

SPECIAL FEATURE REVIEW

Hyper IgE syndromes: clinical and molecular characteristics

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Abstract

Hyper IgE syndromes comprise a group of rare primary immunodeficiency disorders characterized by a triad of atopic dermatitis, recurrent skin and lung infections along with elevated IgE levels. Job syndrome or autosomal dominant hyper IgE syndrome because of heterozygous loss-of-function mutations with dominant negative effect in *signal transducer and activator of transcription-3* is the prototype of these disorders. However, several other genetically characterized immunodeficiency disorders have been identified over the past decade and joined the umbrella of hyper IgE syndromes including autosomal recessive mutations in the *DOCK8*, *ZNF431* and *PGM3* genes and heterozygous mutations with dominant negative effect in the *CARD11* gene. Moreover, a number of phenotypically distinct immunodeficiency disorders can mimic hyper IgE syndromes, adding to the diagnostic challenge. Herein, we will concisely review these disorders, their molecular bases, highlighting key distinguishing clinical and laboratory findings and therapeutic options.

INTRODUCTION

Hyper IgE syndromes (HIES) belong to a group of primary immunodeficiency disorders characterized by a triad of eczema, recurrent skin and pulmonary infections, and elevated IgE levels. Most cases are sporadic, but autosomal recessive (AR), autosomal dominant (AD) and X-linked variants were described.

In 1966, Davis *et al.*¹ reported two unrelated fair-skinned girls with early onset severe eczema and recurrent pulmonary and staphylococcal skin abscesses “or boils” that lacked the cardinal inflammation signs of rubor, calor and dolor, and were hence described as “cold abscesses,” defining Job syndrome. Six years later, Buckley *et al.*² described two teenage boys with features of Job syndrome but additionally noted dysmorphic facial features and exceptionally high IgE levels defining “Buckley syndrome.” In 1974, Hill *et al.*³ demonstrated defective granulocyte chemotaxis and elevated IgE levels in four female children including the two girls initially reported by Davis *et al.*

showing that Job and Buckley syndromes are in fact one disease entity, and later coined the controversial but still widely accepted term “hyper-IgE syndrome.” In 1999, Grimbacher *et al.*⁴ characterized HIES as an AD multisystem disease with both immune and non-immune manifestations that included skeletal, dental and connective tissue abnormalities (OMIN#147060).

While AD inheritance was subsequently well established in multiple families,⁴ sporadic cases of HIES were more common, and in some kinships, AR inheritance was recognized. In 2004, Renner *et al.* described 13 patients from six consanguineous families who fulfilled the HIES clinical triad but were phenotypically distinct by their heightened susceptibility to cutaneous viral infections and by their lack of skeletal and connective tissue abnormalities, therefore defining yet another disease entity, the AR-HIES with combined immunodeficiency (OMIN#243700).

Over the past decade, progress in genetic testing allowed the identification of the underlying genetic causes

for both the AD- and AR-HIES. Heterozygous mutations in the *signal transducer and activator of transcription-3* (*STAT3*) gene with dominant negative effect were recognized as the cause for AD-HIES,⁵ and biallelic mutations in the *dedicator of cytokinesis-8* (*DOCK8*) gene were identified as the most common cause for AR-HIES.⁶ Over the past 5 years, other monogenic disorders with the HIES phenotype were described (mutations in *PGM3*, *CARD11* and *ZNF431*),⁷⁻¹² expanding the genetic heterogeneity of this syndrome. Moreover, the HIES triad is frequently present in other clinically distinct primary immunodeficiency disorders and in primary skin disorders. While phenotypically similar, treatment strategies for these syndromes do differ. Patients with hypogammaglobulinemia and/or documented functional antibody deficiency are expected to benefit from immunoglobulin replacement therapy. Hematopoietic stem cell transplantation (HSCT) is curative in *DOCK8*-deficient patients,¹³ but is less effective or at least controversial for patients with AD-HIES because of *STAT3* mutations,¹⁴ demonstrating a compelling need to distinguish these molecularly heterogeneous disorders.

In this review, we describe primary immunodeficiency disorders associated with markedly elevated IgE and their underlying molecular bases (Figures 1 and 2), highlighting key distinguishing clinical and laboratory findings and therapeutic options (Table 1).

STAT3 LOSS-OF-FUNCTION MUTATIONS WITH DOMINANT NEGATIVE EFFECT

The classic AD-HIES (also known as Job syndrome) is caused by heterozygous mutations with dominant negative effect in the *STAT3* gene.⁵ *STAT3*, a member of the *STAT* protein family, is a transcription factor involved in signal transduction of multiple cytokines, most notably interleukin (IL)-6, IL-10, IL-11 and IL-21.

