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REVUE DE LA LITTERATURE

Hétérogénéité génétique des syndromes d'Hyper IgE

Genetic heterogeneity of Hyper IgE Syndromes

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MOTS CLÉS

Syndromes d'hyper-IgE ;
Erreurs innées de l'immunité ;
Hétérogénéité génétique

Résumé

Introduction : Les syndromes hyper-IgE (HIES) sont des erreurs innées de l'immunité rares caractérisées par une élévation marquée des IgE sériques, un eczéma, des infections récurrentes et un large éventail de manifestations immunologiques et extra-immunologiques. Au cours des deux dernières décennies, l'identification de nouveaux gènes responsables a profondément modifié la compréhension de ces maladies et mis en évidence une importante hétérogénéité génétique.

Méthodes : Les syndromes hyper-IgE (HIES) sont des erreurs innées de l'immunité rares caractérisées par une élévation marquée des IgE sériques, un eczéma, des infections récurrentes et un large éventail de manifestations immunologiques et extra-immunologiques. Au cours des deux dernières décennies, l'identification de nouveaux gènes responsables a profondément modifié la compréhension de ces maladies et mis en évidence une importante hétérogénéité génétique.

Résultats : Les HIES résultent d'anomalies affectant plusieurs voies biologiques. Les altérations de l'axe IL-6/STAT3, impliquant notamment STAT3, IL6R, IL6ST et ZNF341, représentent une part importante des cas et sont associées à un déficit de l'immunité Th17. D'autres formes sont liées à des anomalies de la signalisation TGF- β , de l'activation de NF- κ B, de l'intégrité de la barrière épithéliale, de la glycosylation ou encore de l'organisation du cytosquelette. Des découvertes récentes, telles que le déficit en OSMR, ont élargi le spectre des affections associées à une hyper-IgE. Malgré des manifestations cliniques communes, ces maladies diffèrent par leur susceptibilité infectieuse, leurs manifestations allergiques, leurs atteintes extra-immunitaires et leurs options thérapeutiques. Plusieurs autres erreurs innées de l'immunité peuvent également s'accompagner d'une élévation importante des IgE et doivent être envisagées dans le diagnostic différentiel.

Conclusion : Les HIES constituent un groupe hétérogène de maladies monogéniques plutôt qu'une entité unique. L'identification précise du défaut génétique sous-jacent est essentielle pour le diagnostic, le conseil génétique, l'évaluation pronostique et l'orientation thérapeutique.

KEYWORDS

Hyper-IgE syndromes ;
Inborn errors of
immunity ;
Genetic heterogeneity

Abstract

Introduction : Hyper-IgE syndromes (HIES) are rare inborn errors of immunity characterized by elevated serum IgE levels, eczema, recurrent infections, and a broad spectrum of immunological and extra-immunological manifestations. Over the past two decades, the identification of new disease-causing genes has substantially changed our understanding of these disorders and revealed considerable genetic heterogeneity.

Methods : We reviewed the literature on the genetic causes of HIES and HIES-like disorders, focusing on the molecular pathways involved, genotype–phenotype relationships, and current diagnostic classification. Both autosomal dominant and autosomal recessive forms were included.

Results : HIES are caused by defects affecting several biological pathways. Alterations of the IL-6/STAT3 axis, involving STAT3, IL6R, IL6ST, and ZNF341, account for a substantial proportion of cases and are associated with impaired Th17 immunity. Other forms result from abnormalities in TGF- β signaling, NF- κ B activation, epithelial barrier function, glycosylation, or cytoskeletal organization. Recent discoveries, including OSMR deficiency, further expand the spectrum of disorders associated with elevated IgE levels. Although these conditions share common clinical features, important differences exist regarding infectious susceptibility, allergic manifestations, connective tissue involvement, neurological abnormalities, and treatment options. In addition, several other inborn errors of immunity may present with marked IgE elevation and should be considered in the differential diagnosis.

Conclusion : HIES represent a diverse group of monogenic disorders rather than a single disease entity. Recognition of the underlying genetic defect is essential for accurate diagnosis, genetic counseling, prognostic evaluation, and selection of the most appropriate therapeutic strategy.

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Introduction

Hyper IgE syndromes (HIES) are rare inborn errors of immunity (IEI) defined by a classic triad: markedly elevated serum IgE, recurrent infections (especially staphylococcal), and eczema presenting as "cold" cutaneous abscesses without typical inflammatory signs. Dental, skeletal, and connective tissue abnormalities are also common, along with susceptibility to viral skin infections (1–3). Normal adult serum IgE is generally below 140 UI/mL, whereas HIES patients often show levels up to ten-fold higher (1).

Recent advances in molecular genetics have considerably expanded the spectrum of disorders associated with the HIES phenotype. To date,

pathogenic variants in multiple genes involved in cytokine signaling, immune-cell differentiation, epithelial barrier integrity, cytoskeletal organization, and tissue homeostasis have been identified, revealing marked genetic and immunological heterogeneity (4–6). Although these disorders share overlapping clinical features, their underlying pathogenic mechanisms and immunological profiles differ substantially. This improved understanding has refined disease classification, leading to the recognition of distinct molecular subtypes and the reclassification of some entities, such as DOCK8 deficiency, within the broader category of combined immunodeficiencies. Together, these discoveries

have provided important insights into the pathophysiology of HIES and underscore the complexity of its molecular landscape, with a clinical spectrum extending beyond infections to include immunological and extra-hematopoietic manifestations (5–7).

The review aims to distinguish the genetic basis of autosomal dominant (AD) and autosomal recessive (AR) forms of HIES to improve diagnosis, clinical management, and targeted therapy.

