



The Child with Elevated IgE and Infection Susceptibility

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Abstract

Purpose of Review Over the last 13 years, the genetic etiologies have been determined for multiple conditions causing elevated serum IgE, infection susceptibilities, and variable other features. In this review, we discuss the clinical presentation, laboratory features, and genetics of these diseases caused by mutations in STAT3, DOCK8, PGM3, IL6ST, ZNF341, IL6R, IL6ST, CARD11, and CARD14, with particular focus given to STAT3LOF and DOCK8 deficiency.

Recent Findings Defining the phenotype of each of these syndromes with high IgE and infection susceptibility shows that some have a pronounced connective tissue phenotype such as STAT3LOF and IL6ST deficiency, some have worse viral susceptibility such as DOCK8 deficiency and heterozygous LOF CARD11, and some have more severe allergy and eczema such as LOF CARD14.

Summary Studying these distinct but overlapping monogenic diseases will allow a better understanding of more common disease processes such as allergy, eczema, infection susceptibility, scoliosis, and aneurysm.

Keywords Hyper IgE syndrome · IgE · STAT3 · ZNF341 · DOCK8 · PGM3 · CARD11 · CARD14 · IL6ST · IL6R

Introduction

Elevated serum IgE occurs in many conditions of immune dysregulation, with atopic disease being the most common. Primary immune deficiencies previously referred to as hyper IgE syndromes were defined by the constellation of eczema, recurrent infections, and elevated serum IgE. Over the last 13 years, multiple monogenic diseases that share these clinical findings have been defined, with each being a distinct disease, with specific clinical considerations and, for some, therapeutic interventions. It is no longer as meaningful to define these diseases as HIES, or by whether they are autosomal dominant or autosomal recessive “versions”, but rather by the more

specific and meaningful genetic causes, when known. That said, some of these disorders do have phenotypic similarities which in some cases are likely due to mutations within a particular pathway, and as such in understanding patients with elevated IgE and infection—whether due to a known or yet to be discovered cause, it is important to recognize the types of phenotypic features which may appear and cluster.

In this review, we will discuss the main clinical features of genetically defined immune dysregulatory syndromes characterized by the classic triad of eczematoid dermatitis, recurrent skin and lung infections, and elevated serum IgE, including the frequent laboratory and immunologic findings, the pathogenesis, and the approach to therapy. The main focus will be on dominant negative STAT3 (Job’s syndrome) mutations and DOCK8 deficiency (bi-allelic), with a shorter review of more recently described defects including PGM3 deficiency, IL6ST (bi-allelic and heterozygous) deficiency, IL6R (bi-allelic) deficiency, ZNF341 (bi-allelic) deficiency, and dominant negative heterozygous mutations in CARD11 and CARD14 (Table 1). There are many other immune dysregulation disorders that are not covered in this review but frequently have elevated serum IgE such as, but not limited to, Wiskott-Aldrich syndrome (WAS), IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked), Omenn syndrome, and Netherton syndrome caused by SPINK5 mutations. Also not covered are

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Table 1 Comparison of main clinical features of monogenic diseases causing high serum IgE, eczematoid dermatitis, and recurrent infections

	DN STAT3	DOCK8	PGM3	LOF CARD11	LOF CARD14 ^a	ZNF341 ^a	IL6ST bi- allelic ^a	DN IL6ST ^a	IL6R ^a
Allergic hypersensitivity	++	+ / +++	+++	+++	+++	+	ND	+	+
Eczema	++	+ / +++	++	+++	+++	+++	++	+	+++
Bronchiectasis/pneumatoceles	++	++	++	+	—	++	+++	+++	+
Mucocutaneous candidiasis	+++	+	—	—	—	+++	ND	+	—
Cutaneous viral infections	+	+++	++	++	+	—	—	—	—
Neurologic deficits	+ / —	+ / —	+++	—	—	—	—	—	—
Vascular abnormalities	++	+	+	—	—	—	—	—	—
Skeletal/connective tissue changes	+++	—	++	—	—	+	+++	+	—
Retained primary teeth	+++	—	—	—	—	—	ND	++	—
Immunoglobulins (except IgE)	Typically normal	Low IgM	High	Some low IgG	Some low IgG	Some increased IgG	Normal	Normal	Low normal/slightly decreased IgG
T lymphopenia	+	++	++	+	—	—	—	—	—
Lymphoma	+	++	+	++	—	—	—	—	—

^a Limited reports of patients making assessment of relative frequency of clinical phenotype difficult

some phagocytic defects such as chronic granulomatous disease (CGD), which often have mildly elevated serum IgEs.