IL-6 is an inflammatory cytokine that promotes the release of prostaglandin E in the brain causing fever,¹⁵ and is crucial for both T-helper-17 cell (Th17) and early stages of T follicular helper cell (Tfh) differentiation.¹⁶ Th17 cells, a distinctive T-cell subset that is markedly reduced in AD-HIES,¹⁷ secrete IL-17 and IL-22, two cytokines that induce keratinocytes and epithelial cells to produce various chemokines and antimicrobial peptides, demonstrating the importance of Th17 cells in eliminating extracellular bacterial and fungal pathogens.¹⁸⁻²⁰ Tfh is a T-cell subset involved in immunoglobulin class switching and affinity maturation.²¹ In contrast, IL-10, a cytokine with anti-inflammatory and broad immunosuppressive effects, interferes with the release of proinflammatory cytokines including IL-1, IL-6 and TNF- α .^{22,23} Being crucial for both IL-6 (proinflammatory) and IL-10 (anti-

inflammatory) signaling, *STAT3* plays a role in fine-tuning the inflammatory response. IL-21 promotes B-cell differentiation to IgG-secreting plasma cells, and IL-10 and IL-21 suppress IgE production by B cells.^{22,24,25}

STAT3 function reaches well beyond the immune system. *STAT3* regulates IL-11 signaling and metalloprotease generation,²⁶⁻²⁸ both being important for timely primary teeth exfoliation and ossification of skull sutures. Thus, *STAT3* deficiency explains the delayed shedding of primary teeth, susceptibility to bone fractures, development of aneurysms and the coarse facial features²⁹ which are hallmarks of Job syndrome. It is therefore not surprising that patients with AD-HIES because of *STAT3* mutations present with broad immunological and non-immunological manifestations.^{4,5,17,30}

A large number of missense and in-frame insertion/deletion mutations in *STAT3* have been identified, all exerting a dominant negative effect. These mutations are mostly confined to the DNA binding and SH2 domains of the *STAT3* gene.¹⁷ The latter domain is important for *STAT3* homodimerization with each other or heterodimerization with other *STAT* proteins, required for its transfer across the nuclear membrane. The DNA-binding domain mediates the interaction of the dimerized *STAT3* with specific DNA sequences. While one would expect a genotype–phenotype correlation, this does not seem to be the case, except for slightly increased prevalence of non-immunologic features (high palate, increased interalar distance and scoliosis) among those with mutations involving the SH2 domain.³¹

Clinical features

Neonatal onset eczema (present in 57% of patients), recurrent cutaneous staphylococcal infections with abscess formation (74%), recurrent pneumonias caused by *Staphylococcus aureus* (72%) and *Aspergillus fumigatus* (27%) often resulting in pneumatoceles, deep organ abscesses, mucocutaneous candidiasis (MCC), along with skeletal, dental and connective tissue abnormalities sum up the clinical features of AD-HIES.^{4,5,17,30} While thought to be uncommon, a recent report listed food (37%) and environmental (18%) allergies as being present in a cohort of 58 patients with AD-HIES collected in the USIDnet registry; nonetheless this is less frequent than reported by patients with *DOCK8* deficiency, possibly related to impaired mast cell degranulation.³² While it is not surprising for patients with reduced Th17 cell numbers to develop chronic MCC, the heightened susceptibility of skin and lung tissues to bacterial, predominantly staphylococcal infections remains puzzling, but highlights the importance of Th17 deficiency for the development of these