Genetic classification

HIES arises from de novo or inherited variants, following either AD or AR inheritance pattern (8). Most AD-HIES are caused by mutations in STAT3, whereas most AR-HIES cases involve DOCK8 deficiency (2). The first gene associated with HIES was identified in 2006 as AR TYK2 deficiency (9), which highlighted the role of the JAK/STAT pathway and paved the way for the discovery of dominant-negative STAT3 mutations as the main cause of AD-HIES in 2007 (10).

The most recent International Union of Immunological Societies (IUIS) classification recognizes thirteen genetic defects across ten genes, including AD STAT3 loss-of-function (LOF), AR IL6R, AR and AD IL6ST partial deficiency, AR IL6ST complete deficiency, AR ZNF341, AD ERBIN, AD TGFBR1/2, AR SPINK5, AR PGM3, AD CARD11 LOF, and AD STAT6 gain-of-function (GOF) (7).

Although DOCK8 deficiency is no longer classified as HIES in the latest IUIS update, it is retained in this review due to its well-established HIES-like clinical phenotype. The currently recognized genetic causes are summarized in Table 1.

Molecular and immunological basis of hyper-IgE syndrome

Despite this heterogeneity, HIES converges on shared pathogenic mechanisms that result in elevated serum IgE levels, eczema, recurrent infections, and allergic manifestations. The IL-6/STAT3 signaling pathway represents the best-characterized axis of HIES pathogenesis and is marked by genetic heterogeneity at multiple levels of the cascade, including ligand–receptor interaction (IL6R), signal transduction (IL6ST), and downstream transcriptional regulation (STAT3 and ZNF341). These defects ultimately converge on impaired STAT3 activation, defective Th17-cell differentiation, and compromised mucocutaneous immunity (11).

Other forms of HIES involve dysregulation of TGF- β signaling (TGFBR1, TGFBR2, ERBIN), NF- κ B signaling (CARD11), or cytokine signaling due to STAT6 gain-of-function variants. DOCK8 deficiency affects cytoskeletal dynamics and lymphocyte survival, leading to impaired immune synapse formation and combined immunodeficiency with a HIES-like phenotype. In

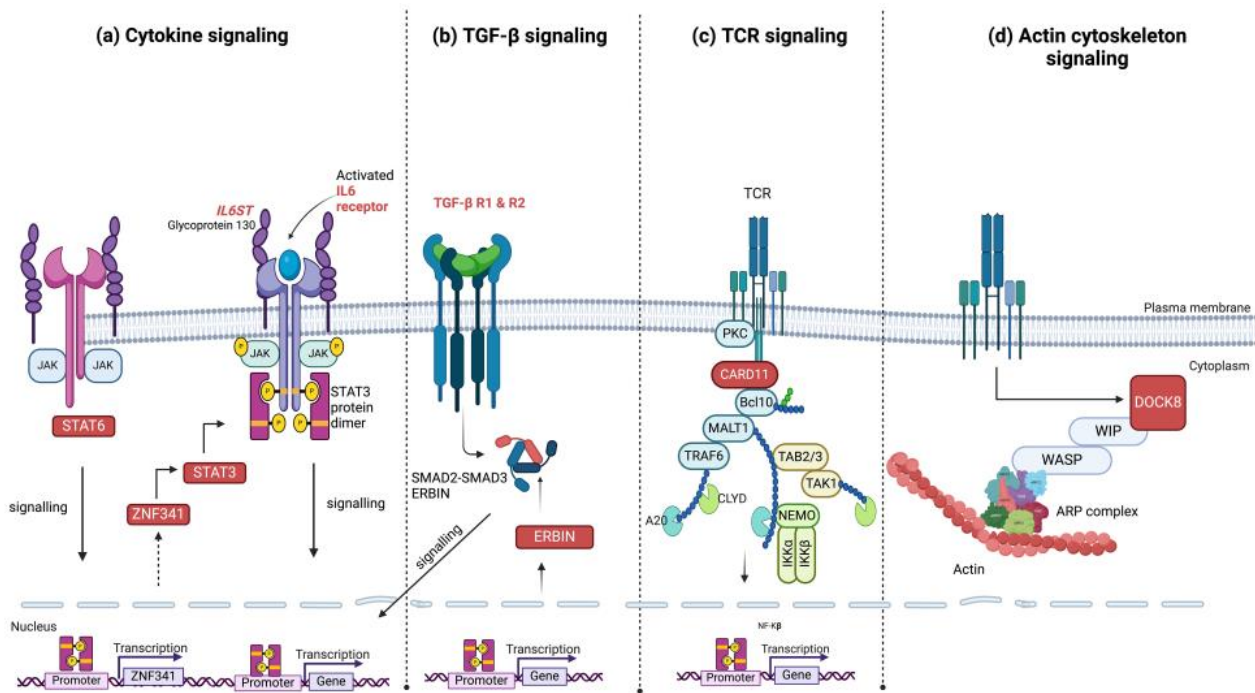


Figure 1. Signaling pathways and associated genes in hyper-IgE syndrome (6). (A) Cytokine signaling; (B) TGF- β signaling; (C) antigen receptor signaling; and (D) cytoskeletal organization. This figure summarizes the major molecular pathways implicated in hyper-IgE syndrome (HIES). Genes associated with HIES are highlighted in red, and phosphorylation events are indicated by yellow circles. Together, these pathways illustrate the key mechanisms underlying the clinical manifestations of HIES: CARD11, caspase recruitment domain-containing protein 11; ERBIN, ErbB2 interacting protein; IL, interleukin; JAK, Janus kinase; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; NF- κ B, nuclear factor kappa B; PKC, protein kinase C; SMAD, mothers against decapentaplegic homolog; STAT, signal transducer and activator of transcription; TAK1, TGF- β activated kinase 1; TCR, T cell receptor; TGFBR, transforming growth factor beta receptor; TRAF6, TNF receptor-associated factor 6; ZNF, zinc finger.

addition, defects in glycosylation (PGM3) or epithelial barrier integrity (SPINK5) may also present with HIES-like phenotypes (11). Collectively, these findings highlight how distinct molecular pathways converge toward a shared clinical phenotype, underscoring the central role of cytokine signaling, Th17 immunity, and barrier homeostasis in HIES (Figure 1).

