The Genetic Basis for Inborn Errors of Immunity: A Clinical Guide

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ABSTRACT Inborn errors of immunity (IEI) are a heterogeneous group of monogenic disorders affecting immune function, associated with a broad clinical spectrum including recurrent infections and immune dysregulation consisting of poly-autoimmunity, multiple allergies, and malignancies. To date, more than 550 causative genes have been identified, with inheritance patterns that may be autosomal dominant, autosomal recessive, or X-linked. Pathogenic variants may result in loss-of-function, dominant-negative, or gain-of-function effects, leading to variable phenotypic presentations and, at times, incomplete penetrance. Despite advances in genomic technologies, a definitive molecular diagnosis is reached in only 30–35% of cases. Early and accurate genetic diagnosis is crucial for guiding targeted therapy and providing effective genetic counseling. This review presents an updated overview of IEI from the geneticist's perspective and offers a practical approach to the genetic evaluation and diagnosis of these conditions.

IMAJ 2026; 28: 528–534

KEY WORDS: immunodeficiency, inborn errors of immunity (IEI), genetics

Inborn errors of immunity (IEI) are monogenic disorders of the immune system that can lead to increased susceptibility to infections and immune dysregulation including increased risk for malignancy, atopy, and autoimmune manifestations. The prevalence of IEI is currently estimated to range between 1 in 1000 and 1 in 5000 individuals. However, these figures are likely an underestimation, and it is speculated that the true prevalence may be as high as 1 in 500 [1,2].

There are several distinct types of IEI, each resulting from pathogenic variants in different genes. These variants were classified by the International Union of Immunological Societies (IUIS), with the most recent update issued by an expert committee in 2024 [3]. In this framework, IEI are organized into 10 categories: bone marrow failure disorders; severe combined immunodeficiencies (SCID); combined immunodeficiencies (CID); CID with associated or syndromic features; predominantly antibody deficiencies (PAD); diseases of immune dysregulation; congenital defects of phagocyte number, function, or both; defects in intrinsic and innate immunity; autoinflammatory disorders; and complement deficiencies [3].

A list of variants associated with each IEI category can be found in the IUIS guidelines [3]. SCID represents a heterogeneous group of inherited disorders characterized by profound defects in T cell development and/or function, often resulting in life-threatening infections during early infancy [4]. Important examples are variants in IL-2RG and RAG [4]. In contrast, PAD are characterized by impaired antibody production and reduced levels of immunoglobulins. One form of PAD is common variable immunodeficiency (CVID), a heterogeneous group of hypogammaglobulinemia syndromes. CVID is typically defined by reduced serum levels of IgG, IgA, and/or IgM, along with absent or deficient antibody responses to either protein or polysaccharide antigens [5].

An increasing number of patients with IEI present clinical manifestations affecting distal organ systems, including severe dysfunction of the central nervous, gastrointestinal, renal, and pulmonary systems. This combination of immune and non-immune manifestations may result from pathogenic variants in immune-related genes or in broadly expressed genes that affect multiple organ systems beyond the immune system. Such widespread gene expression often results in marked pleiotropy, whereby a single genetic defect produces diverse and clinically significant manifestations across multiple tissues. [1].

Genes associated with the immune system include those encoding the type I interferon receptor, which is expressed by most–if not all–cell types and illustrates how disruption of an immune-related gene can lead to pleiotropic effects. In such cases, immune-related genes expressed in non-immune tissues have normal physiological, non-immune roles in resident tissue cells. Pathogenic mutations may disrupt these functions and induce aberrant immune pathway activation, either within the tissue cells themselves or via secondary stimulation of immune system cells, resulting in an immunological phenotype accompanied by multi-organ clinical involvement [1,6].

Last, non-immune or general genes may also contribute to IEI-like syndromes. For example, mutations in genes encoding nucleases, such as those implicated in Aicardi–Goutières syndrome (AGS), lead to the accumulation of endogenous nucleic acids and subsequent activation of the innate immune system. Although AGS is classified as an IEI, it is primarily characterized by neurological manifestations [1].