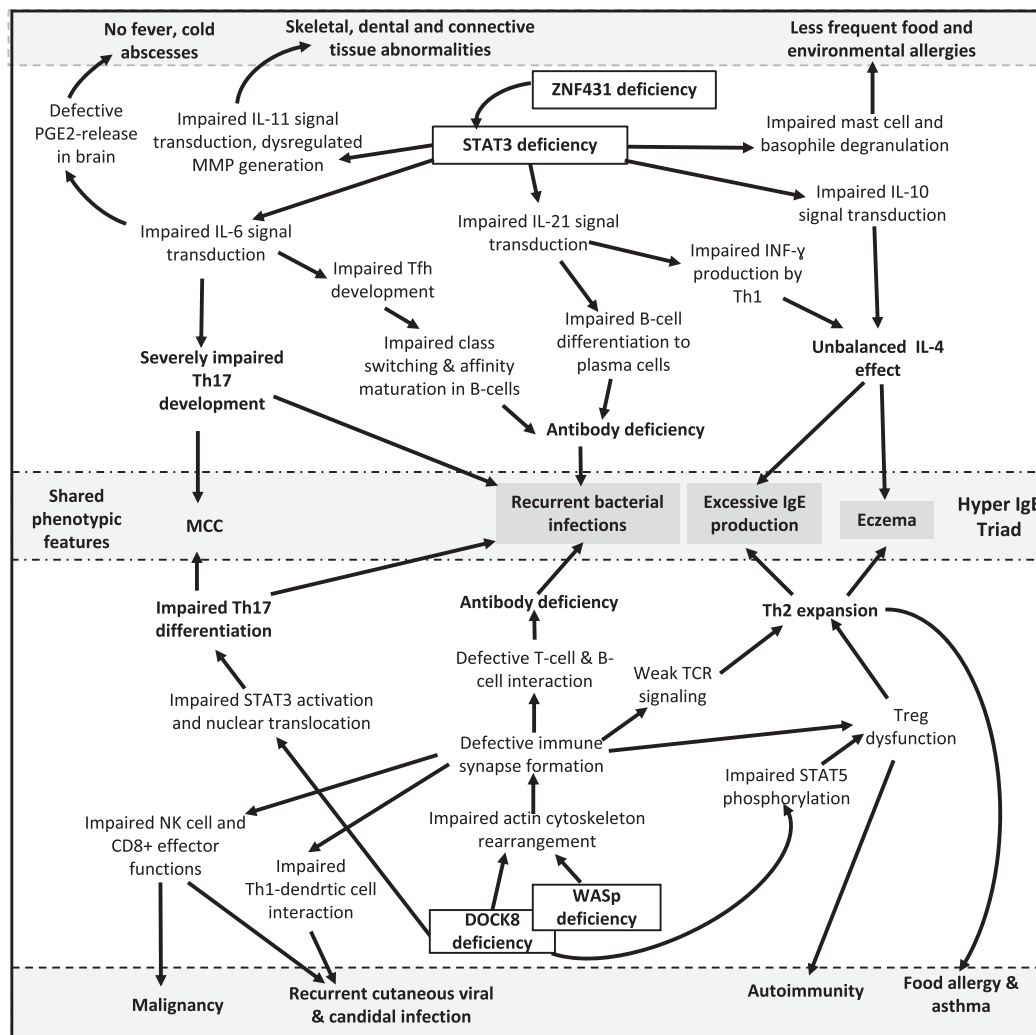


Figure 1. Schematic representation showing the molecular basis for the shared clinical and immunological phenotypes between AD-HIES because of heterozygous mutations in *STAT3* with dominant negative effect and AR-HIES because of *DOCK8* deficiency. While in AD-HIES the defective signal transduction via multiple cytokines is considered to be the cause of the multiple immunological and non-immunological features, the combined immunodeficiency characteristic of *DOCK8* deficiency is related to defective actin cytoskeleton rearrangement. The production of *STAT3* protein is regulated by the *ZNF431* transcription factor. Wiskott–Aldrich syndrome because of *WASp* deficiency shares the molecular basis and some clinical features with *DOCK8* deficiency. MCC, mucocutaneous candidiasis; PGE2, prostaglandin E2; TCR, T-cell receptor; MMP, matrix metalloproteases; *STAT3*, signal transducer and activator of transcription-3.

complications. Since inflammatory responses are mostly absent (hence the term “cold abscesses”), bacterial infections can be easily overlooked.

Non-immunological manifestations such as skeletal, dental and connective tissue abnormalities are key distinguishing features. These include characteristic facial features (increased interalar distance, prominent forehead and facial asymmetry), retained primary teeth (41%), hyperextensible joints (4%), scoliosis (34%), recurrent pathological fractures (39%) and vascular anomalies.^{4,17,30,31,33} It is important to recognize that these

features accumulate over time, and may be absent early in life, posing a diagnostic challenge.

The combination of pulmonary infections and impaired connective tissue remodeling may lead to the development of pulmonary structural abnormalities including pneumatoceles and bronchiectasis setting up the anatomical milieu suitable for colonization with a wide spectrum of pathogens such as *Pseudomonas aeruginosa*, nontuberculous *mycobacteria* and *A. fumigatus*. The latter complication is a major cause of morbidity and mortality.³⁴

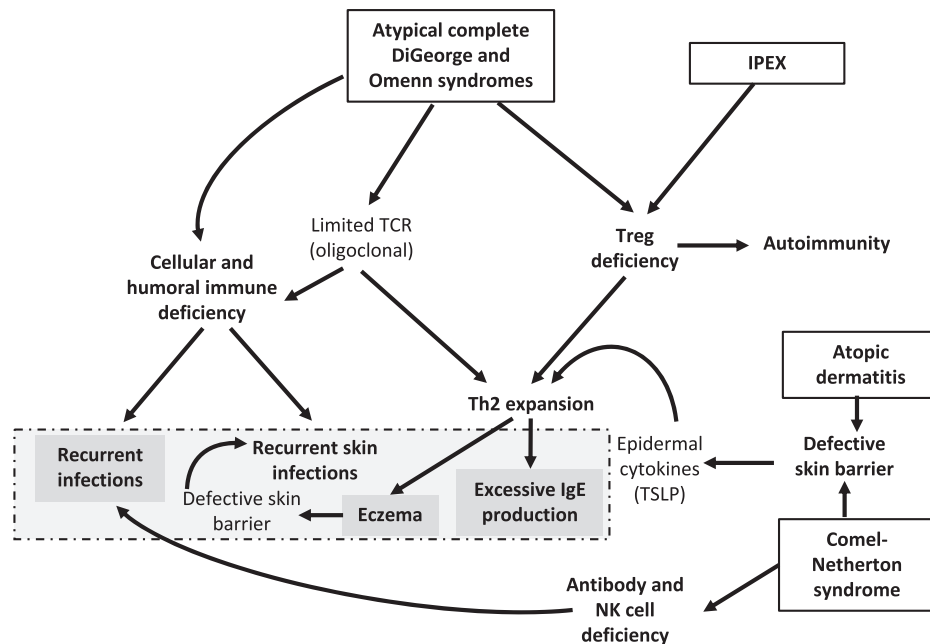


Figure 2. Schematic representation showing the molecular basis underlying the hyper IgE syndrome triad in atypical complete digeorge, Omenn syndrome, IPEX, atopic dermatitis and Comel–Netherton syndrome. While T-regulatory (Treg) cell deficiency allows for the dysregulated Th2 expansion in IPEX, Omenn syndrome and atypical complete DiGeorge, the predominant skin findings in atopic dermatitis and Comel–Netherton syndrome is the result of defective skin barrier. TSLP, Thymic stromal lymphopoietin.