Autosomal dominant HIES

AD-HIES STAT3 deficiency (Job's syndrome)

Autosomal dominant STAT3 deficiency (Online Mendelian Inheritance in Man (OMIM) #147060), also known as Job syndrome, represents the most common form of hyper-IgE syndrome and accounts for more than 90% of AD-HIES cases.

Since the identification of STAT3 as the causative gene in 2007, more than 400 patients have been reported worldwide (3,10,12). The disease results from heterozygous dominant-negative (DN) variants in STAT3, located on chromosome 17q21.2. Most pathogenic variants are missense mutations affecting the DNA-binding and SH2 domains, emphasizing the critical role of these regions in STAT3-mediated transcriptional activity (Figure 2) (3,6).

STAT3 is a key mediator of signaling downstream of IL-6, IL-21, and IL-23 and is essential for Th17-cell differentiation. Consequently, patients exhibit profoundly reduced Th17-cell numbers, often representing less than 0.3% of circulating CD4⁺ T

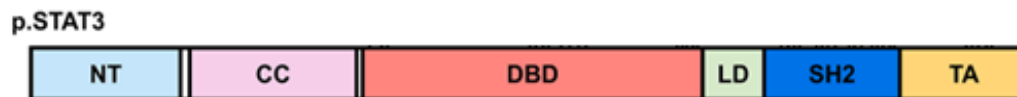


Figure 2. Structural domains of STAT3 (3). DBD, DNA-binding domain; LD, linker domain; NT, N-terminal; SH2, Src homology 2; TA, transactivation

cells, leading to impaired neutrophil recruitment and increased susceptibility to recurrent *Staphylococcus aureus* and fungal infections. In addition, abnormalities of memory B cells and CD8+ T-cell function contribute to the broader immunological phenotype (13,14). Clinically, STAT3 deficiency is characterized by severe eczema, recurrent skin and pulmonary infections, chronic mucocutaneous candidiasis, eosinophilia, and markedly elevated serum IgE levels. Extra-hematopoietic manifestations are common and include characteristic facial features, retained primary teeth, scoliosis, osteoporosis, pathological fractures, and vascular abnormalities such as coronary artery ectasia and aneurysms (3,15–17). Although genetic testing is the diagnostic gold standard, the National Institutes of Health (NIH) scoring system remains useful in identifying patients with a typical clinical phenotype (18). Management remains largely supportive; however, emerging data suggest that hematopoietic stem cell transplantation (HSCT) may improve immune function and reduce infectious complications in selected patients (19).

AD-IL6ST partial deficiency

IL6ST encodes GP130, the common signal-transducing receptor subunit shared by several members of the IL-6 cytokine family, including IL-6, IL-11, IL-27, oncostatin M (OSM), and leukemia inhibitory factor (LIF). Consequently, the clinical manifestations of IL6ST deficiency depend on both the nature of the genetic defect and the cytokine pathways affected. Three distinct forms have been described: complete biallelic LOF causing a severe

Stüve-Wiedemann-like syndrome, biallelic hypomorphic variants causing AR HIES, and heterozygous DN variants causing AD HIES (20). An overview of the affected signaling pathways and HIES-associated phenotypes is shown in **Figure 3**. Autosomal dominant IL6ST deficiency (OMIM #619752) was first reported in 2020 in 12 patients from eight unrelated families and remains an exceptionally rare cause of hyper-IgE syndrome. All reported variants are heterozygous truncating mutations, including nonsense, frameshift variants, and small insertions/deletions, located in the intracellular C-terminal region of GP130 downstream of the transmembrane domain. These mutations remove the intracellular STAT3-binding sites and receptor recycling motifs while preserving cell-surface expression of the mutant protein, thereby leading to a DN effect through interference with signaling by the wild-type receptor. As a result, downstream STAT3 activation is impaired. Signaling through IL-6 and IL-11 is preferentially affected, whereas LIF responses are relatively preserved. Clinically, affected individuals present with a variable HIES phenotype closely resembling DN STAT3 deficiency, including elevated IgE, eosinophilia, eczema, recurrent bacterial and fungal infections, and skeletal and dental abnormalities such as scoliosis and retained primary teeth. Defective signaling downstream of IL-6 family cytokines leads to impaired STAT3 activation and reduced Th17-cell differentiation. However, unlike disorders with profound impairment of IL-11 signaling, craniosynostosis is typically absent, likely reflecting partial preservation of IL-11–

dependent signaling. These findings support the concept that upstream defects affecting the IL-6/STAT3 pathway can reproduce many, but not all, features of STAT3-HIES (6,20–23).

TGFBR deficiency (TGFBR1/TGFBR2)

Autosomal dominant Loeys–Dietz syndrome (LDS; OMIM #609192, #610168) is caused by heterozygous pathogenic variants in TGFBR1 or TGFBR2, which encode the type I and type II receptors of transforming growth factor- β (TGF- β). Reported variants are predominantly missense mutations, most of which affect the intracellular serine/threonine kinase domains, although nonsense, splice-site, and small insertion/deletion variants have also been described, leading to dysregulated downstream signaling. LDS is characterized by aortic aneurysms, arterial tortuosity, and craniofacial abnormalities, including cleft palate (6,24,25).

Dysregulated TGF- β signaling drives Th2 skewing and elevated serum IgE levels, resulting in allergic features that can mimic STAT3-HIES in some patients (26). This expands the phenotypic overlap between connective tissue disorders and inborn errors of immunity.

