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## The Hyper IgE Syndromes

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### Abstract

**Synopsis**—The hyper IgE syndromes (HIES) are rare primary immune deficiencies characterized by elevated serum IgE, rash and recurrent bacterial infections of the skin and lung. Autosomal dominant HIES, the most common disease in this group, results from *STAT3* mutations and has a variety of connective tissue and skeletal abnormalities. The genetic etiologies of the more rare autosomal recessive form(s) still need delineation. Treatment of these syndromes has relied on prophylactic and therapeutic antimicrobials and aggressive skin care. The new and evolving genetic and immunologic understandings of this previously elusive set of diseases should lead to more effective disease-specific therapies.

### Introduction

The Hyper-immunoglobulin E syndromes (HIES) are rare primary immune deficiencies characterized by elevated serum IgE, dermatitis and recurrent skin and lung infections. There are two forms of HIES: a dominant form caused by mutations in *STAT3*, and a recessive form, for which a genetic cause is unclear<sup>1-4</sup>. These two different syndromes have distinct presentations, courses, and outcomes and share very little in terms of pathogenesis other than the IgE elevation. The dominant form is characterized by non-immunologic features including skeletal, connective tissue, and pulmonary abnormalities in addition to recurrent infections and eczema. In contrast, the recessive form lacks the somatic features and has marked viral infections and neurologic complications. We will discuss the diagnostic, laboratory and clinical aspects of these disorders as well as their genetic etiologies.

### Autosomal Dominant Hies (*STAT3* deficiency)

The disease subsequently identified as Hyper IgE Recurrent Infection syndrome (HIES) was first described as Job's syndrome by Davis et al in 1966,<sup>5</sup> referring to the Biblical Job, who was “smote with sore boils”. The syndrome was refined by Buckley et al in 1972, who recognized extremely high serum IgE levels<sup>6</sup>. Since that time, the classic triad of eczema, recurrent skin and lung infections and high serum IgE has been expanded to include skeletal, connective tissues, cardiac and brain abnormalities<sup>7-9</sup>. Until 2007, HIES remained the last of the major immune deficiencies without neither a known genetic etiology nor a comprehensive understanding of the associated immune dysfunction. We now know that *STAT3* mutations are responsible for most, if not all, cases of autosomal dominant HIES, and these mutations have

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begun to explain the multi-system nature of the disease<sup>2,3</sup>. To distinguish this dominant disease due to *STAT3* mutation from the recessive forms of hyper IgE syndromes, and to distinguish this disease from other syndromes of IgE elevation, we will also refer to this disease as *STAT3* deficiency.

### Clinical Manifestations

*STAT3* deficiency is a disease of multi-organ dysfunction (Table 1). Although what brings patients to initial attention is usually eczema and recurrent infections, these individuals have abnormalities in vessels, connective tissue and skeleton. Prior to genetic testing, the diagnosis of HIES has typically been difficult to confirm until both immunologic and somatic features exist. A clinical scoring system has been developed which includes both of these categories<sup>10</sup>.

#### Skin

A newborn rash is usually the first manifestation of *STAT3* deficiency<sup>8,9</sup>. Pustular and eczematoid rashes usually begin within the first month of life, typically first affecting the face and scalp. In a series of 43 patients, 8 babies (19%) were born with the rash, and 23 (53%) acquired the rash within the first week of life<sup>9</sup>. Biopsies typically show an eosinophilic infiltrate and bacterial culture usually grows *Staphylococcus aureus*. The rash can be quite significant, especially in childhood. To achieve and maintain good control, anti-staphylococcal therapies (antibiotics or topical antiseptics, such as bleach) are often essential.

Boils are a classic finding in this disease, and characteristic of the diagnosis. The degree of inflammatory symptoms, such as tenderness and warmth is often quite variable. The “cold” abscesses initially described by Davis et al are common. However, despite the absence of external signs of inflammation, upon aspiration, there is frank pus, and *S. aureus* is usually cultured. With prophylactic antibiotics, the occurrence of these boils typically substantially diminishes. Trouble areas may persist in intertriginous areas such as the axillae, the inguinal region or under the breasts.

