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STAT3 Hyper IgE Syndrome

Synonyms: Job Syndrome, STAT3-Deficient Hyper-IgE Syndrome, STAT3 Deficiency, *STAT3*-HIES, *STAT3* Loss-of-Function Hyper-IgE Syndrome (*STAT3* LOF HIES)

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Summary

Clinical characteristics

STAT3 hyper IgE syndrome (*STAT3*-HIES) is a primary immune deficiency syndrome characterized by elevated serum IgE, eczema, and recurrent skin and respiratory tract infections, together with several nonimmune features. This disorder typically manifests in the newborn period with a rash (often diagnosed as eosinophilic pustulosis) that subsequently evolves into an eczematoid dermatitis. Recurrent staphylococcal skin boils and bacterial pneumonias usually manifest in the first years of life. Pneumatoceles and bronchiectasis often result from aberrant healing of pneumonias. Mucocutaneous candidiasis is common. Nonimmune features may include retained primary teeth, scoliosis, bone fractures following minimal trauma, joint hyperextensibility, and characteristic facial appearance, which typically emerges in adolescence. Vascular abnormalities have been described and include middle-sized artery tortuosity and aneurysms, with infrequent clinical sequelae of myocardial infarction and subarachnoid hemorrhage. Gastrointestinal (GI) manifestations include gastroesophageal reflux disease, esophageal dysmotility, and spontaneous intestinal perforations (some of which are associated with diverticuli). Fungal infections of the GI tract (typically histoplasmosis, *Cryptococcus*, and *Coccidioides*) also occur infrequently. Survival is typically into adulthood, with most individuals now living into or past the sixth decade. Most deaths are associated with gram-negative (*Pseudomonas*) or filamentous fungal pneumonias resulting in hemoptysis. Lymphomas occur at an increased frequency.

Diagnosis/testing

The diagnosis of *STAT3*-HIES is established in a proband with typical clinical findings and a heterozygous dominant-negative pathogenic variant in *STAT3* identified by molecular genetic testing.

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Management

Treatment of manifestations: The mainstay of treatment is prevention of staphylococcal abscesses and pneumonias with anti-staphylococcal prophylactic antibiotics as well as early aggressive treatment of infections. Use of antibiotics and antifungal agents depends on the nature of the infection and the extent of involvement. Antiseptic therapies for the skin such as dilute bleach baths and chlorhexidine are beneficial. Medications such as histamine-1 antagonists to control pruritus are helpful for more significant eczema. There is no known treatment or prevention for the nonimmunologic characteristics, although optimization of calcium and vitamin D intake may be considered to improve bone health. The role of hematopoietic cell transplantation (HSCT) in *STAT3*-HIES is emerging; while successful transplant recipients have improved infection phenotype, the effect of HSCT on the nonimmunologic aspects of the disease remains unclear.

Surveillance: Periodic chest imaging and high clinical suspicion assist in early detection of lung infections. Culture of skin lesions and sputum samples helps direct therapy. Routine screening of adolescents for early signs of scoliosis is recommended. Dental monitoring is necessary to ensure timely removal of primary teeth to allow eruption of secondary teeth. Evaluation for coronary artery and cerebral aneurysms every three years in adulthood is recommended as well as monitoring for lymphadenopathy in case of increased incidence of lymphoma.

Genetic counseling

STAT3-HIES is inherited in an autosomal dominant manner. The majority of affected individuals have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with *STAT3*-HIES has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible once the *STAT3* pathogenic variant in the family has been identified.

Diagnosis

Suggestive Findings

STAT3 hyper IgE syndrome (*STAT3*-HIES) **should be suspected** in individuals with the following findings:

- Newborn rash and typically eczematous rash at least through childhood
- Recurrent skin boils (often "cold," manifesting little inflammatory reaction)
- Cyst-forming pneumonias
- Mucocutaneous candidiasis
- Nonimmune features such as three or more retained primary teeth, scoliosis, bone fractures following minimal trauma, hyperextensibility of joints, characteristic facial appearance, increased nasal width, high palate
- Laboratory test results showing:
  - Elevations of serum concentration of immunoglobulin E (IgE) to levels above 2000 IU/mL (normal <100 IU/mL in adults);
  - Eosinophilia (>700/µL);
  - Diminished circulating memory T and B cells and near absence of IL-17-producing Th17 cells.

Note: Not all features need to be present to suspect *STAT3*-HIES, and because features accrue over time, the clinical diagnosis can be uncertain in young children. Moreover, early institution of effective prophylactic antibiotics can attenuate or prevent many of the infectious complications that would otherwise facilitate suspicion of the diagnosis.

A clinical scoring system was devised by the NIH group who recognized *STAT3*-HIES (then known as autosomal dominant HIES) to be a multisystem disorder [Grimbacher et al 1999b]. Woellner et al [2010] have

developed guidelines that include the NIH clinical feature scoring system as well as determination of IL-17-producing T cells.

However, molecular genetic testing for *STAT3* pathogenic variants, readily available on a clinical basis, is the only reliable diagnostic approach. Prior to the genetic diagnosis, a HIES scoring system was developed to assist in the diagnosis [Grimbacher et al 1999b]. The scoring system components included both immunologic/infectious manifestations and skeletal / connective tissue abnormalities. The scoring system may still be helpful in identifying individuals in whom to perform genetic testing, or for considering the diagnosis if resources do not allow for genetic testing.

Establishing the Diagnosis

The diagnosis of *STAT3* hyper IgE syndrome (*STAT3*-HIES) **is established** in a proband with typical clinical findings and a heterozygous dominant-negative pathogenic (or likely pathogenic) variant in *STAT3* identified by molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *STAT3*-HIES is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical clinical findings in whom the diagnosis of *STAT3*-HIES has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *STAT3*-HIES, molecular genetic testing approaches can include **single-gene testing** (especially if there is a positive family history) or, more typically, the use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *STAT3* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. Since *STAT3*-HIES occurs through a dominant-negative mechanism (see Molecular Genetics), the detection of a large intragenic deletion or duplication is unexpected; however, one in-frame deletion of exons 22 and 23 has been reported [Schimke et al 2010]. Therefore, while it is unlikely to identify a disease-causing variant, testing for intragenic deletions or duplication may be considered.
- **A multigene panel** that includes *STAT3* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes

specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of *STAT3*-HIES is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *STAT3* Hyper IgE Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
STAT3	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	1 reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. An in-frame deletion of exons 22 and 23 has been reported [Schimke et al 2010].
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

STAT3 hyper IgE syndrome (*STAT3*-HIES) is a primary immune deficiency syndrome characterized by elevated serum IgE, eczema, and recurrent skin and respiratory tract infections, together with several connective tissue and skeletal abnormalities.