To date, more than fifty patients with LDS-associated TGFBR1/2 variants presenting immunological features have been reported in the literature (6,24,25).

ERBIN deficiency

ERBIN (encoded by ERBB2IP, OMIM #606944) is a scaffold protein involved in epithelial organization and regulation of TGF- β /SMAD signaling. Autosomal dominant ERBIN deficiency is caused by heterozygous loss-of-function variants, including nonsense and frameshift mutations, leading to reduced protein expression and impaired control of downstream signaling pathways (1,6,27).

Loss of ERBIN results in dysregulated TGF- β signaling, enhanced Th2 cytokine responses, elevated serum IgE levels, and a severe allergic phenotype, often associated with eosinophilic gastrointestinal disease. Only a few unrelated patients have been reported, highlighting the extreme rarity of this entity. This condition expands the HIES-like spectrum by linking epithelial homeostasis and immune dysregulation through altered TGF- β -dependent signaling networks and contributes to clinical overlap with STAT3 deficiency-associated HIES phenotypes (1,6,27).

Clinically, some patients have shown marked improvement with IL-4 receptor blockade (dupilumab), supporting the central role of Th2-driven inflammation (28).

CARD11 deficiency

CARD11-associated atopy with dominant interference of NF- κ B signaling (CADINS) is caused by heterozygous DN variants in CARD11 (OMIM #617638), a key scaffold protein required for antigen receptor-induced NF- κ B activation in lymphocytes. Most reported variants affect the coiled-coil or CARD domains and impair signalosome assembly, resulting in defective downstream NF- κ B signaling (1,6,29).

To date, approximately 60 patients carrying more than 15 distinct CARD11 variants have been reported. The clinical phenotype is characterized by atopy, recurrent infections, hypogammaglobulinemia, and variable cytopenias, reflecting combined B- and T-cell dysfunction (1,6,29).

Serum IgE levels are frequently elevated but are generally lower than those observed in STAT3 deficiency, helping to distinguish CADINS from classic STAT3 deficiency-associated HIES (1,6,27,29).

STAT6 GOF

Gain-of-function variants in STAT6 (OMIM #620532) result in constitutive activation of IL-4/IL-13-dependent signaling, leading to enhanced Th2 differentiation and increased IgE class-switch recombination. Most reported variants affect the DNA-binding or SH2 domains, consistent with a gain-of-function mechanism that amplifies cytokine-driven transcriptional programs (6,30,31).

To date, approximately 20 patients carrying STAT6 GOF variants have been described (11). The clinical phenotype is dominated by severe early-onset allergic disease, including atopic dermatitis, anaphylaxis, eosinophilic gastrointestinal disorders, and, in some cases, lymphoproliferative complications such as follicular lymphoma has been reported (32).

Autosomal recessive HIES

DOCK8 deficiency

DOCK8 deficiency (OMIM #243700) is the most common AR form of hyper-IgE syndrome and is caused by biallelic loss-of-function variants in DOCK8. Pathogenic variants include nonsense, frameshift, splice-site mutations, as well as large intragenic and whole-exon deletions, many of which result in absent or severely reduced protein expression. About 250 patients have been reported worldwide, making DOCK8 deficiency one of the best-characterized monogenic causes of elevated IgE (6,33–35).

DOCK8 encodes a guanine nucleotide exchange factor involved in actin cytoskeleton remodeling, lymphocyte migration, immune synapse formation, and the survival of T, B, and NK cells. Consistent with its role in adaptive immunity, DOCK8 deficiency was reclassified by the 2022 IUIS update as a combined immunodeficiency with low T-cell numbers rather than a classical HIES (4).

Clinically, patients present with severe eczema, marked eosinophilia, extremely elevated IgE levels, recurrent bacterial infections, chronic viral skin infections, severe food allergies, and an increased risk of malignancy. Unlike STAT3 deficiency, skeletal and connective tissue abnormalities are generally absent (6,33–35). HSCT remains the treatment of choice and substantially improves survival and clinical outcomes (36).

ZNF341 deficiency

ZNF341 deficiency (OMIM #618282) is caused by biallelic LOF variants in ZNF341, a zinc-finger transcription factor that regulates both basal and inducible STAT3 expression. Most reported pathogenic variants are nonsense, frameshift, or splice-site mutations generating truncated proteins and resulting in complete loss of ZNF341 function. To date, approximately 20 genetically confirmed patients have been reported worldwide, highlighting the rarity of this condition (6,37,38).

By impairing STAT3 transcription and autoinduction, ZNF341 deficiency produces a clinical and immunological phenotype closely resembling STAT3-HIES. Patients typically exhibit elevated IgE levels, eosinophilia, recurrent bacterial and fungal infections, and defective Th17-cell differentiation. However, extra-immunological manifestations are generally less pronounced than in STAT3 deficiency, whereas low NK-cell counts appear to be a distinctive feature (37,38). These findings identify ZNF341 deficiency as a genetic phenocopy of STAT3-HIES and highlight the central role of the ZNF341–STAT3 pathway in the pathogenesis of HIES.

IL6R deficiency

IL6R deficiency (OMIM #618944) is a rare AR IEI caused by biallelic LOF variants in IL6R, including nonsense, frameshift, and splice-site mutations leading to absent or severely reduced expression of

the interleukin-6 receptor. Fewer than 15 patients have been reported to date, highlighting the extreme rarity of this condition (6,20,39).

IL6R encodes the membrane-bound α -chain of the IL-6 receptor complex, which is essential for classical IL-6 signaling and downstream STAT3 activation. Accordingly, IL6R deficiency results in impaired acute-phase responses, defective B-cell differentiation, and susceptibility to recurrent bacterial infections (20,39).