Similarly, Coffin–Siris syndrome (CSS) illustrates pleiotropy and immune dysregulation arising from mutations in a broadly expressed, non-classical immune gene. CSS is caused by autosomal dominant variants in the ARID1B gene and is primarily associated with intellectual disability, dysmorphic features, and a variable clinical phenotype. Musculoskeletal abnormalities, such as prominent interphalangeal joints, and potentially reflecting autoinflammatory arthritis, are commonly observed. Furthermore, approximately 33% of children diagnosed with CSS experience recurrent infections, suggesting underlying immune dysregulation [6].

ADVANCES IN GENOMIC TECHNOLOGIES HAVE MARKEDLY EXPANDED THE NUMBER OF GENES IDENTIFIED IN ASSOCIATION WITH INBORN ERRORS OF IMMUNITY.

GENETIC PRINCIPLES OF IEI

Complete vs. incomplete penetrance

In some IEI, the genetic variant is rare, the phenotype is severe, and penetrance is complete, meaning that all individuals carrying the pathogenic variant exhibit clinical manifestations of immunodeficiency. In such cases, establishing a causal relationship between the identified genetic variant and the clinical phenotype is relatively straightforward [1,7].

However, pronounced complexity arises when penetrance is incomplete. In such cases, not all individuals harboring the variant develop clinical symptoms of IEI, and the variant itself may be more common in the general population. Penetrance rates in specific IEI range from as low as 5–10% to nearly 100%. Furthermore, affected individuals often display variable expressivity such as heterogeneous clinical phenotypes with differing severity. In these scenarios, it becomes considerably more challenging to determine whether, and to what extent, the genetic variant contributes to the observed immunological phenotype [1,8].

Modifier genes and environmental factors

The underlying causes of incomplete penetrance in IEI involve complex interactions between environmental influences, the individual's genetic background, and the nature of the genetic variant itself. Environmental factors, such as exposure to pathogens, commensal microorganisms, or vaccines, can influence disease expression in individuals with congenital immune deficiencies [1,7,9]. Environmental triggers play a particularly important role when genetic variants confer susceptibility to specific pathogens, as clinical manifestations may develop only after relevant exposure. Individuals carrying a predisposing variant may therefore remain asymptomatic if they are never exposed to the triggering infectious agent or strong immune stimulus such as vaccination. This exposure-dependent effect provides a mechanistic explanation for incomplete penetrance [1,7,8]. In addition, the genetic background of an individual, including common polymorphisms, mild variants in genes operating within the same biological pathways, or non-coding variants that regulate expression of other pathogenic alleles, can impact disease penetrance. These so-called modifier genes are typically insufficient to cause IEI independently but can alter pathway activity thresholds and immune regulatory set-points, thereby modulating the severity, onset, and phenotypic variability of the disease [1,7,10].

Variant type and location

The type and predicted functional severity of a genetic variant also influence penetrance, but this relationship is not absolute. Loss-of-function mutations, such as nonsense, frameshift, or canonical splice-site variants, are often associated with higher penetrance, particularly when they disrupt essential functional protein domains. However, even among loss-of-function variants, clinical penetrance and expressivity may vary substantially due to modifier genes, environmental exposures, epigenetic regulation, and path-

way redundancy. Missense variants, in contrast, may result in partial loss of function altered protein activity, or context-dependent effects. They are more frequently associated with variable or reduced penetrance. In addition, the position of a variant within the gene is important. Changes affecting critical protein domains, interaction interfaces, or regulatory regions are more likely to have significant phenotypic consequences. Epigenetic mechanisms, such as differences in DNA methylation or chromatin state, may further modify gene expression and contribute to phenotypic heterogeneity [1,7].

Mosaicism and intrafamilial variability

Last, post-zygotic somatic mosaicism, defined as the presence of a genetic variant in only a subset of the body's cells, has been reported in approximately 23% of patients with IEI and may account for intrafamilial variability. Mechanistically, somatic mosaicism represents an important and often overlooked cause of IEI, particularly in apparently sporadic or late-onset cases, because pathogenic variants may be confined to specific immune cell lineages and escape detection by standard germline-focused analyses. Mosaic variants can act through both gain-of-function and loss-of-function mechanisms. In some settings, a second somatic event or acquired loss of heterozygosity of the wild-type allele can convert a low-penetrance germline state into a clinically manifest disease, as for FAS-associated immune dysregulation. In such cases, asymptomatic or mildly affected individuals with mosaicism involving only a subset of cells may transmit a fully penetrant germline mutation to their offspring, who may present with a severe clinical phenotype [1,8].