Presentation

Individuals with *STAT3*-HIES typically manifest in the newborn period with a rash, often diagnosed as eosinophilic pustulosis. The rash evolves into an eczematoid dermatitis that is often driven by staphylococcal infection [Chamlin et al 2002, Eberting et al 2004].

Immunologic Characteristics

Recurrent skin and sinopulmonary infections are noted in early childhood.

- Recurrent staphylococcal boils usually manifest in the first few years of life, and may be "cold," lacking the cardinal features of inflammation, warmth, redness, and pain.

- Recurrent pneumonias begin as well in the first few years, with the most common bacterial isolates being *Staphylococcus aureus, Streptococcus pneumoniae*, and *Haemophilus influenzae*. Abnormal healing of these pneumonias frequently leads to pneumatoceles and bronchiectasis.
- Staphylococcal infections outside of the skin and lung, such as osteomyelitis or liver abscess, occur but much less frequently.
- Mucocutaneous candidiasis affecting the oropharynx, vagina, fingernails, and toenails is common.
- Opportunistic infections including *Pneumocystis jiroveci* pneumonia, disseminated histoplasmosis and *Cryptococcus*, and secondary infection of the pneumatoceles with molds such as *Aspergillus fumigatus* or *Scedosporium* species may occur. Histoplasmosis most frequently disseminates to the intestinal tract and can mimic inflammatory bowel disease. *Coccidioides* and *Cryptococcus* have caused meningitis [Odio et al 2015].
- Decreased central memory T-cells may lead to increased incidence of varicella zoster virus (VZV) reactivation and modestly increased levels of circulating Epstein-Barr virus [Siegel et al 2011].

Nonimmunologic Characteristics

Individuals with *STAT3-HIES* may have several additional nonimmunologic findings.

Facial. A characteristic facial appearance including facial asymmetry, deeply set eyes, a broad nose, and prominent skin pores typically emerges by adolescence [Borges et al 1998, Grimbacher et al 1999a].

Oral findings include a high arched palate and oral mucosal variants including prominent palatine ridges [Domingo et al 2008]. Failure of primary teeth exfoliation is common; secondary tooth development is normal if the primary teeth are removed.

Skeletal abnormalities include osteoporosis, minimal trauma fractures, scoliosis, joint hyperextensibility, and craniosynostosis.

- Osteoporosis and minimal trauma fractures start in early childhood.
- Scoliosis typically develops through childhood and adolescence, and may require surgical correction.
- Joint hyperextensibility is common, and adults may have degenerative joint disease.
- Varying degrees of craniosynostosis can be seen, although surgical correction is rarely required. Skull radiographs often have a "beaten copper" appearance. Mild craniosynostosis is frequently noted in skull imaging.

Brain imaging reveals Chiari 1 malformations in approximately 20% of individuals and focal hyperintensities prominent on T_2-weighted images in approximately 70% of individuals.

- The focal hyperintensities are usually localized to the white matter and tend to increase in number with age.
- Both the Chiari 1 malformations and the hyperintensities are usually asymptomatic [Freeman et al 2007a].

Vascular abnormalities including tortuosity of middle-sized arteries and aneurysms have been described [Ling et al 2007, Freeman et al 2011, Chandesris et al 2012]. The coronary arteries have been the most completely studied.

- The combination of tortuosity and dilatation is found in approximately 50% of affected individuals; either abnormality is present in approximately 70%.
- Clinical sequelae have been rare but include myocardial infarction.

Cerebral artery aneurysm has also been described and is infrequently associated with subarachnoid hemorrhage.

Gastrointestinal issues vary [Arora et al 2017]:

- Symptoms of esophageal dysmotility are present in more than 50% of individuals and manifest as gastrointestinal reflux and dysphagia.
- Upper endoscopy frequently shows eosinophilic esophagitis.
- Diverticula can occur at a relatively young age and may be associated with bowel perforation [Stover et al 2010].
- Spontaneous intestinal perforations have also been described.
- Significant gastrointestinal bleeds can occur from aneurysms and Dieulafoy lesions (abnormally large artery in the lining of the gastrointestinal system).

Major Causes of Morbidity and Mortality

Survival is typically into adulthood, but a shortened life span was typical in the past. Most individuals are now living into or past the sixth decade.

- Most deaths of individuals with *STAT3*-HIES are associated with gram-negative (*Pseudomonas*) or filamentous fungal pneumonias (most commonly *Aspergillus*) infecting damaged lung parenchyma (i.e., preexisting pneumatoceles, bronchiectasis) [Freeman et al 2007b]. Fungi may invade the pulmonary vasculature leading to massive hemoptysis, or may disseminate to multiple organs.
- Myocardial infarction may be related to coronary artery aneurysms and subarachnoid hemorrhage may be related to intracranial aneurysms [Fathi et al 2011].
- Lymphomas occur at an increased frequency; treatment with standard chemotherapy has been successful.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *STAT3* missense pathogenic variants have been identified.

Penetrance

Intrafamilial variability is minimal and penetrance appears to be complete.

Nomenclature

Dominant-negative pathogenic variants in *STAT3* were identified as the cause of autosomal dominant hyper IgE syndrome (AD-HIES) and "Job syndrome" in 2007. Since this time, other clinically overlapping dominant genetic disorders have been characterized and the term AD-HIES is no longer specific to the dominant-negative *STAT3* phenotype. Multiple terms are currently used to refer to the dominant-negative *STAT3* phenotype: *STAT3*-HIES (used in this *GeneReview*), *STAT3*-mutated HIES, dominant-negative *STAT3*, LOF *STAT3*, and *STAT3* LOF.