Distinguishing these monogenic disorders of atopy and immune deficiency from more common atopic disease can be difficult, especially early in life. Those with atopic dermatitis are predisposed to Staphylococcal skin infections, and even viral skin infections can be recurrent and more severe. Through this review, we will highlight the features that distinguish disease—such as the extra-immunologic features associated with dominant negative STAT3 mutations, or the severity of the viral infections and lymphopenia associated with DOCK8 deficiency. But early in life, there can be overlap in clinical features, or a lack of other features such as infection or connective tissue abnormality, and as such, genetic testing may be necessary to arrive at a specific diagnosis, when a known monogenic disease is present. Importantly, there are likely many congenital causes of severe atopy and infection which have yet to be identified, and as such genetic testing that yields no results in the clinical sphere may require follow-up analysis in research settings.

Dominant Negative Mutations in STAT3 (STAT3LOF) Job's syndrome was initially described in 1966 with two sisters with recurrent boils reminiscent of the Biblical prophet Job [1]. Several years later, IgE was identified and noted to be quite elevated in those fitting this clinical description leading to the definition by Dr. Buckley of autosomal dominant hyper IgE recurrent infection syndrome (AD-HIES) [2]. In 2007, dominant negative mutations in STAT3 were identified as the cause of what is recognized as a multi-system disorder characterized by recurrent sino-oto-pulmonary infections, eczema, boils,

connective tissue and skeletal abnormalities, vasculopathy, and elevated serum IgE [3•, 4•].

Clinical Features STAT3LOF presents in almost all children within the first few weeks of life with a pustular or eczematoid rash that typically appears in the face and scalp, and is characterized by eosinophilic infiltrate [5]. The newborn rash differs from atopic dermatitis, which typically presents around the second or third month of life. The eczematoid rash with STAT3LOF tends to be driven by *Staphylococcus aureus* colonization and is usually mild when antiseptics and/or anti-*S. aureus* antimicrobials are used. The rash tends to be greatly improved by adult years. Recurrent *S. aureus* boils start usually in the first few years of life and may be “cold” lacking the typical characteristics of inflammation including rubor, calor, and dolor, although aspiration does reveal neutrophils. Similar to the eczematoid rash, with *S. aureus* suppressive antibiotics, the boils are infrequent.

Recurrent bacterial pneumonias typically start early in life, with the most common organisms being *S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* [6]. Similar to the boils, these pneumonias may present with minimal signs of inflammation, with minimal to no fever, and white blood cell counts and inflammatory markers may be normal. Less frequently, the initial pneumonia in infancy is *Pneumocystis jirovecii* [7]. Healing after pyogenic pneumonias is often aberrant and bronchiectasis and pneumatoceles may result and persist (Fig. 1). The altered lung architecture leads to changes in infection susceptibility, with more frequent Gram-negative bacilli such as *Pseudomonas*, molds such as *Aspergillus* and nontuberculous mycobacteria [6, 8•, 9]. These

