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Review

Human germline gain-of-function in STAT6:
from severe allergic disease to lymphoma
and beyondSTAT6 Gain-of-Function International Consortium^{1,*}

Signal transducer and activator of transcription (STAT)-6 is a transcription factor central to pro-allergic immune responses, although the function of human STAT6 at the whole-organism level has long remained unknown. Germline heterozygous gain-of-function (GOF) rare variants in *STAT6* have been recently recognized to cause a broad and severe clinical phenotype of early-onset, multi-system allergic disease. Here, we provide an overview of the clinical presentation of STAT6-GOF disease, discussing how dysregulation of the STAT6 pathway causes severe allergic disease, and identifying possible targeted treatment approaches. Finally, we explore the mechanistic overlap between STAT6-GOF disease and other monogenic atopic disorders, and how this group of inborn errors of immunity (IEIs) powerfully inform our fundamental understanding of common human allergic disease.

Rapid growth in the discovery of human primary atopic disorders

IEIs (see [Glossary](#)) are a group of genetic disorders in which products of immunity genes are missing or dysfunctional. They are typically caused by monogenic germline variants that result in altered expression or function of the encoded protein [1–3]. Driven by recent advances in the accessibility, affordability, and efficiency of **next-generation sequencing (NGS)** technology, the number of recognized human IEIs is rapidly increasing [4,5]. As of 2022, the International Union of Immunological Societies (IUIS) listed 485 single-gene defects as IEIs, with 55 novel defects identified since 2020 [2]. Although individually rare diseases, as a group, the cumulative prevalence of human IEIs is now estimated to be at least 1 in 1000 in the general population [6,7]; and probably higher, as attested, for example, by homozygosity for the P1104A variant in the TYK2 protein that may underlie TB in ~1% of European patients [8,9].

While IEIs were first recognized in patients with increased susceptibility to infection, notable allergic inflammation occurs in many classic IEIs [10]. Indeed, the term **‘primary atopic disorders’ (PADs)** was coined in 2018 to highlight a subset of IEIs with the predominant phenotype of allergic inflammation [11]. Today, PADs encompass a group of more than 40 IEIs in which allergic inflammation is caused by single-gene defects that alter an array of key immune mechanisms, including T cell signaling, cytokine signaling, glycosylation, tolerance induction, mast cell function, and skin barrier integrity [10–12]. The identification of affected pathways provides important insights into the fundamental human biology of allergic inflammation and uncovers new treatment targets for both patients with PADs and the general population harboring an allergic diathesis [13].

Here, we have united the investigators who independently discovered a new PAD caused by GOF variants in *STAT6* [14–18]. As a consortium, we now share the growing evidence implicating

Highlights

Primary atopic disorders (PADs) are a subset of monogenic inborn errors of immunity (IEIs) characterized by severe allergic diseases. Recently, a new PAD was discovered that was caused by germline heterozygous gain-of-function (GOF) variants in human *STAT6*.

Signal transducer and activator of transcription (STAT)-6-GOF disease was recently diagnosed in 21 individuals with severe allergic disease from birth. These patients presented with severe treatment-resistant atopic dermatitis, eosinophilic gastrointestinal disease, skin and respiratory infections, and other non-allergic manifestations.

This discovery follows decades of fundamental biological research into STAT6, establishing it as a molecule that is central to T helper type 2 (T_H2) immunity. This builds on a large body of knowledge, integrating both mouse models and genome-wide association studies, linking STAT6 function with allergic disease.

The mechanism of STAT6-GOF disease emphasizes the central role of enhanced STAT6 activity, via increased phosphorylation, delayed dephosphorylation, as well as increased nuclear translocation and transcription of STAT6 targets and T_H2 polarization.

Early results indicate that precision medicine approaches targeting the IL4R/Janus kinase (JAK)/STAT6 pathway, particularly dupilumab and JAK inhibitors, might be effective in treating STAT6-GOF disease.

Significance

Germline heterozygous GOF *STAT6* variants have been recently discovered



STAT6 in allergic disease, integrate the rapidly accumulating clinical and molecular characteristics defining **STAT6-GOF disease**, and briefly outline certain treatment approaches that we have found to be effective in these patients. Our take-home message is that patients with severe allergic disease that begins in infancy should be assessed for STAT6-GOF disease, and that the detailed study of these individuals can provide powerful insights into the role of STAT6 in human physiology.

IEIs that disrupt the JAK-STAT signaling cascade

Defining human monogenic disorders has provided essential insights into the biology of the Janus kinase (JAK)-STAT signaling cascade (Box 1). Autosomal dominant **hyper-IgE syndrome (HIES)** is a classic IEI that was first described in 1966 [19] and is now known to be caused by dominant-negative variants in STAT3 [20,21]. STAT1 is notable for the fact that all four possible forms of genetic disease have been reported in humans: (i) autosomal recessive (AR) complete STAT1 deficiency [22]; (ii) AR partial STAT1 deficiency [23]; (iii) autosomal dominant (AD) STAT1 deficiency [24]; and (iv) AD STAT1-GOF disease [25]. Building on this legacy of patient-driven discovery, recent additions to this family of disorders include GOF variants in STAT4 causing a severe autoinflammatory disorder called disabling pansclerotic morphea (DPM) [26], and GOF variants in STAT6 causing a severe multi-system atopic disorder [14–18]. IEIs that disrupt the JAK/STAT pathway are presented in Figure 1 [14–18,20–22,25–37].

STAT6 and allergic inflammation

The body of evidence, generated mostly from cell lines and mouse models, indicates that STAT6 has a key role in the signaling pathways involving the IL-4 and IL-13 cytokines, which are central to the pathology of many allergic diseases [38]. However, it should be acknowledged that STAT6-deficient humans have not yet been identified; thus, the function of STAT6 in the whole human organism is yet to be formally defined.

From studies mostly conducted in mouse models, we know that, in lymphocytes, STAT6 signaling induces proliferation [39] and activation of **group 2 innate lymphoid cells (ILC2s)** [40] and differentiation of **T helper type 2 (T_H2)** cells from naïve CD4⁺ T cells [41]. When activated, these T_H2 immune cells secrete type 2 cytokines, such as IL-4, IL-5, and IL-13, resulting in the induction of eosinophilic inflammation in tissues. In **T follicular helper (T_{FH})** cells, which are crucial for B cell **affinity maturation** and immunoglobulin (Ig) **class-switch recombination** (CSR) in the germinal center [42], STAT6 is involved in IL-4 production [43]. This further induces STAT6 signaling in B cells, leading to germinal center formation [44,45], and CSR to IgE [46]. In non-immune cells, IL-4/IL-13-STAT6 is involved in triggering the proliferation and collagen production of fibroblasts [47], the development of mucus-secreting goblet cells [48], eosinophil-attracting

to cause a broad and severe human clinical phenotype of asthma, atopic dermatitis, food and drug allergies, eosinophilic gastrointestinal disease, as well as skeletal and vascular anomalies. Moving forward, as more patients are found to have STAT6-GOF disease and the mechanisms of disease are fully defined, we may appreciate the full clinical phenotype and optimal treatment approaches for this newfound primary atopic disorder.

