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**INVITED REVIEW**
**MEDICAL REVIEW**

# Hyper IgE (Job's) syndrome: a primary immune deficiency with oral manifestations

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**Autosomal dominant hyper IgE (HIES or Job's) syndrome is a rare primary immune deficiency characterized by eczema, recurrent skin and lung infections, extremely elevated serum IgE, and a variety of connective tissue and skeletal abnormalities. Individuals with HIES share a characteristic facial appearance and many oral manifestations including retained primary dentition, a high arched palate, variations of the oral mucosa and gingiva, and recurrent oral candidiasis. Mutations in *STAT3* account for the majority, if not all, of the cases of autosomal dominant HIES, but the pathogenesis of the many varied features remains poorly understood. In this review, we discuss the clinical phenotype of HIES including immunologic and non-immunologic features, the genetics of HIES, and treatment.**
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## Introduction

Autosomal dominant hyper IgE (HIES or Job's) syndrome was first described by Davis *et al* (1966) in two sisters with eczema, cold boils, and pneumonias. The syndrome was further delineated by Buckley *et al* (1972) with the recognition of extremely high serum levels of IgE. Since that time, HIES has been increasingly recognized as a multisystem immune deficiency characterized not only by the classic triad of high serum IgE levels, eczema, skin and lung infections, but also by retained primary dentition, variations of oral mucosa and gingiva, osteopenia, minimal trauma fractures, scoliosis, a characteristic facial appearance, central nervous system abnormalities, and arterial aneurysms (Grimbacher *et al*, 1999a,b; Freeman *et al*, 2007a,b; Ling *et al*, 2007; Domingo *et al*, 2008). Recently, missense or in-frame deletions resulting in one amino acid change or loss in *STAT3* have been identified as the etiology for the majority, if not all, of the cases of the autosomal dominant form of this disease (Holland *et al*, 2007; Minegishi *et al*, 2007); however, the pathogenesis of the many manifestations remains poorly understood. In this review, we will discuss both the immunologic and non-immunologic features of HIES including the many oral manifestations.

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*Immunologic manifestations*

Hyper IgE syndrome is characterized by the triad of eczema, recurrent skin and lung infections, and high serum levels of IgE (Table 1). In almost all cases, the rash presents in the newborn period, and often at or within days of birth. The rash usually starts as papules or pustules on the scalp and face and later progresses over the rest of the body (Chamlin *et al*, 2002; Eberting *et al*, 2004). As the rash progresses, it most commonly mimics eczema, but is typically driven by *Staphylococcus aureus* infection. Control and resolution of the rash typically occurs with anti-staphylococcal antibiotics or topical therapies such as bathing in diluted bleach or swimming in chlorinated pools. Abscesses of the skin (boils) are characteristic of HIES, but typically well controlled with prophylactic antibiotics. Although the abscesses may lack some of the external cardinal features of inflammation including warmth, redness, and tenderness, when incised, pus is present, and *S. aureus* is usually cultured.

Pneumonias typically present within the first few years of life. *Staphylococcus aureus* is the most common etiology, with other pyogenic bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* occurring frequently (Grimbacher *et al*, 1999a,b; Buckley, 2001). Similar to the presentation of the boils, systemic signs of illness are often less than would be expected by the degree of purulence in the airways. Airway remodeling associated with infection appears to be abnormal, and pneumatocoeles and bronchiectasis often follow the pyogenic pneumonias. These chronic lung parenchymal changes then allow infection by gram-negative bacteria

**Table 1** Immunologic characteristics of Hyper IgE syndrome (% frequency)

| |
|---|
| Newborn rash (81) |
| Eczema (100) |
| Boils (87) |
| Recurrent pneumonias (87) |
| Pneumatocoeles (77) |
| Mucocutaneous candidiasis (83) |
| Peak serum IgE > 2000 IU ml$^{-1}$ (97) |
| Eosinophilia (93) |
| Increased incidence of lymphoma (approximate increased relative risk of 259) |

such as *Pseudomonas aeruginosa* and molds, with *Aspergillus fumigatus* predominating. The mold and *Pseudomonas* infections have been a significant source of morbidity and mortality for these individuals, both through dissemination of infection as well as life-threatening hemoptysis following fungal invasion into bronchial vessels (Freeman *et al*, 2007a,b).

