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# Human hyper-IgE syndrome: singular or plural?

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## Abstract

Spectacular progress has been made in the characterization of human hyper-IgE syndrome (HIES) over the last 50 years. HIES is a primary immunodeficiency defined as an association of atopy in a context of very high serum IgE levels, characteristic bacterial and fungal diseases, low-level clinical and biological inflammation, and various non-hematopoietic developmental manifestations. Somewhat arbitrarily, three disorders were successively put forward as the underlying cause of HIES: autosomal dominant (AD) STAT3 deficiency, the only disorder corresponding to the original definition of HIES, and autosomal recessive (AR) DOCK8 and PGM3 deficiencies, in which atopy and high serum IgE levels occur in a context of manifestations not seen in patients with typical HIES. Indeed, these three disorders disrupt different molecular pathways, affect different cell types, and underlie different clinical phenotypes. Surprisingly, several other inherited inborn errors of immunity in which serum IgE levels are high, sometimes almost as high as those in HIES patients, are not considered to belong to the HIES group of diseases. Studies of HIES have been further complicated by the lack of a high serum IgE phenotype in all mouse models of the disease other than two *Stat3* mutant strains. The study of infections in mutant mice has helped elucidate only some forms of HIES and infection. Mouse models of these conditions have also been used to study non-hematopoietic phenotypes for STAT3 deficiency, tissue-specific immunity for DOCK8 deficiency, and cell lineage maturation for PGM3 deficiency. We review here the history of the field of HIES since the first clinical description of this condition in 1966, together with the three disorders commonly referred to as HIES, focusing, in particular, on their mouse models. We propose the restriction of the term “HIES” to patients with an AD STAT3 deficiency phenotype, including the most recently described AR ZNF341 deficiency, thus excluding AR DOCK8 and PGM3 deficiencies from the definition of this disease.

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## Introduction

Hyper-IgE syndrome (HIES) has a rich history, but no universal definition. Three disorders were successively designated as HIES. Job's syndrome was first described in 1966 [1], shown to be autosomal dominant (AD) in 1999 [2], and shown to be due to monoallelic loss-of-function (LOF) *STAT3* mutations in 2007 [3]. Autosomal recessive (AR) forms of HIES we described in 2004 [4], with biallelic mutations of *DOCK8* described in 2009 [5, 6] and of *PGM3* in 2014 [7-9]. However, many other inborn errors of immunity leading to high serum IgE levels and severe infections, including Wiskott-Aldrich syndrome (*WAS* or *WIPF1* mutations), DiGeorge Syndrome (22q11.2DS), Omenn Syndrome (hypomorphic mutations in genes for which null alleles underlie SCID), immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX, *FOXP3* mutations), and Netherton/Comèl-Netherton syndrome (*SPINK5* mutations), have never been considered to belong to the HIES group. AD STAT3, AR DOCK8, and AR PGM3 deficiencies are currently considered to be *bona fide* forms of HIES by some investigators [6, 10-12], but not others [5, 11, 13-15]. Only Job's syndrome and PGM3 deficiency are recognized as HIES in the International Union of Immunological Societies 2018 classification, which considers DOCK8 deficiency to be a combined immunodeficiency (CID) [11]. These three disorders have related, but different immunological and clinical phenotypes, with only a modest overlap. We review here the history of HIES, and what is currently known about its three proposed genetic forms, and we discuss the contribution of the corresponding mouse models to studies of the pathogenesis of this disease. Like other investigators [14, 15], we suggest that the term "HIES" best applies to patients with a phenotype of AD STAT3 deficiency.

## The history of IgE and HIES in human diseases

The definition of "HIES" has been revised and extended on many occasions over the years. Paradoxically, HIES was first described before the discovery of IgE. In May 1966, Ralph J. Wedgwood and coworkers described two red-haired girls with recurrent "cold" staphylococcal abscesses, eczema, and respiratory infections [1]. They named the disease "Job's syndrome", based on the skin boils of the patients. A month later, Robert A. Good and coworkers discovered that X-linked chronic granulomatous disease (CGD) was caused by an inborn error of phagocytic cells resulting in a failure to destroy the bacteria taken up by phagocytosis [16]. At the time, some argued that Job's syndrome was a variant of CGD [17], but this view was overturned in 1969, when Wedgwood demonstrated normal nitroblue tetrazolium (NBT) reduction, indicating that superoxide anion production in phagocytes was normal after phagocytosis in the leukocytes of patients with Job's syndrome, at odds with the characteristic features of CGD [18]. Job's syndrome was subsequently recognized as a distinct condition, different from CGD. IgE was discovered two months after the first description of Job's syndrome in 1966 [19, 20] and it was not until 1971 that serum IgE levels were first reported to be high in patients with Job's syndrome [21]. In 1972, Buckley and coworkers described "hyper-IgE syndrome with recurrent infections", a new syndrome consisting of recurrent cutaneous, pulmonary, and joint abscesses, growth retardation, coarse facies, chronic dermatitis, and extremely high serum IgE levels [22]. Between 1972 and 1980, Job's syndrome and "hyper-IgE syndrome with recurrent infections" were considered to be different conditions, although similarities between them, including high serum IgE

levels and specificity, anti-staphylococcal IgE antibodies, and leukocyte chemotaxis, were recognized and analyzed [23-35]. At the start of the 1980s, researchers in the field finally agreed that Job's syndrome was not restricted to red-haired females and was identical to "hyper-IgE syndrome with recurrent infections" [33, 35-40]. The term and the acronym HIES emerged in 1983 [39-42].