Clinically, patients present with eczema, recurrent skin and respiratory infections, and a blunted inflammatory response, with a phenotype partially overlapping with hyper-IgE syndromes but lacking the full connective tissue manifestations of STAT3 deficiency-associated HIES (20,39). Immunoglobulin replacement therapy and infection prophylaxis represent the main therapeutic approaches (40).

IL6ST-partial LOF

Autosomal recessive HIES caused by biallelic hypomorphic IL6ST variants (OMIM #618523) was first described in 2021 (23). Most reported variants are missense substitutions affecting membrane-proximal extracellular domains of GP130, occasionally in compound heterozygosity, resulting in hypomorphic receptor function with cytokine-selective signaling defects (6,20,23,44). These variants selectively impair signaling downstream of IL-6, IL-11, IL-27, and OSM while largely preserving LIF responses. Clinically, affected individuals present with a milder HIES phenotype characterized by elevated serum IgE, eosinophilia, recurrent skin and pulmonary infections and eczema. Skeletal and dental abnormalities include scoliosis, retained primary teeth, and craniosynostosis resembling STAT3 deficiency-associated HIES. Impaired signaling

through IL-6 family cytokines results in defective STAT3 activation, reduced Th17-cell differentiation, and increased susceptibility to bacterial and fungal infections (6,20,23,41).

IL6ST complete deficiency

Complete biallelic IL6ST deficiency was first reported in 2020 in five patients from three unrelated families (42). The reported variants are biallelic loss-of-function alleles (OMIM #619751), including nonsense and canonical splice-site mutations, resulting in complete absence of GP130 function. These variants abolish signaling by all GP130-dependent cytokines, including LIF, resulting in a severe multisystem disorder overlapping extended Stüve-Wiedemann syndrome. Clinical manifestations include profound skeletal dysplasia, dysautonomia, respiratory complications, thrombocytopenia, and high early mortality. The marked phenotypic divergence from HIES highlights the critical role of residual GP130 signaling, particularly through the LIF pathway (20,41,42).

PGM3 deficiency

PGM3 deficiency (OMIM #615816) is caused by biallelic hypomorphic variants in PGM3, which encodes phosphoglucomutase 3, a key enzyme involved in the biosynthesis of UDP-N-acetylglucosamine and protein glycosylation. Reported pathogenic variants include predominantly missense mutations, although splice-site variants and compound heterozygous genotypes have also been described. To date, approximately 40 patients from fewer than 20 families have been reported worldwide (6,27,43).

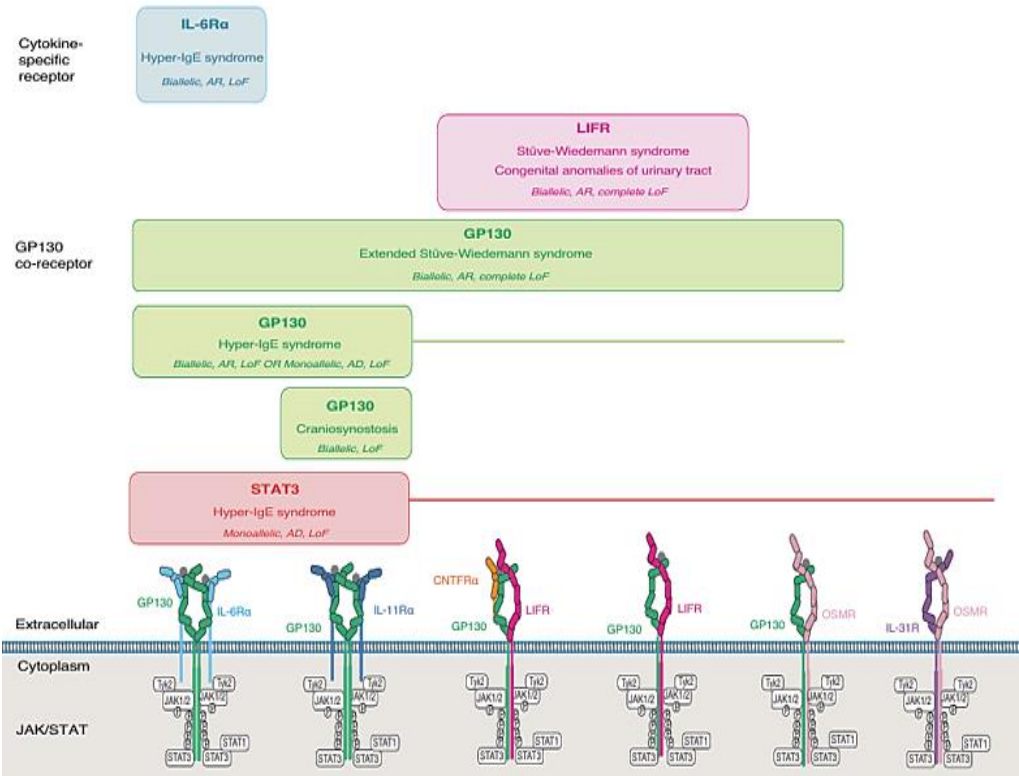


Figure 3. Spectrum of IL6ST/GP130 deficiency and associated hyper-IgE phenotypes (20) modified.

AD : Autosomal dominant; AR : Autosomal recessive; CNTF : Ciliary neurotrophic factor; LIF: Leukemia inhibitory factor; OSM : Oncostatin M

Unlike the classical forms of HIES, PGM3 deficiency combines immunodeficiency with multisystem manifestations resulting from defective glycosylation. Patients typically present with elevated IgE levels, eczema, recurrent infections, eosinophilia, and variable immune dysregulation, often accompanied by neurodevelopmental abnormalities, hypomyelination, developmental delay, and skeletal involvement. The presence of neurological manifestations is a particularly useful feature for distinguishing PGM3 deficiency from STAT3- and DOCK8-related disease (6,27,43). Preliminary studies have suggested that N-acetylglucosamine supplementation may partially restore enzymatic activity, although clinical experience remains limited (44).