Individuals with HIES also suffer from a small number of opportunistic infections. *Pneumocystis jiroveci* pneumonia has been reported, and can occur in infancy with a presentation similar to that seen in congenital HIV infection (Freeman *et al*, 2006). Mucocutaneous candidiasis including candidal fingernail infections can be prominent and recurrent, requiring chronic antifungal therapies. Disseminated histoplasmosis and cryptococcosis, often isolated to a non-pulmonary location such as the gut, have been described (Jacobs *et al*, 1984; Hutto *et al*, 1988).

As is seen in many other primary immune deficiencies, the incidence of malignancy appears to be higher in HIES. Non-Hodgkin's lymphoma has been described most frequently, and is usually of B-cell origin with aggressive histology (Leonard *et al*, 2004). Treatment with chemotherapy is usually effective, and often curative. Other described malignancies include Hodgkin's lymphoma, leukemia, and vulva, liver and lung cancers (Gorin *et al*, 1989; Oztop *et al*, 2004).

The most consistent laboratory abnormalities in HIES are high serum IgE and eosinophilia (Grimbacher *et al*, 1999a,b; Buckley, 2001). The serum IgE typically peaks at >2000 IU ml$^{-1}$, and may even be elevated at birth. Over time, however, serum IgE may decrease, even reaching normal levels (Grimbacher *et al*, 1999a,b); therefore, an extremely elevated serum IgE is not necessary for diagnosis. Other laboratory values are not consistently abnormal in HIES. White blood cell counts are usually normal, although the typical rise in bacterial infections may not be present. The other serum immunoglobulins (IgA, IgM, IgG) are usually normal.

The mechanism of the immune deficiency of HIES remains poorly understood. There have been multiple reports with small numbers of patients and conflicting data as to whether a chemotactic defect is present and whether there is a T helper (Th) 1/Th2 cytokine imbalance (Hill *et al*, 1974; Rodriguez *et al*, 1998; Borges *et al*, 2000; Chehimi *et al*, 2001). More recent data suggest that proinflammatory cytokines, such as TNF-$\alpha$ and interferon-$\gamma$ are elevated at rest and after stimulation, consistent with mouse models of STAT3 immune regulation (Holland *et al*, 2007). Naïve T cells have been shown to be unable to differentiate into IL-17-producing T helper cells (Th17 cells), thus resulting in absent IL-17 production (Milner *et al*, 2008). Th17 cells and IL-17 appear to be critical in control of both extracellular bacteria and fungal infections; their absence may help explain some of the infections in HIES.

*Non-immunologic manifestations of HIES*

Since the initial descriptions of HIES, it has become abundantly evident that HIES is a multi-system disorder. Individuals often share a common facial appearance characterized by asymmetry, a fleshy nasal tip, deep-set eyes, and a prominent forehead (Borges *et al*, 1998; Grimbacher *et al*, 1999a,b; Buckley, 2001) (Table 2). The skin of the face typically has a coarse appearance with pronounced pores. This characteristic facial appearance usually develops during childhood and adolescence.

Musculoskeletal abnormalities include scoliosis, osteopenia, minimal trauma fractures, degenerative joint disease, and craniosynostosis (Smithwick *et al*, 1978; Hoger *et al*, 1985; Grimbacher *et al*, 1999a,b). Scoliosis occurs in about 75% of patients, and typically worsens during adolescence in a pattern similar to idiopathic scoliosis. Minimal trauma fractures, usually of the long bones, occur in about half of the patients, and osteopenia and osteoporosis are common, although not necessarily associated with the minimal trauma fractures. Hyperextensibility of the small and large joints is frequent and may relate to later degenerative joint disease. Craniosynostosis is often observed, but typically does not require corrective surgery (Smithwick *et al*, 1978; Hoger *et al*, 1985).

Abnormalities on brain magnetic resonance imaging are frequent and include punctate hyperintensities particularly of the white matter observed on T2-weighted images (Freeman *et al*, 2007a,b). These abnormalities are typically incidental imaging findings and not associated with any neurologic or developmental abnormalities. Chiari I malformations are relatively common and lacunar infarcts have occurred at younger ages than in the general population.

Vascular abnormalities include dilation, tortuousity, and aneurysms, predominantly of the medium-sized arteries, including the coronary arteries (Ling *et al*, 2007). Interestingly, atherosclerosis appears not to be a feature of HIES, even in older males (A. Freeman, A. Gharib, unpublished data).

