankle and bilateral knees, accompanied by fever and generalized erythematous rash. Laboratory evaluation revealed elevated C-reactive protein (CRP) and hypercytokinemia. MRI showed fasciitis and peritendinitis extending from the lower leg to the foot, without clear evidence of osteomyelitis or arthritis. She was treated with cephalexin and prednisolone for presumed bacterial tenosynovitis and an excessive immune response resembling systemic juvenile idiopathic arthritis, with good clinical improvement and no recurrence to date.
Case 3: The father, who carries the same variant, remains asymptomatic.
Discussion: This family demonstrates a novel N-terminal AD STAT1 LOF variant with experimentally confirmed functional impairment and marked phenotypic heterogeneity, ranging from osteomyelitis to soft tissue inflammation and an asymptomatic carrier state. Further studies are needed to elucidate the factors determining phenotypic variability.

https://doi.org/10.70962/JSIAD2026abstract.26
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.26

A Case with *STAT1* GoF: Secondary Analysis of Gene Panel Test Is a Promising Method for Diagnosis of Inborn Errors of Immunity

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Aim: To present a case with *STAT1* gain-of-function (GoF) mutations absent of chronic mucocutaneous candidiasis (CMC) and to discuss the use of unanalyzed data from genetic panel testing.
Case Presentation: The male patient initially had stomatitis at age 3 and experienced sepsis-like symptoms at age 4. During his school-age years, he repeatedly had fevers 4 to 5 times a year, each episode lasting 7 to 10 days. At age 13, he developed ileocecal enteritis two times; while antibiotics were not effective, glucocorticoid (GC) showed marked response. Considering the possibilities of auto-inflammatory diseases such as familial Mediterranean fever, he was treated with low-dose GC, colchicine, and adalimumab. At age 14, he suffered from *Pneumocystis jirovecii* pneumonia, *Cryptococcus neoformans* fungemia/meningitis, and herpes zoster, successively. A chest CT scan revealed bronchiectasis. After age 18, he hemoptysed several times. He was diagnosed with *STAT1* GoF by genetic testing at age 19. Elevated antinuclear antibodies (x 640, speckled pattern) were detected at age 13, and a proteome-wide antibody array analysis (HuPEX) identified 176 kinds of autoantibodies. Though most had unknown clinical significance, anti-PSME3 (anti-Ki) antibody has been reported as an autoantibody associated with Sicca syndrome in male systemic lupus erythematosus (SLE) patients. Our patient did not have dry symptoms; however, inflammatory cell infiltration was observed in some small salivary glands.
Discussion: In this case, autoinflammatory-like symptoms emerged in early childhood and autoimmune symptoms and susceptibility to infectious diseases became apparent from around adolescence. Ultimately, a heterozygous p.R274Q mutation was identified in the *STAT1* gene, and he was diagnosed with *STAT1* GoF, but no CMC symptoms were observed throughout the clinical course. For cases difficult to diagnose clinically, we believe that genetic testing should be actively pursued to facilitate early diagnosis. The genetic testing for hereditary autoinflammatory diseases (conducted by Kazusa DNA Research Institute), which is covered by health insurance, provides results for about 10 target genes. However, in the background, sequencing data for more than 242 genes is obtained using next-generation sequencers and stored without analysis. We have successfully established definitive diagnoses through the secondary analysis of these unused data.
Conclusion: We reported a case of *STAT1* GoF without CMC. Genetic analysis has a crucial role in the diagnosis of inborn errors of immunity. Promoting the secondary use of unanalyzed data could lead to enhanced diagnostic rates.

https://doi.org/10.70962/JSIAD2026abstract.27
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.27

An Adult Case of Chronic Mucocutaneous Candidiasis and Autoimmune Hepatitis Due to *STAT1* Gain-of-Function Variant

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A 23-year-old woman presented with a history of recurrent oral and vaginal candidiasis and herpes zoster since childhood. In year X–1, she was diagnosed with autoimmune hepatitis (AIH) based on elevated liver enzymes, hypergammaglobulinemia, and histopathological findings of lymphocytic and plasmacytic infiltration in the portal tracts. Despite an initial response to high-dose glucocorticoids (GCs), the AIH relapsed during tapering. Immunological workup revealed impaired T cell proliferative capacity, undetectable T cell receptor excision circles (TREC) and kappa-deleting recombination excision circles (KREC), and a reduced proportion of Th17 cells. Genetic analysis identified a previously reported heterozygous *STAT1*-gain-of-function (GOF) variant (c.821G>A), establishing the diagnosis of symptomatic chronic mucocutaneous candidiasis (CMC) associated with *STAT1*-GOF. Given the increasing evidence for the efficacy of JAK inhibitors in *STAT1*-GOF, ruxolitinib therapy is planned in our patient following institutional ethical approval. The clinical severity of *STAT1*-GOF is

highly variable among affected individuals. *STAT1*-GOF can present with a broad spectrum of autoimmune manifestations. While AIH has been reported in pediatric patients, adult-diagnosed cases remain relatively rare. Insufficient awareness of this entity in adult medicine may lead to significant diagnostic delays. In the present case, the diagnosis of *STAT1*-GOF was established based on a clinical history of recurrent candidiasis and herpes zoster since childhood, appearing alongside GC-dependent AIH. We believe that documenting the clinical course of adult-diagnosed cases is essential for improving the recognition of the diverse clinical spectrum of *STAT1*-GOF among physicians caring for adult patients.

https://doi.org/10.70962/JSIAD2026abstract.28
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.28