¹The collaboration members, names only, can be found in the special section ‘STAT6 Gain-of-Function International Consortium authors’ near the end of the paper. For a full list of author names and affiliations, please see the supplemental information online.

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Box 1. STAT6 is the central mediator of IL-4 signaling

STAT6 is a member of the STAT family of transcription factors. It shares a similar N-terminal domain (N-ter), coiled-coil domain (CC), DNA-binding domain (DBD), linker domain (Linker), Src homology 2 domain (SH2), and C-terminal transcription activation domain (TAD) with the other STAT molecules. Canonically, in response to cytokine–receptor interactions, intracellular membrane receptor-associated JAK proteins undergo activation, leading to receptor tyrosine phosphorylation, which then phosphorylates cytosolic STAT molecules [93]. Each STAT molecule has unique functions and characteristics regulating the expression of genes involved in cellular activation, proliferation, and differentiation [93]. The distinct functional profile of STAT6 is delineated through its unique position downstream of IL-4 signaling pathways [94], the presence of a conserved tyrosine residue at its amino acid position 641 [95], its ability to exert nuclear functions in an unphosphorylated state [76], and its DBD capability to specifically recognize and bind to palindromic DNA sequences with a four base-pair (bp) spacer, conforming to the pattern TTCNNNGAA [96]. This multifaceted functionality underscores the pivotal role of STAT6 in cellular signaling and gene expression regulation leading to expression of key genes, including GATA3 and CCL26 [97,98].

chemokine production from epithelial cells [49,50], barrier dysfunction in epithelial cells [51,52], and induction of bronchial smooth muscle hyper-responsiveness [53]. Together, these processes contribute to shaping the pathophysiology of classic allergic diseases, such as asthma and atopic dermatitis.

Transgenic mouse models link STAT6 and allergic disease

The essential role of mouse STAT6 in delivering T_H2 responses has been documented in several complementary mouse models. Specifically, STAT6-deficient mice (*Stat6*^{-/-}) are highly resistant to allergic airway inflammation compared with wild-type (WT) mice [54–56]. By contrast, two separate mouse models engineered to have increased activity of the IL-4/STAT6 pathway exhibited exaggerated allergic inflammation.

The first was the STAT6VT mouse. STAT6VT is an experimental *STAT6*-GOF variant generated through mutational analysis to contain alanine substitutions at amino acid positions V547 and T548 in the STAT6 SH2 domain (designated STAT6VT) [57]. Compared with WT STAT6, STAT6VT has GOF activity that is independent of IL-4 stimulation, as documented by higher STAT6 phosphorylation, higher DNA binding, and higher transcription of an IL-4-responsive promoter in HEK293 cells [57,58]. When STAT6VT was studied *in vivo*, lymphoid tissue-restricted Stat6VT expression (CD2:Stat6VT mice) resulted in an atopic dermatitis-like phenotype and allergic pulmonary inflammation with eosinophilic infiltration compared with WT controls [59,60]. IL-4-induced proteins were also higher in Stat6VT mice compared with WT controls, including enhanced surface expression of FcεRII (CD23) on B cells, and high serum titers of IgG1 and IgE [59].

The second mouse model relied on a GOF mutation in IL-4Rα to activate STAT6. Specifically, IL-4Rα^{Y709F} disrupts the immunotyrosine inhibitory motif (ITIM) in the cytoplasmic domain of the IL-4Rα chain to enhance STAT6 phosphorylation following exposure to IL-4 and IL-13 [61]. In the ovalbumin (OVA) model of antigen-induced allergic airway inflammation, C.129.*Il4ra*^{F709/F709} mice exhibited increased allergic airway inflammation, as assessed via histology and cellular infiltration, as well as increased airway hyper-responsiveness following methacholine challenge compared with C.129.*Il4ra*^{Y709/Y709} controls [61].

Together, these complementary mouse models place STAT6 at the center of allergic inflammation: namely, loss of STAT6 activity protects against allergic inflammation, while enhanced STAT6 activation exaggerates the allergic response.

Human STAT6 single nucleotide polymorphisms are associated with multiple allergic diseases

Building upon the insights gained from mouse models, numerous human **single nucleotide polymorphisms (SNPs)** linked to *STAT6* have now been associated with various atopic disorders [14]. These **genome-wide association studies (GWAS)** provide another body of evidence supporting the involvement of genetic variation of *STAT6* in human allergic diseases. However, the common SNPs implicated by these GWAS typically have very small effect sizes and often require very large sample sizes to be detected; this is in marked contrast to the functionally damaging and highly penetrant genetic variants that cause IELs. Since many GWAS associations have been reported between *STAT6* and human allergic disease [14], we only provide an illustrative example using the allergic condition, **eosinophilic esophagitis**. A GWAS totalling 936 cases and 4312 controls in an imputed data set that included ~2.3 million variants implicated *STAT6* in eosinophilic esophagitis, with the top SNP (rs167769) having an odds ratio (OR) of 1.49 [62]. Recently, a prospective longitudinal cohort study focusing on children aged 2–16 years with eosinophilic esophagitis found that *STAT6* SNPs (rs324011, rs167769, or rs12368672) were linked to an increased risk of relapse following **proton pump inhibitor (PPI) therapy** [63].

Glossary

Affinity maturation: process by which activated B cells produce antibodies with increased affinity and avidity through somatic hypermutation of Ig genes.

Allergic eosinophilic gastroenteritis: chronic condition characterized by eosinophilic infiltration of the gastrointestinal tract, affecting any part of the gastrointestinal system, including the esophagus, stomach, and intestine, and resulting in gastrointestinal distress and dysfunction.

Allergic march: typical progression of allergic disorders, which begins with atopic dermatitis and food allergies in infancy and subsequent development of allergic rhinitis and asthma during later childhood and adulthood.

Catalog of Somatic Mutations in Cancer (COSMIC): online database of reported somatically acquired variants found in human cancer.

Class-switch recombination (CSR): CSR of Ig heavy chains is a biological process by which a B cell switches from the production of IgM to that of IgG, IgE, or IgA.