#### Lungs

Recurrent pyogenic pneumonias are the rule. Pneumonias typically start in childhood, and the most frequent bacteria isolates are *S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (Box 1). Similar to the occurrence of cold abscesses, these pneumonias may present with fewer symptoms (e.g., cough, sputum production) than would be expected in a normal person given the extent of disease. This dearth of symptoms and subsequent delay in clinical presentation may contribute to advanced disease and significant tissue damage prior to identification and initiation of appropriate therapy. Upon sputum inspection or bronchoscopy, pus is clearly present.

Although the pneumonias typically respond promptly to appropriate antimicrobial therapy, the healing of the lungs is aberrant. Pneumatocoeles and bronchiectasis form during the healing process and usually persist once the infection has cleared. These persistent structural abnormalities, which can be quite significant, then predispose to Gram-negative bacterial infection (typically *Pseudomonas*) and fungal infections (typically *Aspergillus* or *Scedosporium* species) in addition to the primary pathogens in *STAT3* deficiency (Figure 1). The secondary infections are typically indolent and difficult to clear. These long-term infections are more frequently associated with mortality than the acute pyogenic infections, causing rupture into large pulmonary vessels with life-threatening hemoptysis or fungal dissemination to the brain<sup>13</sup>.

## Other Infections

Mucocutaneous candidiasis is common in *STAT3* deficiency, manifesting typically as oral thrush, vaginal candidiasis or onychomycosis<sup>1</sup>. Systemic *Candida* infections are very rare, and most likely nosocomial in origin (such as an indwelling catheter infection). Disseminated *Cryptococcus* and *Histoplasma* infections also occur, although less frequently than candidiasis. These uncommon yeast infections are often localized, such as histoplasmosis of the tongue, or intestinal cryptococcal infection<sup>14-15</sup>. *Pneumocystis jiroveci* pneumonia (PCP) also occurs, albeit infrequently, and may present in infants in a way similar to the initial presentation of PCP in infants infected with HIV<sup>16</sup>.

## Musculoskeletal Abnormalities

Skeletal abnormalities in *STAT3* deficiency include scoliosis, osteopenia, minimal trauma fractures, hyperextensibility, and degenerative joint disease. Scoliosis occurs in about 75% of patients, typically emerging during adolescence in a pattern similar to that of idiopathic scoliosis<sup>1</sup>. In some patients, there is associated leg length discrepancy; in others scoliosis develops or worsens after thoracotomy for lung infections. The scoliosis varies in severity, and some individuals have required surgical stabilization or correction.

Hyperextensibility of both the large and small joints is frequent, and may be related to the early development of severe degenerative joint disease, particularly of the spine, that we have seen in several patients in their 20s-40s. Several patients have required stabilization procedures as early as in their 3<sup>rd</sup> decade, and many suffer from chronic pain due to extensive arthritis. Minimal trauma fractures and decreased bone mineral density are also common, but may occur independently of one another<sup>1</sup>. Fractures tend to be of the long bones, ribs and pelvic bones. Bone resorption has been shown to be abnormally increased in patients with HIES due to abnormalities in the prostaglandin synthetic pathway, and is responsive to non-steroidal agents<sup>17,18</sup>. Healing appears to be normal following surgery or fractures.

## Cranial Abnormalities

Craniosynostosis of varying degrees occurs, but typically does not require surgical repair<sup>19, 20</sup>. Chiari 1 malformations also occur fairly frequently; in one study of 50 individuals, 9 (18%) had Chiari 1 malformation on brain MRI<sup>7</sup>. The Chiari malformations observed typically do not require surgical repair and are usually incidental findings.

## Dental Abnormalities

The majority of individuals with *STAT3* deficiency retain at least some, if not all, of their primary teeth past the age of normal primary dental exfoliation<sup>1,21</sup>. This appears to be a failure of the primary teeth to exfoliate, not of the secondary teeth to develop or to erupt. Once the primary teeth do exfoliate, whether by dental extraction or naturally, the secondary teeth, which are normally formed, emerge. At times, layers of both primary and secondary teeth are simultaneously present when the secondary teeth emerge despite the primaries having not fallen out. There are also characteristic findings of the oral mucosa, tongue, roof of the mouth and cheeks<sup>22</sup>. Central depressions in the tongue (central rhomboid glossitis) may be caused by or become secondarily infected with candida. The palate typically has a high arch with varying degrees of a central band-type protrusion. Abnormally prominent wrinkles are often observed on the oral mucosa.