X-Linked Agammaglobulinemia with Variants in 5'-Untranslated Region

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X-linked agammaglobulinemia (XLA) is an X-linked inborn error of immunity caused by variants in the *BTK* gene. Variants in the 5'-untranslated region (UTR) of the *BTK* gene account for approximately 2% of all cases, but their detailed molecular pathogenesis remains unclear. In this study, we identified 5'-UTR variants in two XLA families and examined promoter activity. Whole-exome sequencing revealed the 5'-UTR variants (patient 1: c. -358-3G>T; patients 2 and 3: c. -356-6_-3del AAAG) in three patients from two families with XLA. Reduced BTK protein expression by flow cytometry and reduced mRNA expression by quantitative PCR were observed in all three patients. Quantitative PCR on nascent RNA identified a marked decrease in *BTK* transcriptional activity. Assay for transposase-accessible chromatin using sequencing (ATAC-seq) confirmed that the region near the variants adopts a closed chromatin structure. Chromatin immunoprecipitation-quantitative PCR (ChIP-qPCR) results confirmed that the variants reduce the binding of the transcription factor PU.1. The 5'-UTR variants observed in these two families were identified as critical sites for PU.1 binding, suggesting that these sites are important for promoter activity. Further elucidation of the pathogenesis is anticipated through the accumulation of cases with variants in the 5'-UTR of the *BTK* gene.

https://doi.org/10.70962/JSIAD2026abstract.29
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.29

Clinical Characteristics of Low KREC Cases in Newborn Screening for Primary Immunodeficiency

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Background: In Saitama Prefecture, newborn screening (NBS) for severe combined immunodeficiency (SCID) was initiated as a pilot program since September 2024. Immunoglobulin kappa chain-deleting recombination excision circles (KREC) reflect newly generated B cells and enabled NBS for B cell deficiencies. However, clinical characteristics and managements of low KREC cases in Japan has not been sufficiently clarified. We investigated the clinical features of low KREC cases referred to our institution.
Methods: We retrospectively reviewed infants with low KREC levels who were referred to our hospital between April 2024 and October 2025 due to positive NBS results. Diagnoses, immunological findings, and clinical courses were analyzed.
Results: Six cases were identified, including two cases of X-linked agammaglobulinemia (XLA), two cases of secondary immunodeficiency associated with maternal medications, one case suspected of primary immunodeficiency, and one case in which B cell levels had returned to the normal range. Both XLA patients had a positive family history, and flow cytometric analysis revealed B cell deficiency. In the two cases of secondary immunodeficiency, their mothers had received immunosuppressive medications during pregnancy. One mother was treated with azathioprine for ulcerative colitis, and the other received azathioprine and tacrolimus following kidney

transplantation. In the former case, the number of B cells improved to 11.0% at 2 months. In the latter case, the number of B cells improved to 14.5% at 24 days of age. Vaccinations proceeded in both cases. The infant suspected of primary immunodeficiency showed decreased lymphocyte subsets at 17 days of age, with B cells at 1.4% and natural killer (NK) cells at 2.2%. Only inactivated vaccines were administered, and further etiological evaluation is ongoing. One infant referred as a low KREC level was found to have a B cell proportion of 6.5% at 1 month of age, which was within the normal range.

Conclusion: The effects of maternal immunosuppressive medications appear to be transient, and periodic FACS evaluation may help determine the appropriate timing for live vaccination. However, some infants may exhibit persistent B cell lymphopenia. Therefore, early immunological evaluation and continued postnatal monitoring using FACS are essential for appropriate clinical management.

https://doi.org/10.70962/JSIAD2026abstract.30
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.30

One-Year Outcomes of Expanded Newborn Screening for Primary Immunodeficiency in Saitama Prefecture, Japan

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Introduction: In November 2023, the Children and Families Agency announced the implementation of newborn screening (NBS) for severe combined immunodeficiency (SCID), which has since been expanded nationwide in Japan. In Saitama Prefecture, expanded NBS using T cell receptor excision circles (TREC) and kappa-deleting recombination excision circles (KREC) was initiated in September 2024. We report the first-year outcomes of expanded NBS for primary immunodeficiency (PID) in Saitama Prefecture.

Methods: Expanded NBS was initiated in Saitama Prefecture (excluding Saitama City) in September 2024 and in Saitama City in April 2025. A regional consortium was established to coordinate sample collection, laboratory testing, and confirmatory evaluation. PID screening was performed using the NeoMDx kit (Revvity). Cutoff values for positive screening were defined as TREC <300 copies/10^5 cells and KREC <250 copies/10^5 cells.

Results: Between September 1, 2024, and August 31, 2025, a total of 35,248 newborns were screened. The recall rate for retesting was 58 cases (0.16%), repeat sampling was required in 42 cases (0.12%), and 12 cases (0.03%) required further diagnostic evaluation. Among these, two PID cases were identified and successfully treated: one case of complete DiGeorge syndrome/CHARGE syndrome and one case of X-linked agammaglobulinemia. Additional diagnoses included three infants born to mothers receiving immunosuppressive therapy, one infant born to a mother treated with biologic agents, one case of Langerhans cell histiocytosis, one case of trisomy 21 with transient abnormal myelopoiesis, one case of fetal hydrops/cardiofaciocutaneous (CFC) syndrome, one case of neonatal asphyxia with steroid exposure, and two cases of B cell lymphopenia.

Conclusion: Expanded NBS enabled not only the life-saving identification of two patients with PID but also appropriate clinical management of infants with positive screening results. Continued efforts to improve public awareness, quality control, and regional collaboration are essential to further optimize early diagnosis and treatment.

https://doi.org/10.70962/JSIAD2026abstract.31
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.31

Novel *TBX1* Variants of Uncertain Significance in Two Infants with Abnormal T Cell Receptor Excision Circles on Newborn Screening

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Background: T cell receptor excision circle (TREC)-based newborn screening enables early detection of severe combined immunodeficiency (SCID), but it also identifies infants with mild or asymptomatic non-SCID primary immunodeficiencies, for whom optimal management remains unclear.

Cases: We identified two female infants with heterozygous novel *TBX1* variants after abnormal TREC-based newborn screening. Case 1, born at 38 weeks and 5 days of gestation, was admitted on day 13 of life because of low TRECs. She showed T cell lymphopenia (CD4+ 483/μL, CD8+ 161/μL, CD4+CD45RA+ 15.2%, phytohemagglutinin stimulation index 42.5) and hypocalcemia due to hypoparathyroidism, without structural cardiac abnormalities. G-banding and fluorescence in situ hybridization for 22q11.2 were normal. Genetic testing identified a heterozygous novel *TBX1* variant (NM_080647.1:c.1439C>T), classified as a variant of uncertain significance (VUS). The same variant was detected in her mother, whose T cell counts were normal. Case 2, born at 40 weeks and 6 days of gestation, was evaluated on day 18 of life because of mildly low TRECs. She showed mild T cell lymphopenia (CD4+ 1,416/μL, CD8+ 650/μL, CD4+CD45RA+ 22.3%) without cardiac abnormalities or hypocalcemia. G-banding and fluorescence in situ hybridization for 22q11.2 were normal. Genetic testing identified a heterozygous novel *TBX1* variant (NM_080647.1:c.1446_1464del), also classified as a VUS. The same variant was detected in her mother, whose T cell counts were normal.