Before Job's syndrome and "hyper-IgE syndrome with recurrent infections" were combined under the same umbrella as HIES, other conditions had been shown to be associated with high serum IgE levels. Between 1966 and 1980, extremely high serum IgE levels were observed in patients with several other PIDs, including Wiskott-Aldrich syndrome, DiGeorge syndrome, and Omenn syndrome. These conditions were rightly seen to be very different from both Job's syndrome and "hyper-IgE syndrome with recurrent infections", and were, therefore, not included in the definition of HIES. Following the recognition of HIES as a single disorder, efforts were made to evaluate its clinical phenotypes by a scoring system and to define its mode of inheritance and map the genetic defect [39, 43, 44]. HIES was first shown to be autosomal dominant in 1999 [2]. Its clinical features were characterized and found to include recurrent skin and pulmonary abscesses, extremely high serum IgE levels, and facial and skeletal features [2]. In 2004, Grimbacher and coworkers proposed the classification of HIES into two subgroups: the AD form as classical Job's syndrome, and the AR form, which lacks skeletal and dental abnormalities but includes recurrent viral and fungal infections [4]. Soon after this report, mutations of *TYK2* (AR, 2006) [45], *STAT3* (AD, 2007) [3, 46, 47], *DOCK8* (AR, 2009) [5, 6], and *PGM3* (AR, 2014) [7-9] were sequentially reported as genetic causes of disease in patients enrolled in "HIES" cohorts. STAT3 deficiency has since been universally recognized as the major AD form of HIES [48, 49]. By contrast, the suggestion that DOCK8 deficiency is the major AR form of HIES has remained controversial [50-52]. Indeed, DOCK8 deficiency has also been categorized as a combined immunodeficiency (CID) (i.e. a T- and B-cell deficiency) by one of the two groups that discovered it [5] and by the International Union of Immunological Societies [11]. PGM3 deficiency is very rare and its classification as a form of HIES has not been contested [12]. Finally, TYK2 deficiency, which has been shown to underlie HIES in two families [45, 53], has been tentatively redefined as a cause of mycobacterial and viral diseases in a context of normal serum IgE levels, based on its identification in multiple families with this phenotype [11, 54]. The meaning of the term "HIES" has thus evolved considerably over the last 50 years. Before reviewing STAT3, DOCK8 and PGM3 deficiencies in humans and mice, and discussing their relevance to HIES, we will begin by briefly reviewing the current state of knowledge regarding IgE.

## IgE and its production

IgE was first isolated in 1966 [19, 20, 55, 56], in the same year as Job's syndrome was first described. The existence of IgE was actually suspected 45 years before its physical discovery [57]. In 1921, Prausnitz and Küstner found that allergies could be transferred to previously unaffected individuals by the transfer of serum from allergic patients. Erythema-wheal assays were used to test for this serum fraction, which was named "reagin". IgG, IgM, IgA and IgD were discovered sequentially between the 1930s and 1960s. However, the name IgE ("E" for the erythema-wheal assays) was coined by Ishizaka and coworkers, who

eventually isolated it from human serum in 1966. Mouse IgE was identified a couple of years later [58]. Its low abundance probably accounts for IgE being the last human Ig isotype to be discovered. In the general population, serum IgE concentrations are at least three orders of magnitude lower than those of any other type of Ig. Despite this low abundance, IgE typically exerts rapid, potent, and broad effects on a wide range of cell types, through FcεRI/FCER1 and CD23/FCER2 [59]. Abnormally high serum IgE levels are, therefore, an alarming trait. It is not rare for Job's syndrome patients to have serum IgE levels as high as 10,000 IU/ml, a thousand times higher than the upper limit of the normal range and almost in the range normally recorded for IgM. Nevertheless, the diagnostic cutoff for HIES is >1,000 IU/ml, which can overlap with atopic diseases and parasitic infections [60, 61]. The name "HIES" may have contributed to the setting of this diagnostic cutoff. Most HIES patients have extremely high IgE levels, but a small proportion of patients with clear genetic diagnoses present with relatively low IgE levels (see below for further discussion). "HIES" therefore requires a relatively low cutoff point, resulting in some overlap with other common diseases, to prevent the exclusion of patients with the same genetic defects but lower levels of IgE. The situation is rendered even more complicated by the normal serum IgE concentrations observed in some HIES patients later in life [2]. Thus, high IgE levels are very good indicators, but are not absolutely required for the diagnosis of HIES.

The molecular and cellular basis of IgE production in humans remains poorly understood due to a number of technical challenges. Most of what we know has been gleaned from mouse models, even though mouse IgE was not discovered until 1972, six years after the discovery of human IgE [58]. We now understand that the Iε promoter is activated by IL-4, acting in synergy with IL-13 and CD40-CD40L signaling [59, 62, 63]. The origin of IgE-producing B cells and plasma cells remains unclear. In antibody responses involving other isotypes, germinal center B cells undergo clonal expansion, somatic hypermutation (SHM), and class switch recombination (CSR), and long-term memory B cells are generated. The process appears to be different for IgE-producing B cells. Following their activation and initial expansion, IgE-expressing B cells are either rapidly becoming plasma cells at the expense of memory B cells, or immediately undergo apoptosis. High-affinity IgE is generated through a unique process, in which B cells first undergo IgM to IgG CSR, and then IgG to IgE CSR, also known as sequential CSR [59, 64-67]. Any abnormality of these processes could potentially lead to the unregulated production of IgE, and thus to hyper-IgE, with or without allergic manifestations. Given the complexity of these processes, the difficulties involved in studies of the synthesis of IgE and pathogenesis of HIES in humans might best be overcome by the use of new emerging mouse models. Conversely, the discovery of genetic causes of HIES, or perhaps eventually of isolated IgE deficiency, may shed light on the mechanisms controlling human IgE production. A very elegant review on inborn errors of atopic disorders and their relationship to abnormal IgE production was recently published [55].