Laboratory findings

While marked elevation in serum IgE (2000–100,000 IU mL⁻¹) is observed in almost all patients (because of impaired IL-10 and IL-21 signaling²⁵), IgE levels start to rise only after birth and decrease or even normalize during adulthood, being inversely correlated with patient age.³⁰ Hence, a normal or an IgE level <2000 is not exclusive of the diagnosis. Eosinophilia is present in more than 90% of patients (usually ≥ 700 cells μL^{-1}). Neither IgE concentration nor eosinophilia correlate with disease activity.^{4,33} Aside from an elevated IgE level, serum immunoglobulin concentrations are unexpectedly normal considering the importance of STAT3 for both Tfh (IL-6 signaling) and plasma cell differentiation (IL-21 signaling). Most patients with AD-HIES, however, exhibit diminished vaccine responses, associated with abnormal B-cell maturation as exemplified by decreased CD27⁺ switched memory B cells.³⁵ Except for decreased central memory T cells,³⁶ T-cell number and function are usually normal.

Diagnosis

The NIH scoring system, based on the presence and severity of 21 clinical and laboratory findings, was developed specifically for identification of AD-HIES.⁴ In

an observational study evaluating 48 AD-HIES patients with STAT3 mutations, 96% scored ≥ 40 ,³⁷ a score indicating high probability for this diagnosis. In the same study, a decreased percentage of Th17 cells ($<0.3\%$ of CD4⁺ T cells) was found to correlate strongly with the presence of STAT3 loss-of-function mutations as opposed to atopic dermatitis patients who had increased percentages of Th17 cells.³⁷

Treatment

Proactive and meticulous skin care, prophylactic anti-staphylococcal and antimycotic agents represent the mainstay of therapy. Vigilance and early institution of antimicrobials for skin and pulmonary infections are key measures, as AD-HIES patients do not display the classic inflammatory signs. Since cutaneous staphylococcal infections contribute to the extent and severity of atopic dermatitis, systemic anti-staphylococcal antibiotics combined with conventional topical agents are recommended. While the efficacy of high dose intravenous immunoglobulin in improving eczema is controversial,^{38,39} replacement doses of immunoglobulin are effective in AD-HIES patients with documented antibody deficiency. The role of HSCT is being explored, so far with conflicting results,^{40,41} at best correcting the immune defect.⁴²

Table 1. Key clinical, laboratory findings and therapeutic options.

Disorder	Mode of inheritance	Mechanism for excessive IgE production	Unique clinical finding(s)	NIH HIES score (prevalence)	IgG, IgA, IgM	Vaccine responses	T- and B-cell numbers	Memory B cell	Mitogen response	Treatment
STAT3 deficiency (Job syndrome)	AD (dominant negative effect)	Impaired IL-10 and IL-21 signal transduction	Skeletal, dental and connective tissue abnormalities	≥40 (96%)	NL	↓	NL	↓	NL	Prophylactic antibiotics, skin care, ±IVIg/SCIG
ZNF431 deficiency	AR	Impaired IL-10 and IL-21 signal transduction	Phenocopy of STAT3 deficiency	≥40 (26%)	NL	↓	NL	↓	NL	Prophylactic antibiotics, skin care, ±IVIg/SCIG
DOCK8 deficiency	AR	Weak TCR signaling favoring Th2 polarization, impaired Treg function	↑↑↑ Cutaneous viral infections, food allergy, ↑ malignancy, combined immunodeficiency	≥40 (67%)	↓ IgM ⁺ , ↑ IgA	↓	↓ T-cell number	↓	↓	Prophylactic antimicrobials, IVIg/SCIG HSCT
PGM3 deficiency	AR	Unknown, possibly weak TCR signaling	Developmental delay, neurologic deficits, skeletal abnormalities, combined immunodeficiency, neutropenia	≥40 (87%)	↑ IgG, IgA, and IgM	NL	↓ T-cell number (↓ CD4:CD8 ratio), ↓ B-cell number	↓	Possibly ↓	GlcNAc supplementation (not clinically explored), HSCT
CARD11 deficiency	AD (dominant negative effect)	Weak TCR signaling favoring Th2 polarization	Similar to DOCK8 deficiency but less cutaneous viral infections and MCC	<40 (always)	Possibly ↓ IgG, ↑ IgA	↓	NL	NL	↓	IVIg/SCIG
Wiskott-Aldrich syndrome	X-linked	↓ Treg function, weak TCR signaling favoring Th2 polarization	Similar to DOCK8 deficiency, but with bleeding tendency (bloody stool), microthrombocytopenia, ↑↑ autoimmunity, malignancy	<40 (always)	↓ IgM, ↑ IgA	↓	↓ With age	↓	↓ Anti-CD3 responses	IVIg/SCIG, HSCT, GT
IPEx syndrome	X-linked	↓ ↓ Treg number and function	Autoimmune enteropathies, endocrinopathies, failure to thrive)	<40 (always)	↑ IgA	NL	NL	NL	NL	IS, HSCT
Omenn syndrome	AR, X-linked (depending on genetic defect)	↓ Treg number and function, limited TCR repertoire, ↑ Th2 cytokine production	Symptoms of SCID, erythroderma, lymphadenopathy, diarrhea, hepatosplenomegaly, autoimmunity	<40 (always)	↓ or absent	Absent	T-cell number reduced, highly restricted, may undergo oligoclonal expansion, B cells ↓ or absent	Absent	↓↓↓ or absent	IS, HSCT
Atypical complete DiGeorge syndrome	Sporadic or AD	↓ Treg number and function, limited TCR repertoire, ↑Th2 cytokine production	Omenn-like, but with characteristic facial features, ↓ PTH/Ca ⁺⁺ and cardiac defects ^a	<40 (always)	↓ or absent	Absent	Similar to Omenn syndrome, but NL B-cell number	↓↓↓	↓↓↓ or absent	IS, thymic tissue transplantation