**Table 2** Non-immunologic characteristics of Hyper IgE syndrome (% frequency)

| |
|---|
| Retention of primary teeth (72) |
| Characteristic face (83) |
| Minimal trauma fractures (71) |
| Scoliosis >10 degrees (63) |
| Hyperextensibility (68) |
| Oral mucosal and gingival abnormalities (77) |
| Hyperintensities on brain magnetic resonance imaging (70) |
| Chiari I malformations (18) |
| Craniosynostosis (unknown) |
| Arterial aneurysms (unknown) |

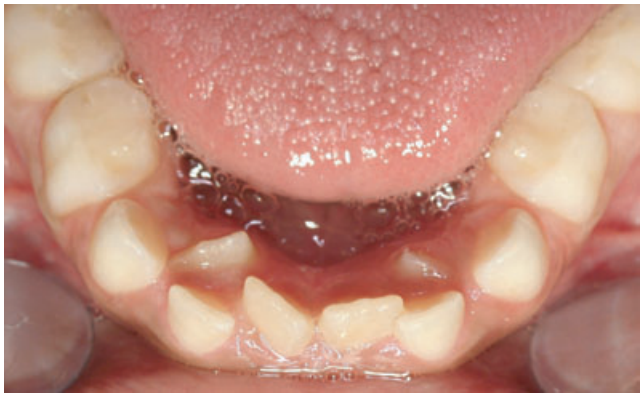

**Figure 1** Eight-year-old girl with Hyper IgE syndrome and mixed dentition with retained primary lateral incisors and lingually erupted permanent lateral incisors

*Oral manifestations of HIES*

The majority of HIES individuals (64%) exhibit failure of primary teeth exfoliation, often preventing the eruption of succedaneous teeth (O'Connell *et al*, 2000; Domingo *et al*, 2008). This prolonged retention of primary teeth can lead to permanent tooth impaction or formation of 'double rows', in which succedaneous teeth erupt lingual of the deciduous teeth and predispose to malocclusion (Figure 1). Abnormal persistence of Hertwig's epithelial root sheath in primary teeth was suggested by an early case, but the actual frequency and underlying mechanisms remain to be confirmed (O'Connell *et al*, 2000).

Lesions of the oral mucosa and gingiva, involving the hard palate, dorsal tongue, buccal mucosa, and lip mucosa, have been identified in over 75% of patients (Domingo *et al*, 2008). The majority of HIES individuals manifest palatal lesions which consist of a midline fibrotic bridge, either linear or multilobular, and occasionally surrounded by grooves or clefts (Figure 2). Even more prevalent are tongue lesions, consisting of surface grooves of varying depths which may be localized or distributed over the entire tongue surface (Figure 3). The most significant tongue lesion is a deep midline cleft anterior to the circumvallate papillae, which may or may not have an overlying tissue flap. On the lips and cheeks, mucosal lesions consist of surface fissures and non-rubabble keratotic striations, patches, or plaques, some of which resemble lichenoid formations (Figure 4). All intraoral lesions are asymptomatic and require no intervention. These oral characteristics manifest earlier than the characteristic facial features, highlighting the potential role of oral phenotypes in early diagnosis (Domingo *et al*, 2008). These oral lesions may represent developmental abnormalities, reactive lesions arising from chronic infections associated with the syndrome, or be manifestations of the role of the HIES gene, *STAT3*, in epithelial development. Oral candidiasis (pseudomembranous, erythematous, median rhomboid glossitis, and angular cheilitis) is also common.

*Diagnosis and genetics of HIES*

Until very recently, the genetic etiology of HIES was unknown, forcing the diagnosis to be based solely on