## Job's syndrome

Most patients with Job's syndrome suffer from infections, atopic disease, and abnormalities of the joints, skeletal, dental, and vascular systems. The clinical features of Job's syndrome

have been reviewed extensively in more than 200 patients worldwide [39, 49, 68-70]. Two related scoring systems, the “NIH score” and the “STAT3 deficiency score” [44, 69], have been proposed to assist clinical diagnosis, because many of the early manifestations are nonspecific and the penetrance of each phenotype is both age-dependent and incomplete. The early signs of Job’s syndrome are mostly atopic disorders, including neonatal rash and chronic atopic dermatitis. Patients with Job’s syndrome are susceptible to two key pathogens: *Staphylococcus aureus* and *Candida albicans.* The typical “cold” skin and lung abscesses are mostly caused by *S. aureus* or, more rarely, *Streptococcus pneumoniae,* whereas lung infections, particularly if secondary, can also be caused by *Aspergillus* and *Pseudomonas* [49]. Typically, patients also display chronic mucocutaneous candidiasis (CMC) (43-85%). Although severe, the fungal infections are usually limited to mucocutaneous surfaces and the lungs. A hallmark of STAT3-deficient patients is poor or delayed clinical and biological inflammation, as best exemplified by the cold abscesses observed in these patients [49]. Non-hematopoietic abnormalities include dental abnormalities (retention of the primary teeth), facial abnormalities (coarse appearance), osteopenia (resulting in multiple fractures), and various vascular malformations (including coronary artery aneurysms). About 7-9% of the patients also develop malignancies, especially various types of lymphoma, including Burkitt, non-Hodgkin, histiocytic lymphoma, peripheral T-cell and other B-cell lymphomas.

The immunological phenotypes include high IgE levels, eosinophilia, low levels of Th17 cells, and B memory lymphopenia. Almost all patients have extremely high total IgE levels accompanied with eosinophilia. However, patients with normal IgE levels have occasionally been reported [2, 49]. Serum IgE levels decline with age, particularly in adult patients [2]. T-cell differentiation, particularly for Th17 cells [71-75], is disrupted, T-cell activation and proliferation in patients is normal overall, distinguishing this condition from SCID or CID. Despite the wide range of immunological and non-immunological phenotypes [76, 77], around 80% of patients live to an age of at least 50 years [49]. Minegishi and coworkers, as well as several other groups, discovered that Job’s syndrome is caused by heterozygous, LOF, and dominant-negative (DN) *STAT3* mutations [3, 46, 47]. About 90 different mutations of *STAT3* have been reported, the vast majority of which are missense [70]. No more than ten mutations have been demonstrated experimentally to be dominant-negative. However, no stop-gain mutations have been proven to cause Job’s syndrome, suggesting that the underlying mechanism in Job’s syndrome is not one of haploinsufficiency. Three individuals are heterozygous for a mutation that creates a premature stop, which has however not been proven to underlie haploinsufficiency and Job’s syndrome [78]. Interestingly, three families with mosaic mutations in multiple tissues have been described. The mosaic carriers presented intermediate phenotypes when compared with their heterozygous offspring family members [79, 80]. The complexity of STAT3 signaling and the broad expression of *STAT3* in many tissues have made it harder to understand the mechanism of disease, but both human cells and mouse models have recently been used to elucidate this mechanism.

The complexity of Job’s syndrome is not surprising, because STAT3 is pleiotropic [81]. There are seven STATs (signal transducer and activator of transcription, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6), and four JAKs (Janus kinase, JAK1, JAK2,

JAK3, TYK2) in humans and mice. More than 50 different cytokines and their receptors make selective use of a combination of JAKs and STATs to transmit signals regulating tissue development, organism homeostasis, and host defense [76, 77, 81, 82]. STAT3 is ubiquitous and involved in many cytokine responses, including IL-6. The canonical transcriptional activity of STAT3 has been studied intensively for over 20 years. Following cytokine binding to the receptors, the Y705 residue at the C-terminus of STAT3 is phosphorylated by JAK tyrosine kinases. Phosphorylated STAT3 (p-STAT3) molecules then form homodimers or heterodimers with other STATs via the SH2 domain and are translocated to the nucleus, where they bind directly to DNA and promote transcription. S727 phosphorylation further increases the transcriptional activity of the molecule [81]. Unphosphorylated STAT3 was recently shown to bind to DNA and to exert transcriptional activities not normally associated with tyrosine kinase-mediated signaling [83-86]. Moreover, STAT3 has been shown to have non-transcriptional functions in mitochondria, including electron transport chain regulation, gamma-glutamyl cycle control, and reactive oxygen species (ROS) regulation [83, 87, 88]. Mitochondrial STAT3 has also been implicated in Ras-mediated oncogenic transformation [83, 89, 90]. However, it remains unclear whether these non-canonical functions of STAT3 are related to human disease.

The discovery of AD LOF STAT3 deficiency paved the way for studies of the many defective pathways in Job's syndrome patients [91]. A patient with an AR deficiency of GP130 (also known as IL6ST), a receptor chain common to the receptors for IL-6, IL-11, IL-27, OSM, and LIF was recently shown to suffer from a disease resembling Job's syndrome, but with normal numbers of Th17 cells [92]. Meanwhile, defects in IL-11RA [93-95] and LIFR [96] have been discovered in patients with craniosynostosis and congenital anomalies of the kidneys and urinary tract (CAKUT), respectively. The GP130-deficient patient also presented with high IgE levels, susceptibility to bacterial infections, eczema, and skeletal abnormalities, suggesting that GP130 signaling through STAT3 is responsible for these defects, which are seen in patients with both these disorders. Inborn errors affecting specific cytokines and their receptors facilitated further dissection of the phenotypes seen in patients with Job's syndrome. The discovery of defective Th17 cell differentiation in patients with this syndrome [71-75], together with inborn errors of IL-12Rβ1, IL-17A/F, and the IL-17RA/IL-17RC receptor complex, RORC, and ACT1 [97-107], strongly suggested that IL-17 activity played a key role in attracting neutrophils to the tissues and controlling mucocutaneous fungal infections [97, 99]. The recent discovery of an ERBIN-deficient family has bridged the gap between STAT3 and TGF-β signaling [108]. STAT3 promotes the expression of ERBIN, which impairs TGF-β signaling, thereby skewing $CD4^+$ T-cell differentiation and impairing Treg functions. Two out of three ERBIN-deficient patients have slightly high serum IgE levels and allergic disease, implying that other STAT3 pathways contribute to the extremely high serum IgE concentrations in patients with Job's syndrome. LOF defects of IL-21 and IL-21R lead to inflammatory bowel diseases and cryptosporidial infections, respectively [109-112]. Patients with these defects also display defective Ig class switching and slightly high serum IgE levels, suggesting that insufficient IL-21 signaling is not the only cause of hyper-IgE syndrome [109-114]. Other inborn errors have been used to analyze the non-hematopoietic phenotypes, which are much more difficult to study in patients, due to the lack of access to primary cells [91]. Studies of