(Continued)

Table 1. Continued.

Disorder	Mode of inheritance	Mechanism for excessive IgE production	Unique clinical finding(s)	NIH HIES score (prevalence)	IgG, IgA, IgM	Vaccine responses	T- and B-cell numbers	Memory B cell	Mitogen response	Treatment
Cornel-Netherton syndrome	AR	Defective skin barrier, epidermal cytokines promote Th2 polarization	Ichthyosis, bamboo hair	<40 (always)	NL	↓	NL	↓	NL	Meitulous skin care, IVIG
Atopic dermatitis	Multifactorial	Defective skin barrier, epidermal cytokines promote Th2 polarization	Infections are limited to the skin, without deep abscesses, severe infections or MCC; most common cause of hyper IgE	<40 (always)	NL	NL	NL	NL	NL	Meitulous skin care

TCR, T-cell receptor; Th2, T-helper cell type-2; Treg, T-regulatory cell; MCC, mucocutaneous candidiasis; PTH, parathyroid hormone; HSCT, hematopoietic stem cell transplant; IVIG/SCIG, intravenous immunoglobulin or subcutaneous immunoglobulin; IS, immunosuppression; GT, gene therapy; NL, normal.

^aIgM level decreases with age.

^bLow set ears, hypertelorism, fish mouth, hypoplastic thymic tissue with the absence of AIRE gene expression and Treg cells.

DISRUPTED STAT3 TRANSCRIPTION BY NULL MUTATIONS IN THE *ZNF431* GENE

Recently, a functional STAT3-deficient state was described caused by biallelic mutations in the gene coding for the transcription factor *ZNF431*, which resides in the nucleus, where it binds to a specific DNA motif found in various genes, including the STAT3 promoter.^{11,12} All affected patients were consanguineous and homozygous for truncating mutations in *ZNF431*, and had low constitutive levels of STAT3 mRNA, which is in part because of impaired autoinduction of STAT3 generation and function by the cytokines that activate STAT3. The autoinduction process acts as a response acceleration process and appears to be essential for proper STAT3-dependent B- and T-cell function, resulting in decreased Th17, excess Th2 and decreased memory B cells typically observed in AD-HIES patients. However, this process appears to be redundant for STAT3-dependent functions in monocytes and other cell types, explaining the absence of cold abscesses and low incidence of skeletal, dental and/or connective tissue abnormalities. Accordingly, dysmorphic facial features, raised palate, primary teeth retention, scoliosis, joint hyperextensibility and pneumatocoles were infrequently observed among these patients. Given the low prevalence of extra-immune manifestations, only 25% of *ZNF431*-deficient patients had an NIH score of ≥ 40 , which raises a diagnostic challenge and mandates genetic testing as the only way to confirm the diagnosis.^{11,12} There is as yet no consensus or experience on how to treat affected patients effectively. Based on the more prominent immune defect, HSCT may be more effective in *ZNF431* deficiency than in AD-HIES.

DOCK8 deficiency

AR-HIES was initially described in consanguineous families with heightened susceptibility to cutaneous viral infections and neurological complications,⁴³ and was subsequently attributed to deleterious biallelic mutations in the *DOCK8* gene.^{6,44} *DOCK8* is a member of the *DOCK180* superfamily of guanine nucleotide exchange factors which interacts with Rho GTPases. *DOCK8* works upstream of Wiskott–Aldrich syndrome protein and regulates cytoskeletal rearrangement required for cellular migration and immune synapse formation. In dendritic cells, *DOCK8* regulates Cdc42 activity. In *DOCK8* knockout mice, dendritic cells failed to migrate to lymph node parenchyma where they are expected to prime T cells.⁴⁵ *DOCK8* is also important for proper T-cell development. *In vitro* studies suggest that *DOCK8*-deficient memory CD4⁺ T cells are biased toward