Prevalence

The prevalence of *STAT3*-HIES is unknown. The condition is rare, likely around 1:1,000,000 population. Enrichment in a specific population group has not been reported.

Genetically Related (Allelic) Disorders

Germline gain-of-function *STAT3* pathogenic variants have been described in a multisystem disorder characterized by lymphoproliferation, autoimmunity and frequently short stature. Chronic lung disease, liver disease, and enteropathy were common findings [Milner et al 2015].

There have been three individuals with heterozygous null variants, all of whom lacked the hallmark features of *STAT3*-HIES; however, each had invasive fungal infections [Natarajan et al 2018].

Somatic *STAT3* pathogenic variants have been described in large granular lymphocytic leukemia [Koskela et al 2012]. See Cancer and Benign Tumors.

Differential Diagnosis

Table 2. Disorders with Elevated Serum Concentration of IgE to Consider in the Differential Diagnosis of *STAT3* Hyper IgE Syndrome

Gene(s)	Disorder	MOI	Additional Clinical Features of Differential Disorder	
			Overlapping w/*STAT3*-HIES	Distinguishing from *STAT3*-HIES
CARD14 [1] *FLG* [2]	Atopic dermatitis [3]	AD AR [4]	Recurrent staphylococcal skin infections	• Absence (typically) of other features of AD-HIES • Individuals w/severe atopic dermatitis often have more (& more severe) allergies (e.g., environmental, food that may lead to anaphylaxis) than those w/AD-HIES.
CARD11	Immunodeficiency 11B w/ atopic dermatitis [5] (OMIM 617638)	AD	Early-onset eczema (frequently)	↑ viral skin infections; variable hypogammaglobulinemia
DCLRE1C *RAG1* *RAG2*	Omenn syndrome [6] (OMIM 603554)	AR	Presents in newborn period w/ rash & typically ↑ serum IgE	• Affected infants are usually sicker than those w/HIES. • Lymphadenopathy, hepatosplenomegaly, opportunistic infections
DOCK8	DOCK8 deficiency (*DOCK8* AR HIES [7]) (OMIM 243700)	AR	• Eczema • Recurrent skin & lung infections [8]	• ↑ occurrence of viral skin infections (e.g., *Molluscum contagiosum*, warts); ↑ malignancies (lymphoma, squamous cell CA); ↑ vasculitis • Absence of nonimmunologic findings of *STAT3*-HIES (e.g., retention of primary teeth) [8]
IL6ST	IL6ST deficiency [9] (OMIM 618523)	AR	• Recurrent skin & lung infections • Craniosynostosis & scoliosis	Limited cases but potentially more serious infections
PGM3	PGM3 deficiency [10] (OMIM 615816)	AR	Recurrent skin & sinopulmonary infections; bone defects incl scoliosis	• Developmental delays (common) • Cytopenias w/lymphopenia & neutropenia
SPINK5	Netherton syndrome (OMIM 256500)	AR	Rash	• Rash typically more ichthyotic in appearance w/assoc trichorrhexis invaginata (bamboo hair) • Enteropathy w/failure to thrive frequently present

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Additional Clinical Features of Differential Disorder	
			Overlapping w/*STAT3*-HIES	Distinguishing from *STAT3*-HIES
WAS	Wiskott-Aldrich syndrome (See *WAS* Disorders.)	XL	Eczema & recurrent infections	• Thrombocytopenia w/small platelets; high incidence of autoimmune disease & lymphoma in later childhood & adulthood; typically more opportunistic infections than in HIES • Typically seen in males (isolated cases of affected females w/skewed X-inactivation resulting in disease phenotype reported)
ZNF341	ZNF341 deficiency [11] (OMIM 618282)	AR	Eczema & recurrent infections	Fewer nonimmunologic manifestations; stronger inflammatory responses w/infection

AD = autosomal dominant; AR = autosomal recessive; HIES = hyper IgE syndrome; MOI = mode of inheritance; XL = X-linked

1. Peled et al [2019]

2. OMIM 605803

3. Atopic dermatitis has many causes (many of which are unknown); *FLG*- and *CARD14*-related atopic dermatitis represent selected examples of heritable atopic dermatitis.

4. Atopic dermatitis caused by *FLG* pathogenic variants can be inherited in an autosomal dominant or autosomal recessive manner; atopic dermatitis caused by *CARD14* pathogenic variants is inherited in an autosomal dominant manner.

5. Dorjbal et al [2019]

6. Omenn syndrome is a form of SCID (severe combined immunodeficiency) that can result from pathogenic variants in *RAG1*, *RAG2*, *DCLRE1C* (previously known as Artemis), *IL2RG*, and additional combined immunodeficiency genes that allow residual functional activity.

7. Most individuals initially described as having autosomal recessive hyper IgE were found to have biallelic pathogenic variants in *DOCK8*. DOCK8 deficiency is a combined immunodeficiency characterized by eczema, allergies, sinopulmonary infections, and viral skin infections including herpes simplex virus, varicella-zoster virus, Molluscum contagiosum, and human papillomavirus [Zhang et al 2009, Engelhardt et al 2009]. Affected individuals are at increased risk for malignancy; squamous cell carcinomas and lymphoma have been reported. DOCK8 deficiency is frequently associated with lymphopenia which often progresses with age, and serum IgM levels may be low or undetectable. Eosinophilia and IgE are both variable, but can be extremely elevated.