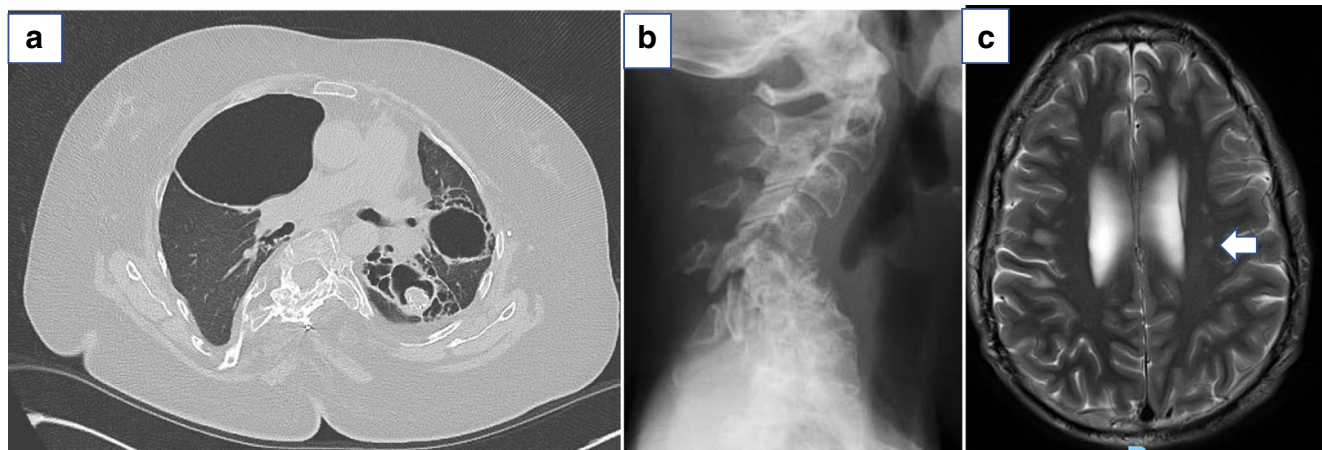


Fig. 1 **a** Pneumatocoles, including one with Aspergilloma, along with scoliosis in a 49-year-old woman with STAT3LOF. **b** Degenerative cervical spine disease in a 54-year-old woman with STAT3LOF prior to

surgical correction. **c** Brain MRI of a 33-year-old man with STAT3GOF with multiple focal hyperintensities on T2-weighted images (arrow, example)

infections can be the source of great morbidity and mortality, with hemoptysis being a serious complication. Aspergillus, and other molds, not only cause chronic infection in pneumatoceles and bronchiectasis, but can also cause an allergic bronchopulmonary Aspergillosis (ABPA) type pattern with significant mucus plugs.

Chronic or recurrent mucocutaneous candidiasis can manifest with thrush, esophageal, vaginal, and nail disease. Endemic fungi can cause disseminated infection, including *Cryptococcus* meningitis or gastrointestinal disease, *Coccidioides* meningitis, and *Histoplasmosis* disseminated typically to the gastrointestinal tract [10].

Viral infections tend not to be particularly severe for these patients. However, reactivation of latent viruses is increased, leading to a higher incidence of zoster as well as asymptomatic EBV viremia [11].

Despite the quite elevated serum IgE, food allergy and anaphylaxis are not as high as expected. Compared with the general population, food allergies are more frequent, occurring in 38% of STAT3LOF patients in our cohort, but they are significantly less frequent than others with similarly elevated serum IgE, at 58.3% [12•]. Anaphylaxis is infrequent, with an 8.5% incidence in STAT3LOF, compared with 33.3% in non-STAT3 atopic individuals.

STAT3LOF mutations lead to many extra-immunologic findings [13]. The joints are usually hyperextensible, leading to significant arthritis often in adulthood, with some individuals requiring spine stabilization surgeries or joint replacements (Fig. 1). Most individuals fail to lose their primary teeth, which need to be extracted to allow the secondary teeth to emerge normally [14]. About half of individuals have osteoporosis, and similar numbers have minimal trauma fractures; however, those with frequent fractures do not always have osteoporosis [15]. About ¾ of individuals have scoliosis, which may be significant enough to require rod placement.

There is a characteristic facial appearance with deep-set eyes, bulbous nose, some asymmetry, and coarse features [13], as well as frequently some degree of craniosynostosis, rarely requiring correction. Brain imaging reveals about one quarter of patients with Chiari 1 malformations, typically asymptomatic, as well as focal hyperintensities on T2-weighted images, which may relate to small vessel disease (Fig. 1) [16]. Tortuous and aneurysmal medium-sized arteries infrequently cause myocardial infarction from coronary artery aneurysm, subarachnoid hemorrhage from cerebral aneurysm, and intestinal hemorrhage from mesenteric aneurysm [17, 18]. Intestinal perforations have occurred either with or without associated diverticuli. Eosinophilic esophagitis can lead to dysphagia and dysmotility [19].