LIFR deficiency, a severe AR disease also known as Stuve-Wiedemann syndrome (SWS), have suggested that many of the skeletal abnormalities may be associated with insufficient LIF signaling [96, 115-117]. Moreover, the features of patients with AR IL-11RA deficiency suggest that the craniosynostosis and supernumerary teeth seen in Job's syndrome patients may result from insufficient IL-11 signaling [93-95]. These signaling pathways may interact and overlap in Job's syndrome patients, thereby contributing jointly to the various phenotypes. Studies in both Job's syndrome patients and patients with defects of the STAT3 pathways have begun to resolve the various functions of human STAT3 and the pathogenesis of the various phenotypes of Job's syndrome.

The only mouse model of Job's syndrome currently available was reported in 2013: a transgenic mouse reproducing some of the features of Job's syndrome in humans [118, 119]. The AD mode of inheritance for this disease was mimicked by introducing the V463del mutation, which is common in patients, into the mice via a BAC transgene. The mutant mouse carried two copies of wildtype *Stat3* (wt-Stat3) and two copies of the mutant *Stat3* gene (mut-Stat3). Total Stat3 (both wt-Stat3 and mut-Stat3) protein levels were similar to those in the parental mouse strain. The V463del mutation affects the DNA-binding domain. It impairs transcriptional activity but does not affect the normal phosphorylation of the Y705 residue on activation. This study did not report the levels of the mut-Stat3 protein in mice, but the mutation was dominant, as shown by the level of transcriptional activity upon stimulation with IL-6. The mouse reproduced several of the main features of Job's syndrome, including high IgE levels and a failure to generate Th17 cells. The mutant mouse also displayed impaired control of intestinal *Citrobacter* infection, and a higher mortality on challenge with LPS. More interestingly, bone marrow transplantation restored the production of IL-17 and IL-22 in the mutant mouse, whereas the control of *Citrobacter* infection was only partially rescued, suggesting that non-hematopoietic functions of STAT3 play an important role in host defense [118]. Studies in the same mouse model also demonstrated that the mast cell degranulation induced by IgE receptor cross-linking was impaired in mut-Stat3 mice, consistent with the low levels of food allergy and anaphylaxis in patients despite their high IgE levels [118]. Overall, this mouse model had a phenotype similar to that of patients, including high IgE levels, and is therefore promising for future studies of this multifaceted disease.

In addition to the attempts made to model AD Job's syndrome, murine recessive STAT3 deficiency models have taught us much about the functions of STAT3 (Table 1). Germline *Stat3* deletion is embryo-lethal [83]. However, it is unclear whether heterozygous animals are entirely normal or harbor certain defects. Due to the lethality of the germline knockout in mice, four separate floxed mouse strains have been established with the cre-LoxP system. The canonical transcriptional activity of Stat3 is abolished in all four strains. Many tissue/cell-specific knockout strains have been generated from these four floxed strains and analyzed. Both the myeloid and lymphoid lineages of the immune system have been studied, and these analyses have yielded intriguing results. It has long been debated whether neutrophils from patients with Job's syndrome display impaired chemotaxis [23-32, 34, 120]. Conflicting results have been obtained in human studies, whereas mouse studies have clearly shown that G-CSF-induced emergency granulopoiesis is defective in Stat3-deficient neutrophils, together with chemotaxis towards CXCR2 ligands [121-123]. During the acute

phase of infection, particularly in candidiasis, the endothelial cells produce G-CSF, triggering the immediate mobilization of neutrophils from the bone marrow and expansion of the immature granulocyte population to increase the neutrophil reserve. This results in a rapid increase in the number of circulating neutrophils. This G-CSF-mediated acute response is Stat3-dependent. A failure to mobilize neutrophils, together with the lack of Th17 cells in Job's syndrome patients [73], may contribute to their susceptibility to bacterial and fungal infections, especially at mucocutaneous surfaces [102].