Conclusions: These cases suggest that infants with abnormal TRECs may have novel *TBX1* variants even in the absence of 22q11.2 deletion or major cardiac anomalies. However, both variants were classified as VUS and were also present in mothers with normal T cell counts and no apparent immunodeficiency; therefore, their pathogenic significance remains uncertain. As newborn screening increasingly identifies infants with non-SCID immunological abnormalities and variants of uncertain clinical relevance, standardized management strategies and careful longitudinal follow-up are needed.

https://doi.org/10.70962/JSIAD2026abstract.32
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.32

CHARGE Syndrome with Athymia Diagnosed by Newborn Screening and Treated with Cord Blood Transplantation: A Case Report

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Background: CHARGE syndrome is caused by pathogenic variants in the *CHD7* gene and is characterized by coloboma, congenital heart defects, choanal atresia, growth retardation/developmental delay, genital hypoplasia, and ear anomalies with hearing loss. CHARGE syndrome with athymia can present with complete absence of the thymus, leading to T cell deficiency and a clinical phenotype of severe combined immunodeficiency (SCID). Early therapeutic intervention is required after diagnosis. Thymic transplantation is the curative treatment; however, when access is limited, hematopoietic stem cell transplantation (HSCT) may be an alternative. In Japan, reports of cord blood transplantation for CHARGE syndrome with athymia are limited, and cases diagnosed and treated before infectious complications through newborn screening (NBS) are extremely rare.

Case: A male infant was born at 41 weeks' gestation, weighing 3,632 g. Expanded NBS at day 6 revealed T cell receptor excision circle (TREC) 0 copies, reported on day 16. Positive-pressure management, cessation of breastfeeding, antifungal and anti-CMV prophylaxis, and immunoglobulin replacement were promptly initiated. Genetic testing identified a known frameshift variant in *CHD7*, and together with imaging findings of thymic aplasia, the patient was diagnosed with CHARGE syndrome with athymia. On day 30, he underwent aortic arch repair for coarctation of the aorta. On day 66, he received a 7/8 HLA allele–matched cord blood transplant without conditioning. T cells appeared in peripheral blood on day 14 post-transplant. At 1 month, he developed stage 2 skin graft versus host disease (GVHD), currently managed with adjustment of immunosuppressive therapy; no other transplant-related complications or infections have occurred.

Conclusion: Although long-term outcomes after HSCT require further follow-up, this case demonstrates that diagnosis of CHARGE syndrome with athymia by NBS prior to infectious complications enabled early appropriate supportive care and treatment planning, which likely contributed to a reduced risk of transplant-related mortality.

https://doi.org/10.70962/JSIAD2026abstract.33
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.33

Successful Second Transplantation with Thiotepa-Containing Reduced-Intensity Conditioning in Hypomorphic RAG1 Deficiency

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Background: Busulfan (Bu)-containing conditioning regimens are widely used in hematopoietic stem cell transplantation for severe combined immunodeficiency (SCID), including recombination-activating gene (RAG) deficiency, because they facilitate the achievement of stable donor chimerism. However, when Bu cannot be administered due to complications such as pulmonary toxicity, the optimal alternative conditioning strategy remains unclear.
Case Presentation: A patient was diagnosed with hypomorphic RAG1 deficiency at 4 months of age following the onset of Pneumocystis pneumonia. During the clinical course, autoimmune hemolytic anemia (AIHA) developed and required prolonged management before adequate disease control was achieved. At 18 months of age, after stabilization of the patient's general condition, HLA 6/6 antigen–matched cord blood transplantation was performed using fludarabine (Flu), melphalan (LPAM), antithymocyte globulin (ATG), and low-dose total body irradiation (TBI) as the conditioning regimen. After transplantation, the patient developed severe diarrhea due to mucosal injury, followed by stage 4 intestinal graft-versus-host disease (GVHD). GVHD improved after treatment with human bone marrow–derived mesenchymal stem cells (hMSC-BM), and the patient was discharged at 2 years and 2 months of age. However, mixed donor chimerism persisted. At approximately 2 years and 6 months of age, the patient was readmitted with recurrent respiratory infections. Concurrently, watery diarrhea and hematochezia developed, and lower gastrointestinal endoscopy revealed multiple ulcerative lesions consistent with gastrointestinal GVHD. Steroid-refractory GVHD progressed despite treatment with ruxolitinib, vedolizumab, and additional hMSC-BM infusions. Because of persistent immune dysfunction with recurrent airway infections, progressive pulmonary impairment, and declining donor chimerism, re-transplantation was indicated. At 3 years and 7 months of age, bone marrow transplantation from an HLA-matched older sibling was performed using a conditioning regimen consisting of Flu, LPAM, ATG, low-dose TBI, and thiotepa (TT). Neutrophil engraftment was achieved on day 17. Gastrointestinal GVHD resolved after re-transplantation, and recurrent respiratory infections disappeared. Four years after transplantation, the patient remains well with sustained 100% donor chimerism.
Conclusion: In this case, thiotepa-containing conditioning enabled successful re-transplantation and durable full donor chimerism without severe adverse events when Bu could not be used. This regimen may represent a potential alternative conditioning strategy for SCID patients with similar clinical constraints.

https://doi.org/10.70962/JSIAD2026abstract.34
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.34

A Case of Allogeneic Hematopoietic Stem Cell Transplantation in a Patient with POLE2 Deficiency

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Background: DNA polymerase epsilon (POLE) plays a critical role in DNA replication, DNA damage repair, and cell cycle regulation. POLE2, a subunit of this enzyme complex, is associated with an extremely rare deficiency characterized by facial dysmorphism, combined immunodeficiency, and autoimmune disease. To date, only a single case has been reported by Frugoni et al (1). There are no

previous reports of hematopoietic stem cell transplantation (HSCT) for POLE2 deficiency. We report the case of an 18-month-old female with POLE2 deficiency who developed a hepatocellular malignant neoplasm (HMN) following HSCT from an HLA-matched sibling donor.