Coarse facies: characterized by facial features lacking in delicacy or precision, often appearing more rounded and heavier. This can manifest in the facial structure, such as the eyebrows, nose, lips, mouth, and chin, and not having the typical sharp or fine qualities. Coarse facies are a feature of some hyper-IgE syndromes.

Dominant interference: phenomenon caused by a genetic mutation on a single allele resulting in a variant protein that interferes with the normal function of the WT protein translated from the other allele.

Eosinophilic esophagitis: chronic allergic condition of the esophagus that becomes inflamed due to eosinophilic infiltration, resulting in esophageal dysfunction.

Eosinophilic gastrointestinal diseases (EGIDs): group of chronic, immune-mediated diseases characterized by pathological eosinophilic infiltration of the gastrointestinal tract, resulting in gastrointestinal symptoms.

Exudative ascites: characterized by the abnormal accumulation of ascitic fluid in the peritoneal cavity, featuring an elevated concentration of proteins.

Genome-wide association studies (GWAS): studies that identify

Beyond these genetic associations, some studies have functionally characterized germline variants in genes aligned with the STAT6 pathway, further emphasizing its importance in atopic diseases. For example, a notable glutamine to arginine substitution at position 576 (Q576R) of IL-4R α was documented to be prevalent in individuals with allergic inflammation [64,65], and this variant was also functionally assessed in mice. C.129.*Il4ra*^{R576/R576} mice carrying the R576 substitution exhibited an increase in the airway inflammatory response to allergen in the OVA model and upregulated transcription of a subset of IL-13-responsive genes, including genes involved in mucus secretion and airway inflammation, compared with C.129.*Il4ra*^{Q576/Q576} controls [66]. This evidence from human population genetics further reinforces the relationship between STAT6 function and allergic inflammation.

Discovery and characterization of severe allergic human disease caused by germline STAT6-GOF variants

Unifying the clinical phenotype

Building on the substantial body of evidence emphasizing the pivotal role of STAT6 in the pathogenesis of allergic diseases, in 2022 our research groups began independently reporting the discovery of germline heterozygous GOF variants in *STAT6* in patients with severe allergic disease [14–18] (Table 1). STAT6-GOF disease was recently added to the Online Mendelian Inheritance in Man (OMIM) database as ‘Hyper-IgE syndrome 6, autosomal dominant, with recurrent infections’ (OMIM #620532). STAT6-GOF disease is a rare and severe multi-system disorder driven by exaggerated pro-allergic immune responses that cause symptoms that begin within the first few weeks of life. Its unifying clinical features include the presence of:

- (i) Severe early-onset atopic disease featuring treatment-refractory atopic dermatitis (or eczema) with **lichenification**, multiple food allergies, and severe or recurrent anaphylaxis, accompanied by a notable increase in serum IgE titers and eosinophilia [14–18]. Patients also show features of the ‘**allergic march**’, with the sequential onset of asthma, allergic rhinitis, and drug allergies during later childhood and adulthood [14,15,17].
- (ii) **Eosinophilic gastrointestinal diseases (EGIDs)**, particularly **allergic eosinophilic gastroenteritis** and eosinophilic esophagitis; the involvement of different layers of the intestinal wall result in diverse clinical manifestations, including the mucosal form (vomiting, abdominal pain, diarrhea, blood loss in stools, and protein-losing enteropathy) [14,15,17], and the serosal form (**exudative ascites**) [15].
- (iii) Lymphoproliferation, characterized by lymphadenopathy [16], cobblestone-like appearance of the buccal mucosa [15], polypoid nodules in the intestinal tract [15,17], and notably, recurrent B cell lymphomas [18].
- (iv) Non-immunological features resembling those observed in autosomal dominant HIES caused by heterozygous *STAT3* variants, such as coarsening and thickening of facial features, osteoporosis, pathological fractures, joint hyperextensibility, and cerebral aneurysms [14,16].
- (v) Additional features in which the relationship to the *STAT6*-GOF variant will be determined through the recognition of additional patients, including recurrent skin and respiratory tract infections [14], renal fibrosis [15], short stature [14,16], and **hypotrichosis** [15].

Genotype

To date, 21 individuals from 13 distinct families have been identified with germline heterozygous *STAT6*-GOF variants [14–18] (Figure 2). All affected individuals carried heterozygous missense variants in *STAT6*, either through *de novo* occurrences or autosomal dominant inheritance patterns. *STAT6*-GOF disease demonstrated complete penetrance, although some clinical variability was observed. At the time this review was written, none of the *STAT6* GOFs had been reported in large population databases (e.g., gnomAD). However, *in silico* tools predicted all the variants to

associations between SNPs and phenotypic traits.

Group 2 innate lymphoid cells

(ILC2s): innate immune cells that arise from common lymphoid progenitors and produce the type 2 cytokines IL-4, IL-5, IL-9, and/or IL-13. ILC2s contribute to allergic inflammation at multiple barrier surfaces, such as the skin, airways, and gut.

Hyper-IgE syndrome (HIES): rare multi-system inborn error of immunity characterized by high serum IgE, atopic disease, recurrent bacterial infections, and various nonleukocytic anomalies. It can be autosomal recessive (e.g., *ZNF341*) or autosomal dominant (e.g., *STAT3*).

Hypotrichosis: medical condition characterized by sparse hair growth beginning early in life.

Inborn errors of immunity (IEI): group of monogenic human disorders caused by damaging germline variants in immunity genes causing susceptibility to infection, allergy, autoinflammation, autoimmunity, and/or malignancy.

JAK inhibitors: class of small-molecule inhibitors with immune modulatory activity; inhibit one or more of the JAK enzymes; currently used clinically in the treatment of psoriasis, atopic dermatitis, rheumatoid arthritis, systemic lupus erythematosus, and pathological inflammation triggered by infection.

Lichenification: skin condition characterized by skin thickening, hyperpigmentation, and exaggerated skin lines; often caused by excessive scratching.

Next-generation sequencing (NGS): high-throughput technology used to determine the sequence of nucleic acids and study genetic variation(s) associated with disease. NGS enables parallel sequencing of many nucleic acid strands instead of one (such as in traditional Sanger sequencing).

Organoids: *in vitro* 3D structures derived from pluripotent stem cells or primary tissue that resemble the anatomy and physiology of organ; used to approximate *in vivo* conditions to study disease and therapeutics.

Primary atopic disorders (PADs): subcategory of IEIs in which patients present with severe allergic disease.