## Vascular abnormalities

Arterial aneurysms are an important recently appreciated aspect of *STAT3* deficiency<sup>8</sup>. Bilateral berry aneurysms of the internal carotid arteries and mycotic aneurysm have been reported in an autopsy series of HIES<sup>13</sup>. A large aneurysm in the left anterior descending

coronary artery resulted in myocardial infarction in one adult male patient<sup>8</sup>. That case prompted us to look more closely at our other adult patients with HIES. We have been surprised at the frequency of coronary artery anomalies, including arterial tortuosity, dilation and aneurysms. Of 18 individuals studied by either cardiac CT or MRI, 14 had one of these abnormalities, with tortuosity and dilation predominating and aneurysms being present in only 4 (unpublished data). It is important to note that there has been a paucity of significant atherosclerosis in the individuals studied by CT and MR angiography, despite their having coronary artery disease risk factors. The fact that one of the patients had a myocardial infarction due to his aneurysm clearly indicates that these can be medically important. Whether and when these aneurysms require therapy, and if so with what, is unclear. Whether the coronary and extracoronary aneurysms are reflections of the same underlying pathophysiology also remains to be determined.

Lacunar infarcts have been reported at a younger age than is typical, and have had varying clinical consequences, ranging from thalamic infarction to no symptoms<sup>7</sup>. T2 weighted hyperintensities seen on brain MRI are similar to incidental findings that accumulate in otherwise healthy adults as they age, but seen at much younger ages than in the general population<sup>7</sup>. Similar hyperintensities in elderly otherwise healthy adults are thought to reflect small vessel abnormalities, which may be signs of subtle vascular abnormalities, or demyelination. Gross neurologic abnormalities are not detected in the majority of patients with these findings.

### Face

The characteristic facial appearance that individuals with *STAT3* deficiency share may make patients look more like one another than their family members<sup>1,12,23</sup>. Facial asymmetry, broad nose, and deep-set eyes with a prominent forehead are common. The facial skin has a rough appearance with exaggerated pore size. This characteristic appearance typically develops during childhood and adolescence.

### Malignancies

There is an increased risk of malignancy associated with *STAT3* deficiency<sup>24-26</sup>. Both Hodgkin's and non-Hodgkin's lymphoma (NHL) have been described, with the majority of the NHL being of B cell origin with aggressive histology. Individuals have been successfully treated and apparently cured with chemotherapy. In one study of 11 individuals, 7 died, but two for reasons other than lymphoma<sup>24</sup>. The increased mortality may reflect a delay in diagnosis. Other cancers described in HIES have included leukemia and those of the vulva, liver and lung<sup>26</sup>.

### Laboratory abnormalities of *STAT3* Deficiency

The two most consistent laboratory findings of Job's syndrome are elevated serum IgE and eosinophilia; otherwise there is a lack of pathognomic laboratory signs. Therefore, the diagnosis has historically been more syndromic than laboratory-based. The serum IgE typically peaks above 2,000 IU/ml, and is usually elevated even at the time of birth. It is important to keep in mind the natural change in IgE levels over time: they are usually undetectable in cord blood, and rise to the adult range slowly over the years. In adulthood the IgE level may diminish over time in some individuals and can actually normalize, despite persistence of the clinical abnormalities of *STAT3* deficiency (in one report 20%)<sup>1</sup>. Eosinophilia is almost always present in these patients at least at some point, but is not correlated with the serum IgE.

Other laboratory findings are variable in *STAT3* deficiency. Total white blood cell counts are typically normal, but may not increase appropriately during acute infection. Neutropenia has

been reported, but is uncommon. Serum IgG, IgA, IgM are typically normal, although there are some individuals with deficiencies in one or more of these immunoglobulins.