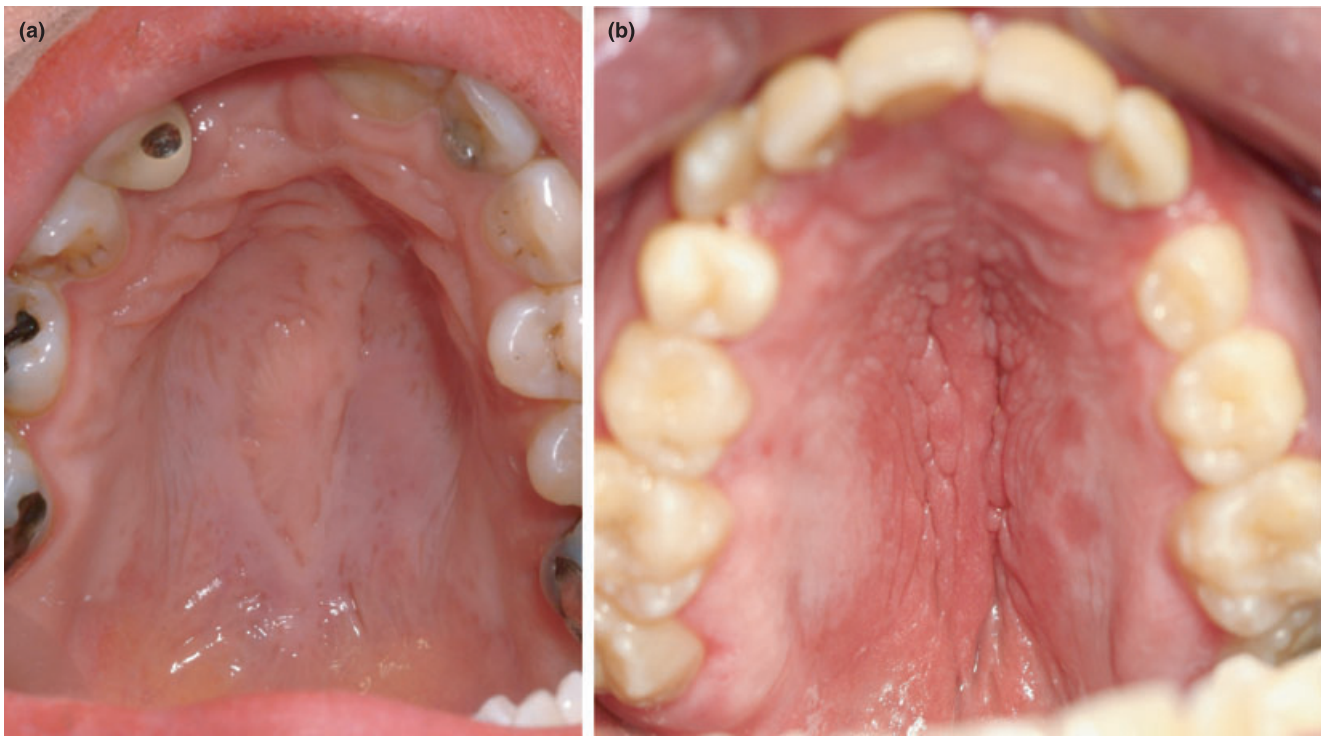


**Figure 2** (**a**) Hard palate with irregular midline fibrotic thickening. (**b**) Hard palate with diffuse palatal midline fibrotic bands and nodules with surrounding erythema