SPINK5 deficiency (Comel-Netherton syndrome)

SPINK5 deficiency (OMIM #256500), the molecular basis of Netherton syndrome, is caused by biallelic loss-of-function variants in SPINK5, which encodes the serine protease inhibitor LEKTI. Reported pathogenic variants include predominantly nonsense, frameshift, and splice-site mutations that result in absent or severely reduced LEKTI expression. More than 200 patients have been described worldwide, making SPINK5 deficiency one of the best-characterized inherited disorders associated with elevated IgE (45,46,6).

Loss of LEKTI disrupts epidermal barrier integrity and promotes excessive protease activity, leading to chronic skin inflammation and marked Th2 skewing. Clinically, patients present with

Table 1. Genetic classification of hyper-IgE syndromes

Gene	Inheritance	Variant type	Pathway	Key clinical features
STAT3	AD	DN LOF	IL-6 / STAT3 signaling	Eczema, recurrent bacterial and fungal infections, skeletal and dental abnormalities, pneumatocoles
ZNF341	AR	LOF	STAT3 transcriptional regulation	STAT3-HIES-like phenotype
IL6ST	AD	DN LOF	IL-6 family signaling (GP130)	STAT3-HIES-like phenotype, absence of craniosynostosis
	AR	Hypomorphic LOF		Craniosynostosis, skeletal abnormalities, eczema, recurrent infections
		Complete LOF		Stüve-Wiedemann-like syndrome, severe developmental abnormalities
IL6R	AR	LOF	IL-6 signaling	Recurrent bacterial infections, impaired acute-phase response, eczema
TGFBR1/2	AD	LOF	TGF- β signaling	Aortic aneurysms, arterial tortuosity, craniofacial abnormalities, allergic manifestations
ERBB2IP	AD	LOF	TGF- β / epithelial-immune regulation	Atopy with STAT3-HIES-like manifestations
CARD11	AD	DN LOF	NF- κ B signaling	Severe atopy, food allergy, eczema, asthma
DOCK8	AR	LOF	Cytoskeletal dynamics / immune synapse	Severe viral skin infections, allergy, malignancy risk, CID
PGM3	AR	hypomorphic LOF	Glycosylation pathway	Neurodevelopmental abnormalities, atopy, skeletal involvement
STAT6	AD	GOF	IL-4 / IL-13 signaling	Severe allergic disease, eosinophilia, food allergy, anaphylaxis
SPINK5	AR	LOF	Epithelial barrier integrity	Netherton syndrome, bamboo hair, severe skin barrier defect

congenital ichthyosiform erythroderma, trichorrhexis invaginata (“bamboo hair”), severe atopic manifestations, and elevated serum IgE levels. In addition to barrier dysfunction,

immunological abnormalities including reduced memory B cells, impaired NK-cell cytotoxicity, and suboptimal vaccine responses have been reported (45,46). Recent studies suggest that biologic

therapies such as dupilumab may provide clinical benefit in selected patients (46).

Oncostatin M deficiency

OSMR deficiency has recently been proposed as a novel AR form of HIES-like disease, clinically resembling STAT3-HIES but primarily arising from stromal rather than hematopoietic dysfunction (47). This was illustrated by a patient presenting with elevated IgE, eczema, recurrent infections, chronic pulmonary aspergillosis, and bone fractures, who carried a homozygous missense variant in OSMR (V436D). The variant leads to reduced cell-surface expression of OSMR and impaired oncostatin M-induced STAT3 activation. Immunological studies revealed alterations in B- and T-cell compartments consistent with a germinal center defect driven by a non-hematopoietic, fibroblast-intrinsic abnormality. Importantly, functional rescue experiments confirmed that reconstitution of OSMR in patient fibroblasts restores the cellular phenotype (47).

Differential diagnosis of high IgE disorders

Beyond classical HIES, several inborn errors of immunity (IEI) may present with elevated serum IgE, making differential diagnosis particularly challenging. Omenn syndrome, Wiskott–Aldrich syndrome, WIP deficiency, and ARPC1B deficiency are characterized by increased IgE levels associated with eosinophilia and allergic manifestations, although each displays a distinct immunological and hematological profile. IPEX syndrome, caused by FOXP3 loss-of-function mutations, is marked by profound regulatory T cell deficiency and often results in markedly elevated IgE in the context of severe multiorgan autoimmunity rather than recurrent infections. STAT5b deficiency disrupts signaling downstream of multiple cytokines and growth hormone, leading

to growth failure, immune dysregulation, and increased IgE levels (48).

Defects affecting lymphocyte activation, such as STK4 and MALT1 deficiencies, may also present with hyper-IgE phenotypes accompanied by variable immune dysfunction. Similarly, IL21 deficiency impairs T cell help for B cell differentiation and has been associated with elevated IgE and defective humoral immunity. In addition, 22q11.2 deletion syndrome (DiGeorge syndrome), characterized by thymic hypoplasia and T cell lymphopenia, may occasionally present with elevated IgE and eczema-like skin involvement (48).

Beyond IEI, disorders affecting epithelial barrier integrity, such as filaggrin deficiency and epidermolysis bullosa, can also mimic HIES by inducing secondary IgE elevation due to increased allergen exposure through a disrupted skin barrier rather than a primary immune defect (6,11).

Because of this broad overlap, accurate diagnosis relies on integrated clinical evaluation, immunophenotyping, and genetic testing to identify the underlying defect and guide appropriate management.