### Immunology of *STAT3* deficiency

The mechanisms of the immune deficiencies in *STAT3* deficiency remain elusive. Multiple reports with small numbers of patients have conflicted regarding whether a neutrophil chemotactic defect is present, and whether there is a T helper 1 (Th-1)/Th2 cytokine imbalance<sup>27-32</sup>.

*STAT3* is a key regulator of many immunologic pathways. Mouse *Stat3* homozygous knock-outs die *in utero*, reflecting the absolute necessity of some *Stat3* function for survival. Therefore, most experiments in mice have used organ-specific or conditional knock-out animals. Animals with a myeloid-specific deletion of *Stat3* had upregulation of TNF-alpha and interferon-gamma, and down-regulation of IL-6 and IL-10<sup>33-34</sup>. Consistent with these mouse data, microarray analysis of leukocytes from *STAT3* deficient humans showed significant upregulation of pro-inflammatory genes both at rest and after stimulation<sup>2</sup>. Similarly, patients showed excessive proinflammatory cytokine production in response to innate immune agonists, consistent with the impaired regulation of these cytokines by *STAT3*<sup>2</sup>. After incubation with lipopolysaccharide (LPS), levels of TNF-alpha and Interleukin (IL)-12 were elevated. Interferon-gamma was also increased after the mitogen phytohemagglutinin (PHA). As expected for a defect in *STAT3*, upon which the signaling of IL-6 and IL-10 depend, there are impaired responses to these cytokines. Monocyte chemoattractant protein-1 (MCP-1) levels are diminished after IL-6 stimulation of HIES patient leukocytes<sup>2</sup>.

Many of the specific immune defects of *STAT3* deficiency remain somewhat unexplained. The predominance of infections of the lung and skin may be because *STAT3* is a key regulator of beta-defensins of the skin and lung through IL-22 signalling<sup>35</sup>. The high IgE may result from defects in *STAT3* mediated IL-21 receptor signaling, as heterozygous IL-21 receptor knock-out mice have increased IgE<sup>36</sup>. HIES is not exclusively a disorder of too little inflammation and resulting inability to control invading microorganisms. It is also surprisingly a disorder of too much inflammation. The increased inflammation is evident in the lung, where tissue breakdown leading to pneumatoceles may be a consequence of exuberant inflammation. In contrast, there are aspects of *STAT3* deficiency that are more consistent with too little inflammation, such as the frequent "cold" abscesses, and the relative paucity of symptoms compared to the extent of disease. Exploration and charting of these areas of aberrant regulation, both too little and too much, should be highly informative about the nature of the early and late aspects of inflammation.

### Genetics of *STAT3* Deficiency

*STAT3* mutations cause most, if not all, cases of autosomal dominant HIES. So far, mutations have been found in only 2 regions of the *STAT3* gene: the SH2 domain (mediating protein-protein interaction) and the DNA binding domain (mediating the interaction of protein with DNA). There are mutational hot spots in both the SH2 and DNA binding domains, as shown by multiple independent families carrying the same mutation<sup>2,3</sup>. Many of the same mutations have been found in multiple ethnic groups among Caucasians, Africans, and Asians, indicating recurrent *de novo* mutations. All mutations so far have been missense mutations or in frame deletions, allowing the production of full-length mutant *STAT3* protein able to exert a dominant negative effect. The importance of the production of mutant protein with dominant negative effect is shown by the fact that mice with heterozygous deletions of *STAT3* have no apparent phenotype, suggesting that having a single copy of a functional gene is adequate for most functions. This suggests that the development of human HIES requires an inhibition of function below that afforded by a single allele. The mutations have no intrinsic function on their own,

but act in a dominant-negative manner to inhibit the function of the normal allele<sup>3</sup>. Consistent with this in vitro phenotype, HIES is transmitted in an autosomal dominant manner. Importantly, somatic mosaicism has been recognized in a male who had an intermediate HIES score but had 2 HIES affected children. His peripheral blood showed evidence for 2 populations of cells: one population with the mutant allele and one population without it<sup>2</sup>. Efforts to define the existence of somatic mutations that cause intermediate types of disease are underway. Despite the existence of only 2 mutated domains of *STAT3* that are thought to mediate such different effects as DNA and protein binding, genotype/phenotype correlations have yet to be determined.