8. Renner et al [2004]

9. Schwerd et al [2017]

10. Stray-Pedersen et al [2014], Zhang et al [2014]

11. Béziat et al [2018]

Note: A single report of human TYK2 deficiency described moderately high serum concentration of IgE in conjunction with disseminated bacillus Calmette-Guérin infection and susceptibility to viral and other infections [Minegishi et al 2006]. However, subsequent reports of TYK2 deficiency have not been associated with the AR-HIES phenotype [Kilic et al 2012, Kreins et al 2015].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *STAT3* hyper IgE syndrome (*STAT3*-HIES), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *STAT3* Hyper IgE Syndrome

System/Concern	Evaluation	Comment
Skin	Dermatologic exam	Newborn rash & eczema during childhood; often improves w/age
Pulmonary	Chest imaging	Detection of bronchiectasis & pneumatoceles
Skeletal	Eval for scoliosis & osteoporosis	• Scoliosis typically progresses through adolescence. • Osteoporosis can be present in children & adults; DXA screening recommended.
Dental	Dental exam for possible retention of primary teeth	
Vascular	Screening for coronary artery & cerebral artery aneurysms	• Aneurysms much more common in adults than in children • Screening by brain MRA & heart CTA or coronary artery MRA every 3 yrs recommended for adolescents & adults
Other	Consultation w/clinical geneticist &/or genetic counselor	

DXA = dual-energy x-ray absorptiometry

Treatment of Manifestations

Currently, there is no complete cure or targeted treatment for *STAT3*-HIES. The mainstay of therapy is prevention of staphylococcal abscesses and pneumonias with prophylactic anti-staphylococcal antibiotics as well as early aggressive treatment of infections. It is important to institute antibiotic therapy at the earliest sign of infection. Many affected individuals progress from minor to major infection rapidly, and systemic signs of infection may be minimal.

There is no known treatment or prevention for the nonimmunologic characteristics.

The role of hematopoietic cell transplantation (HSCT) in *STAT3*-HIES is emerging. It is clear that successful transplant recipients have improved infection phenotype. The effect of HSCT on the nonimmunologic aspects of the disease remains unclear [Goussetis et al 2010, Patel et al 2015, Yanagimachi et al 2016].

Table 4. Treatment of Manifestations in Individuals with *STAT3* Hyper IgE Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Eczema & recurrent boils	Topical antiseptics, e.g., dilute bleach baths [1] & chlorhexidine; frequent swimming in chlorinated pool	Adequate skin lubrication is needed after bleach.
	Anti-staphylococcal prophylaxis, e.g., w/2x/day TMP/SMX	
	Histamine-1 antagonists (e.g., hydroxyzine) to control pruritus	Helpful for more significant eczema
Recurrent pneumonias	Antibiotic prophylaxis, typically w/2x/day TMP/SMX	Targeting *Staphylococcus aureus* & other pyogenic bacteria to prevent the pneumonias & their complications
	In *Coccidioides* endemic regions use of prophylactic antifungals (e.g., fluconazole) can be considered.	To prevent disseminated severe infection

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
	• If structural damage to the lungs (e.g., bronchiectasis &/or pneumatoceles) has occurred, the breadth of antimicrobial coverage may need to be extended, incl antifungals, as these structural abnormalities become secondarily infected w/gram-negative bacteria (e.g., *Pseudomonas*) or fungi (e.g., *Aspergillus*). • In the setting of bronchiectasis, consideration of azithromycin to prevent exacerbations if no mycobacterial infection present	Sputum samples for bacteria, fungi, & mycobacteria (typically nontuberculous) should be obtained for microbiology during lung infections to help guide antimicrobial choice.
	Intravenous or subcutaneous IgG replacement can be considered.	Has been used w/anecdotal improvement for some individuals, esp those who fail to make protective levels of specific antibodies following vaccination challenge; prospective, randomized controlled studies of immunoglobulin supplementation have not been performed.
	Airway clearance w/bronchiectasis	Airway clearance techniques incl airway clearance devices, hypertonic saline nebulizers.
Chronic mucocutaneous candidiasis	Antifungal prophylaxis	Consider fluconazole prophylaxis if living in a *Coccidioides* endemic region.
Osteoporosis & Minimal trauma fractures	Optimize calcium & vitamin D intake	The role of bisphosphonates for those w/this disorder w/osteoporosis is unclear; some improvement seen in bone density but unclear improvement in fractures [Sowerwine et al 2014].
Arterial aneurysms	Optimal blood pressure mgmt	
	Antiplatelet or anticoagulation therapies may be considered for individuals w/significant coronary artery aneurysms to prevent myocardial infarction related to clotting w/in the aneurysm.	This must be weighed against risk of hemoptysis, a complication of fungal or bacterial lung disease in persons w/*STAT3*-HIES.

TMP/SMX = trimethoprim/sulfamethoxazole
1. 1/2-1 cup bleach per bathtub of water for 15 minutes three times weekly

Surveillance

Table 5. Recommended Surveillance for Individuals with *STAT3* Hyper IgE Syndrome

System/Concern	Evaluation	Frequency
Skin	Dermatology exam & culture of skin lesions	As needed
Pulmonary	High index of suspicion for infection	Lifelong
	Periodic chest imaging	With ↑ pulmonary symptoms
	Sputum samples	With ↑ pulmonary symptoms
Skeletal	Scoliosis eval	Through adolescence
Dental	Monitor for emergence of secondary teeth & possible need for removal of primary teeth	Every 6-12 mos during childhood
Vascular	• Brain MRA for cerebral aneurysm • CTA or MRA for coronary artery aneurysm	Every 3 yrs in adults

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Other	Monitor for lymphadenopathy, or masses due to ↑ incidence of lymphoma	Annually

Evaluation of Relatives at Risk

Molecular genetic testing of at-risk relatives of a proband with a known *STAT3* pathogenic variant allows for early diagnosis and prompt initiation of treatment and preventive measures.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Cessation of prophylactic antimicrobials is often advised during pregnancy. This may increase the risk of infection and should be taken into consideration. There have been pregnancies without complication, but also instances in which lung disease has worsened after pregnancy, potentially from limited antimicrobial use, delayed radiographic diagnosis, and impaired pulmonary clearance.