Conclusion

Hyper-IgE syndromes represent a genetically heterogeneous group of inborn errors of immunity resulting from disruption of multiple molecular pathways, including cytokine signaling, antigen receptor signaling, epithelial barrier function, and immune homeostasis. This expanding genetic landscape highlights that IgE-associated phenotypes arise from distinct but converging molecular mechanisms rather than a single unified disease entity, and that a proportion of patients with a typical HIES phenotype still lack an identifiable genetic cause, suggesting that additional disease genes remain to be discovered.

Accurate molecular diagnosis using next-generation sequencing approaches, including targeted gene panels and whole-exome sequencing, is therefore essential for precise classification, early diagnosis, and improved patient management. Beyond confirming the diagnosis, genetic characterization provides key insights into disease mechanisms and supports risk stratification and therapeutic decision-making.

From a therapeutic perspective, allogeneic hematopoietic stem cell transplantation remains a genotype-driven intervention with proven benefit in selected disorders such as DOCK8 deficiency, while emerging gene-based and targeted immunomodulatory approaches are reshaping future management strategies.

Overall, the integration of clinical, immunological, and genetic data continues to refine the definition of HIES and reinforces the central role of molecular diagnosis in improving patient outcomes.

Declaration of interests

The authors declare that they have no conflicts of interest.

References

1. Gracci S, Novelli T, D'Elia S, Bernardini R, Peroni D. Hyper IgE Syndromes. *Curr Pediatr Rev*. 2024;20(3):253-64.
2. Minegishi Y. Hyper-IgE syndrome, 2021 update. *Allergol Int*. oct 2021;70(4):407-14.
3. Freeman AF, Wang C, Urban A, Martin I, Dang L, Davis J, et al. Clinical features, genetics, treatment, and long-term outcomes of STAT3 hyper-IgE syndrome: Single-center cohort analysis. *Journal of Allergy and Clinical Immunology*. 28 avr 2026.
4. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. oct 2022;42(7):1473-507.
5. Zhang Q, Boisson B, Béziat V, Puel A, Casanova JL. Human hyper-IgE syndrome: singular or plural? *Mamm Genome*. août 2018;29(7-8):603-17.
6. AlYafie R, Velayutham D, van Panhuys N, Jithesh PV. The genetics of hyper IgE syndromes. *Front Immunol*. 18 févr 2025;16.
7. Poli MC, et al. Human inborn errors of immunity: 2024 update. *J Hum Immun*. 2025;1(1):e20250003.
8. Ishizaka K, Ishizaka T. Physicochemical properties of reaginic antibody. 1. Association of reaginic activity with an immunoglobulin other than gammaA- or gammaG-globulin. *J Allergy*. mars 1966;37(3):169-85.
9. Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity*. nov 2006;25(5):745-55.
10. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 30 août 2007;448(7157):1058-62.
11. Salehi M, Neshati Z, Ahanchian H, Tafrishi R, Pasdar A, Safi M, et al. Hyper IgE Syndromes: Understanding, Management, and Future Perspectives: A Narrative Review. *Health Sci Rep*. 19 mars 2025;8(3):e70497.
12. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 18 oct 2007;357(16):1608-19.
13. Siegel AM, Heimall J, Freeman AF, Hsu AP, Brittain E, Brechley JM, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. *Immunity*. 23 nov 2011;35(5):806-18.
14. Deenick EK, Pelham SJ, Kane A, Ma CS. Signal Transducer and Activator of Transcription 3 Control of Human T and B Cell Responses. *Front Immunol*. 2018;9:168.

15. Tsilifis C, Freeman AF, Gennery AR. STAT3 Hyper-IgE Syndrome—an Update and Unanswered Questions. *J Clin Immunol*. 2021;41(5):864-80.
16. Freeman AF, Avila EM, Shaw PA, Davis J, Hsu AP, Welch P, et al. Coronary artery abnormalities in Hyper-IgE syndrome. *J Clin Immunol*. juin 2011;31(3):338-45.
17. Retained primary teeth in STAT3 hyper-IgE syndrome: early intervention in childhood is essential | Orphanet J Rare Dis. 2020.
18. Schimke LF, Sawalle-Belohradsky J, Roesler J, Wollenberg A, Rack A, Borte M, et al. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *J Allergy Clin Immunol*. sept 2010;126(3):611-617.e1.
19. Tsilifis C, Raedler J, Renke J, Medinger M, Laberko A, Haraldsson Á, et al. Allogeneic hematopoietic stem cell transplantation for STAT3 hyper-IgE syndrome: a worldwide study. *Blood Adv*. 23 juin 2025;9(16):4126-35.
20. Chen YH, Spencer S, Laurence A, Thaventhiran JE, Uhlig HH. Inborn errors of IL-6 family cytokine responses. *Curr Opin Immunol*. oct 2021;72:135-45.
21. Béziat V, Tavernier SJ, Chen YH, Ma CS, Materna M, Laurence A, et al. Dominant-negative mutations in human IL6ST underlie hyper-IgE syndrome. *J Exp Med*. 1 juin 2020;217(6):e20191804.
22. Ashihara K, Asano T, Takeuchi K, Noma K, Tsumura M, Wang W, et al. Fine mapping of heterozygous IL6ST nonsense variants underlying autosomal dominant hyper-IgE syndrome. *JCI Insight*. 22 juill 2025;10(14).
23. Arlabosse T, Materna M, Riccio O, Schnider C, Angelini F, Perreau M, et al. New Dominant-Negative IL6ST Variants Expand the Immunological and Clinical Spectrum of GP130-Dependent Hyper-IgE Syndrome. *J Clin Immunol*. oct 2023;43(7):1566-80.
24. Pees C, Michel-Behnke I, Hagl M, Laccone F. Detection of 15 novel mutations in 52 children from 40 families with the Marfan or Loeys-Dietz syndrome and phenotype-genotype correlations. *Clin Genet*. déc 2014;86(6):552-7.
25. Nakajima T, Iba Y, Shibata T, Hosaka I, Nakazawa J, Kawaharada N. Ten-year follow-up study of a young woman with loeys-dietz syndrome: a case report. *J Cardiothorac Surg*. 4 juill 2023;18:209.
26. Rodari MM, Cerf-Bensussan N, Parlato M. Dysregulation of the immune response in TGF- β signalopathies. *Front Immunol*. 2022;13:1066375.
27. Milner JD. ERBIN and phosphoglucomutase 3 deficiency. *Curr Opin Immunol*. 2023;84:102353.
28. Droghini HR, Abonia JP, Collins MH, Milner JD, Lyons JJ, Freeman AF, et al. Targeted IL-4R α blockade ameliorates refractory allergic eosinophilic inflammation in a patient with dysregulated TGF- β signaling due to ERBIN deficiency. *J Allergy Clin Immunol Pract*. juill 2022;10(7):1903-6.
29. García-Martínez E, Schiaffino MT, Di Natale M, Díaz Luna M de las M, Viteri Álvarez DA, Mejía González MA. From syndromic clues to diagnosis: understanding CARD11-driven disorders. *Front Immunol*. 23 juin 2025;16:1626065.
30. Sharma M, Leung D, Momenilandi M, Jones LCW, Pacillo L, James AE, et al. Human germline heterozygous gain-of-function STAT6 variants cause severe allergic disease. *J Exp Med*. 1 mai 2023;220(5):e20221755.
31. Takeuchi I, Yanagi K, Takada S, Uchiyama T, Igarashi A, Motomura K, et al. STAT6 gain-of-function variant exacerbates multiple allergic symptoms. *The Journal of allergy and clinical immunology*. mai 2023;151(5).
32. STAT6 Gain-of-Function International Consortium. Electronic address: sturvey@bccr.ca; STAT6 Gain-of-Function International Consortium. Human germline gain-of-function in STAT6: from severe allergic disease to lymphoma and beyond. *Trends Immunol*. 2024 Feb;45(2):138-153.
33. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol*. déc 2009;124(6):1289-1302.e4.
34. Aydin SE, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, et al. DOCK8 deficiency: clinical and