*STAT3* is a major signal transduction protein involved in diverse pathways including wound healing, angiogenesis, immune pathways, and cancer. Homozygous *STAT3* knock-out mice are not viable, but organ- and tissue-specific knock-outs are and have been informative. In mice with *STAT3* deficiency of the pulmonary epithelium, there is excessive inflammation and airspace enlargement when exposed to hyperoxia, reminiscent of the pneumatoceles that form in HIES patients following bacterial pneumonia<sup>37</sup>. Mice with hematopoiesis-specific *STAT3* deficiency develop osteopenia and increased osteoclast generation, reminiscent of the osteopenia and fractures of HIES patients<sup>38</sup>. Mice with brain-specific *STAT3* have increased inflammation, demyelination, and astrogliosis, reminiscent of the hyperintensities seen in HIES patient brain MRIs<sup>7,39</sup>. *STAT3* is also involved in vascular remodeling and atherosclerosis, which may be relevant to the coronary artery aneurysms and lack of atherosclerosis in HIES patients<sup>40</sup>.

### Therapy of Hyper IgE syndromes

Specific therapies for *STAT3* deficiency are only now being developed but successful supportive care has been well honed. Effective skin care often depends on control of both superficial and invasive *S. aureus* infection. Bleach baths (120 ml bleach in a tub of water, soaked in for 15 minutes 3 times weekly) and swimming in chlorinated pools are highly effective. Systemic immune suppression (such as corticosteroids) to treat the eczema are usually not necessary, as there is typically an excellent response to antimicrobials, but topical steroids help in difficult cases. Antimicrobial prophylaxis to prevent *S. aureus* skin and lung infection (such as trimethoprim-sulfamethoxazole 2.5 mg/kg twice daily), may be broadened if Gram-negative lung infections occur. Antifungal prophylaxis to prevent pulmonary aspergillosis remains attractive but unproven, but it is highly effective to treat and prevent mucocutaneous candidiasis. Treatment of pneumonia is ideally guided by the etiologic agent. Bronchoscopy is helpful to recover the pathogen and to assist with clearance of mucus and pus, as these patients often do not have an adequate cough response. Since *STAT3* deficient patients often feel well and have minimal fever despite significant infection, it is good to have a low threshold to investigate slight changes, like new cough, chest discomfort, or fatigue, even in the absence of fever. The decision to resect the large pneumatoceles that sometimes form following pneumonia is complex. These large cysts may become secondarily infected and be a source of infection, bleeding, and possibly death. On the other hand, thoracic surgery can be complicated by poor expansion of the remaining lung after surgery, often resulting in thoracoplasty.

Before the identification of *STAT3* deficiency as the cause of HIES, there were only a few immunomodulator trials. Levamisole is an unusual antihelminthic that also stimulates T cell and NK cell function. In a blinded randomized study it was found to be inferior to placebo<sup>41</sup>. Interferon-gamma has been used with mixed results. In vitro it improved neutrophil chemotaxis, but in vivo it had inconsistent effects on IgE levels<sup>42</sup>. Intravenous immunoglobulin (IVIG) may decrease the number of infections for some patients<sup>43</sup>. Case reports and small case series have extolled cyclosporine and histamine-2 receptor

blockade<sup>44,45</sup>. Omalizumab (the monoclonal antibody against IgE) has not yet been studied, and it is unclear whether there may be any benefit.

Two bone marrow transplants in HIES patients have been reported<sup>46,47</sup>. An adult died 6 months after transplantation<sup>47</sup>. His death was thought to be due to complications of the transplant, but he had a decrease in serum IgE and improvement in HIES related symptoms in the post-transplant interval. A 7 year old girl was transplanted because of her severe HIES. Although she initially had a good response, when post-transplant immune suppression was weaned, her serum IgE once again became elevated and infections recurred despite engraftment of the donor cells<sup>46</sup>. Subsequently she appears to be doing well, leaving open issues of short and long term benefits to transplant (A. Cant, personal communication).