A DIAGNOSIS OF INBORN ERRORS OF IMMUNITY REQUIRES A COMPREHENSIVE, MULTIDISCIPLINARY APPROACH INTEGRATING CLINICAL, IMMUNOLOGICAL, AND GENETIC EVALUATIONS.

INHERITANCE PATTERNS IN IEI

Chromosomal abnormalities

IEI may originate either from structural variants or single nucleotide variants. Some syndromes characterized by immunodeficiency, among other clinical features, result from structural variations, such as microdeletions or microduplications. For example, DiGeorge syndrome is caused by a microdeletion of chromosome 22q11.2, leading to abnormal development of several organs, including the thymus [1]. Trisomy 21 is another example of a chromosomal condition associated with immune dysregulation [11].

Single nucleotide variants

Variants in more than 550 genes have been identified as causative of IEI. The mode of inheritance of these conditions can be autosomal dominant (AD), X-linked, or autosomal recessive, depending on the gene and variant involved [2,4].

HAPLOINSUFFICIENCY AND DOMINANT-NEGATIVE EFFECTS IN AUTOSOMAL DOMINANT IEI

AD inheritance in IEI arises when a single mutated allele is sufficient to produce a clinical phenotype. Two distinct molecular mechanisms underlie AD inheritance in monogenic IEIs: haploinsufficiency and dominant-negative effects.

The more common mechanism of autosomal dominant inheritance in IEI is haploinsufficiency, in which a single functional allele fails to produce enough protein required to sustain immune homeostasis. This loss-of-function (LOF) mechanism leads to disease due to an inadequate dosage of a critical immunoregulatory gene product. A well-characterized example is CTLA4 haploinsufficiency, which results in a complex syndrome of immune dysregulation. Affected individuals may present with a wide range of clinical features including hypogammaglobulinemia, lymphoproliferation, and autoimmunity, as well as lymphocytic infiltration in multiple organs such as the lungs, gastrointestinal tract, central nervous system, bone marrow, kidneys, and retroperitoneal tissues [1,2].

In contrast, a dominant-negative mechanism involves a mutant protein that actively interferes with the function of the wild-type counterpart, often by forming non-functional or antagonistic complexes. This defect leads to immune dysfunction despite the presence of one normal allele. A well-characterized example is *STAT3*, a transcription factor essential for Th17 cell differentiation and cytokine-mediated signaling. Certain mutations in *STAT3*, such as p.Thr38Ile, prevent phosphorylation and dimerization of the protein, thereby blocking downstream gene transcription. The mutant *STAT3* protein interferes with the activity of the wild-type protein, leading to a dominant-negative effect [12].

While both mechanisms result in autosomal dominant inheritance, they differ fundamentally in their molecular basis: haploinsufficiency reflects insufficient gene dosage, whereas dominant-negative mutations involve active disruption of normal protein function. This issue also affects possible treatment modalities [1,12].

GAIN-OF-FUNCTION VARIANTS

Gain-of-function (GOF) mutations, which enhance or alter protein activity, contribute to autosomal dominant IEIs. STAT1 dysfunction is a well-characterized example. STAT1 GOF variants are inducers of immune dysregulation including autoimmunity and malignancies. In addition, the heterozygous GOF mutations lead to increased susceptibility to chronic mucocutaneous candidiasis (CMCC) through *STAT1* hyperphosphorylation, exaggerated IFN-γ signaling, and impaired Th17 differentiation [13].