There is an increased rate of predominantly large B cell lymphoma [20, 21]. It is unclear whether the decreased STAT3 activity will be protective against any malignancies associated with increased STAT3 activity such as colon carcinoma.

Laboratory Findings In most individuals, the serum IgE is quite elevated, often greater than 2000 IU/μL. However, there are cases with only mildly elevated IgE, in the hundreds and in some adults, the IgE can fall into the normal range. The degree of IgE elevation does not appear to correlate with whether eosinophilia is present, or the clinical severity of disease. The other immunoglobulins tend to be normal, and antibody responses to vaccination are variable. Mild neutropenia (approximately 500–1500 cell/μL) occurs in some individuals.

Lymphocyte phenotyping typically shows low memory T and B lymphocytes. Ex vivo Th17 expression is also impaired [22•].

STAT3 mutations are localized largely to the SH2 and DNA binding domains, with fewer falling in the transactivation domain [3•, 4•]. Mutations are missense or

short in-frame deletion, and therefore STAT3 protein is present, but abnormal leading to diminished STAT3 signaling.

Pathogenesis STAT3 is a major signal transduction molecule that is expressed widely and is involved in host defense, wound healing, and vascular remodeling. Expression of STAT3 protein is essential for survival, and thus, only those with some residual protein production are expected to survive. Many cytokines and chemokines with varying functions signal through STAT3 leading to the multi-system phenotype, including IL-6, IL-10, IL-11, IL-17, IL-21, IL-22, IL-23, leukemia inhibitory factor, oncostatin M, cardiotrophin-1, cardiotrophin-like cytokine, and ciliary neurotrophic factor.

One of the most consistent findings in STAT3LOF is the failure of Th17 cell differentiation [22•], leading to a defect in epithelial immunity with impaired antimicrobial peptide up-regulation [23]. Although this likely explains the mucosal candida susceptibility, the predisposition to *S. aureus* is less clear. In part, this may relate to increased TNF alpha production in the epithelium with impaired epithelial function as is evident by abnormal migration after injury and impaired epithelial-to-mesenchymal (EMT) transition [24]. The defect in central memory T cells explains the viral reactivation, such as the increased incidence of zoster [11]. NK function is impaired as well, with decreased expression of NKG2D, which may also contribute to the increased rate of zoster and EBV viremia, as well as lymphoma predisposition [25]. The B cell defect, manifesting as low memory B lymphocytes and variable specific antibody responses, may be explained by STAT3's role in follicular T cell differentiation [26].

While it is not clear exactly why the IgE is elevated in these patients, it does appear to be B cell intrinsic. In addition, the lack of more severe allergic symptoms despite this high IgE may be attributable to poor mast cell degranulation, as well as poor vascular responses to histamine when STAT3 mutation is present [12•, 27•]. Tissue remodeling abnormalities likely explain the lung pneumatocele formation and poor healing after surgery as well as the vascular aneurysm [28]. Matrix metalloproteinases (MMP) are dysregulated which likely explains this finding in part, as well as the impaired EMT which is essential for wound healing [29•, 30].

Therapy Therapy for STAT3LOF is largely supportive. Antimicrobial prophylaxis is directed against *S. aureus* to prevent the pneumonias that lead to the large pneumatoceles. Trimethoprim/sulfamethoxazole (TMP/SMX) is frequently prescribed, dosed around TMP 5–6 mg/kg divided twice daily with a maximum of 160 mg of TMP twice daily. Antiseptics such as dilute bleach baths or swimming in chlorinated pools can decrease the *S. aureus* skin colonization and minimize the eczema and skin abscesses. Antifungal prophylaxis is given for those with chronic or frequently recurring Candida infections, typically with fluconazole. Antifungal prophylaxis