Risks associated with pregnancy should be discussed with affected females who have pulmonary compromise, severe scoliosis, or other complications of *STAT3*-HIES.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Parents have reported that because of the severe eczema of their child, there have been occasions when the health care providers have alerted Child Protective Services reporting that the child is not being kept clean. While skin hygiene is very important, in spite of the best efforts of caregivers, sometimes the skin flares are severe. Questions about parental neglect/abuse have also arisen when a toddler or young child appears with evidence of repeated fractures. Health care providers who are attuned to these possibilities can serve as important advocates for the parents and family.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

STAT3 hyper IgE syndrome (*STAT3*-HIES) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals with *STAT3*-HIES reported to date have had the disorder as the result of a *de novo* pathogenic variant; simplex cases (i.e., a single occurrence in a family) are common.

- Some individuals diagnosed with *STAT3*-HIES have an affected parent.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include clinical evaluation and/or molecular genetic testing.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or mosaicism in a parent. * Individuals with some findings of hyper IgE syndrome have had somatic and germline mosaicism for a *STAT3* pathogenic variant and have transmitted the variant to offspring [Holland et al 2007, Hsu et al 2013].

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with *STAT3*-HIES may appear to be negative because of failure to recognize the disorder in family members with a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly affected [Holland et al 2007, Hsu et al 2013].

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *STAT3* pathogenic variant that cannot be detected in the leukocyte DNA of either parent and the parents are clinically unaffected, the recurrence risk to sibs is still greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *STAT3*-HIES has a 50% chance of inheriting the *STAT3* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *STAT3* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *STAT3* pathogenic variant has been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing for *STAT3*-HIES are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Job Research Foundation**
  459 Columbus Avenue
  Suite 509
  New York NY 10024
  Email: info@jobresearchfoundation.org
  www.jobresearchfoundation.org
- **ImmUnity Canada**
  Canada
  Phone: 250-381-7134; 877 -607-2476
  Email: info@immunitycanada.org
  immunitycanada.org
- **International Patient Organization for Primary Immunodeficiencies (IPOPI)**
  United Kingdom
  Phone: +44 01503 250 668
  Fax: +44 01503 250 668
  Email: info@ipopi.org
  ipopi.org
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  Email: info@jmfworld.org
  info4pi.org
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **United States Immunodeficiency Network (USIDNET) Registry**
  Email: contact@usidnet.org
  Enrolling Institutions

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. STAT3 Hyper IgE Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
STAT3	17q21.2	Signal transducer and activator of transcription 3	STAT3 database Mutation registry for Hyper-IgE syndrome (STAT3) STAT3base-NIH	STAT3	STAT3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for STAT3 Hyper IgE Syndrome (View All in OMIM)

102582	SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3; STAT3
147060	HYPER-IgE SYNDROME 1, AUTOSOMAL DOMINANT, WITH RECURRENT INFECTIONS; HIES1

Molecular Pathogenesis

STAT3 encodes signal transducer and activator of transcription 3 (STAT3), a major signal transduction protein involved in many diverse pathways such as wound healing, immunity, cancer, and vascular remodeling.

Expression of an abnormal gene product with a dominant-negative effect is associated with *STAT3* hyper IgE syndrome (*STAT3*-HIES). Its complex immunologic and somatic features reflect STAT3's critical role in signaling for the gp130-dependent cytokines including IL-6 (inflammation, fever, CRP elevation, wound healing), IL-11 (tooth deciduation), IL-23 (IL-17 production), and TNF (vascular remodeling and wound healing).

Mechanism of disease causation. Almost all cases of *STAT3*-HIES are caused by missense variants that interfere with STAT3 function, conferring a dominant-negative effect that leads to impaired STAT3 signaling. In-frame splice variants and in-frame insertions/deletions have also been reported, as well as a single in-frame deletion of exons 22 and 23 [Schimke et al 2010].

Null alleles have not been detected, consistent with the dominant-negative mechanism. Homozygous *Stat3* knockout mice are embryonic lethal while the heterozygous mice are reported to be phenotypically normal [Takeda et al 1997], supporting the dominant-negative mechanism of disease.

***STAT3*-specific laboratory considerations.** The *STAT3* mechanism of disease complicates variant interpretation. It is important to note that dominant gain-of-function variants cause lymphoproliferation, autoimmunity, lung disease, and infection (see Genetically Related Disorders). These variants have been reported in the same codons as the dominant-negative variants, meaning that determining whether a missense variant in *STAT3* will confer a dominant-negative or gain-of-function effect cannot be based on codon alone.

Table 6. Notable *STAT3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_139276.2 NP_644805.1	c.1144C>T	p.Arg382Trp	Recurrent & most frequently observed pathogenic variants [Holland et al 2007]
	c.1145G>A	p.Arg382Gln	
	c.1268G>A	p.Arg423Gln	
	c.1387_1389delGTG	p.Val463del	
	c.1909G>A	p.Val637Met	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Somatic variants in *STAT3* are associated with multiple cancers. Of the hematologic malignancies, activating pathogenic variants in *STAT3* occur most frequently in T-cell large granular lymphocyte leukemia [Koskela et al 2012]. Somatic *STAT3* variants have also been described in skin cancers including melanomas, gastrointestinal cancers, and neural tumors [Shahmarvand et al 2018].

References

Literature Cited

Arora M, Bagi P, Strongin A, Heimall J, Zhao X, Lawrence MG, Trivedi A, Henderson C, Hsu A, Quezado M, Kleiner DE, Venkatesan AM, Holland SM, Freeman AF, Heller T. Gastrointestinal manifestations of STAT3 deficient hyper IgE syndrome. J Clin Immunol. 2017;37:695–700. PubMed PMID: 28803389.

Béziat V, Li J, Lin JX, Ma CS, Li P, Bousfiha A, Pellier I, Zoghi S, Baris S, Keles S, Gray P, Du N, Wang Y, Zerbib Y, Lévy R, Leclercq T, About F, Lim AI, Rao G, Payne K, Pelham SJ, Avery DT, Deenick EK, Pillay B, Chou J, Guery R, Belkadi A, Guérin A, Migaud M, Rattina V, Ailal F, Benhsaien I, Bouaziz M, Habib T, Chaussabel D, Marr N, El-Benna J, Grimbacher B, Wargon O, Bustamante J, Boisson B, Müller-Fleckenstein I, Fleckenstein B, Chandesris MO, Titeux M, Fraitag S, Alyanakian MA, Leruez-Ville M, Picard C, Meyts I, Di Santo JP, Hovnanian A, Somer A, Ozen A, Rezaei N, Chatila TA, Abel L, Leonard WJ, Tangye SG, Puel A, Casanova JL. A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. Sci Immunol. 2018;15:3(24).