T-helper cell 2 (Th2) cytokines at the expense of Th17 cytokines. This is thought to be related to attenuated T-cell receptor (TCR) signaling favoring Th2 differentiation,⁴⁶ and to impaired activation and nuclear translocation of STAT3, a key transcription factor for Th17-cell differentiation.⁴⁷ DOCK8 is required for optimal T-regulatory (Treg) cell function through modulation of IL-2 signaling.⁴⁸ Treg dysfunction itself may result in further dysregulated Th2-cell expansion in addition to predisposing patients to autoimmunity. DOCK8 is important for the survival and function of CD8⁺ T cells, particularly for the generation of memory CD8⁺ T cells.⁴⁹ Natural killer (NK) cells from DOCK8-deficient patients have reduced production of IFN- γ and TNF- α upon Nkp30 stimulation resulting in inefficient NK cell effector function.⁵⁰ Defects in CD8⁺ T cells and/or NK cells may predispose patients to viral infections and impaired tumor surveillance. Finally, immune synapse formation which depends on DOCK8 is crucial for B-cell activation by activated T cells, germinal center formation and generation of memory B cells.⁵¹ Taken together DOCK8 deficiency is expected to have a broad effect on the immune system resulting in combined immunodeficiency, autoimmunity and atopy. DOCK8 deficiency is caused by homozygous or compound heterozygous deletions spanning multiple exons, or less frequently by point mutations resulting in premature stop codons or deleterious splice sites.^{6,44}

Clinical features

Similar to AD-HIES, eczema is an invariable finding in DOCK8-deficient patients who are truly atopic and develop allergies, particularly to food (85%), and most patients suffer from asthma. In addition to recurrent sinopulmonary infections, staphylococcal skin infections and MCC, DOCK8-deficient patients are highly susceptible (81%) to cutaneous viral infections (herpes simplex, human papillomavirus and molluscum contagiosum).¹³ Susceptibility to human papillomavirus infection coupled with defective tumor surveillance are likely contributing to the high prevalence of vulvar and anal squamous cell carcinomas. Skeletal, dental and connective tissue abnormalities are virtually absent, but neurologic manifestations including infectious and noninfectious manifestations (vasculitis, vascular aneurysm and brain infarcts) are frequent complications.¹³ The mechanisms for these noninfectious neurologic manifestations remain elusive.

Laboratory findings

Besides eosinophilia and elevated IgE levels, DOCK8-deficient patients often develop lymphopenia, especially T-

cell lymphopenia and less frequently B-cell lymphopenia. Lymphocyte proliferation in response to mitogens is generally reduced. Quantitative immunoglobulin levels are variable. Low IgM levels are frequently observed and seem to decline further with age. IgG and IgA are usually normal or elevated.¹³ Poor vaccine responses are a common finding.^{13,44}

Diagnosis

Although NIH scores of ≥ 40 are often obtained, this is less frequent than in patients with AD-STAT3 deficiency. Flow cytometric analysis for DOCK8 protein expression is a reliable diagnostic test since most patients have mutations that interfere with normal protein expression. Mutational analysis by Sanger sequencing may be difficult because of the prevalence of large deletion in *DOCK8*; assessing for copy number variation is a more effective strategy.

Treatment

Supportive care consisting of proper identification and treatment of infections, prophylactic antimicrobials and immunoglobulin replacement therapy should be attempted. However, prognosis without HSCT remains poor (median survival ~20 years). Contrary to STAT3 loss-of-function mutations, the exclusive effect of DOCK8 deficiency on the immune system explains the highly successful outcome of early HSCT.¹³

TYK2 DEFICIENCY

AR mutation in the *Tyk2* gene was reported in one patient with AR-HIES⁵² who had an NIH score of 48, and also experienced BCG infection and *Salmonella* gastroenteritis. Tyk2 is a nonreceptor tyrosine kinase of the Janus kinase family involved in signaling through multiple cytokines including type 1 interferon, IL-6, IL-10, IL-12 and IL-23. Impaired IL-12 signaling explains the susceptibility to intracellular organisms in patients with Tyk2 deficiency. Patients subsequently reported with Tyk2 deficiency presented with atypical mycobacterial and viral infections, but did not develop the HIES triad, raising the question if the atopic diathesis observed in the original patient was merely a coincidental finding.⁵³

PHOSPHOGLUCOMUTASE-3 DEFICIENCY

In 2014, Sassi *et al.* and Zhang *et al.* described 17 patients with homozygous hypomorphic mutations in the phosphoglucomutase-3 (*PGM3*) gene featuring an AR-HIES phenotype with preponderance of neurologic

manifestations.^{7,8} PGM3 is required for the synthesis of uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc), an essential precursor for protein glycosylation, but the mechanism by which this glycosylation defect results in HIES remains to be elucidated. One can speculate that UDP-GlcNAc which is a substrate for O-GlcNAc transferase can modulate cellular signaling including TCR signaling via NF- κ B and NFAT, contributing to Th2 expansion.⁵⁴ Like other congenital disorders of glycosylation, PGM3 deficiency causes a broad spectrum of clinical manifestations extending beyond the immune system.