should also be strongly considered for those living in areas with high risk of disseminated endemic fungi, such as fluconazole prophylaxis for those living in the US Southwest where *Coccidioides* is endemic. For those with pneumatoceles, mold-active azoles are considered for prophylaxis, such as itraconazole. Posaconazole, voriconazole, or isavuconazole should be considered for those with chronic pulmonary mold infections, with awareness given to long-term complications of voriconazole, such as photosensitivity, skin cancers, and hyperfluorosis. Lung surgeries have a high rate of complications with frequent bronchopleural fistulas, and thus should be avoided if possible. There appears to be a role for immune globulin supplementation, at least for some patients with poor specific antibody production, with decreased infections [31]. Vaccinations, including live vaccines, are well tolerated, with the exception of the 23 valent polysaccharide pneumococcal vaccine, which appears to have a poorly understood increased rate of significant large local reactions [32]. Multi-disciplinary care for bone and dental health is essential.

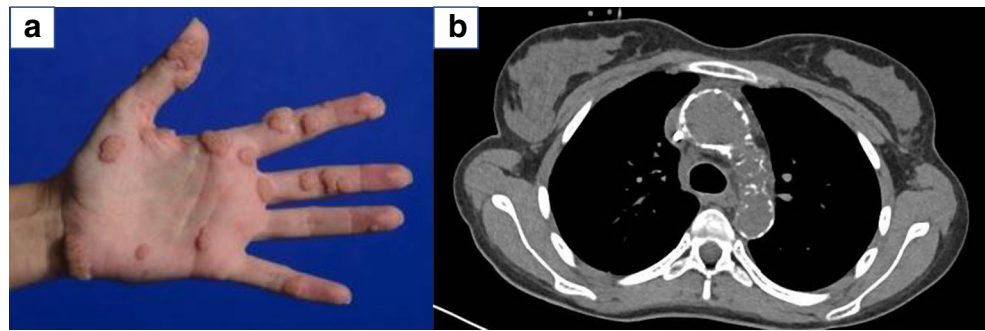
Hematopoietic stem cell transplantation (HSCT) remains controversial. The initial report of HSCT stated that it was not successful in correcting the phenotype [33]. Recent reports are promising; however, it appears that at least the infection susceptibility can be ameliorated [34••]. As the STAT3 mutations are dominantly negative, excellent donor chimerisms are essential, and progressive lung disease has been reported with mixed chimerism [35]. The overall prognosis and life expectancy appear to be improving with improved antimicrobials and recognition of the infections, and thus deciding which patients should proceed to HSCT is difficult.

DOCK8 Deficiency

DOCK8 deficiency was described in 2009 in individuals previously described as having autosomal recessive HIES [36••]. Bi-allelic mutations lead to a disease characterized primarily by sino-oto-pulmonary infections, eczema, rash, viral skin infections, and increased malignancy. Prognosis is worse in DOCK8 deficiency than in STAT3LOF, with about half of affected individuals dying by the age of 20 years, and about 75% having life threatening medical events by 20 years [37•].

Clinical Manifestations DOCK8 deficiency presents typically in young children with eczema and recurrent infections [36••, 37•, 38]. The atopy in DOCK8 infection is variable ranging from minimal to quite severe and debilitating. *S. aureus* skin infections are common. Cutaneous viral infections typically start in childhood, with recalcitrant human papillomavirus (HPV) and molluscum infections, and recurrent herpes simplex virus (HSV) and zoster (Fig. 2a). More severe viral infections, including progressive multifocal leukoencephalopathy (PML) from JC virus, occur, but are less common. Recurrent bacterial

Fig. 2 **a** Severe warts in a 25-year-old woman with DOCK8 deficiency. **b** Calcified ascending and descending aorta in a 19-year-old with DOCK8 deficiency



pneumonias lead to bronchiectasis in about one third of patients; PCP also occurs but less frequently [39]. *Cryptosporidium* can lead to persistent GI infection and cause cholestatic liver disease, which can be severe and increase the risks of HSCT. Vasculitis, typically of the aorta and/or cerebral arteries, occurs in a subset of patients, sometimes with a clear viral etiology, such as Varicella zoster, but other times with no etiology identified [39]. Aortic vasculitis can lead to dilation, calcification, and aneurysm (Fig. 2b). Cerebral vasculitis can lead to stroke and Moyamoya pathology. Malignancies relate to the poor control of virus, with HPV leading to squamous cell carcinomas, and EBV leading to lymphomas; however, EBV-negative lymphoma occurs as well [36•, 37•, 38, 39].