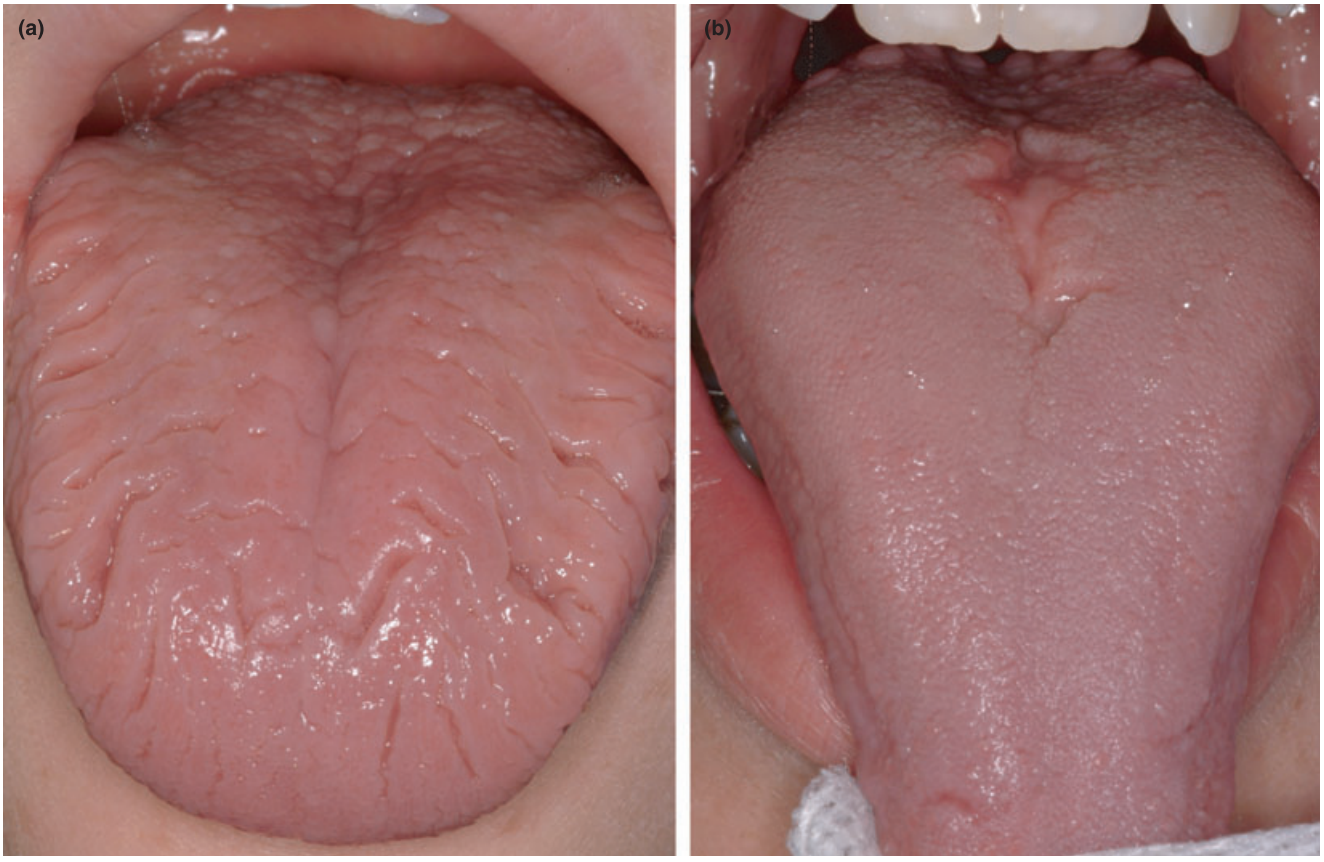


**Figure 3** (**a**) Deep fissures distributed over the entire lingual surface. (**b**) Very deep midline tongue cleft anterior to the circumvallate papillae

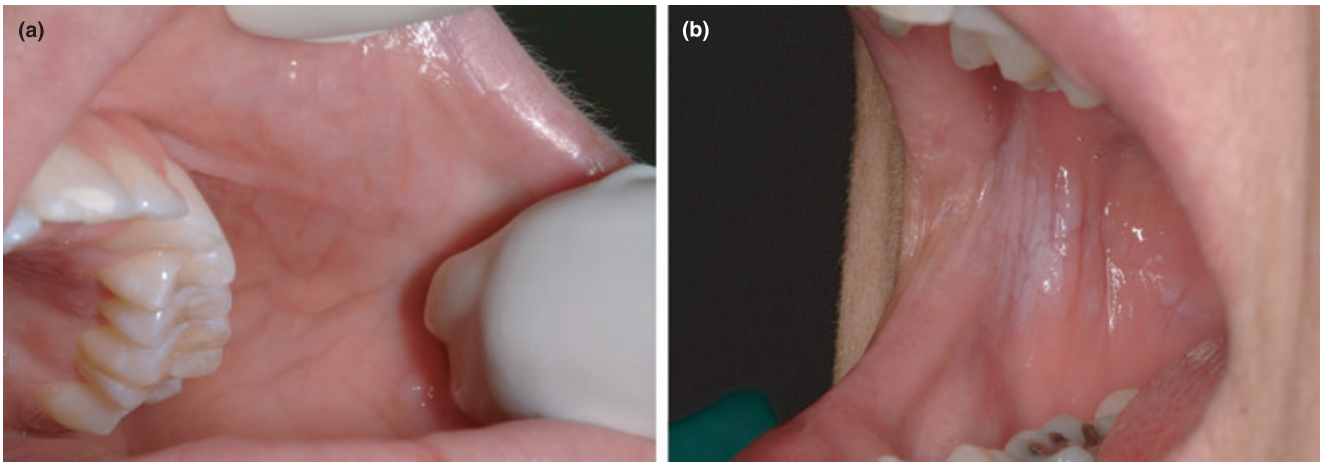


**Figure 4** (**a**) Surface fissures on the buccal and lip mucosae. (**b**) Keratotic patches and plaques on the buccal mucosa

clinical and laboratory features. A scoring system was developed to assist in the diagnosis and included many of the immunologic and non-immunologic features discussed above (Grimbacher *et al*, 1999a,b). Since the finding of *STAT3* mutations, the diagnosis may be based on a high level of clinical suspicion and confirmed through *STAT3* mutational analysis (Holland *et al*, 2007; Minegishi *et al*, 2007). Although *STAT3* is the only gene so far identified to cause autosomal dominant HIES, it remains possible that more than one genetic etiology exists.