Other functions of Stat3 have also been revealed by studies of conditional knockout mouse models (Table 1). Several Stat3-dependent signaling pathways, including the Flt3, G-CSF, IL-6, and IL-10 pathways, govern the maturation and differentiation of dendritic cells (DCs) [83]. DCs can be classified as conventional DCs (cDCs), which migrate into tissues to perform phagocytosis and present antigens, and plasmacytoid DCs (pDCs), which produce large amounts of type I interferon (IFN). Stat3 overexpression drives the development of hematopoietic progenitors into cDCs and pDCs. The Stat3-dependent Flt3 signal is particularly important for the differentiation of pDCs. The conditional deletion of Stat3 in CD11c-expressing cells selectively impairs pDC differentiation, with little effect on the cDC compartment [124, 125]. By contrast, Stat3-mediated IL-6 signaling and IL-10 signaling have been shown to suppress DC maturation and activation by reducing the expression of MHC II, costimulation molecules, SA100A9, and PD-L1, and by limiting TLR-induced pro-inflammatory responses [83, 124, 126-129]. Stat3 also restrains the RANK and TLR4 pathways by directly inhibiting the expression of a key E2 ubiquitin-conjugating enzyme, Ubc13, in these pathways [130]. Macrophages and osteoclast precursors from Stat3-deficient mice display enhanced osteoclast development following RANK stimulation, potentially accounting for the skeletal abnormalities seen in Job's syndrome patients. Lymphocyte counts are normal in Job's syndrome, but studies of mouse models have shown that Stat3-dependent signaling pathways are indispensable in many lymphoid lineages, including the Flt3L signaling pathway in common lymphocyte progenitors [131], IL-6 and TGF-β signaling in Th17 cell differentiation [83, 132], and IL-21 signaling in the expansion and maturation of B cells and plasma cells [133, 134]. Intriguingly, B cell specific deletion of Stat3 in mouse models challenged with antigen resulted in elevated IgE, suggesting that the hyper-IgE in Job's patients might be B cell-intrinsic [135]. Studies of the conditional deletion of Stat3 in multiple lineages have improved our overall understanding of the mechanisms underlying the various phenotypes seen in Job's syndrome patients.

## DOCK8 deficiency

Inherited DOCK8 deficiency was first reported in 2009 [5, 6]. Years earlier, Bodo Grimbacher's group had already distinguished AR-HIES from Job's syndrome, and described AR-HIES as a condition characterized by susceptibility to viral and fungal infections rather than bacterial infections [4]. We now know that a sizeable proportion of the AR-HIES patients known at the time were actually DOCK8-deficient. Most patients present with severe allergy, chronic infections, and early-onset cancer. The clinical presentation and treatment of this condition were recently extensively reviewed; about 200 patients have been reported worldwide [15, 136, 137]. The first sign suggestive of DOCK8 deficiency is usually severe allergies, including atopic dermatitis soon after birth, asthma, multiple food and

respiratory allergies. However, despite this initial presentation of severe allergy in DOCK8-deficient patients, the hallmark of the disease is a broad spectrum of infections, including chronic cutaneous viral infections, recurrent respiratory infections, and mucocutaneous candidiasis. More than half the patients have been reported to have life-threatening infections, with overall survival was as low as 37% at 30 years of age [136]. It is, therefore, unsurprising that DOCK8 deficiency is increasingly considered to be a CID rather than a form of HIES, as proposed by Helen Su in her seminal paper [5, 15]. The immunological phenotypes of DOCK8 deficiency include high serum IgE levels, eosinophilia, and T- and NK-cell lymphopenia. Serum IgE levels are high in almost all patients, with a median value of about 2000 IU/ml [136]. DOCK8, which is mostly expressed in hematopoietic cells, belongs to the dedicator of cytokinesis (DOCK) family. All 11 members of this family function as atypical guanine nucleotide exchange factors (GEFs), activating small Rho GTPases, such as RAC1, RAC2, and CDC42 [138]. DOCK8 was first isolated and cloned in 2004 as a CDC42-interacting protein of the DOCK family [139]. As a newly identified protein, the *in vivo* functions of DOCK8 were then characterized by studying human disease and the corresponding mouse models [5, 6, 139, 140].

All the mutations identified in patients with DOCK8 deficiency to date are LOF, and heterozygous carriers are clinically healthy. AR DOCK8 deficiency has two specific genetic features. The first is the high frequency of large deletions (CNVs), which have been identified in more than half the patients. The mechanism for the unusually high frequency of deletions probably involves frequent homologous recombination between repetitive DNA sequence elements over a large stretch of the DOCK8 locus close to the telomere [15]. This high frequency of homologous recombination also accounts for the other specific feature of DOCK8 deficiency, including its unusually high frequency of somatic reversion. In DOCK8-deficient patients, homologous recombination may repair the mutant allele by gene conversion or intragenic single crossover. Five years after the first discovery of DOCK8 deficiency, reversion was detected in 17 of the 23 families followed at the NIH [141]. Reversion has also been reported in other PIDs, such as WAS [142-147] and X-linked lymphoproliferative disease (XLP) [148] in particular, in which reversion has been reported in up to 10-30% of patients. Nevertheless, the frequency of reversion in DOCK8 deficiency is unprecedented among PIDs. Careful investigations of different cell populations also revealed that T and NK cells in which DOCK8 defects were repaired were at a significant advantage in terms of growth. The clonal expansion of these cell populations eventually resulted in the reversion becoming clinically detectable [141]. Reversion resulted in no particular growth advantage in the B cells of patients, but it has been shown that DOCK8 may also regulate the activation and IgE production triggered by TLR9-MYD88 signaling in a STAT3-dependent pathway, which might explain the B cell defects and hyper IgE shared by DOCK8-deficient and Job’s syndrome patients [149, 150]. Similar to Job’s syndrome patients, DOCK8-deficient patients also presented with defective Th17 cell differentiation, which has been suggested to be caused by defective STAT3 phosphorylation and translocation [151]. In addition to its role in the expansion of T- and NK-cell populations, DOCK8 has been shown to participate in NK cell effector functions, T-cell activation, Th1, and Th2 cell differentiation, although conflicting results have been obtained in different studies [138, 151-157]. The high frequency of somatic reversion modifies the clinical

presentation of the disease in an unpredictable, but often beneficial way. Conversely, somatic reversion does not occur in mouse models, which have nevertheless become a key tool for studies of the underlying mechanisms of disease.