Case Presentation: The patient presented with recurrent respiratory infections and was referred to our hospital due to pancytopenia. Clinical evaluation revealed decreased counts of $CD8^+$ T cells and $CD56^+$ cells, diminished natural killer (NK) cell activity, and low T cell receptor excision circle (TREC) levels. Given a family history of fatal immunodeficiency in her older sister, genetic analysis was performed, confirming POLE2 deficiency in both siblings. While both parents carried a monoallelic HLA deletion, the younger sister was wild type and was selected as the donor. Neutrophil engraftment was achieved on day 20 post-transplantation. Although the patient developed stage 4 acute gastrointestinal graft-versus-host disease (GVHD) on day 35, it was successfully managed without secondary infectious complications. After HSCT, $CD3^+$, $CD8^+$, and $CD56^+$ cell counts recovered and NK cell activity normalized, whereas recovery of $CD19^+$ cells remained absent. At 25 months after HSCT, the patient was diagnosed with HMN.

Discussion: POLE is increasingly recognized for its role in genomic stability, and its mutations are frequently linked to an elevated risk of malignancies, particularly colorectal cancer. In this case, the POLE2 mutation likely contributed to post-transplantation oncogenesis. Since POLE-mutated tumors often exhibit a high tumor mutational burden (TMB), which suggests potential efficacy of immune checkpoint inhibitors, we intended to perform comprehensive cancer genomic profiling to evaluate the TMB in this patient. These findings may inform future therapeutic strategies.

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https://doi.org/10.70962/JSIAD2026abstract.35
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.35

Serum Leucine-Rich Alpha-2 Glycoprotein in Inflammatory Bowel Disease Complicated by Wiskott-Aldrich Syndrome

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Background: Serum leucine-rich α-2 glycoprotein (LRG) is widely used as a biomarker of disease activity in the management of inflammatory bowel disease (IBD). While its utility has been demonstrated in pediatric IBD, the role of serum LRG in monogenic IBD remains unclear. This report describes the association between the clinical course of gastrointestinal symptoms and serum LRG levels before and after allogeneic hematopoietic cell transplantation (HCT) in an infant with Wiskott-Aldrich syndrome (WAS) complicated by IBD.

Case: A 57-day-old male infant presented to our hospital with subcutaneous hemorrhage, thrombocytopenia, and generalized eczema as the primary complaints; genetic testing confirmed a diagnosis of WAS. At 3 months of age, he developed bloody stools, and lower gastrointestinal endoscopy revealed ulcers and erosions in the colon. Histopathological examination showed infiltration of inflammatory cells and a reduction in goblet cells, leading to a diagnosis of WAS-associated IBD. Despite treatment with an elemental diet, oral 5-aminosalicylic acid, and prednisolone, poor weight gain and bloody stools persisted. Cytomegalovirus (CMV) viremia worsened despite antiviral therapy, and systemic complications of WAS, such as thrombocytopenia and colitis, remained uncontrolled; therefore, at 10 months of age, the patient underwent HCT from an HLA-matched unrelated donor following conditioning with fludarabine and busulfan. Neutrophil engraftment was achieved on day 24. No acute graft-versus-host disease was observed. Bloody stool resolved after the start of conditioning, and remission stabilized following engraftment of donor cells. Serum LRG concentration peaked at 50.2 μg/mL prior to HCT but gradually decreased after the start of conditioning, reaching 14.0 μg/mL by day 90. No recurrence of colitis has been observed during the 5 months following HCT.

Discussion: In this case, disease activity in WAS-associated IBD showed a good correlation with serum LRG levels. Since clinical significance may vary depending on the underlying genetic defect and the immune pathways involved, further cases are needed to establish the interpretation of serum LRG in IEI-associated IBD.

https://doi.org/10.70962/JSIAD2026abstract.36
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.36

Severe Colitis in X-Linked Chronic Granulomatous Disease Bridged to Hematopoietic Cell Transplantation with Tacrolimus and Biologic Agents

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Case: A 22-month-old boy presented with hematochezia beginning in infancy. He had a history of lymphadenitis after Bacille Calmette-Guérin vaccination. Based on absent neutrophil oxidative burst activity, absent gp91phox expression (0%), and a CYBB variant (c.252G>A), he was diagnosed with X-linked chronic granulomatous disease (X-CGD). Colonoscopy revealed ulcerative colitis-like pancolitis characterized by diffuse loss of the vascular pattern, fine mucosal granularity, and friability, without perianal fistula. Histopathology showed neither foamy histiocytes nor granulomas.

Treatment with 5-aminosalicylic acid (5-ASA) was discontinued because of intolerance. Vedolizumab (VED) was insufficiently effective, and prednisolone (PSL) and tacrolimus (Tac) were added. Although Tac induced remission at higher trough concentrations, relapse recurred as the trough concentration was lowered. After mirikizumab (MRK) was introduced, clinical remission could be maintained at lower Tac trough concentrations. However, colitis remained difficult to fully control, and prolonged Tac use led to renal dysfunction and septic shock secondary to a catheter-related infection. He therefore underwent unrelated donor bone marrow transplantation at 32 months of age. Conditioning consisted of fludarabine, dose-adjusted busulfan, antithymocyte globulin, and 3-Gy total body irradiation. For graft-versus-host disease (GVHD) prophylaxis, Tac and short-course methotrexate were used. At the start of conditioning, MRK was replaced with VED. Neutrophil engraftment was achieved on day 17 after transplantation, and hematochezia resolved. Although skin GVHD and vomiting developed, endoscopy showed improvement of colitis. Erythema in the stomach and duodenum prompted the addition of PSL while VED was continued, resulting in prompt symptom improvement. VED was discontinued 4 months after transplantation, Tac 9 months after transplantation. He remains alive without recurrence of colitis 1 year after transplantation.