The role of bisphosphonates in treating the osteoporosis and minimal trauma fractures is undefined. Although we have treated several patients with bisphosphonates leading to improved bone mineral density without adverse events, it is unclear whether this will translate into fewer fractures. Possible dental adverse events from bisphosphonates also remain unclear. The proper therapy for coronary artery aneurysms, or other blood vessel abnormalities, if any, is undefined. Coronary artery aneurysms from Kawasaki disease are typically treated with anticoagulation depending on the size of aneurysm (from aspirin to warfarin). However, the development, progression, and significance of the arterial abnormalities in *STAT3* deficiency are unknown. The hypothetical benefits of anticoagulation must be weighed against the real risks of pulmonary hemorrhage. Close attention to blood pressure and other cardiovascular risk factors seems sensible.

A complex multisystem disease like *STAT3* deficiency requires a sophisticated multidisciplinary approach. In addition to close infectious disease management, other subspecialists are often required. The orchestrated expertise of orthopedists for scoliosis, fractures and degenerative joints; dentists to address the retained primary teeth; and pulmonologists for diagnostic and therapeutic bronchoscopy and pulmonary toilet.

## Autosomal Recessive Hies (AR-HIES)

In 2004, Renner et al described 13 patients from six consanguineous families who had a disease similar to, but distinct from, what we now know to be autosomal dominant HIES (*STAT3* deficiency).<sup>4</sup> Their patients had elevated serum IgE, eczema and recurrent skin and cutaneous viral infections, but lacked the connective tissue and skeletal findings characteristic of *STAT3* deficiency. One patient has been described with a recessive disease similar to AR-HIES due to a homozygous mutation in Tyrosine kinase 2 (*Tyk2*), a major signal-transducing molecule for IL-12, IL-6, and interferon alpha<sup>48</sup>. However, *Tyk2* deficiency is distinct from AR-HIES, and patients with AR-HIES have normal *Tyk2* and *STAT3* sequences<sup>49</sup>.

## Clinical Manifestations (Box 2)

The predominant clinical manifestations of AR-HIES are severe eczema and recurrent skin and lung infections<sup>4</sup>. All of the patients described with AR-HIES have had severe eczematoid rashes, starting early in life, although not necessarily in the newborn period. Skin abscesses do occur, and are typically from *S. aureus*. However, the skin disease of AR-HIES differs from *STAT3* deficiency in the much higher incidence of cutaneous viral infections including *Molluscum contagiosum*, herpes simplex and varicella zoster virus infections. AR-HIES and *STAT3* deficient patients share the propensity towards mucocutaneous candidiasis. Sinopulmonary infections are common in AR-HIES, with etiologies including *S. aureus*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Cryptococcus*. However, as opposed to *STAT3* deficient patients, in whom pneumatoceles complicate

pneumonias, AR-HIES patients heal their lung infections without pneumatoceles. Fatal sepsis occurs in AR-HIES from both Gram positive and negative bacteria.

The AR-HIES patients have more symptomatic neurologic disease than those with *STAT3* deficiency<sup>4</sup>. In the Renner series, seven had neurologic symptoms, ranging from facial paralysis to hemiplegia. The etiology of the neurologic complications was not clear for all patients, but one had a cerebral cryptococcoma with meningitis, while others had severe central nervous system vasculitis.

AR-HIES lacks the connective tissue and skeletal abnormalities of *STAT3* deficiency. AR-HIES has normal primary tooth exfoliation, no fractures and normal facies.

### Immunologic Manifestations

Patients with AR-HIES have high serum IgE, comparable to those with *STAT3* deficiency<sup>4</sup>. Their eosinophilia is typically higher than in *STAT3* deficiency. Autoimmune phenomena, including hemolytic anemia may occur. Lymphocyte phenotyping and function are inconsistent in AR-HIES, although decreased lymphocyte proliferation was seen in response to a staphylococcal antigen. Neutrophil chemotaxis and nitroblue-tetrazolium reduction are normal.