Interestingly, Dock8-deficient mice were discovered independently through unbiased screening for antibody responses, a model for common variable immunodeficiency (CVID) rather than CID or HIES [140]. Using N-ethyl-N-nitrosourea (ENU)-induced mutation in mice, the Goodnow group discovered two independent mouse pedigrees (*cpm* and *pri*) with LOF mutations of *Dock8* [140]. Other total knockout mice were subsequently established [138, 158]. All these mouse strains have LOF mutations and present similar phenotypes (Table 1). For the sake of clarity, we refer to all these mouse strains hereafter as “Dock8-deficient” mice. Unlike human patients, Dock8-deficient mice do not have high IgE levels. Instead, they fail to form or maintain marginal zone B (MZB) cells in germinal centers, resulting in impaired affinity maturation and failure to maintain IgG responses to T cell-dependent antigens [140]. A similar phenotype has been described in human patients, with patients having low titers of antibodies against T cell-dependent vaccines although their total IgG levels are often normal or even elevated [5]. In mice, this defect was not rescued by normal T cells, implying that it was intrinsic to Dock8-deficient B cells. The survival defect was found not only in Dock8-deficient MZB cells, but also in many other cell types, including T cells [159, 160], NKT cells [161], Tregs [162, 163], and ILCs [164]. Studies of these defects in mice have helped to explain the wide spectrum of pathogens to which DOCK8-deficient patients are susceptible. However, the mechanisms underlying the survival defect of these different cell types remain unclear.

By contrast, studies focusing on the migration defect of Dock8-deficient mice have clearly elucidated the mechanisms underlying susceptibility to cutaneous viral infections and the survival defect of DCs and T cells [138, 158, 165-167]. Another DOCK family member, DOCK2, has been shown to play a key role in Rho GTPase-mediated chemotaxis and to cause severe immunodeficiency in patients [168, 169]. The group that first reported the chemotaxis defect Dock2-deficient cells, discovered a different type of migration defect in Dock8-deficient DCs [158], with poor interstitial migration during immune responses, 10 years after their initial discovery. Coincidentally, this migration defect of Dock8-deficient DCs was confirmed by an incidental second mutation occurring in an unrelated mouse strain [166]. Several years later, similar migration defects were also discovered in DOCK8-deficient human and mouse T cells [138, 165]. The migration defects of both T cells and DCs have been linked to CDC42, suggesting that a specific DOCK8 pathway may operate during cell migration [138, 158]. Interstitial cell migration is impaired in both DOCK-deficient DCs and T cells, but the underlying mechanisms differ between these two cell types. Dock8-deficient DCs fail to transmigrate through the subcapsular sinus floor to the lymph nodes for T-cell priming. This deficiency therefore results in a general defect of T-cell responses during immune responses [158]. Dock8-deficient T cells maintain their ability to migrate to infected tissues, but undergo catastrophic morphological changes and cell death when migrating in dense tissues, such as those of the skin. This results in a considerable loss of tissue-resident memory T cells in the skin, compromising the immunity of the skin to HSV [138, 165]. The tissue-specific defect of Dock8-deficient T cells provides clues to a new disease mechanism accounting for the prominent skin-tropism of viral infections in

patients. The migration defects of DCs and T cells also suggest that similar migration defects may occur in other cell types, such as B cells and NKT cells. In general, it is very difficult to study migration defects, particularly those concerning interstitial migration, directly in patients. Mouse models have proved highly useful for elucidating the disease mechanisms relevant to DOCK8 deficiency.

## PGM3 deficiency

AR PGM3 deficiency was first reported in 2014, in patients with HIES or SCID/CID [7-9]. Shortly afterwards, more patients were reported from both types of cohort [14, 170, 171]. To date, 29 patients from nine families (including 16 patients from 4 families carrying identical mutations) have been identified with HIES, and 8 patients from 5 families with SCID/CID. Patients from these two cohorts have clinical features in common, including severe infections (recurrent respiratory infections, and, less commonly, abscesses, and candidiasis), glomerulonephritis (possibly due to autoimmunity), allergies and eczema, and multiple severe non-immunological phenotypes, including dysmorphic features, skeletal dysplasia, developmental delay, and neurological impairment. Common immunological phenotypes include neutropenia, lymphopenia, and eosinophilia (with or without high IgE levels), of variable severity. Serum IgE levels were normal in patients from the SCID/CID cohort, whereas they were high in most patients from the HIES cohort. Almost all patients from both these cohorts displayed impaired T-cell proliferation in response to stimulation with PHA/PMA or TCR [7, 9, 170]. This feature is also observed in DOCK8 deficiency but not Job’s syndrome, providing strong support for the classification of PGM3 deficiency as a CID rather than a form of HIES. Moreover, the presentation of PGM3 deficiency varies among patients, ranging from SCID to HIES. Patients carrying the same mutation often present with similar phenotypes. For example, all 16 Tunisian patients from four families carrying the same homozygous E340del mutation presented with similar HIES phenotypes, and the two unrelated Tunisian patients carrying the same homozygous N246S mutation presented with similar SCID phenotypes and dysmorphic features. However, too few data are currently available to analyze the correlation of genotype with cellular and clinical phenotypes in patients. Surprisingly, measurements of residual PGM3 expression and function did not differentiate between the patients of these two cohorts [7-10, 14, 170, 171]. It would, nevertheless, be very interesting to compare the deleteriousness of biallelic PGM3 genotypes with that of various cellular, immunological, and clinical phenotypes. Indeed, all patients identified to date carry hypomorphic mutations, which are likely to differ in severity, thereby resulting in immunological and clinical defects of different severities.