Laboratory Findings Serum IgE and eosinophils range from normal to extremely elevated, and there appears to be more correlation with the degree of atopic disease than is seen with STAT3LOF. Serum IgG is usually normal, but the specific antibody responses to vaccination are often poor. Serum IgA is variable and serum IgM is frequently low. Lymphopenia tends to progress with age, with lower memory B lymphocytes and lower naïve T lymphocytes.

Bi-allelic DOCK8 mutations frequently include large deletions and frameshift mutations [36•]. DOCK8 is a large gene and heterozygous missense mutations leading to variants are common, and generally not thought to be pathogenic. The carriers of pathogenic mutations do not have a phenotype.

Pathogenesis DOCK8 belongs to the DOCK180 protein family group of guanine exchange factors involved in the actin cytoskeleton. Of note, other disorders of actin polymerization are associated with atopic disease as well, such as ARPC1B loss of function and WAS [40–42]. DOCK8 is expressed almost exclusively by the lymphocytes, and thus, HSCT should be curative, and the multi-center experience supports excellent long-term outcomes [43•]. The impaired actin cytoskeleton causes impaired accumulation of adhesion molecules and cytotoxic granules at the immunologic synapses resulting in impaired lymphocyte function and survival. The actin cytoskeleton impairment also causes a migration defect of the lymphocytes through matrices such as the skin, likely explaining the

high incidence of viral skin infections [44•]. In some patients, reversion mutations in DOCK8 lead to some amelioration of disease manifestations, such as allergy, but significant infections still occur and the long-term prognosis likely remains poor [45]. Therefore, HSCT is still recommended despite reversion mutations.

Treatment With the poor long-term prognosis as well as the relative restriction of DOCK8 protein expression to hematopoietic cells, HSCT should be recommended upon diagnosis due to the progressive nature of the disease and the high mortality [43•, 46, 47]. Long-term survival after transplant is reported in a large multi-center study to be about 85% [43•]. It is prudent to perform the HSCT as soon as the diagnosis is confirmed, as the co-morbidities increase with age and can be significant, with cryptosporidium related liver disease, bronchiectasis, vasculitis, and malignancy.

While awaiting HSCT, patients are maintained on antimicrobial prophylaxis, typically with TMP/SMX for both bacterial and PCP prophylaxis. Viral prophylaxis with acyclovir or valacyclovir should be strongly considered for patients who have had recurrent HSV or VZV. Immune globulin replacement should be provided if there are poor specific antibodies. IFN alpha has been used with some success for persistent viral skin infections, but has significant adverse events including depression and cytopenias, and is not a long-term replacement for HSCT [48, 49].

PGM3 Deficiency

Bi-allelic mutations in phosphoglucomutase 3 (PGM3) were described in 2014 in patients with phenotypes ranging from SCID-like to a hyper IgE phenotype [50, 51•, 52•, 53•, 54•]. PGM3 deficiency is a glycosylation defect, thereby affecting the majority of the proteins in the body and causing a diverse phenotype. Defects are hypomorphic as PGM3 expression is essential for survival.

The clinical phenotype ranges from early onset bone marrow failure with a SCID-like phenotype to a more indolent course characterized by allergic disease of all sorts, atopic

dermatitis, infection susceptibility, and autoimmunity [50, 51, 52, 53, 54]. Similar to other glycosylation defects, some degree of developmental defect is common, as well as skeletal abnormalities including osteoporosis, scoliosis, and long bone length abnormalities (Fig. 3a). Recurrent bacterial skin and lung infections usually start in early childhood and bronchiectasis may develop (Fig. 3b). Skin viral infections, such as molluscum contagiosum, as well as poor control of herpes viruses have been seen, and there is an increased risk of lymphoma. Autoimmunity including cytopenias, vasculitis, and kidney disease has been described.