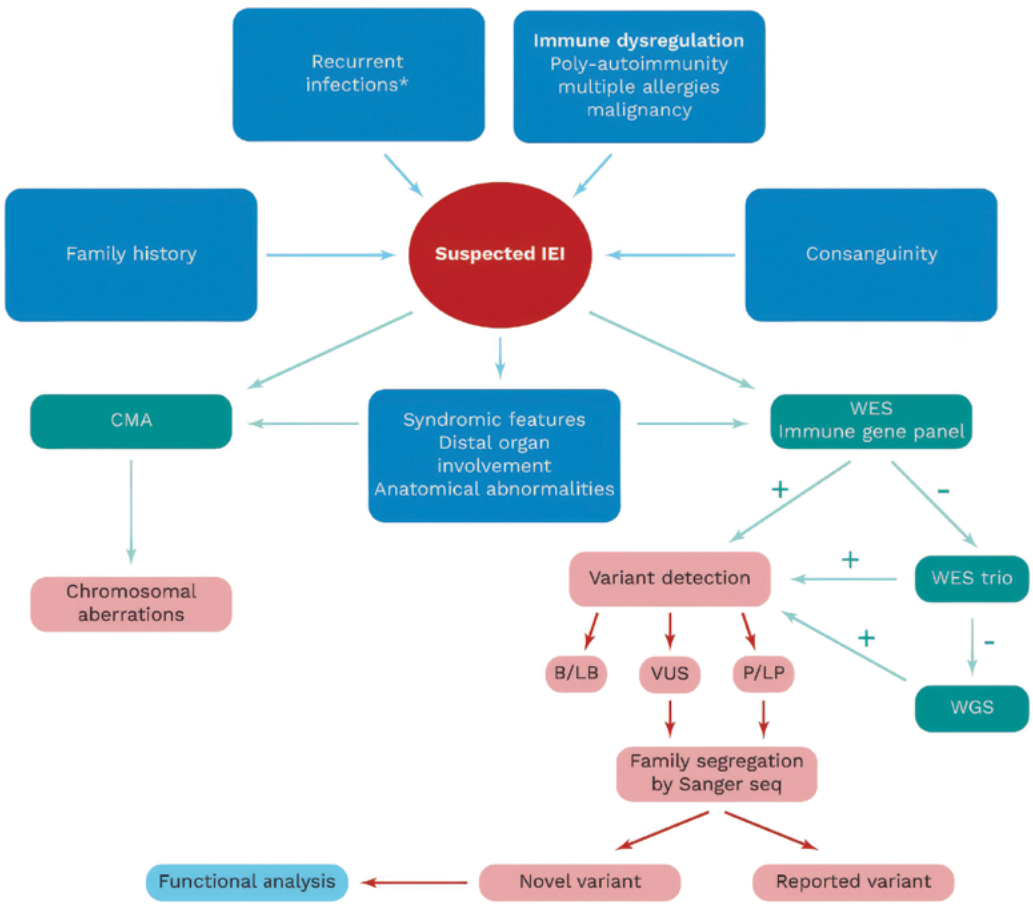
3.2.3 X-LINKED INHERITANCE

The most well-known form of X-linked SCID is caused by pathogenic variants in the *IL2RG* gene localized to chromosome Xq13.1, which encodes the common gamma chain shared by multiple cytokine receptors including IL-2, IL-7, IL-21, IL-15, IL-4, and IL-9. Over 200 pathogenic mutations in *IL2RG* have been described, leading to absent T and NK cells and functionally abnormal B cells [4]. Another example of an X-linked IEI is X-linked agammaglobulinemia (XLA) caused by mutations in the *BTK* gene. *BTK* is essential for pre-B cell receptor signaling, and its deficiency leads to a block in B cell maturation and profound hypogammaglobulinemia.

Most pathogenic variants are located in the coding region (80%), with a smaller proportion (14%) in splice sites, while the remaining variants include deep intronic, regulatory, or structural alterations [14].

Figure 1. Clinical approach to genetic diagnosis of inborn errors of immunity

Recurrent bacterial, viral, or fungal infections, including recurrent abscesses and severe, invasive, or persistent infections, represent key clinical features that should raise suspicion for inborn errors of immunity [2]
B = benign, CMA = chromosomal microarray analysis, IEI = inborn errors of immunity, P/LP = pathogenic/ likely pathogenic, VUS = variant of uncertain significance, WES = whole exome sequencing, WGS = whole-genome sequencing



AUTOSOMAL RECESSIVE INHERITANCE

Most IEI-related genetic defects are inherited in an autosomal recessive (AR) manner, typically resulting from homozygous pathogenic variants, often observed in individuals born to consanguineous parents, or from compound heterozygosity where biallelic pathogenic variants affect the same gene [15].