Clinical features

PGM3-deficient patients share features of both STAT3 and DOCK8 deficiency. Early onset atopic dermatitis is a typical finding. Like DOCK8 deficiency, PGM3 deficiency facilitates allergies but the prevalence of food allergy is lower. Recurrent bacterial skin and sinopulmonary infections are hallmarks and complement the HIES triad. Viral cutaneous infections and MCC are occasionally observed but are less prevalent compared to DOCK8 deficiency. Like AD-STAT3 deficiency, patients with mutations in PGM3 present with facial dysmorphism (wide nostrils and prominent lips) and skeletal abnormalities (scoliosis, joint hypermobility) but primary teeth retention is not a feature. As observed in other glycosylation disorders, neurological manifestations, notably developmental delay, intellectual impairment and motor symptoms (ataxia, hypotonia) are characteristic and distinguish PGM3-deficient patients from other HIES disorders.^{7,8} Other findings include renal manifestations (membranoproliferative glomerulonephritis), erythema multiforme major and rarely T⁺B⁺NK⁺ severe combined immunodeficiency-like phenotype.⁵⁵

Laboratory findings

Besides eosinophilia and elevated serum IgE, PGM3-deficient patients can present with B-cell lymphopenia, decreased memory B-cell percentage and hypergammaglobulinemia. Antibody titers to protein and carbohydrate antigens are mostly protective. T-cell lymphopenia is a common finding affecting predominantly the CD4⁺ subset, resulting in reversed CD4:CD8 ratio.⁷ Lymphocyte proliferative responses to mitogens are variable.^{7,8} Neutropenia has also been observed.⁸

Diagnosis

Given the considerable overlap with AD-HIES, a high proportion (87%) of these patients have an NIH score of

≥ 40 ,^{7,8} which is higher than in DOCK8 deficiency. PGM3 protein level may be normal, but its activity is decreased in PGM3-deficient fibroblasts, a useful diagnostic criteria.⁸

Treatment

Oral *N*-acetyl-galactosamine (GlcNAc) supplementation could theoretically bypass the metabolic defect and ameliorate the pathologic phenotype. Clinical data are not available to guide such therapy, but GlcNAc supplementation did restore in vitro intracellular UDP-GlcNAc levels in PGM3-deficient cells.⁸ Immunoglobulin replacement therapy may not be helpful considering the observed hypergammaglobulinemia and normal antibody responses to vaccinations. Two patients with a severe combined immunodeficiency phenotype were successfully treated with HSCT.⁵⁵

DOMINANT NEGATIVE MUTATIONS IN CARD11

Caspase recruitment domain family member 11 (CARD11) plays a critical role as a scaffold protein in the assembly of CARMA1-BCL-9-MALT1 complex which is essential for T- and B-cell receptor signaling via NF- κ B and mTORC activation. Experiments using mouse models have shown that reduction in the efficiency of TCR-NF- κ B signaling differentially compromise Treg versus Th2 effector cells resulting in allergic manifestations.⁵⁶

Heterozygous mutations in *CARD11* with dominant negative effect, allowing for some residual CARD11 activity, have been recently reported as cause of severe atopy, recurrent infections associated with combined immunodeficiency and elevated IgE levels, joining the umbrella of HIES.^{9,10} To date, 12 patients with AD-CARD11 deficiency were identified.^{9,10} While atopic dermatitis, food and environmental allergies and asthma were the predominant clinical manifestations, the majority also suffered from recurrent sinopulmonary and cutaneous bacterial infections, and half the patients reported viral infections with molluscum contagiosum being the most common. Autoimmunity including colitis, lichen planus and autoimmune ovarian failure were also observed, and one patient developed T-cell lymphoma. Fungal infections were infrequent with only 1 of the 12 patients reporting oral candidiasis. Skeletal, dental and connective tissue abnormalities were absent and only two patients displayed mild facial dysmorphism with a wide nasal bridge and a prominent forehead.

IgE levels, although elevated in all patients, were generally lower than those observed in STAT3 deficiency. Eosinophilia was a consistent finding. Quantitative

immunoglobulin levels were mostly normal with moderately reduced IgG and elevated IgA levels being infrequently observed. Antibody responses to vaccines varied with consistently reduced responses to carbohydrate antigens. B- and T-cell numbers were normal, but proliferative response to PHA and anti-CD3 were subnormal.

The clinical and immunological phenotypes of patients with AD-CARD11 mutations overlap considerably with DOCK8-deficient patients but cutaneous viral infections and MCC are less common, and only one affected patient had neurologic complications (seizures and nystagmus). None of the patients with *CARD11* mutations scored ≥ 40 in the NIH scoring system.

HIES IMPERSONATORS

In addition to the “classic” HIESs with a common clinical phenotype and interconnected molecular mechanisms, there are a number of primary immunodeficiency disorders with distinct clinical symptoms and laboratory findings that resemble HIES. Examples of these disorders include complete DiGeorge syndrome,⁵⁷ Omenn syndrome,⁵⁸ Wiskott–Aldrich syndrome⁵⁹ and immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX).⁶⁰ Primary skin disorders like Comel–Netherton syndrome⁶¹ and severe atopic dermatitis can also result in recurrent skin infections and elevated IgE levels, imitating their HIES counterparts.⁶²

Omenn syndrome and atypical complete DiGeorge syndrome

Omenn syndrome, an inflammatory variant of severe combined immunodeficiency, is caused by hypomorphic mutations in a number of severe combined immunodeficiency-causing genes especially those involved in TCR recombination (*RAG1*, *RAG2*, *ARTEMIS* and *DNA ligase IV*).⁵⁸ DiGeorge syndrome is caused by hemizygous 22q11 deletion, resulting in variable developmental defects affecting the thymus, heart and parathyroid glands. Athymic patients are classified as having complete DiGeorge syndrome and ~1/3 of those patients can present with an Omenn-like phenotype.⁵⁷