Proton pump inhibitor (PPI) therapy: refers to use of hydrogen–potassium ATPase channel inhibitors for gastrointestinal conditions by inhibiting stomach acid production.

be damaging, as demonstrated by the high Combined Annotation Dependent Depletion (CADD) scores in Figure 2B. With the exception of p.P643R, the other variants face the DNA-binding groove and are located in the DNA-binding domain, linker domain, or SH2 domain [14–16]. Although it is yet to be established experimentally for all variants, we hypothesize that STAT6-GOF variants likely exhibit increased binding affinity to DNA since, in general, the missense variants result in the conversion to an amino acid that decreases the electronegativity of the DNA-binding interface, potentially promoting enhanced interactions between the variant STAT6 transcription factor and the negatively charged DNA backbone. p.D419 is a notable amino acid residue in STAT6, a mutational hotspot for functional genetic change in patients with STAT6 GOFs [14, 17, 18], and the most commonly affected residue for somatic variation in follicular lymphoma [67] (Figure 2A). In addition to p.D419, other germline amino acid changes causing STAT6-GOF disease were also enriched as somatic mutations in cancer, including p.E373, p.E377, p.D519, and p.P643. This concordance is biologically plausible since the IL-4/JAK/STAT6 axis is known to be a driver of follicular lymphoma pathogenesis [67].

STAT6-GOF disease and the risk of lymphoma

To date, one patient found to have STAT6-GOF disease has developed lymphoma [18]. This individual, who was heterozygous for *STAT6* c.1255G>C p.D419H, was found to have follicular lymphoma at the age of 49 years. After initially responding to standard therapy, they experienced a relapse with diffuse large B cell lymphoma at the age of 60 years [18]. Although more individuals with STAT6-GOF disease need to be diagnosed before the true lymphoma risk can be established, the biological relationship between STAT6 and lymphoma is compelling.

STAT6 is frequently and recurrently mutated in follicular lymphomas and other B cell lymphomas [67–72]. STAT6 p.D419, and the amino acids in its vicinity, define a mutational hotspot [67–69]; however, somatic mutations in multiple other STAT6 sites in different domains have been documented in the **Catalog of Somatic Mutations in Cancer** (COSMIC[®]) [14, 73] (Figure 2). That there are other peaks in STAT6 on COSMIC, which have not yet been identified in patients with germline STAT6-GOF disease, suggests that additional patients will be found to have germline variants at these recurrently mutated residues. Parallels can also be drawn to the related signaling molecules, JAK1 and STAT5B. Specifically, the first two reported germline *JAK1*-GOF variants [27, 74] were previously noted as mutational hotspots in the JAK1 autoinhibitory pseudokinase domain [73]. Similarly, one of the reported *STAT5B*-GOF variants, p.N642H [36], was also reported to be a mutational hotspot, although a second reported variant, p.R217H [75], was not. These reports suggest that identification of additional germline *STAT6*-GOF variants will benefit from the incorporation of somatic mutations as part of the algorithm predicting variant pathogenicity. However, rigorously controlled functional validation should still be undertaken, because it is the gold standard for the evaluation of new variants of uncertain significance.

Identified mechanisms of STAT6-GOF pathology

Under physiological conditions, unphosphorylated STAT6 (uSTAT6) monomers shuttle between the cytoplasm and nucleus, without binding DNA [76]. After IL-4 stimulation, phosphorylated STAT6 (pSTAT6) dimers are formed and translocated to the nucleus, where they bind DNA to activate a pro-allergic transcriptional response. pSTAT6 is then eventually dephosphorylated, de-dimerized, and recycled as uSTAT6 monomers back to the cytoplasm (Figure 3A, Key figure) (see also Box 1).

While experimental data are limited at this early stage since the initial recognition of STAT6-GOF disease, for germline *STAT6*-GOF variants studied to date, the most clear and consistent finding is that they exhibit increased *STAT6* transcriptional activity relative to WT, measured by luciferase

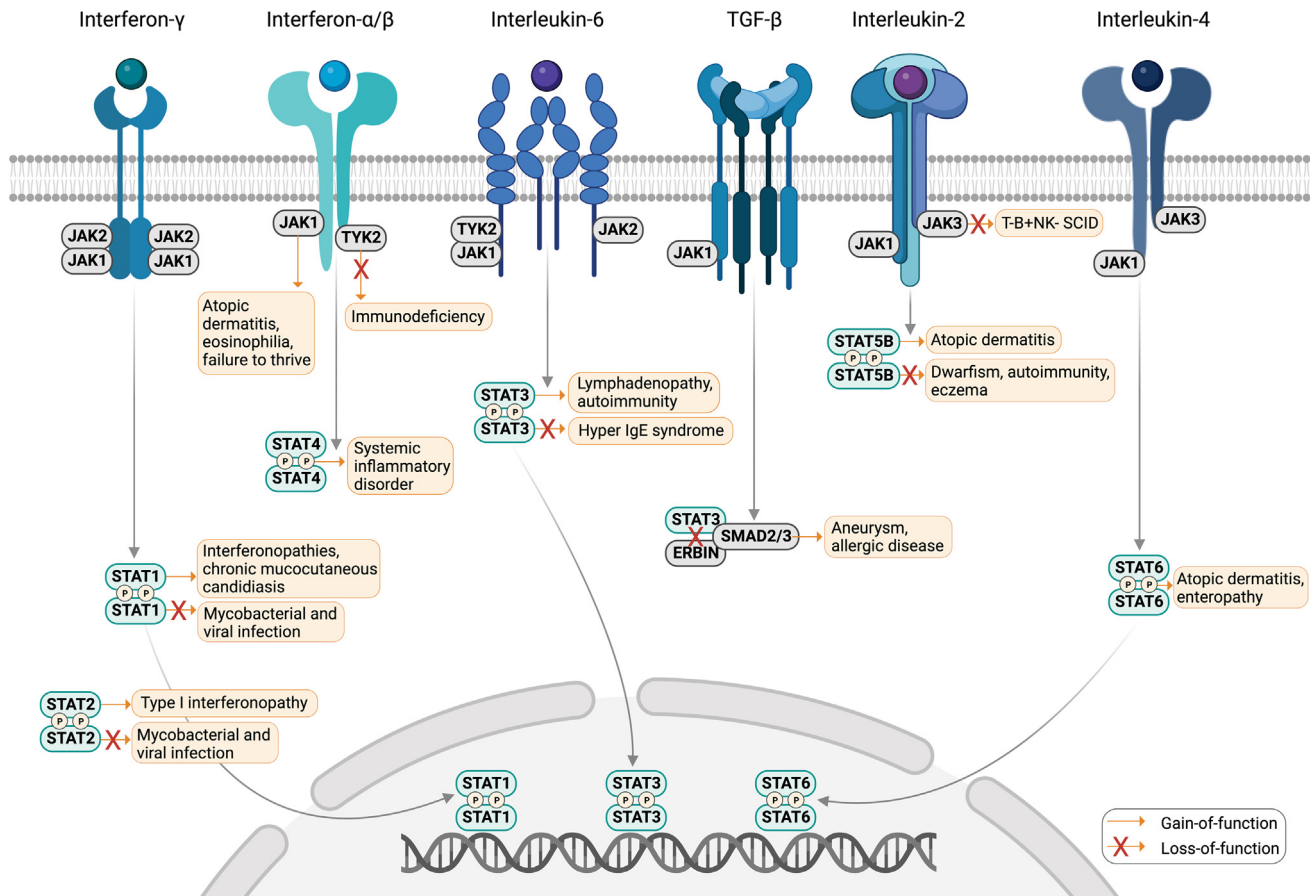
Signal transducer and activator of transcription 6—gain of function (STAT6-GOF) disease:

STAT6-GOF disease is a recently discovered PAD that is characterized by severe, early-onset treatment-resistant atopic dermatitis and other allergic/non-allergic manifestations; designated in the Online Mendelian Inheritance in Man (OMIM) database as ‘Hyper-IgE syndrome 6, autosomal dominant, with recurrent infections’ (OMIM #620532).

Single nucleotide polymorphisms (SNPs): genomic variants at single base positions in DNA with a minor allele frequency (MAF) >0.01.

T follicular helper (T_{FH}) cells: specialized subset of CD4⁺ T helper cells found in secondary lymphoid tissues that support B cells and drive humoral immunity; crucial for B cell affinity maturation and Ig CSR.

T helper 2 (T_H2) cells: adaptive effector cells arising from naïve CD4⁺ T cells; secrete type 2 cytokines IL-4, IL-5, and IL-13; not only facilitate protective type 2 immune responses, but also contribute to chronic inflammation observed in asthma and allergy.



Trends in Immunology

Figure 1. Human inborn errors of immunity (IEIs) caused by defects in the Janus kinase–signal transducer and activator of transcription (JAK–STAT) signaling pathway. Known defects in the JAK and STAT molecules and in their related pathways are presented alongside the primary clinical presentations of patients with these defects. The presented IEIs include: JAK1-gain of function (GOF)-associated severe atopic disease [27], predisposition to mycobacteria and viral infections in TYK2 deficiency [28], JAK3 deficiency causing severe combined immunodeficiency (SCID) [29], broad spectrum of STAT1-GOF disease often associated with chronic mucocutaneous candidiasis (CMC) [25,30], susceptibility to mycobacterial and viral infections in STAT1 and STAT2 deficiencies [22,31], STAT3-GOF disease causing a broad spectrum of immunodeficiencies and autoimmunity [32,33], dominant-negative STAT3 variants associated with hyper immunoglobulin (Ig)E syndrome (DN-HIES) [20,21], STAT5B-loss of function (LOF)-associated growth failure, and autoimmune disease [34,35], STAT5B-GOF disease causing atopic dermatitis and eosinophilia [36], STAT2-GOF-mediated type I interferonopathy leading to autoinflammation [37], STAT4-GOF causing autoinflammatory syndrome [26], and STAT6-GOF variants causing severe allergic disease [14–18]. Orange arrows indicate clinical signs of a GOF in the molecule/pathway. Orange arrows with an X on them represent clinical presentation due to LOF in the molecule/pathway. Figure created using BioRender ([biorender.com](https://www.biorender.com)).

assays [14–18]. Compared with WT STAT6, after IL-4 stimulation, there is both increased phosphorylation of STAT6 GOF [14,17] and increased pSTAT6 nuclear localization [15,16]. These enhanced STAT6 activation processes in STAT6-GOF disease culminate in the upregulation of key downstream genes. Specifically, upregulated expression of the genes encoding X-box binding protein 1 (*XBP1*), endothelial PAS domain-containing protein 1 (*EPAS1*), B cell lymphoma 6 (*BCL6*), cytokine-inducible SH2-containing protein (*CISH*), and IL4 receptor (*IL4R*) was noted in both primary patient CD4⁺ T lymphocytes and STAT6 GOF-transduced Jurkat CD4⁺ T cell lines [14,18]. At the protein level, upregulation of several STAT6-targeted molecules was documented in STAT6-GOF cells compared with WT controls, including: IL-4R α on both CD4⁺ T cells and B cells, and CD23 on B cells. Patients with STAT6-GOF disease also exhibited higher concentrations (compared with healthy controls) of the T_H2 cytokines, IL-4, IL-5, and IL-13, as

Table 1. STAT6 Gain-of-Function International Consortium Recommendations for the clinical diagnosis and management of STAT6-GOF disease^a