GENETIC DIAGNOSTIC APPROACHES

Given the clinical and genetic heterogeneity of IEI, a precise molecular diagnosis is essential for guiding clinical management. Consequently, genetic analysis is increasingly considered an early step in the diagnostic workup, facilitating earlier and sometimes unexpected diagnoses [2]. A suggested diagnostic algorithm is presented in Figure 1.

Chromosomal microarray analysis (CMA) is a genome-wide method for detecting copy number variations, including deletions, duplications, and unbalanced translocations, based on hybridization of patient DNA to microarray probes. Although widely used in prenatal testing, CMA also has important value in immunology, particularly in patients with syndromic or multisystem presentations and dysmorphic features, where large genomic imbalances may underlie the phenotype. However, CMA does not detect single nucleotide variants or small insertions and deletions, and its yield is therefore limited in non-syndromic IEI cases [16].

THE INTEGRATION OF IMMUNE-GENETICS INTO INBORN ERRORS OF IMMUNITY MANAGEMENT ENABLES PRECISION MEDICINE AND INDIVIDUALIZED PATIENT CARE.

While CMA is useful for detecting large copy number variations, it cannot identify single nucleotide variants or small insertions and deletions (indels). Therefore, its diagnostic yield is limited to non-syndromic patients. The increasing availability of next generation sequencing technologies, including targeted gene panels, whole exome sequencing (WES), and whole genome sequencing (WGS), has significantly improved the molecular diagnosis of IEIs, particularly in complex or atypical cases [2,17,18].

WES targets protein-coding regions, which comprise approximately 1–2% of the genome but harbor most currently known disease-causing variants. It is highly effective for detecting coding single nucleotide variants and small indels but has limited ability to detect noncoding, regulatory, and deep intronic variants. WGS provides more uniform genomic coverage and improves detection of copy number variants, structural rearrangements, and deep intronic or splice-altering variants across coding and noncoding regions [2,19,20].

Comparative cohort studies show that WES achieves diagnostic yields comparable to or higher than targeted gene panels, while also enabling detection of newly described disease genes and facilitating periodic reanalysis as knowledge evolves. Both WES and WGS have demonstrated clear clinical utility in IEI cohorts, including impact on treatment decisions. In large cohorts, including studies of approximately 1000 families (approximately 1500 patients) and a multinational cohort of 878 patients, targeted panels achieved yields around 56%, whereas WES provided additional diagnoses in previously unresolved cases. These data support WES as a first-line comprehensive approach, particularly in genetically heterogeneous or atypical IEI phenotypes [21,22].

Expanded newborn screening (NBS) using genome sequencing is emerging as a complementary approach to traditional biochemical screening and may enable early detection of actionable monogenic conditions, including immune disorders. Recent large prospective studies demonstrated the feasibility of genome sequencing-based NBS with high parental acceptance and reliable turnaround, identifying clinically actionable findings and, in some cases, immune-related conditions not captured by standard screening assays, thereby enabling earlier intervention [23]. However, implementation of NGS-based NBS raises important challenges, including criteria for gene and condition selection, definition of clinical actionability, reporting policies in phenotype-free settings, confirmatory testing and follow-up burden, turnaround-time requirements, data privacy, and equitable variant interpretation across diverse populations [24].

Genome sequencing interpretation remains challenging for noncoding and structural variants and often requires complementary approaches. Transcriptome sequencing (TS), an RNA-based method that evaluates gene expression levels and splicing patterns, can provide functional support by revealing aberrant splicing or expression outliers. Because immune cells are readily accessible, TS is particularly suitable in IEI evaluation. Combined genome and transcriptome (multi-omics) approaches have produced additional diagnoses in unresolved IEI cases (approximately 14%), although the incremental yield over exome sequencing alone is moderate [25,26].

Long-read sequencing further enhances detection of complex variation, including structural rearrangements, repeat expansions, variants in difficult genomic regions, allele phasing, and methylation signatures. In rare disease co-

horts, including suspected IEI, long-read approaches identified pathogenic genomic and epigenomic variants missed by exome sequencing and provided additional diagnoses in previously negative cases (approximately 10%) [25,27].