PGM3 deficiency has more features in common with other inherited glycosylation defects than with HIES [172]. PGM3 (phosphoglucomutase 3), also known as AGM1 (N-acetylglucosamine-phosphate mutase 1), is one of the five ubiquitously expressed hexose phosphate mutases identified in humans [173, 174]. Anecdotally, before the identification of PGM3 as a phosphoglucomutase, it was known for its polymorphism and used as a genetic marker in forensic science [175, 176]. PGM3 is one of the key enzymes in glycosylation, a process that modifies proteins and lipids by adding glycans [177]. About 50% of the proteins in our bodies are glycosylated, and there are hundreds to thousands of different types of glycans, forming a complicated network affecting almost all physiological processes in all

living organisms [178]. An estimated 1-2% of the genome encodes proteins involved in glycosylation. It is therefore unsurprising that 105 of the genetic diseases identified to date, including PGM3 deficiency, have been shown to involve glycosylation defects, also known as congenital disorders of glycosylation (CDGs) [13, 178]. These CDGs affects different steps of the glycosylation process in different tissues, resulting in a wide spectrum of phenotypes. In brief, when glucose enters the cell, it is mostly converted to fructose-6-phosphate and used for glycolysis to produce energy. However, a small amount of fructose-6-phosphate instead enters the hexosamine biosynthesis pathway (HBP), to produce uridine diphosphate N-acetylglucosamine (UDP-GlcNAc). PGM3, together with several other enzymes, such as GFPT, GNPNAT1, and UAP1, is required for the HBP. PGM3 catalyzes the isomerization of GlcNAc-6-phosphate to GlcNAc-1-phosphate, which is followed by a final reaction to yield UDP-GlcNAc. The newly synthesized UDP-GlcNAc is then transferred to the Golgi apparatus and used as a substrate in various glycosylation processes, including N-glycosylation, O-glycosylation, and O-GlcNAcylation, or converted into UDP-GalNAc [179]. PGM3 deficiency would therefore be expected to decrease cellular UDP-GlcNAc levels and to affect many downstream glycosylation processes.

Mouse models are of great potential value, given the diversity of hypomorphic mutations and biallelic genotypes in PGM3-deficient patients. Mice with hypomorphic and LOF mutations were generated years before the discovery of the human disease. In 2007, Kile's group discovered a Pgm3-deficient mouse strain through the screening of mice with ENU-induced mutations (Table 1). The mutation in this mouse strain led to aberrant mRNA splicing and the production of Pgm3 proteins with less than 1% the wild-type level of enzyme activity. Mice homozygous for this mutation had a mild phenotype, consisting of smaller than normal numbers of lymphocytes, red blood cells, and platelets, and were therefore named *Pgm3*$^{mld1/mld1}$. The same group also generated mice with a LOF mutation of *Pgm3,* named *Pgm3*$^{gt/gt}$. Homozygosity for the LOF mutation is embryo-lethal. Both *Pgm3*$^{mld1/wt}$ and *Pgm3*$^{gt/wt}$ mice were apparently normal, indicating that most, if not all Pgm3 deficiency phenotypes are inherited in an AR manner. Interestingly, when the authors crossed the two mutant strains to generate *Pgm3*$^{mld1/gt}$ mice, these mice had even less enzyme activity and a more severe phenotype than the *Pgm3*$^{mld1/mld1}$ mouse, but they were nevertheless alive. Both *Pgm3*$^{mld1/mld1}$ and *Pgm3*$^{mld1/gt}$ mice display many of the phenotypes of human patients, including anemia, impaired B-cell maturation and low T-cell numbers. Surprisingly, the *Pgm3*$^{mld1/gt}$ mouse more closely resembles patients with a SCID phenotype, with only very small numbers of peripheral T cells and a total absence of mature B cells. The *Pgm3*$^{mld1/gt}$ mouse also had other phenotypes in common with patients, such as dysmorphic features, and, more interestingly, glomerulonephritis. Overall, studies of mouse models have shown that incremental changes in Pgm3 activity lead to a graded series of pathological changes in different tissues [177]. It is, therefore, possible that the different phenotypes seen in PGM3-deficient patients originate from residual enzyme activities. HIES patients with PGM3 deficiency probably have a T-cell disorder with Th2 bias, similar to that in DOCK8-deficient patients. It has been shown that the paucity of Th cells is often accompanied, by default, by a Th2 phenotype [55, 180]. Another clinical feature common to patients from HIES and SCID/CID cohorts was neutropenia, which probably contributes to the wide spectrum of infections found in these patients [7-9, 170]. Pgm3-deficient mice had

normal neutrophil numbers, but neutrophil defects are common in CDGs. Seven of the 10 CDGs classified as immunodeficiencies include either neutropenia or neutrophil trafficking/chemotaxis defects [172]. The hematopoietic defects in the mouse models were rescued by bone marrow transplantation, consistent with the encouraging results obtained for the few human patients to have undergone transplantation. Overall, the mouse models are promising and complementary to human research.

## Other syndromes in which IgE levels are high

Several other PIDs from the CID category are also characterized by high IgE levels, at least in some patients. These syndromes, including Wiskott-Aldrich syndrome, DiGeorge Syndrome, and Omenn Syndrome, are all characterized by large decreases in T-cell numbers and a severe impairment of T-cell function. The high serum IgE levels may result from the clonal expansion of certain T/B cells, weak TCR affinity and signaling, or an imbalance in the differentiation of Th1/Th2 cells [180]. The more recent discovery of high IgE levels in IPEX patients suggests that the lack of functional Tregs, as observed in other CIDs, may trigger excessive IgE production [181]. As IgE levels vary among patients with these diseases, it is not easy to establish mouse models that faithfully reproduce the phenotype. Recently, Ma et al. reported a new cohort of AD, hypomorphic CARD11 deficient patients, who presented with eczema, recurrent infections, and elevated IgE was found in 5/7 of the patients [182]. The patients' T cells displayed defects in both NF-κB and mTORC1 activation, which might underlie their abnormal IgE production. Whether this disorder should be classified as CID or HIES is unclear. Defects other than T-cell defects may also results in high serum IgE levels. Comèl-Netherton syndrome is one such defect. It is caused by biallelic *SPINK5* mutations, leading to aberrant epidermal desquamation and an impairment of epidermal barrier function [183-186]. Patients suffer from congenital erythroderma, a specific hair-shaft abnormality (bamboo hair), and atopic manifestations, with high IgE levels. Some patients also experience severe sepsis and cutaneous infections with viruses such as HPV, presumably because of the skin lesions. The phenotype, genotype, and mouse models have all recently been reviewed [185, 187-190]. In addition, filaggrin (*FLG*) deficiency can lead to impaired keratinization and defective skin barriers, which result in ichthyosis vulgaris and in some patients with elevated serum IgE [191-193]. It is usually categorized as an inherited disorder of keratinization.