Serum IgE is usually elevated, and eosinophilia is variable. Neutropenia is common, as is lymphopenia, predominantly of the CD8 lymphocytes. Bone marrow findings are variable ranging from hypocellular to hypercellular, and autoimmune cytopenias have been seen. Th17 lymphocyte numbers are usually elevated, likely related to the increased autoimmunity [54].

HSCT has been performed successfully in at least two individuals with PGM3 deficiency who presented with bone marrow failure and a SCID-like phenotype [53]. HSCT appears to correct the infection susceptibility but is not expected to correct other non-immunologic manifestations such as the developmental delays. Without HSCT, treatment has been supportive with antimicrobial prophylaxis and a multidisciplinary approach to the varied organs affected. Whether the glycosylation can be bypassed with sugar supplementation requires further investigation.

IL6ST Deficiency

In 2017 and 2019, two individuals were reported with homozygous mutations in IL6ST encoding the GP130 cytokine receptor, which is proximal to STAT3 signaling [55, 56]. Both reported individuals had clinical features overlapping

with STAT3LOF with eczema, recurrent lung infections, as well as nonimmunologic features such as craniosynostosis and scoliosis. In addition to the clinical phenotype overlap with STAT3LOF, there were also immunologic similarities with decreased memory B lymphocytes and impaired acute phase reactant responses.

More recently, dominant negative heterozygous mutations in IL6ST were identified in 12 patients from eight unrelated families [57]. These patients have an overlap with STAT3LOF with destructive lung disease, forming large pneumatoceles (Fig. 4). Although reports are limited, the pneumatoceles seem to occur at younger ages potentially more frequently than with STAT3LOF, with frequent *Aspergillus* infection and an ABPA phenotype. Non-immune features such as retention of primary teeth and skeletal abnormalities appear to be present as well. Notably, however, some of these patients were relatively healthy in their early years, in contrast to many of the other diseases described here.

IL6R Deficiency

Bi-allelic mutations in IL6R, which encodes the IL-6 receptor, have been described in two unrelated patients, one a teenager and one an adult, with severe dermatitis, bacterial skin and lung infections, and elevated IgE [58]. Strikingly, their inflammatory responses were grossly abnormal, with little grossly observable inflammation when infected, and nearly undetectable CRP. They lacked relatively severe disease in general, nor did they have viral, fungal or mycobacterial infection, connective tissue abnormalities, or other developmental issues. Functional data reveals a complete lack of lymphocyte response to IL-6. The clinical presentation likely contrasts with GP130 (IL6ST) deficiency, which has such destructive lung disease, because (a) gp130 is a co-receptor for

Fig. 3 **a** Scoliosis in a 14-year-old boy with PGM3 deficiency. **b** Chest CT of a 14-year-old with PGM3 deficiency, diagnosed with allergic bronchopulmonary aspergillosis (ABPA), with sputum cultures positive for *Aspergillus flavus*, and good clinical response to posaconazole and prednisone

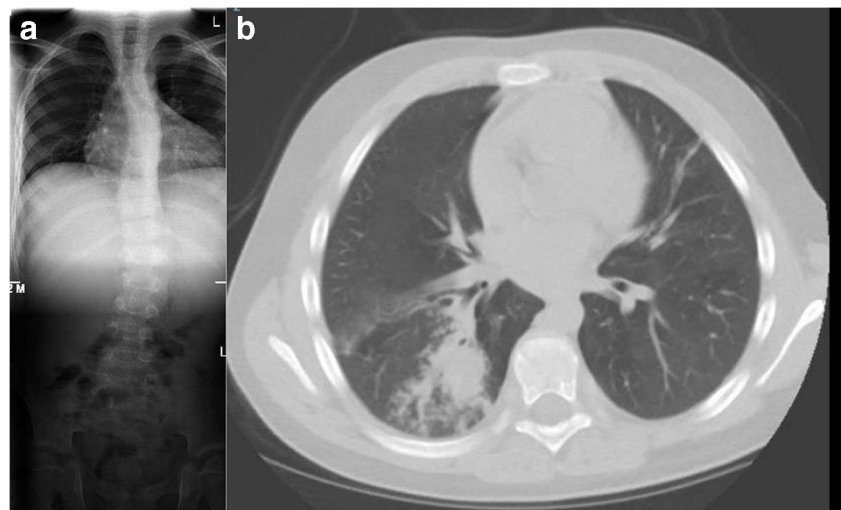




Fig. 4 Chest CT showing large pneumatocele and cystic lung changes in an 18-year-old man with heterozygous IL6ST deficiency with history of ABPA

many other cytokines besides IL-6 and (b) IL-6R expression appears to be more restricted than gp130.