Variants detected by high-throughput sequencing are commonly confirmed by Sanger sequencing, which provides high analytical accuracy and is particularly useful for validating single nucleotide variants and performing familial segregation analysis [2,28].

Identified variants should be classified according to standardized guidelines to ensure consistent interpretation of genetic findings. Variant classification is based on a structured assessment of diverse evidence, including scientific literature, population databases, and silico predictions. The American College of Medical Genetics and Genomics in collaboration with the Association for Molecular Pathology established widely adopted criteria for variant interpretation. These guidelines include the use of five standard terms: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign. They also defined a framework for evaluating the clinical relevance of sequence variants in Mendelian disorders [28].

Despite technological advances, a molecular diagnosis is currently achieved in only about 30–35% of IEI cases. Diagnostic yield varies across cohorts and may be substantially higher in consanguineous families and in patients with multisystem or syndromic features [29,30]. In unresolved cases or when variants of uncertain significance are identified, functional assays are often required to establish pathogenicity, with transcriptome analysis providing additional supportive evidence [19,26]. These experimental validations provide critical evidence to distinguish disease-causing mutations from benign variants, improving diagnostic accuracy and guiding clinical management [1,2]. Moreover, in cases where only common variants are detected, their individual contribution to disease risk may be modest or unclear. In such scenarios, calculating a polygenic risk score can help assess the cumulative impact of multiple low-effect variants and determine whether they collectively contribute to the phenotype. This approach is particularly valuable when no single high-penetrance mutation is identified, yet the genetic background may still impact disease susceptibility [10].

THERAPEUTIC AND COUNSELING IMPLICATIONS

Early molecular diagnosis enables timely treatment, including immunoglobulin replacement therapy, hematopoietic stem cell transplantation, and targeted therapies such as immunosuppression, monoclonal antibodies, small molecule inhibitors, and gene therapy. These interventions can improve patient outcomes and offer important insights into genotype–phenotype correlations with prognostic and therapeutic implications [15].

Moreover, genetic diagnosis enables genetic counseling. For highly penetrant, deleterious variants, such as those causing SCID, options including prenatal and pre-implantation genetic diagnosis and pre-marital carrier testing may be considered as part of preventive reproductive planning. In contrast, for variants with incomplete penetrance or milder phenotypes, counseling should emphasize the importance of the diagnosis for personalized medical treatment [7].

CONCLUSIONS

IEI represent a genetically and clinically heterogeneous group of monogenic disorders that require a multidisciplinary diagnostic approach. The integration of advanced genomic tools with functional studies is essential for achieving accurate diagnoses, guiding personalized therapies, and enabling precise genetic counseling. Continued efforts to interpret variants of uncertain significance and uncover novel pathogenic mechanisms will enhance our ability to diagnose and manage these complex immune conditions.

Acknowledgements

The authors thank Prof. Vardiella Meiner, the director of the Department of Clinical Genetic at Hadassah Medical Center, for her academic support and valuable comments regarding the manuscript.

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Capsule

Efficacy and safety of obinutuzumab in active systemic lupus erythematosus

This phase 3, randomized, placebo-controlled trial by **Furie** and co-authors investigated the efficacy and safety of obinutuzumab, a type II anti-CD20 monoclonal antibody, in patients with active systemic lupus erythematosus (SLE) receiving standard background therapy. Obinutuzumab produces more potent and sustained B-cell depletion than rituximab, providing a strong biological rationale for its evaluation in lupus. The study showed that obinutuzumab significantly improved clinical disease activity compared with placebo, with a greater proportion of patients achieving the primary treatment response endpoint. Treatment resulted in reduced disease flares, improved serologic markers, and allowed greater reduction of glucocorticoid doses. Clinical benefits were observed across multiple organ systems, including musculoskeletal and mucocutaneous manifestations, with encouraging results also seen in patients with lupus nephritis. The safety profile was generally consistent with previous experience using anti-CD20 therapies. Infusion-related reactions and infections occurred more frequently with obinutuzumab but were mostly mild to moderate and manageable. No unexpected safety concerns emerged during the study.

N Engl J Med 2026; 395: 243

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