Discussion: Anti-tumor necrosis factor-alpha agents are generally avoided in chronic granulomatous disease-associated colitis because fatal cases have been reported. The efficacy of VED and ustekinumab, an anti–interleukin-12/23 antibody, has been described in case series, but an optimal treatment strategy for refractory cases has not been established. In this case, MRK reduced the Tac requirement, and VED was safely continued before and after transplantation as bridging therapy. Careful selection of biologic agents with attention to infection risk may facilitate bridging to transplantation in refractory X-CGD–associated colitis. Further accumulation of cases is needed to establish an optimal treatment strategy.

https://doi.org/10.70962/JSIAD2026abstract.37
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.37

A Phase 3 Clinical Study to Evaluate the Long-Term Safety and Tolerability of 20% IGSC for Japanese Patients with PID

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Background: Subcutaneous immunoglobulin (Ig20Gly) is an effective and safe immunoglobulin replacement therapy for primary immunodeficiency disorders (PIDs), allowing home self-administration. While the efficacy and safety of 20% subcutaneous immunoglobulin (Ig20Gly) have been reported in Europe, North America, and Japan, data on long-term administration, particularly biweekly dosing, were limited. This study (TAK-664-3002) is a phase 3 open-label trial evaluating the safety and tolerability of long-term Ig20Gly administration (weekly or biweekly dosing) in Japan.

Methods: Twelve PID patients who completed the preceding study (TAK-664-3001) were enrolled. They continued receiving Ig20Gly in either the weekly group (5 patients) or the biweekly group (7 patients) and were followed. The primary endpoints were long-term safety and tolerability; secondary endpoints included pharmacokinetics, efficacy, and treatment preference.

Results: The median treatment duration was 893.5 days (range: 226–1,037 days). A total of 159 adverse events were reported in all 12 patients; however, only 15 events in 3 patients (25.0%) were judged to be related to the study drug. The majority of reported adverse events were mild to moderate in severity. There were no severe or serious related adverse events and no adverse events leading to discontinuation of the drug or withdrawal from the trial. The overall adverse event rate was 6.0 events per patient-year, and the related adverse event rate was 0.6 events per patient-year, both showing a decreasing trend with long-term administration. Serum IgG trough levels (geometric mean) at the end of the trial were maintained at stable, high levels: 11.0 g/L (1,100 mg/dL) in the weekly group and 8.98 g/L (898 mg/dL) in the biweekly group. No acute serious bacterial infections were observed, with an annual infection rate of 1.32 events per patient. The patient desire to continue treatment was 100% (5/5 patients) in the weekly group and 71% (5/7 patients) in the biweekly group.

Conclusion: Long-term administration of Ig20Gly once weekly or biweekly demonstrated efficacy, safety, and good tolerability in Japanese PID patients. These trial results support the usefulness of long-term Ig20Gly use in Japanese patients and are consistent with existing reports.

https://doi.org/10.70962/JSIAD2026abstract.38
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.38

Immunoglobulin Replacement Therapy for Primary Immunodeficiency Patients in Japan: A PIDJ2 Registry-Based Study

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Primary immunodeficiency diseases (PID) comprise a heterogeneous group of disorders characterized by impaired host defense mechanisms. Increased susceptibility to infection is central clinical feature, and immunoglobulin replacement therapy is widely used for infection prevention. Although meta-analyses have suggested that maintaining serum IgG trough levels above 1,000 mg/dL reduces the risk of pneumonia, the optimal IgG target is thought to vary among individuals. Furthermore, the relationship between IgG levels and other immune dysregulation remains unclear. As therapeutic options have expanded including subcutaneous formulations, there is a growing need to tailor immunoglobulin replacement therapy for individual patients and disease characteristics.

In this context, we analyzed clinical data from the Primary Immunodeficiency Database in Japan ver.2 (PIDJ2) to investigate the status of immunoglobulin replacement therapy in Japan.

As of January 2026, 367 patients receiving immunoglobulin replacement therapy were registered in PIDJ2. The mean age was 27 years (ranging from 0-80 years), with 209 males and 158 females. By disease category, antibody production deficiency accounted for approximately 60% of cases, followed by combined immunodeficiency and immune dysregulation disorders. It was also used in phagocytic disorders, innate immune disorders, and autoinflammatory diseases.

Intravenous immunoglobulin (IVIG) was administered to 136 patients, while subcutaneous immunoglobulin (SCIG) was used in 181 patients; among these, 50 transitioned from IVIG to SCIG during the observation period.

The mean IgG level was higher in patients receiving SCIG (981 mg/dL) than in those receiving IVIG (806 mg/dL). IgG levels at the onset of infectious events were available for 107 events. The mean IgG level during infections requiring hospitalization was 546 mg/dL, whereas it was 760 mg/dL in infections manageable in the outpatient setting. These findings suggest that maintaining higher IgG levels may be beneficial for patients at increased risk of severe infection or hospitalization.

https://doi.org/10.70962/JSIAD2026abstract.39
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.39

Leniolisib, a Selective Phosphoinositide 3-Kinase Delta (PI3Kδ) Inhibitor, in Japanese Patients Aged 12 and Over with Activated PI3Kδ Syndrome (APDS): Data from a 12-Week, Open-Label, Single-Arm Study

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Background: Leniolisib is a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor approved to treat activated PI3Kδ syndrome (APDS) in patients ≥12 years old in the U.S. There are no clinical data on leniolisib in Japanese APDS patients ≥12 years old.
Methods: This prospective, 2-part, open-label, single-arm study (NCT06249997) evaluated bodyweight-adjusted doses of leniolisib in Japanese APDS patients 12–75 years old and ≥35 kg. Part 1 co-primary endpoints were changed from baseline (CFB) to day 85 in log_{10}-transformed sum of product of diameters (SPD) of index lymph nodes and % of naïve B cells ($CD19^+CD20^+IgD^+CD27^-$) out of total B cells.
Results: The study enrolled 3 patients: 2 received leniolisib 70 mg BID, and 1 received 50 mg BID. The mean CFB in log_{10}-transformed index lymph node SPD was −0.41 (SD, 0.26) and mean CFB in % of naïve B cells was 7.2% (SD, 7.0); the corresponding CFB in % of $CD19^+CD27^-CD10^-$ naïve B cells was 32.7% (SD, 17.1). Grades 1 and 2 adverse events (AEs) and treatment-related AEs (all in the system-organ-class "Investigations") were reported in 3 patients. No AEs were serious, and none led to leniolisib discontinuation.
Conclusion: Overall, leniolisib was generally well-tolerated and met the co-primary endpoints, reducing lymphoproliferation and increasing % of naïve B cells. Results in Japanese patients appear consistent with those from the pivotal trial (NCT02435173).