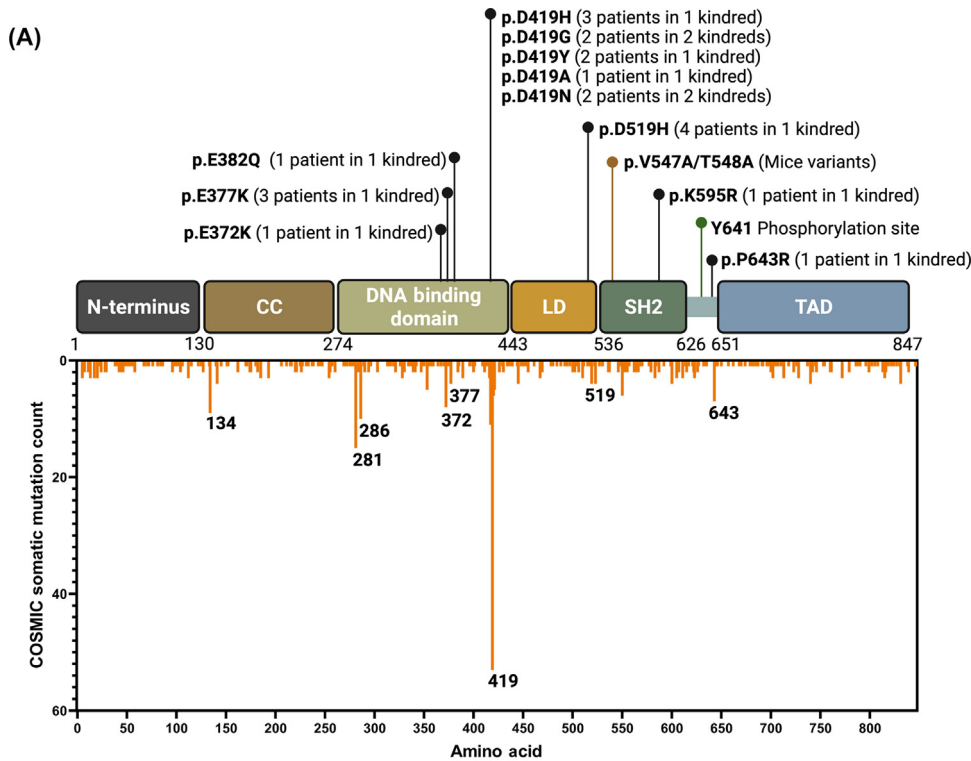
Factor	Description	Refs
Diagnosis		
History and physical examination	Key diagnostic factors: disease onset in early infancy with multiple severe atopic manifestations, such as recalcitrant atopic dermatitis/eczema with severe pruritis, severe asthma, life-threatening anaphylaxis, allergic rhinoconjunctivitis, multiple food allergies, drug allergies, eosinophilic esophagitis and gastroenteritis, protein-losing enteropathy, early gastroesophageal reflux disease	[14–18]
	Other diagnostic factors:	
	Common: recurrent infections, secondary skin infections with <i>Staphylococcus aureus</i> , <i>Candida albicans</i> , and <i>molluscum contagiosum</i> ; pneumonia, superficial abscesses, failure to thrive	[14,16]
	Uncommon: urticaria, pneumothorax, bronchiectasis, interstitial lung disease, retinal detachment, cataract, oral and laryngeal papillary hyperplasia, osteoporosis with pathological fractures, generalized joint hypermobility, joint pain, enamel hypoplasia, generalized lymphadenopathy, coarse facies (broad nasal bridge, increased alar width, and deep-set eyes; mild high palate arch), hypotrichosis	[14–16]
	Risk factors: family history consistent with autosomal dominant pattern of early-onset severe atopic disease (NB: ~50% of cases reported to date are sporadic caused by <i>de novo</i> damaging variants and, hence, lack a family history)	[14–18]
Investigations	Key investigations:	
	Complete blood count with white cell differentials; absolute eosinophil count is typically elevated; other possible abnormalities include anemia, thrombocytosis, and leukocytosis	[14–18]
	IgG/A/M: usually normal; may be raised or reduced	[14–18]
	Total IgE: raised; may exceed upper limit of detection	[14–18]
	Lymphocyte subsets: usually normal	[14–18]
	Next-generation genetic sequencing: most powerful and cost-effective diagnostic approach	[14–18]
	Other investigations:	
	Elevated T _H 2 cell numbers in blood	[14–17]
	Skin biopsy: chronic inflammation with infiltration of eosinophils and other cell types; lichenification	[14–17]
	Upper and lower gastrointestinal endoscopy: swelling, erythema, and erosions of mucosa, polypoid-like lesions; trachealization and furrowing in esophagus; nodularities and lymphonodular hyperplasia in small and large intestines; biopsy demonstrating eosinophilic inflammation	[14–17]
	Growth hormone evaluation and bone age study if there is short stature; delayed bone age and growth hormone deficiency may be found	[14,16,17]
	Specific IgE panels: may be reactive toward multiple common aeroallergens and food allergens	
Skin prick tests: may be reactive toward multiple common aeroallergens and food allergens	[14,15]	
Differential diagnoses	Other primary atopic disorders with overlapping phenotypes:	
	Possibilities include: JAK1 GOF, STAT5B GOF, HIES family of disorders, DOCK8 deficiency, TYK2 deficiency, MALT1 deficiency, IPEX, Omenn syndrome, Wiskott Aldrich syndrome, Netherton syndrome, and others	
	Phenotypic overlap emphasizes value and efficiency of using NGS to simultaneously assess many genes to secure diagnosis	

Table 1. (continued)

Factor	Description	Refs
	Hypereosinophilic syndrome: patients usually 20–50-years old; many overlapping features with STAT6-GOF disease; lymphocytic variant of hypereosinophilic syndrome may also present with mostly dermatological manifestations	[108]
	Eosinophilic granulomatosis with polyangiitis: typically diagnosed in adulthood; triad of tissue eosinophilia, granulomatous inflammation, and vasculitis; may be perinuclear-ANCA positive	[109]
	Parasitic infections: presence in endemic areas, travel and contact history, consumption of raw freshwater fish, contact with domestic cats or dogs; sudden onset; presence of ova in stool specimens, microfilariae on blood film, or positive serology	
	Chronic myeloid leukemia: uncommon in children; eosinophil counts in circulation may be raised, but atopic manifestations are not atypical	[110,111]
Management		
Interventions	Effective therapies in STAT6-GOF disease described to date (any of the following):	
	Anti-IL4R antibodies (dupilumab)	[14]
	JAK inhibitors (ruxolitinib or tofacitinib)	[14,16]
Prevention	Primary: prenatal genetic testing	
	Secondary: allergen avoidance if sensitized, medical record alert, medical alert jewelry, epinephrine autoinjectors; immunization; prophylaxis for bone loss in patients treated with chronic corticosteroids; early genetic testing for offspring of patients	
Discussion	Epinephrine autoinjector: carry at all times because anaphylaxis may be lethal; call emergency services and warn service providers about possibility of biphasic reactions	
	Infections: be aware of signs and symptoms of infections; seek treatment early	
	Prognosis: awareness of potential long-term risk of lymphoma, fatal anaphylaxis, and possibility of increased risk of cerebral aneurysms	[14,18]
Follow-up		
Monitoring	Atopic dermatitis/eczema: can be longitudinally monitored by SCORing Atopic Dermatitis (SCORAD) index or Eczema Area and Severity Index (EASI)	[14–16]
	Eosinophil count: eosinophil count tends to be reduced after dupilumab or JAK inhibitor therapy, and may correlate with treatment efficacy	[14,16]
	Growth chart: should be monitored as integrated measure of overall health	[14,16,17]
Complications	Kidney failure: reported in one patient in adolescence; may require kidney transplantation	[15]
	Cerebral aneurysm: reported in one patient in adulthood; may be fatal	[14]
	Lymphoma: reported in one patient in later adulthood; may relapse	[14,18]
Prognosis	Mortality: two patients out of 21 reported to date have died: causes were cerebral aneurysm (age 35 years) and anaphylaxis (age 20 years)	[14,18]
	Inheritance: autosomal dominant, although ~50% of reported cases were sporadic, caused by <i>de novo</i> STAT6 variants in the affected individual	[14–18]

^aThese clinical recommendations are based on the expert clinical opinion of members of the STAT6 Gain-of-Function International Consortium since STAT6-GOF disease was only first described in 2022 and formal clinical trials have not yet been completed and, in fact, may not be feasible in such a rare disease.