Borges WG, Hensley T, Carey JC, Petrak BA, Hill HR. The face of Job. J Pediatr. 1998;133:303–5. PubMed PMID: 9709729.

Chamlin SL, McCalmont TH, Cunningham BB, Esterly NB, Lai CH, Mallory SB, Mancini AJ, Tamburro J, Frieden IJ. Cutaneous manifestations of hyper-IgE syndrome in infants and children. J Pediatr. 2002;141:572–5. PubMed PMID: 12378200.

Chandesris MO, Azarine A, Ong KT, Taleb S, Boutouyrie P, Mousseaux E, Romain M, Bozec E, Laurent S, Boddaert N, Thumerelle C, Tillie-Leblond I, Hoarau C, Lebranchu Y, Aladjidi N, Tron F, Barlogis V, Body G, Munzer M, Jaussaud R, Suarez F, Clément O, Hermine O, Tedgui A, Lortholary O, Picard C, Mallat Z, Fischer A. Frequent and widespread vascular abnormalities in human signal transducer and activator of transcription 3 deficiency. Circ Cardiovasc Genet. 2012;5:25–34. PubMed PMID: 22084479.

Domingo DL, Freeman AF, Davis J, Puck JM, Tianxia W, Holland SM, Hart TC. Novel intraoral phenotypes in hyperimmunoglobulin-E syndrome. Oral Dis. 2008;14:73–81. PubMed PMID: 18173452.

Dorjbal B, Stinson JR, Ma CA, Weinrich MA, Miraghazadeh B, Hartberger JM, Frey-Jakobs S, Weidinger S, Moebus L, Franke A, Schäffer AA, Bulashevska A, Fuchs S, Ehl S, Limaye S, Arkwright PD, Briggs TA, Langley C, Bethune C, Whyte AF, Alachkar H, Nejentsev S, DiMaggio T, Nelson CG, Stone KD, Nason M, Brittain EH, Oler AJ, Veltri DP, Leahy TR, Conlon N, Poli MC, Borzutzky A, Cohen JI, Davis J, Lambert MP, Romberg N, Sullivan KE, Paris K, Freeman AF, Lucas L, Chandrakasan S, Savic S, Hambleton S, Patel SY, Jordan MB, Theos A, Lebensburger J, Atkinson TP, Torgerson TR, Chinn IK, Milner JD, Grimbacher B, Cook MC, Snow AL. Hypomorphic caspase activation and recruitment domain 11 (CARD11) mutations associated with diverse immunologic phenotypes with or without atopic disease. J Allergy Clin Immunol. 2019;143:1482–95. PubMed PMID: 30170123.

Eberting CL, Davis J, Puck JM, Holland SM, Turner ML. Dermatitis and the newborn rash of hyper-IgE syndrome. Arch Dermatol. 2004;140:1119–25. PubMed PMID: 15381553.

Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, Chen A, Kim HS, Lloret MG, Schulze I, Ehl S, Thiel J, Pfeifer D, Veelken H, Niehues T, Siepermann K, Weinspach S, Reisli I, Keles S, Genel F, Kutukculer N, Camcioğlu Y, Somer A, Karakoc-Aydiner E, Barlan I, Gennery A, Metin A, Degerliyurt A, Pietrogrande MC, Yeganeh M, Baz Z, Al-Tamemi S, Klein C, Puck JM, Holland SM, McCabe ER, Grimbacher B, Chatila TA. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol. 2009;124:1289–302.e4. PubMed PMID: 20004785.

Fathi AR, Vortmeyer A, Holland SM, Pluta RM. Intracranial aneurysms associated with hyperimmunoglobulinaemia E (Job) syndrome: report of two cases. J Neurol Neurosurg Psychiatry. 2011;82:704–6. PubMed PMID: 20861064.

Freeman AF, Avila EM, Shaw PA, Davis J, Hsu AP, Welch P, Matta JR, Hadigan C, Pettigrew RI, Holland SM, Gharib AM. Coronary artery abnormalities in Hyper-IgE syndrome. J Clin Immunol. 2011;31:338–45. PubMed PMID: 21494893.

Freeman AF, Collura-Burke CJ, Patronas NJ, Ilcus LS, Darnell D, Davis J, Puck JM, Holland SM. Brain abnormalities in patients with hyperimmunoglobulin E syndrome. Pediatrics. 2007a;119:e1121–5. PubMed PMID: 17438082.

Freeman AF, Kleiner DE, Nadiminti H, Davis J, Quezado M, Anderson V, Puck JM, Holland SM. Causes of death in hyper-IgE syndrome. J Allergy Clin Immunol. 2007b;119:1234–40. PubMed PMID: 17335882.

Goussetis E, Peristeri I, Kitra V, Traeger-Synodinos J, Theodosaki M, Psarra K, Kanariou M, Tzortzatou-Stathopoulou F, Petrakou E, Fylaktou I, Kanavakis E, Graphakos S. Successful long-term immunologic reconstitution by allogeneic hematopoietic stem cell transplantation cures patients with autosomal dominant hyper-IgE syndrome. J Allergy Clin Immunol. 2010;126:392–4. PubMed PMID: 20584545.

Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, Miller JA, O'Connell AC, Puck JM. Hyper-IgE syndrome with recurrent infections--an autosomal dominant multisystem disorder. N Engl J Med. 1999a;340:692–702. PubMed PMID: 10053178.

Grimbacher B, Schäffer AA, Holland SM, Davis J, Gallin JI, Malech HL, Atkinson TP, Belohradsky BH, Buckley RH, Cossu F, Español T, Garty BZ, Matamoros N, Myers LA, Nelson RP, Ochs HD, Renner ED, Wellinghausen N, Puck JM. Genetic linkage of hyper-IgE syndrome to chromosome 4. Am J Hum Genet. 1999b;65:735–44. PubMed PMID: 10441580.

Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, Anderson VL, Darnell DN, Welch PA, Kuhns DB, Frucht DM, Malech HL, Gallin JI, Kobayashi SD, Whitney AR, Voyich JM, Musser JM, Woellner C, Schäffer AA, Puck JM, Grimbacher B. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007;357:1608–19. PubMed PMID: 17881745.

Hsu AP, Sowerwine KJ, Lawrence MG, Davis J, Henderson CJ, Zarember KA, Garofalo M, Gallin JI, Kuhns DB, Heller T, Milner JD, Puck JM, Freeman AF, Holland SM. Intermediate phenotypes in patients with autosomal

dominant Hyper IgE syndrome caused by somatic mosaicism. J Allergy Clin Immunol. 2013;131:586–93. PubMed PMID: 23623265.

Kilic SS, Hacimustafaoglu M, Boisson-Dupuis S, Kreins AY, Grant AV, Abel L, Casanova JL. A patient with tyrosine kinase 2 deficiency without hyper-IgE syndrome. J Pediatr. 2012;160:1055–7. PubMed PMID: 22402565.

Koskela HL, Eldfors S, Ellonen P, van Adrichem AJ, Kuusanmäki H, Andersson EI, Lagström S, Clemente MJ, Olson T, Jalkanen SE, Majumder MM, Almusa H, Edgren H, Lepistö M, Mattila P, Guinta K, Koistinen P, Kuittinen T, Penttinen K, Parsons A, Knowles J, Saarela J, Wennerberg K, Kallioniemi O, Porkka K, Loughran TP Jr, Heckman CA, Maciejewski JP, Mustjoki S. Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med. 2012;366:1905–13. PubMed PMID: 22591296.

Kreins AY, Ciancanelli MJ, Okada S, Kong XF, Ramírez-Alejo N, Kilic SS, El Baghdadi J, Nonoyama S, Mahdaviana SA, Ailal F, Bousfiha A, Mansouri D, Nievas E, Ma CS, Rao G, Bernasconi A, Sun Kuehn H, Niemela J, Stoddard J, Deveau P, Cobat A, El Azbaoui S, Sabri A, Lim CK, Sundin M, Avery DT, Halwani R, Grant AV, Boisson B, Bogunovic D, Itan Y, Moncada-Velez M, Martinez-Barricarte R, Migaud M, Deswarte C, Alsina L, Kotlarz D, Klein C, Muller-Fleckenstein I, Fleckenstein B, Cormier-Daire V, Rose-John S, Picard C, Hammarstrom L, Puel A, Al-Muhsen S, Abel L, Chaussabel D, Rosenzweig SD, Minegishi Y, Tangye SG, Bustamante J, Casanova JL, Boisson-Dupuis S. Human TYK2 deficiency: mycobacterial and viral infections without hyper-IgE syndrome. J Exp Med. 2015;212:1641–62. PubMed PMID: 26304966.

Ling JC, Freeman AF, Gharib AM, Arai AE, Lederman RJ, Rosing DR, Holland SM. Coronary artery aneurysms in patients with hyper IgE recurrent infection syndrome. Clin Immunol. 2007;122:255–8. PubMed PMID: 17098478.

Milner JD, Vogel TP, Forbes L, Ma CA, Stray-Pederson A, Niemela JE, Lyons JJ, Engelhardt KR, Zhang Y, Topcagic N, Roberson ED, Matthews H, Verbsky JW, Dasu T, Vargas-Hernandez A, Varghese N, McClain KL, Karam LB, Nahmod K, Makedonas G, Mace EM, Sorte HS, Perminow G, Rao VK, O'Connell MP, Price S, Su HC, Butrick M, McElwee J, Hughes JD, Willet J, Swan D, Xu Y, Santibanez-Koref M, Slowik V, Dinwiddie DL, Ciaccio CE, Saunders CJ, Septer S, Kingsmore SF, White AJ, Cant AJ, Hambleton S, Cooper MA. Early onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function STAT3 mutations. Blood. 2015;125:591–9. PubMed PMID: 25359994.

Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, Takada H, Hara T, Kawamura N, Ariga T, Kaneko H, Kondo N, Tsuge I, Yachie A, Sakiyama Y, Iwata T, Bessho F, Ohishi T, Joh K, Imai K, Kogawa K, Shinohara M, Fujieda M, Wakiguchi H, Pasic S, Abinun M, Ochs HD, Renner ED, Jansson A, Belohradsky BH, Metin A, Shimizu N, Mizutani S, Miyawaki T, Nonoyama S, Karasuyama H. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity. 2006;25:745–55. PubMed PMID: 17088085.

Natarajan M, Hsu AP, Weinreich MA, Zhang Y, Niemela JE, Butman JA, Pittaluga S, Sugui J, Collar AL, Lim JK, Zangeneh T, Carr T, Oler AJ, Similuk M, Rosen LB, Desai JV, Freeman AF, Holland SM, Kwon-Chung KJ, Milner JD, Lionakis MS. Aspergillosis, eosinophilic esophagitis, and allergic rhinitis in signal transducer and activator of transcription 3 haploinsufficiency. J Allergy Clin Immunol. 2018;142:993–997. PubMed PMID: 29803798.

Odio CD, Milligan KL, McGowan K, Rudman Spergel AK, Bishop R, Boris L, Urban A, Welch P, Heller T, Kleiner D, Jackson MA, Holland SM, Freeman AF. Endemic mycoses in patients with STAT3- mutated hyper-IgE (Job) syndrome. J Allergy Clin Immunol. 2015;136:1411–3. PubMed PMID: 26292779.

Patel NC, Gallagher JL, Torgerson TR, Gilman AL. Successful haploidentical donor hematopoietic stem cell transplant and restoration of STAT3 function in an adolescent with autosomal dominant hyper-IgE syndrome. J Clin Immunol. 2015;35:479–85. PubMed PMID: 25962528.