https://doi.org/10.70962/JSIAD2026abstract.40
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.40

Successful Sirolimus Therapy in Steroid-Refractory RAS-Associated Autoimmune Lymphoproliferative Disorder with Mosaic KRAS Mutation

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Introduction: Autoimmune lymphoproliferative syndrome (ALPS) is characterized by defective lymphocyte apoptosis caused by abnormalities in the FAS signaling pathway and presents with lymphadenopathy, splenomegaly, and autoimmune manifestations. RAS-associated autoimmune lymphoproliferative disorder (RALD) is classified as an ALPS-related disorder and is caused by somatic mutations in *NRAS* or *KRAS*, resulting in constitutive activation of the RAS signaling pathway. This leads to impaired apoptosis, abnormal lymphocyte proliferation, and autoimmune manifestations. Compared with classic ALPS, RALD may exhibit distinct clinical features such as mild monocytosis or juvenile myelomonocytic leukemia (JMML)-like findings, making accurate differential diagnosis essential. Although glucocorticoids are generally considered first-line therapy, optimal management strategies for glucocorticoid-refractory cases remain to be established.
Case Presentation: A two-year-old boy who had been diagnosed with autoimmune hemolytic anemia at eight months of age developed transient thrombocytopenia and nephrotic syndrome. His cytopenia was unresponsive to glucocorticoid therapy, and he became transfusion dependent. Genetic testing later identified a mosaic *KRAS* variant (p.Gly13Asp), leading to the diagnosis of RALD. Based on recent reports suggesting the possibility of efficacy for mTOR inhibitors in monogenic disorders characterized by immune dysregulation and lymphoproliferation, an investigator-initiated clinical trial using sirolimus was proposed and initiated after obtaining consent. After the introduction of sirolimus, the patient achieved transfusion independence. However, his clinical course was complicated by secondary hypogammaglobulinemia, which currently requires ongoing immunoglobulin replacement therapy.
Discussion: Sirolimus suppresses the activation and proliferation of T and B lymphocytes, thereby controlling pathological lymphoproliferation and autoimmune manifestations in RALD. This case highlights the clinical utility of sirolimus as a promising therapeutic option for glucocorticoid-refractory RALD.

https://doi.org/10.70962/JSIAD2026abstract.41
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.41

Abatacept Enables Steroid Withdrawal in CNS Involvement of LRBA Deficiency: A Case Report

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Introduction: Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency causes a variety of immune abnormalities due to decreased expression of CTLA-4. Various immunosuppressive agents, including prednisolone (PSL), have been used to treat its clinical manifestations; however, their efficacy is often insufficient, and their adverse effects are problematic. Abatacept, which modulates excessive immune responses via CTLA-4–mediated mechanisms, has been reported to be effective.
Case Presentation: Splenomegaly was noted at a routine health checkup at 3 years of age, and the patient was subsequently referred to our hospital due to thrombocytopenia. She was diagnosed with immune thrombocytopenic purpura and recovered following intravenous immunoglobulin (IVIG) therapy. At 4 years and 1 month of age, she developed autoimmune hemolytic anemia. At 4 years and 2 months, she presented with right esotropia and loss of speech; brain MRI revealed inflammatory changes in the brainstem. After methylprednisolone (mPSL) pulse therapy, oral PSL was initiated. At 5 years of age, obesity due to long-term PSL use was observed, and mycophenolate mofetil was started to facilitate PSL tapering. At 6 years, hypogammaglobulinemia (309 mg/dL, below −2 SD of the age-matched reference) was detected, and regular prophylactic IVIG replacement therapy was initiated. PSL was successfully discontinued at 7 years of age. At 9 years, bilateral organizing pneumonia developed, necessitating reinitiation of PSL. Subsequent flow cytometric analysis of peripheral blood mononuclear cells revealed decreased CTLA-4 expression, and genetic testing suggested LRBA deficiency. At 14 years and 3 months, she developed right-sided hearing loss, otalgia, and rotational vertigo; brain MRI demonstrated multiple central nervous system lesions. mPSL pulse therapy and increased PSL dosing were required, resulting in marked deterioration of quality of life due to central obesity and osteoporosis. At 14 years and 5 months, abatacept was initiated, and PSL was gradually tapered and discontinued by 15 years and 9 months. Genetic testing later confirmed compound heterozygous LRBA deficiency. One year after discontinuation of PSL, she remains free of symptoms except for hypogammaglobulinemia, and her quality of life has improved.
Discussion: Abatacept has been reported to have therapeutic efficacy in LRBA deficiency comparable to hematopoietic stem cell transplantation; however, the long-term efficacy and safety of abatacept remain unclear. Meanwhile, the role of hematopoietic stem cell transplantation has not yet been fully established. In this case, we plan to continue abatacept as long as disease control is maintained.

https://doi.org/10.70962/JSIAD2026abstract.42
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.42

Invasive Pulmonary Aspergillosis in an Adolescent with X-Linked Agammaglobulinemia: A Case Report