The mutations in *STAT3* have been described predominantly in two regions of the gene: the DNA binding domain, which mediates DNA–protein interactions, and the SH2 domain, which mediates protein–protein interactions (Holland *et al*, 2007; Minegishi *et al*, 2007). Several mutational hot spots have been identified by virtue of having multiple unrelated families carrying the

same mutation. All of the reported mutations have been missense mutations or in-frame deletions resulting in the change or loss of one amino acid. These mutations occur heterozygously and act in a dominant-negative manner. In *STAT3* knockout mice heterozygotes are clinically unaffected, whereas homozygosity is embryonic lethal, suggesting that one unimpeded copy of the gene can suffice. Therefore, the mutant form of *STAT3* must be causing less than 50% activity.

STAT3 is a major signal transduction protein involved in diverse pathways including wound healing, angiogenesis, cancer, and immunity (Murray, 2007). Although loss-of-function *STAT3* mutations result in HIES, the pathogenesis of the manifestations of the disease remains unknown. Organ-specific knockout mouse models have shown that deficiency of *STAT3* leads to osteoporosis, airspace enlargement after pulmonary injury, and brain demyelination and astrocytosis, all of which are similar to the clinical manifestations of HIES (Hokuto *et al*, 2004; Zhang *et al*, 2005; Okada *et al*, 2006).

*STAT3*-deficient HIES must be distinguished from the distinct syndrome of autosomal recessive HIES (Renner *et al*, 2004), which is characterized by extremely elevated serum IgE and severe eczema, often complicated by bacterial and viral superinfections (e.g., herpes simplex virus, molluscum contagiosum). Autosomal recessive HIES does not share the musculoskeletal and dental manifestations of the autosomal dominant disease, and has a high incidence of neurologic complications resulting from either infection or vasculitis.

*Treatment of HIES*

Treatment of HIES is based on prophylactic antimicrobials and skin care, as there are no directed therapies specific for HIES. Antibiotics are given to prevent *S. aureus* pneumonias and skin infections, and may be broadened if recurrent gram-negative infections occur. For individuals with recurrent mucocutaneous candidiasis, maintenance antifungals such as fluconazole are helpful. Anti-aspergillus antifungals may be needed as prophylaxis or therapy for individuals with parenchymal cystic lung disease.

Skin care typically requires topical therapies for treatment of eczema as well as antiseptics like bleach baths or swimming in chlorinated pools. Bleach baths are remarkably effective at diminishing the staphylococcal colonization of the skin, greatly improving the eczema and reducing the occurrence of boils.

Immunomodulators have been used with varying success in HIES (King *et al*, 1989; Kimata, 1995; Etzioni *et al*, 1997). The only agent studied in a randomized-controlled trial was levamisole, an unusual antiparasitic that stimulates T and NK cell function; it was inferior to placebo (Donabedian *et al*, 1982). Intravenous immunoglobulin has led to anecdotal improvement in some individuals (Kimata, 1995). Bone marrow transplantation has been reported in two individuals (Nester *et al*, 1998; Gennery *et al*, 2000). In one, the transplant was performed for therapy of lymphoma; the individual died of complications 6 months after transplantation, but with a lower serum IgE and fewer HIES-related symptoms (Nester *et al*, 1998). The recipient of the other transplant was a 7-year-old girl who had severe symptoms of HIES (Gennery *et al*, 2000). She had initial improvement in serum IgE and HIES-related symptoms, which waned somewhat after her immunosuppression was weaned despite full engraftment. Therefore, the benefit of transplantation is still unclear.

## Conclusion

Autosomal dominant HIES differs from many primary immune deficiencies in being a truly multisystem disorder. Mutations in the DNA binding and SH2 domains of *STAT3* cause HIES, but the exact mechanism by which these mutations result in the varied manifestations of HIES remains poorly understood. Better understanding HIES at the developmental, biochemical, and molecular levels should help us understand the pathogenesis of many more common conditions, such as eczema, staphylococcal abscesses, retention of primary teeth, scoliosis, and arterial aneurysms. We hope that these insights will lead to therapies for patients with HIES as well as for those with more common conditions.

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### Author contributions

All authors drafted and revised this review.

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