### Genetics of AR-HIES

The patients with AR-HIES and *Tyk2* deficiency were products of consanguineous unions<sup>4, 48</sup>. The *Tyk2* deficient patient shares features of AR-HIES including high serum IgE, eczematoid rash, recurrent skin and sinopulmonary bacterial and viral infections. However, he had Bacille Calmette-Guerin (BCG) and salmonella infections, which are more commonly seen in defects of the Interferon-gamma/IL-12 axis. Indeed, upon cytokine stimulation of the peripheral blood mononuclear cells (PBMCs), defects were found in IL-12 and IFN-alpha signaling. This *Tyk2* deficient patient had a homozygous mutation leading to a four nucleotide deletion resulting in a premature stop codon. His related parents were heterozygous for the same deletion and healthy.

Mutations of *Tyk2* are absent in AR-HIES<sup>48</sup>. Therefore, although it is possible that *Tyk2* mutations may cause some cases of AR-HIES disease, AR-HIES is likely heterogeneous, with more than one gene contributing to its etiology. Since *STAT3* is the genetic etiology of autosomal dominant HIES, related genes in these pathways may cause some of these undefined diseases.

### Therapy of AR-HIES

Therapy of AR-HIES remains supportive and less explored than *STAT3* deficiency. Prophylactic antimicrobials likely help, with anti-staphylococcal agents, antivirals if needed, and antifungals if mucocutaneous candidiasis or invasive fungal disease occur. Aggressive skin care may help to prevent invasive bacterial infection.

Disease severity in AR-HIES is often worse than *STAT3* deficiency. Immunomodulatory therapies and bone marrow transplantation need further exploration.

### Conclusion

Hyper IgE syndromes were first described in 1966, and until recently remained one of the few primary immunodeficiencies without a genetic etiology. However, now two genetic defects have been described: *STAT3* mutations act in a dominant negative manner to cause of autosomal dominant HIES, and *Tyk2* deficiency acts in a recessive manner to cause one of the cases of



AR-HIES. We now need to focus on understanding the pathogenesis of these complicated diseases. Understanding how *STAT3* deficiency leads to the many facets of this disease will hopefully help us understand diseases that are more common, such as idiopathic scoliosis, atopic dermatitis, staphylococcal skin abscesses, and the coronary artery aneurysms of Kawasaki disease. Understanding the pathogenesis of *STAT3* deficiency will allow us to create better therapies to prevent the morbidity and mortality of many diseases, including *STAT3* deficiency.

### Box 1. Pathogens of *STAT3* Deficiency

#### Frequent Pathogens

*Staphylococcus aureus* (lung and skin)

*Streptococcus pneumoniae* (lung)

*Haemophilus influenzae* (lung)

*Candida albicans* (mucocutaneous)

#### Secondary Pathogens of Lung

*Pseudomonas aeruginosa*

*Aspergillus* species

*Scedosporium* species

Nontuberculous mycobacteria

#### Less Frequent Pathogens

*Pneumocystis jiroveci* (lung)

*Histoplasma* (gastrointestinal tract)

*Cryptococcus* (brain and gastrointestinal tract)