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Introduction: X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by abnormalities in the *BTK* gene that impair B cell maturation and antibody production, resulting primarily in susceptibility to encapsulated bacteria. Although invasive fungal infections are considered rare and antifungal prophylaxis is not routinely recommended in XLA, an increasing number of fungal infections have been reported in patients receiving BTK inhibitors, suggesting that BTK may also play a role in innate immune responses. Here, we report a case of invasive pulmonary aspergillosis (IPA) in a patient with XLA.
Case Presentation: An 18-year-old male welder with a history of XLA, who had been diagnosed at age 3, presented with a one-week history of fever. He had been receiving regular immunoglobulin replacement therapy, maintaining serum IgG levels above 1,000 mg/dL. Laboratory findings showed a white blood cell count of 22,600/μL, with 82.0% neutrophils and a C-reactive protein level of 18.57 mg/dL. Chest computed tomography (CT) revealed sinusitis and bilateral pulmonary halo signs. No fungal organisms were detected in sputum, bronchoalveolar lavage fluid, or blood cultures. However, serum β-D-glucan was elevated to 33.8 pg/mL, and the Aspergillus antigen index was 3.2 cut-off index (C.O.I.), leading to a diagnosis of probable IPA. Treatment with voriconazole was initiated, resulting in the rapid resolution of fever and improvement of inflammatory markers. A follow-up CT performed six weeks later showed resolution of the pulmonary lesions. Subsequent neutrophil function testing demonstrated reduced phagocytic activity at 34.7%, while bactericidal activity remained preserved at 99.6%.
Discussion: Recent reports have suggested that BTK is involved not only in B cell differentiation but also in neutrophil functions, including phagocytosis, reactive oxygen species production, and neutrophil extracellular trap formation. In this case, reduced neutrophil phagocytic activity suggests that BTK deficiency-associated neutrophil dysfunction may have contributed to impaired fungal clearance. In addition, environmental exposure to fungi related to chronic sinusitis may have been a contributing factor in the development of IPA. These findings highlight the importance of assessing the risk of fungal infection and implementing appropriate infection control measures in patients with XLA.

https://doi.org/10.70962/JSIAD2026abstract.43
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.43

Identification of a Novel *POLR3F* Gene Variant in a Patient with Susceptibility to Varicella-Zoster Virus Infection

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Varicella-zoster virus (VZV) is a double-stranded DNA virus belonging to the Herpesviridae family that causes chickenpox upon primary infection. It establishes latency in the ganglia and can reactivate as herpes zoster when immunity declines, although it generally confers lifelong immunity. Recurrent or severe disseminated herpes zoster may indicate an underlying immunodeficiency. The patient was a 19-year-old man with a history of five episodes of chickenpox in childhood. He developed Kaposi's varicelliform eruption with headache and was treated with acyclovir after PCR of the cerebrospinal fluid was positive for VZV. Whole-exome sequencing revealed a splice-site variant in *POLR3F* (c.249-2A>G). In a viral infection model using peripheral blood mononuclear cells with intracellular transfection of fragmented nucleic acids, the expression of IFN-α and IFN-β was markedly reduced compared with that in healthy controls. *POLR3F* encodes a subunit of RNA polymerase III (Pol III), which transcribes tRNA and is ubiquitously expressed, including immune cells. Heterozygous variants in genes encoding Pol III subunits have been reported to cause severe VZV infection; however, the c.249-2A>G variant is novel. Immunological investigation of this condition may provide insights not only into the immune response to VZV infection but also into the mechanisms of host defense against DNA viruses and the development of therapeutic strategies.

https://doi.org/10.70962/JSIAD2026abstract.44
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.44

Late-Onset CID (Combined Immunodeficiency) in Families Due to *TRAF3* Variants

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Background: Germline pathogenic *TRAF3* variants were first reported in 2022 as autoimmune lymphoproliferative immunodeficiency disease (ALPID), characterized by autoimmunity and lymphoproliferation. More recently, *TRAF3* variants have also been described in adults with common variable immunodeficiency (CVID). TRAF3 is a key regulator of immune homeostasis that negatively controls the noncanonical NF-κB pathway downstream of CD40 signaling in B cells.
Objective: To characterize the clinical and immunological characteristics of *TRAF3* variants among patients with inborn errors of immunity presenting diverse phenotypes.
Methods: Targeted *TRAF3* sequencing using AmpliSeq was performed in 64 patients with inborn errors of immunity, identifying novel *TRAF3* variants in five patients from two families. Clinical histories, immunophenotypes, plasma cytokines, and TRAF3 protein function were analyzed.
Results: In family A (A1, A2), an ALPID phenotype was observed, characterized by childhood-onset lymphadenopathy and splenomegaly with recurrent respiratory infections, persisting into adulthood. In family B (B1, B2, B3), hypogammaglobulinemia and recurrent infections developed in adulthood, consistent with a CVID-like phenotype. Lymphocyte profiling revealed increased B cell proportions in family A (A1) and reduced B cell proportions in family B (B1–B3). Both families showed decreased naïve T cell proportions and altered Th1/Th2 balance leading to the diagnosis of late onset combined immunodeficiency (LOCID). Plasma cytokine profiling demonstrated elevated

BAFF levels in both families, while IL-5, IL-10, and TNF-α were specifically increased in family A. Functional assays in HeLa cells showed truncated TRAF3 protein expression and activation of the noncanonical NF-κB pathway.
Conclusions: *TRAF3* variants manifest a broad clinical spectrum ranging from ALPID to CVID-like disease, influenced by mutation site, type, and age of onset. It is associated with dysregulated B and T cell differentiation and cytokine imbalance due to increased senescence of T cells. These findings demonstrate the important role of TRAF3 in maintaining immune homeostasis and adaptive immune cell differentiation in humans.

https://doi.org/10.70962/JSIAD2026abstract.45
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.45

Dried Blood Spot (DBS) Proteomic Analysis in Familial Hemophagocytic Lymphohistiocytosis: Exploring Pre-Symptomatic Disease Biology and the Feasibility of Newborn Screening