measured in serum and via intracellular cytokine staining [14]. Moreover, the amount of STAT6-regulated chemokine C-C motif chemokine ligand 24 [CCL24; also known as eosinophil chemoattractant protein 2 (eotaxin-2)] was higher in sera from patients with STAT6 GOF and in gastric



(B) STAT6-GOF variants reported to date

cDNA position (NM_001178079.2)	Protein position (NP_001171550)	Number of patients	Reported in gnomAD (v3.1.1)	CADD (v1.6)
c.1114G>A	p.Glu372Lys	1	No entry	28.0
c.1129G>A	p.Glu377Lys	3	No entry	31.0
c.1144G>C	p.Glu382Gln	1	No entry	27.7
c.1255G>A	p.Asp419Asn	2	No entry	32.0
c.1255G>C	p.Asp419His	3	No entry	32.0
c.1255G>T	p.Asp419Tyr	2	No entry	31.0
c.1256A>G	p.Asp419Gly	2	No entry	29.3
c.1256A>C	p.Asp419Ala	1	No entry	29.3
c.1555G>C	p.Asp519His	4	No entry	28.9
c.1784A>G	p.Lys595Arg	1	No entry	27.5
c.1928C>G	p.Pro643Arg	1	No entry	28.0

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Figure 2. Germline and somatic gain-of-function (GOF) variants in signal transducer and activator of transcription 6 (STAT6). (A) STAT6 protein domains and human germline variants in the protein-coding region of STAT6 are shown in the top of (A) in black lines. Shown in brown is the experimental Stat6-GOF variant generated *in vitro* and validated in a mouse model (Stat6 V547A/T548A aka. Stat6VT [57–59]). At the bottom of (A), somatic variants in human STAT6 aggregated from the Catalog of Somatic Mutations in Cancer (COSMIC) (<https://cancer.sanger.ac.uk/cosmic>) are shown. The length of the line corresponds to the reported number of somatic mutations counts at a particular amino acid position, which includes all the possible changes that are reported at that particular amino acid [e.g., 54 counts at p.D419 includes: p.D419G (28), p.D419H(9), p.D419N(9), p.D419A(3), p.D419V(3), and p.D419Y(2)]. Numbers on the peaks represent particular amino acid locations that are hotspots for somatic mutations. (B) STAT6-GOF variants reported to date. To our knowledge, none of the variants are reported in gnomAD (<https://gnomad.broadinstitute.org/>), a large population database. The *in silico* Combined Annotation Dependent Depletion (CADD) (<https://cadd.gs.washington.edu/>) tool predicted all the variants to be damaging with scores greater than the recommended cut-off of 20. Figure created using BioRender ([biorender.com](https://www.biorender.com)). Abbreviations: CC, coiled-coil domain; LD, linker domain; SH2, Src homology 2; TAD, transcription activation domain.

Key figure

Molecular mechanisms and clinical complications of signal transducer and activator of transcription 6 (STAT6)–gain-of-function (GOF) disease

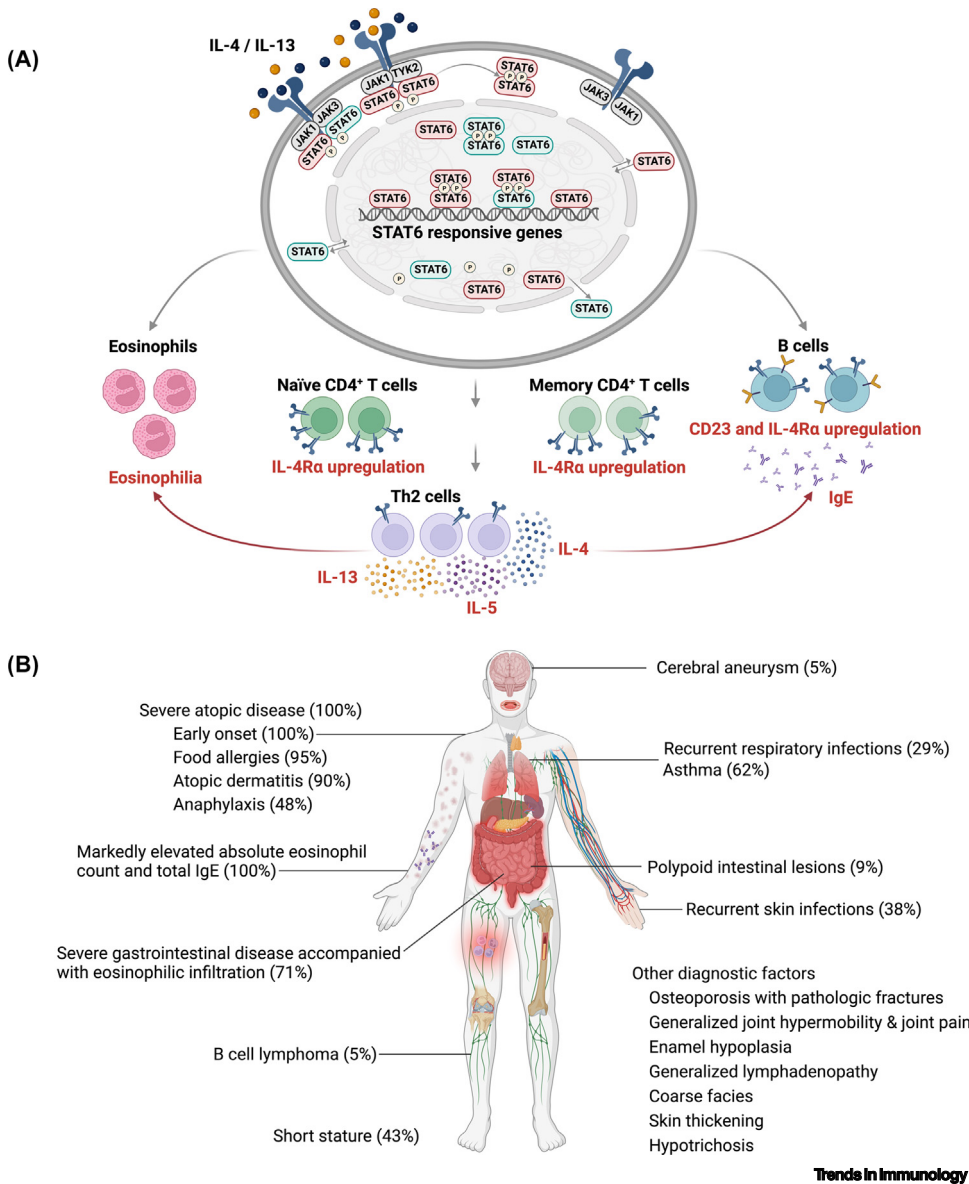


Figure 3. (A) Proposed (hypothetical) mechanistic molecular and cellular model of STAT6-GOF disease. The STAT6-GOF monomer (in red) can shuttle independently of wild-type (WT) STAT6, impacting 50% of nondimerized STAT6 activity. Upon activation and phosphorylation, the STAT6-GOF molecule can either dimerize with itself or with a WT-STAT6 molecule, impairing up to 75% of STAT6 complexes. These complexes can lead to increased STAT6 phosphorylation, delayed dephosphorylation, and increased nuclear retention, with the net result of increased transcription of various STAT6-responsive genes. Higher observed cell surface expression of IL4R α on naïve and memory CD4⁺ T cells, and IL-4R α and CD23 expression on B cells, and corresponding high T helper 2 (T_H2) and immunoglobulin (Ig)E-secreting B cells

(Figure legend continued at the bottom of the next page.)