### Box 2. Clinical Characteristics of AR-HIES

Eczema

Boils

Recurrent pneumonia without pneumatoceles

Sepsis

Mucocutaneous candidiasis

Skin viral infections

Neurologic symptoms

Vasculitis

Increased serum IgE

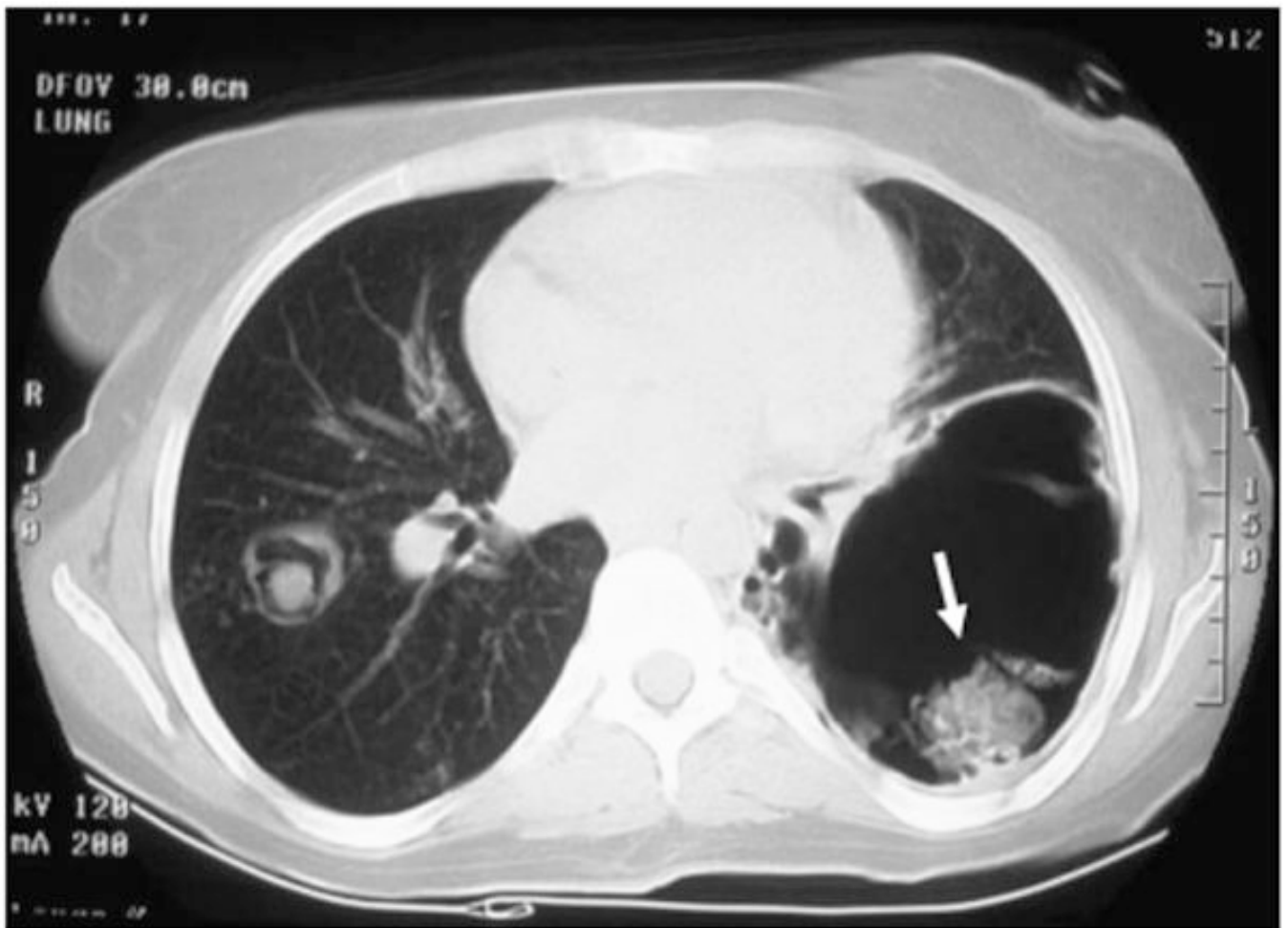
Eosinophilia

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**Figure 1.** Chest CT of an individual with *STAT3* deficiency showing the characteristic pneumatoceles. The pneumatoceles are prone to infection with fungi (arrow indicates an aspergilloma) and Gram-negative bacteria.

**Table 1**

Clinical Characteristics of STAT3 Deficiency.

<b>Immunologic Characteristics (% Frequency)</b>	<b>Non-Immunologic Characteristics (%Frequency)</b>
Newborn rash (81%)	Characteristic face (83%)
Boils (87%)	Retained primary teeth (72%)
Recurrent pneumonias (87%)	Minimal trauma fractures (71%)
Pneumatocoeles (77%)	Scoliosis >10 degrees (63%)
Eczema (100%)	Hyperextensibility (68%)
Mucocutaneous candidiasis (83%)	Focal Brain Hyperintensities (70%)
Peak Serum IgE >2000 IU/ml (97%)	Chiari 1 Malformations (18%)
Eosinophilia (93%)	Craniosynostosis (unknown)
Increased incidence of Lymphoma	Arterial Aneurysms (unknown)