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Background: Familial hemophagocytic lymphohistiocytosis (FHL) is a life-threatening hyperinflammatory disorder caused by inherited defects in lymphocyte cytotoxicity. Because patients are generally asymptomatic before disease onset, preemptive therapeutic intervention remains difficult. However, the existence of fetal-onset cases and cases without an apparent infectious trigger suggests that molecular abnormalities may already be present before overt clinical manifestations. To date, pre-onset studies in FHL have been limited largely to neonatal samples from unaffected siblings, and analyses using multiple patient samples have been challenging.
Objective: To characterize the preclinical disease state of FHL using proteomic analysis of neonatal dried blood spots (DBS) and to explore the potential applicability of this approach to newborn screening for FHL and other inborn errors of immunity.
Methods: Using an optimized high-efficiency DBS proteomics platform, we analyzed archived neonatal DBS samples collected through routine newborn screening from 8 patients with FHL type 3 and 1 patient with FHL type 2. Proteomic profiles were compared with those of 90 healthy neonates to evaluate alterations in disease-causing molecules and related biological pathways.
Results: In patients with FHL3, expression of Munc13-4, the causative protein encoded by *UNC13D*, was significantly reduced, and this decrease was detectable in neonatal DBS obtained before clinical onset. Pathway analysis based on differentially expressed proteins further suggested that, in addition to neutrophil degranulation, pathways related to lipid metabolism and inflammatory responses—some of which are known to be activated after disease onset—were already dysregulated during the neonatal period.
Conclusions: DBS-based proteomic analysis can detect disease-associated protein abnormalities and pathogenic pathway alterations in neonatal samples from patients with FHL before symptom onset. Accumulation of pre-onset DBS proteomic data may deepen our understanding of the pathophysiology of FHL and other inherited disorders, while also supporting the development of novel diagnostic and newborn screening strategies.

https://doi.org/10.70962/JSIAD2026abstract.46
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.46

Clinical Features and Functional Analysis of Compound-Heterozygous *RAB27A* Variants in Griscelli Syndrome Type 2 with Sine Albinism

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Introduction: Griscelli syndrome type 2 (GS2), caused by biallelic variants in *RAB27A*, is classically associated with hypopigmentation and life-threatening hemophagocytic lymphohistiocytosis (HLH). However, a subset of patients exhibits normal pigmentation, a presentation termed GS2 sine albinism. We identified two unrelated Japanese patients with this presentation caused by compound heterozygous *RAB27A* variants, representing the first functionally characterized cases in Japanese patients. We performed functional analysis of the identified *RAB27A* variants, including two that have not been previously reported, to help elucidate the molecular basis of preserved pigmentation in GS2.

Case Presentation: Patient 1 is a previously healthy 3-year-old girl with no history of hypopigmentation, who developed systemic and central nervous system (CNS)-HLH. Targeted next-generation sequencing identified three *RAB27A* missense variants: p.Val143Ala (c.428T>C), p.Gly94Ser (c.280G>A), and the novel p.Trp73Arg (c.217T>C). Flow cytometric CD107a degranulation assays revealed markedly reduced natural killer (NK) and $CD8^+$ T cell degranulation. The patient received HLH-2004 induction therapy, achieving initial remission. Following a CNS relapse, she underwent re-induction with dexamethasone, ruxolitinib, and four weekly intrathecal injections and subsequently received unrelated umbilical cord blood transplantation with reduced-intensity conditioning. She remains relapse-free without graft-versus-host disease or neurologic sequelae 1 year post-transplant. Patient 2 is a previously healthy 11-year-old girl with no history of hypopigmentation, who developed systemic and CNS-HLH during the recurring episodes of HLH-like hyperinflammatory state. Targeted sequencing identified compound-heterozygous *RAB27A* variants: a novel missense p.Ser115Arg (c.345C>G) and a paternal frameshift p.Ser106PhefsTer18 (c.315_316del). CD107a degranulation assays revealed severely impaired NK and $CD8^+$ T cell degranulation. The patient received HLH-2004 induction therapy and subsequently underwent myeloablative conditioning, followed by unrelated umbilical cord blood transplantation. However, HLH remained refractory, and the patient died on post-transplant day 18. Analysis using mouse-derived cell line expressing the variants revealed that Trp73Arg showed loss-of-function to both melanophilin (MLPH) and MUNC13-4 binding, whereas Ser115Arg and Val143Ala retained MLPH binding but exhibited reduced interaction with MUNC13-4. This explains preserved pigmentation despite defective immunity, and both cases were diagnosed with GS2 sine albinism.

Discussion: Compound-heterozygous *RAB27A* variants can impair cytotoxic granule release while preserving melanosome transport, resulting in GS2 with sine albinism and a high risk of HLH. An integrated approach that combines genetic testing with standardized functional assays is important, even in patients with sine albinism.

https://doi.org/10.70962/JSIAD2026abstract.47
J. Hum. Immun. (2026) 2 (JSIAD2026): eJSIAD2026abstract.47

Identification of MMD2 as a Novel Causative Gene for Aggressive Periodontitis and Functional Analysis of Its Pathogenic Role

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Aggressive periodontitis is a rare disease characterized by rapid and severe periodontal tissue destruction, typically developing during the teens to twenties. Because it often leads to early tooth loss, it markedly impairs patient quality of life. Although familial clustering has suggested a genetic contribution, the causative gene has remained unknown. The aim of this study was to clarify the molecular basis of aggressive periodontitis through genetic and functional analyses. We identified a family with aggressive periodontitis showing an autosomal dominant inheritance pattern among patients treated at Hiroshima University Hospital. Whole-exome sequencing of affected family members revealed a heterozygous missense variant in MMD2 as a candidate pathogenic mutation. MMD2 was highly expressed in neutrophils, and patient-derived neutrophils showed significantly impaired chemotaxis toward bacterial stimuli compared with those from healthy controls. Proteomic analysis further demonstrated marked alterations in the protein expression profile of patient

neutrophils, suggesting an underlying molecular basis for neutrophil dysfunction. To investigate the pathogenic significance of this variant in vivo, we generated knock-in mice carrying the corresponding Mmd2 mutation and established an experimental periodontitis model. Mutant mice exhibited significantly greater alveolar bone loss than wild-type mice. In addition, neutrophil infiltration into periodontal tissues was markedly reduced in the mutant mice, accompanied by persistent bacterial colonization. These findings suggest that MMD2 mutations contribute to the pathogenesis of aggressive periodontitis by impairing neutrophil function, thereby increasing susceptibility to infection and promoting destructive inflammation in periodontal tissues. This study is the first to identify MMD2 as a potential causative gene for aggressive periodontitis and to provide insight into its underlying molecular mechanism. Our findings may contribute to future genetic risk assessment, early intervention, and the development of personalized therapeutic strategies.