## Concluding remarks

The transformation of the definition of HIES over the last 50 years reflects continuing progress in biomedical research. From the first description of two red-haired girls with "cold abscesses" in 1966, to that of various inborn errors of immunity, the term "HIES" has taken on a completely new meaning. Many discoveries made thanks to the remarkable advances in molecular biology have shed light on the genetic causes of the disease. Syndromes are now defined by both their clinical characteristics and genetic causes, and molecular defects are more often incorporated into their names than was the case 50 years ago. In this respect, we believe that the two AR forms of HIES, DOCK8 and PGM3 deficiency, would be better classified as CIDs, due to the cytoskeletal and glycosylation defects of T cells, respectively, observed in these forms. The name "HIES" should be reserved for patients with AD STAT3

deficiency or other as yet unknown genetic defects resulting in diseases similar to Job's syndrome, in terms of both clinical features and immunological defects. Surprisingly, the mouse models of DOCK8 and PGM3 deficiencies were established independently of or before the discovery of the corresponding human diseases. The mouse model of Job's syndrome due to STAT3 deficiency is currently the only mouse model reproducing the high IgE levels of the three diseases discussed above. The mechanisms underlying these high levels of IgE remain unclear in these diseases. The DOCK8-deficient mouse reproduces the infectious phenotype well, although further studies are required to improve our understanding of the survival defects in a wide range of cell types and their connections to disease phenotypes. PGM3-deficient mouse models reproduce the incremental changes in enzyme activity. However, further studies are required to explain the allergic and infectious phenotypes in patients. Overall, we suggest that HIES should no longer be considered a mixture of different genetic disorders. The use of well-defined mouse models will improve our understanding of the unique disease mechanisms specific to each entity. We propose restriction of the term "HIES" to patients with AD STAT3 deficiency and phenocopies, and the exclusion from this group of patients with T-cell deficits displaying a Th2 bias, such as those with DOCK8 and PGM3 deficiencies. However, HIES may nevertheless turn out to be plural, rather than singular, despite the exclusion of DOCK8 and PGM3 deficiencies, if novel genetic etiologies of *bona fide* HIES that phenocopy AD STAT3 deficiency are discovered in the future. While this review was being revised, we and others reported patients with AR ZNF341 deficiency, which appears to be a phenocopy of AD STAT3 deficiency. This is understandable, as ZNF341 is a transcription factor that controls the expression, activation, and activity of STAT3 [194, 195]. One can therefore use the plural when referring to HIES, not because of AR DOCK8 and PGM3 deficiency, but because of AR ZNF341 deficiency that closely mimics AD STAT3 deficiency.

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**Table 1.**

Various mouse strains modeling the human diseases of HIES.

| Human disease | Mouse strain | Modeling of human disease |
|---|---|---|
| AD, LOF, STAT3 deficiency (Job's syndrome) | $Stat3^{wt,wt/V463del,V463del}$ (BAC transgene)[118, 119] | High IgE, low Th17;<br>Impaired mast cell degranulation induced by IgE receptor cross-linking;<br>Impaired control of intestinal Citrobacter infection;<br>High mortality upon LPS challenge |
| | Germline knockout [83] | lethal |
| | TIE2-Cre-$Stat3^{\Delta/flox}$ [121-123] | Impaired G-CSF-induced emergency granulopoiesis;<br>Impaired neutrophil chemotaxis towards CXCR2 ligands |
| | CD11c-Cre-$Stat3^{flox/flox}$ [124] | Selectively impaired pDC differentiation |
| | Mx1-Cre-$Stat3^{flox/flox}$, Lyz2-Cre-$Stat3^{flox/flox}$, and TIE2-Cre-$Stat3^{\Delta/flox}$ [83, 125, 126, 129] | Abnormal DC and macrophage maturation and differentiation |
| | CRE-ER-$Stat3^{flox/flox}$and TIE2-Cre-$Stat3^{\Delta/flox}$ [130] | Enhanced osteoclast development mediated by macrophages and osteoclast precursors |
| | Mx1-Cre-$Stat3^{flox/flox}$ [131] | Impaired Flt3L signaling in common lymphocyte progenitors |
| | CD19-Cre-$Stat3^{flox/flox}$ [134, 135] | Impaired IL-21 signaling in maturation of B and plasma cells, Impaired B cell survival and elevated IgE |
| | TIE2-Cre-$Stat3^{\Delta/flox}$ [132] | Impaired IL-6 and TGF-β signaling in Th17 cell differentiation |
| AR, LOF, DOCK8 deficiency | *cpm, pri,* germline knockout (All LOF deficiency)[138, 140, 158-166, 196, 197] | Normal IgE;<br>Defective MZB;<br>Impaired affinity maturation and the persistence of IgG responses to T cell-dependent antigens;<br>Decreased survival in T, NKT, Tregs, ILCs;<br>Increased susceptibility to cutaneous HSV infection;<br>Loss of tissue-resident memory T cells in the skin;<br>Abnormal interstitial T cells and DCs migration |
| AR, hypomorphic, PGM3 deficiency | $Pgm3^{mld1/mld1}$ (hypomorphic) [177] | Low platelets;<br>Anemia;<br>Impaired B cell maturation;<br>Low T cell count |
| | $Pgm3^{gt/gt}$ (LOF) [177] | Embryonic-lethal |
| | $Pgm3^{mld1/gt}$ [177] | SCID-like phenotypes, extremely low peripheral T cell counts, absence of mature B cells;<br>Dysmorphic features;<br>glomerulonephritis |