ZNF341

Bi-allelic mutations in ZNF341 were described in 2018 in eight individuals of six families with elevated serum IgE and infection susceptibility [59•]. ZNF341 is a transcription factor that binds to the STAT3 promotor, and therefore, ZNF341 deficiency leads to diminished STAT3 activity and a disease course that is similar to STAT3LOF. These patients have mucocutaneous candidiasis, elevated IgE, rash, and recurrent infections. Non-immunologic features such as those seen in STAT3LOF were present, though perhaps not as ubiquitously, and there was an abnormal inflammatory phenotype. There is laboratory overlap with STAT3LOF with decreased Th17 cell differentiation and low memory B lymphocytes.

Heterozygous LOF CARD11

CARD11 (also known as CARMA1) is a member of the heterotrimer complex of CARD-BCL10-MALT1, which is involved in NFκB and mTOR activation. Activating mutations have been described in CARD11 to cause a lymphoproliferative disease known as BENTA (B cell expansion with NFκB and T cell anergy), and bi-allelic loss of function mutations causes a SCID-like phenotype [60, 61]. In 2017, heterozygous loss-of-function mutations were described to cause a syndrome with atopy, elevated serum IgE, autoimmunity, infection susceptibility, and lymphoma [62•]. Non-immunologic findings are not nearly as prominent as it is with many of the other disorders described here, and the viral susceptibility is increased in comparison with STAT3LOF with recurrent HPV and molluscum, making this disease have more overlap with DOCK8 deficiency, although generally less severe [63]. In fact, phenotypic variability ranges from asymptomatic carriers to, to

those with infection in the absence of atopy, to those who died of fatal lymphoma. Laboratory investigation shows poor mitogen-stimulated T cell proliferation in most patients, elevated serum IgE, eosinophilia, and low memory B lymphocytes. Serum IgG is variable, with some patients having clinically relevant hypogammaglobulinemia.

Heterozygous LOF CARD14

CARD14 binds with BCL10-MALT1 in a similar manner to CARD11 to activate NFκB, but expression is largely restricted to the keratinocytes. Gain of function mutations in CARD14 causes psoriasis [64], but in 2019, four individuals with dominant negative mutations in CARD14 were described with severe eczema [65•]. These patients had elevated serum IgE, eosinophilia, eczema, some viral and bacterial skin infection, as well as other atopic disease with food allergy and asthma.

Conclusions

In recent years, there have been major advances in our understanding of monogenic causes of the hyper IgE phenotype of recurrent skin and lung infection, eczematoid dermatitis, and elevated serum IgE. Each of these genetic diseases is unique but there are clusters of phenotypes which can define certain patterns of disease likely based on the underlying pathway mutated (Table 1). IL6R, IL6ST, STAT3, and ZNF341 mutations, which all converge on IL-6 signaling, all are associated with high IgE, dermatitis, and bacterial skin and lung infections, but lacking severe viral infection, neurodevelopmental abnormalities, or severe inflammation—allergic or from infection. They also vary in the degree of skeletal or other connective tissue abnormalities. CARD11 and DOCK8 mutations, which affect T cell signaling and function, can be associated with greater viral skin infection, lead to more substantial allergic disease, but lack the connective tissue abnormalities. And PGM3 defects affect many different systems, neurodevelopmentally and otherwise. As more cases accumulate and our knowledge of how the specific defects leads to the varying phenotypes, our understanding of more common disorders will be furthered, such as *S. aureus* skin infections, atopic dermatitis, atherosclerosis and aneurysm, scoliosis, and osteoporosis. In addition, as we delineate the pathogenesis of each of these disorders, our approach to personalized therapy will be optimized.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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