Peled A, Sarig O, Sun G, Samuelov L, Ma CA, Zhang Y, DiMaggio T, Nelson CG, Stone KD, Freeman AF, Malki L, Vidal LS, Chamarthy LM, Briskin V, Mohamad J, Pavlovsky M, Walter JE, Milner JD, Sprecher E. Loss-of-function mutations in caspase recruitment domain containing protein 14 (CARD14) are associated with a severe variant of atopic dermatitis. J Allergy Clin Immunol. 2019;143:173–81. PubMed PMID: 30248356.

Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, Bergmann M, Davis J, Belohradsky BH, Grimbacher B. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr. 2004;144:93–9. PubMed PMID: 14722525.

Schimke LF, Sawalle-Belohradsky J, Roesler J, Wollenberg A, Rack A, Borte M, Rieber N, Cremer R, Maass E, Dopfer R, Reichenbach J, Wahn V, Hoenig M, Jansson AF, Roesen-Wolff A, Schaub B, Seger R, Hill HR, Ochs HD, Torgerson TR, Belohradsky BH, Renner ED. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. J Allergy Clin Immunol. 2010;126:611–7.e1. PubMed PMID: 20816194.

Schwerd T, Twigg SRF, Aschenbrenner D, Manrique S, Miller KA, Taylor IB, Capitani M, McGowan SJ, Sweeney E, Weber A, Chen L, Bowness P, Riordan A, Cant A, Freeman AF, Milner JD, Holland SM, Frede N, Müller M, Schmidt-Arras D, Grimbacher B, Wall SA, Jones EY, Wilkie AOM, Uhlig HH. A biallelic mutation in IL6ST encoding the GP130 co-receptor causes immunodeficiency and craniosynostosis. J Exp Med. 2017;214:2547–62. PubMed PMID: 28747427.

Shahmarvand N, Nagy A, Ahahryani J, Ohgami RS. Mutations of the signal transducer and activator of transcription family of genes in cancer. Cancer Sci. 2018;109:926–33. PubMed PMID: 29417693.

Siegel AM, Heimall J, Freeman AF, Hsu AP, Brittain E, Brenchley JM, Douek DC, Fahle GH, Cohen JI, Holland SM, Milner JD. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. Immunity. 2011;35:806–18. PubMed PMID: 22118528.

Sowerwine KJ, Shaw PA, Gu W, Ling JC, Collins MT, Darnell DN, Anderson VL, Davis J, Hsu A, Welch P, Puck JM, Holland SM, Freeman AF. Bone density and fractures in autosomal dominant hyper IgE syndrome. J Clin Immunol. 2014;34:260–4. PubMed PMID: 24402620.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Stover DG, Freeman AF, Wright PW, Hummell DS, Ness RM. Diverticulitis in a young man with hyper-IgE syndrome. South Med J. 2010;103:1261–3. PubMed PMID: 21037522.

Stray-Pedersen A, Backe PH, Sorte HS, Mørkrid L, Chokshi NY, Erichsen HC, Gambin T, Elgstøen KB, Bjørås M, Wlodarski MW, Krüger M, Jhangiani SN, Muzny DM, Patel A, Raymond KM, Sasa GS, Krance RA, Martinez CA, Abraham SM, Speckmann C, Ehl S, Hall P, Forbes LR, Merckoll E, Westvik J, Nishimura G, Rustad CF, Abrahamsen TG, Rønnestad A, Osnes LT, Egeland T, Rødningen OK, Beck CR, Boerwinkle EA, Gibbs RA, Lupski JR, Orange JS, Lausch E, Hanson IC, et al. PGM3 mutations cause a congenital disorder of glycosylation with severe immunodeficiency and skeletal dysplasia. Am J Hum Genet. 2014;95:96–107. PubMed PMID: 24931394.

Takeda K, Noguchi K, Shi W, Tanaka T, Matsumoto M, Yoshida N, Kishimoto T, Akira S. Targeted disruption of the mouse Stat3 gene leads to early embryonic lethality. Proc Natl Acad Sci USA. 1997;94:3801–4. PubMed PMID: 9108058.

Woellner C, Gertz EM, Schäffer AA, Lagos M, Perro M, Glocker EO, Pietrogrande MC, Cossu F, Franco JL, Matamoros N, Pietrucha B, Heropolitańska-Pliszka E, Yeganeh M, Moin M, Español T, Ehl S, Gennery AR, Abinun M, Breborowicz A, Niehues T, Kilic SS, Junker A, Turvey SE, Plebani A, Sánchez B, Garty BZ, Pignata C, Cancrini C, Litzman J, Sanal O, Baumann U, Bacchetta R, Hsu AP, Davis JN, Hammarström L, Davies EG, Eren E, Arkwright PD, Moilanen JS, Viemann D, Khan S, Maródi L, Cant AJ, Freeman AF, Puck

JM, Holland SM, Grimbacher B. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol. 2010;125:424–432.e8. PubMed PMID: 20159255.

Yanagimachi M, Ohya T, Yokosuka T, Kajiwara R, Tanaka F, Goto H, Takashima T, Morio T, Yokota S. The potential and limits of hematopoietic stem cell therapy for the treatment of autosomal dominant hyper IgE syndrome. J Clin Immunol. 2016;36:511–6. PubMed PMID: 27091139.

Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, Matthews HF, Davis J, Turner ML, Uzel G, Holland SM, Su HC. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med. 2009;361:2046–55. PubMed PMID: 19776401.

Zhang Y, Yu X, Ichikawa M, Lyons JJ, Datta S, Lamborn IT, Jing H, Kim ES, Biancalana M, Wolfe LA, DiMaggio T, Matthews HF, Kranick SM, Stone KD, Holland SM, Reich DS, Hughes JD, Mehmet H, McElwee J, Freeman AF, Freeze HH, Su HC, Milner JD. Autosomal recessive phosphoglucomutase 3 (PGM3) mutations link glycosylation defects to atopy, immune deficiency, autoimmunity and neurocognitive impairment. J Allergy Clin Immunol. 2014;133:1400–9. PubMed PMID: 24589341.

Chapter Notes

Revision History

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