immunological phenotype and treatment options - a review of 136 patients. *J Clin Immunol.* févr 2015;35(2):189-98.

35. Singh N, Ranganath P, Jayaram A, Jhawar P, Kotecha U, Janardhanan J, et al. Clinical and molecular profile of 20 patients with DOCK8 deficiency-a single-center experience from Southern India. *Immunol Res.* 12 déc 2024;73(1):8.

36. Aydin SE, Freeman AF, Al-Herz W, Al-Mousa HA, Arnaout RK, Aydin RC, et al. Hematopoietic Stem Cell Transplantation as Treatment for Patients with DOCK8 Deficiency. *J Allergy Clin Immunol Pract.* mars 2019;7(3):848-55.

37. Frey-Jakobs S, Hartberger JM, Fliegau M, Bossen C, Wehmeyer ML, Neubauer JC, et al. ZNF341 controls STAT3 expression and thereby immunocompetence. *Sci Immunol.* 15 juin 2018;3(24):eaat4941.

38. Béziat V, Fieschi C, Momenilandi M, Migaud M, Belaid B, Djidjik R, et al. Inherited human ZNF341 deficiency. *Curr Opin Immunol.* juin 2023;82:102326.

39. Spencer S, Köstel Bal S, Egner W, Lango Allen H, Raza SI, Ma CA, et al. Loss of the interleukin-6 receptor causes immunodeficiency, atopy, and abnormal inflammatory responses. *J Exp Med.* 2 sept 2019;216(9):1986-98.

40. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol.* avr 2006;117(4 Suppl):S525-553.

41. Chen YH, Zastrow DB, Metcalfe RD, Gartner L, Krause F, Morton CJ, et al. Functional and structural analysis of cytokine-selective IL6ST defects that cause recessive hyper-IgE syndrome. *J Allergy Clin Immunol.* août 2021;148(2):585-98.

42. Chen YH, Grigelioniene G, Newton PT, Gullander J, Elfving M, Hammarsjö A, et al. Absence of GP130 cytokine receptor signaling causes extended Stüve-Wiedemann syndrome. *J Exp Med.* 2 mars 2020;217(3):e20191306.

43. Stray-Pedersen A, Backe PH, Sorte HS, Mørkrid L, Chokshi NY, Erichsen HC, et al. PGM3 mutations cause a congenital disorder of glycosylation with severe immunodeficiency and skeletal dysplasia. *Am J Hum Genet.* 3 juill 2014;95(1):96-107.

44. Brasil S, Pascoal C, Francisco R, Marques-da-Silva D, Andreotti G, Videira PA, et al. CDG Therapies: From Bench to Bedside. *Int J Mol Sci.* 27 avr 2018;19(5):1304.

45. Sprecher E, Amin S, Nielsen K, Pfendner E, Uitto J, Richard G, et al. The spectrum of pathogenic mutations in SPINK5 in 19 families with Netherton syndrome. *J Invest Dermatol.* 2001;117(2):179-87.

46. Reese MS, Nguyen R, Chughtai N, et al. Netherton syndrome: a systematic review of diagnosis and treatment challenges. *Cureus.* 2025;17(12):e98322.

47. Andersen S, Assing K, Jensen J, Rasmussen LD, Laursen CB, Dellgren CD, et al. Oncostatin M receptor deficiency as a novel candidate genetic cause of autosomal recessive hyper-IgE syndrome. *J Hum Immun.* 3 mars 2026;2(3):e20250119.

48. Yaakoubi R, Mekki N, Ben-Mustapha I, Ben-Khemis L, Bouaziz A, Ben Fraj I, et al. Diagnostic challenge in a series of eleven patients with hyper IgE syndromes. *Front Immunol.* 2022;13:1057679.