Patients with Omenn syndrome and complete DiGeorge syndrome have very few T cells at birth with limited TCR repertoire, which can later undergo oligoclonal expansion producing Th2 cytokines and infiltrating peripheral tissues such as skin and gut resulting in eczema, erythroderma, desquamative alopecia, diarrhea and failure to thrive along with eosinophilia and elevated IgE levels. These features, together with their susceptibility to infections, can simulate the HIES triad. One possible explanation for the

oligoclonal Th2 expansion postulates that the limited TCR repertoire prevents sufficient high-affinity competition for antigens, permitting lymphocytes bearing low affinity TCR to be stimulated by self-antigens secrete large quantities of IL-4 leading to proliferation into a Th2 phenotype.⁶³

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome is caused by hemizygous mutations in the *WAS* gene. The *WAS* protein functions downstream of DOCK8 and is involved in the cytoskeletal reorganization necessary for chemotaxis and immune synapse formation. Like DOCK8 deficiency, Wiskott–Aldrich syndrome patients exhibit a mild combined immunodeficiency phenotype; however, the presence of microthrombocytopenia (pathognomonic) and its X-linked inheritance are useful differentiating points. Similar to DOCK8 deficiency, HSCT for Wiskott–Aldrich syndrome is curative.⁵⁹

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked

IPEX is a rare X-linked primary immunodeficiency disorders caused by hemizygous mutations in the *FOXP3* gene which codes for a transcription factor required for the generation of Treg cells. IPEX is an immune regulatory disorder and unlike most HIESs, susceptibility to infections is not a hallmark. Instead, patients present early in life with a triad of autoimmune endocrinopathy (early onset diabetes and hypothyroidism), enteropathy (severe diarrhea resulting in failure to thrive) and eczematous dermatitis. Most patients have eosinophilia, moderately increased serum IgE and IgA levels. T- and B-cell numbers are normal and T cells respond adequately to mitogens. However, most IPEX patients have markedly reduced or absent CD4⁺CD25⁺FOXP3⁺ Treg cells. While Rapamycin and other immunosuppressive agents can tune down the overactive immune system, only HSCT following reduced intensity conditioning is curative.⁶⁰

Comel–Netherton syndrome

Comel–Netherton syndrome is a rare disorder caused by AR mutations in the *SPINK5* gene which codes for the lymphoepithelial Kazal-type-5 related inhibitor which regulates desquamation. Patients usually present early in life with ichthyosiform erythroderma, and many develop characteristic ichthyosis linearis circumflexa and hair shaft abnormalities (easily broken hairs or bamboo hair). These patients are also prone to develop true atopic manifestations (severe atopic dermatitis, hay fever, food allergy and

anaphylaxis). Besides the defective skin barrier which predisposes to cutaneous infections and bacteremia (most commonly with *S. aureus*), patients with Comel–Netherton syndrome were shown to have defective NK cell cytotoxicity, decreased percentage of non-switched and class-switched memory B cells and poor response to the T-cell-dependent neoantigen, bacteriophage phiX174.⁶¹ The functional NK and B-cell defects may further predispose Comel–Netherton syndrome patients to bacteremia and sinopulmonary infections. Elevated IgE levels in view of normal IgG, IgA and IgM levels, eosinophilia, recurrent infections and atopic dermatitis complement the HIES triad, but the presence of hair shaft abnormalities is pathognomonic for this syndrome. Immunoglobulin replacement therapy is indicated in view of the poor antibody responses. In addition, monthly intravenous immunoglobulin injection temporarily corrects the defective NK cell cytotoxicity and improves the skin condition and growth.⁶¹

Atopic dermatitis

The defective skin barrier in atopic dermatitis predisposes patients to recurrent cutaneous bacterial and to disseminated viral infections.⁶⁴ Severe atopic dermatitis is by far the most common cause of elevated IgE levels and can be easily confused with HIES. However, the immune system is generally intact and atopic dermatitis patients have no tendency to develop deep abscesses, severe infections, MCC, nor skeletal or connective tissue abnormalities. Applying the NIH scoring system disqualifies atopic dermatitis patients from a HIES diagnosis.³⁷ In contrast to HIES patients, the IgE levels in atopic dermatitis patients correlate with disease severity and high levels are associated with increased risk of food and environmental allergen sensitization.⁶²

CONCLUSION

Besides presenting with the phenotypic triad of atopic dermatitis, elevated IgE and recurrent skin and pulmonary infections, “classic” HIES disorders appear to share a common molecular basis. They do, however, retain unique flavors specific to their underlying molecular defect, which are useful for keeping them apart and to select optimal therapeutic options. Nonetheless, in view of their significant phenotypic overlap, genetic and functional testing remain the gold standard to establish a definitive diagnosis based on the molecular defect.

As time progresses, more genes responsible for a HIES phenotype will be discovered, possibly revealing exciting new immune pathways, and eventually leading to better understanding and treatment of these disorders.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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