Clinician's corner

Clinical approach to patients with suspected STAT6-GOF disease

Clinical red flags

Patients with STAT6-GOF disease may present to clinical services in pediatric or adult allergy, clinical immunology, dermatology, pulmonology, infectious disease, gastroenterology, or endocrinology units. Such clinical specialists should consider STAT6-GOF disease in patients presenting with severe multi-system allergic disease beginning in early infancy (see Table 1 and Figure 3B in the main text). At the laboratory level, absolute peripheral blood eosinophil counts and total serum IgE titers for such patients are, in general, persistently and markedly elevated [14]. Patients with STAT6-GOF disease often have a poor response to standard first-line treatments, such as corticosteroids, but may have a history of responding positively to medication targeting the IL-4R/JAK/STAT6 pathway, such as dupilumab (a monoclonal antibody that binds IL-4R α and inhibits signaling of both IL-4 and IL-13a) or JAK inhibitors [14,16].

Diagnostic approach

A detailed diagnostic approach is provided in Table 1 in the main text. After routine evaluation, genetic testing with NGS (e.g., targeted immunology panel, whole-exome or whole-genome sequencing) is indicated for all patients with suspected STAT6-GOF disease. There are multiple pathways involved in primary atopic disorders [12], and other conditions, such as JAK1 or STAT5b GOF, share many overlapping clinical and laboratory features with STAT6-GOF disease, emphasizing the value of simultaneous interrogation of multiple genes [27,106]. A definitive diagnosis of STAT6-GOF disease will depend on finding a published, functionally assessed STAT6 variant in a patient with a compatible phenotype. Since this is a newfound disease, novel candidate variants in STAT6 should undergo functional assessment to establish pathogenicity. Familial segregation will also be valuable, given that the STAT6-GOF variants described to date have been fully penetrant [14–18].

tissue-derived patient **organoids** compared with healthy controls, again confirming increased STAT6 activity [15,17]. Patients with STAT6-GOF disease also displayed cellular phenotypes that were consistent with exaggerated STAT6 signaling and pro-allergic immune skewing (compared with healthy controls), including a significant increase in T_H2 lymphocytes and blood eosinophil counts [14–17]. Finally, to further validate the pathogenicity of one of the STAT6-GOF variants, knock-in mice carrying the p.D419N variant were generated using CRISPR/Cas9 [17]. *Stat6*^{D419N/wt} mice spontaneously developed dermatitis characterized by skin thickening and eosinophilic infiltration of the skin, concomitant with high serum IgE titers, high mRNA expression of T_H2 cytokines/chemokines in skin, and high T_H2 cytokine production from cervical lymph node cells compared with WT controls [17]. When considered in aggregate, these data from cell systems, patient primary cells, and mouse models all indicate that STAT6-GOF variants result in an exaggerated pro-allergic phenotype, providing a mechanistic explanation for the severe allergic phenotype experienced by patients.

Mechanistic similarities between patients with STAT6-GOF disease and other IELs affecting JAK-STAT signaling

Further insights into STAT6-GOF disease can be gleaned by studying shared clinical and molecular profiles from patients with other IELs in the JAK-STAT pathway. The prominent allergic features seen in STAT6-GOF disease resemble those observed in patients with JAK1 GOF and STAT5b GOF, including treatment-resistant early-onset atopic dermatitis, severe food allergies, eosinophilic gastrointestinal disorders, and respiratory allergies [27,36,74,75,77]. This overlap suggests that there are common pathways downstream of STAT5 and STAT6 signaling that are involved in T_H2 cell differentiation and proliferation. Indeed, constitutive STAT5 expression in CD4⁺ T cells from *Stat6*^{-/-} mice partially restored STAT6-dependent IL-4 production, as demonstrated via intracellular flow cytometry [78]. Furthermore, a small-molecule inhibitor of the Src homology 2 (SH2) domain, PM-431, targeted both STAT5 and STAT6 to ameliorate airway hyper-responsiveness, and IL-4 production from inflammatory cells that were associated with allergic airway disease in C57BL/6 mice challenged with *Aspergillus niger* [79,80]. This suggests a putative cooperative role of STAT5 and STAT6 activation in contributing to T_H2 polarization and allergic phenotypes, highlighting the importance of studying both their roles in patients with severe allergic diseases.

Furthermore, patients with loss-of-function (LOF) and **dominant interference** in proteins of the IL-6/gp130/STAT3 signaling pathway, including DN-*STAT3* [19–21], AR-*IL6RA* [81,82], AR-*IL6ST* [83–85], DN-*IL6ST* [86], AR-*ZNF341* [87], DN-*TGFBFR1/2* [88], and DN-*ERBB21P* [89], exhibit an array of classic allergic features that are similar to those of patients with STAT6-GOF disease (i.e., eosinophilia, elevated total IgE and specific IgE to foods and aeroallergens, as well as eczema-like rashes). Mechanistically, IL-6 signaling was recently shown to upregulate suppressor of cytokine signaling 3 (SOCS3), suppressing IL-2/STAT5 signaling in early T cell activation and, thus, inhibiting T_H2 priming [90]. Here, stimulation of *Socs3*-deficient naïve CD4⁺ T cells from *CD4^{cre}-Socs3^{fl/fl}* mice in the presence of IL-6 failed to inhibit IL-4 and CD25 expression,

respectively, have been identified. Cytokines produced by these cells can lead to eosinophilic inflammation and IgE-mediated food allergy. (B) Patients with STAT6-GOF disease present with severe, early-onset, multi-system allergic disease. Clinical features include: treatment-resistant atopic dermatitis, food allergies, asthma, and episodes of anaphylaxis. Severe gastrointestinal disease accompanied with eosinophilic infiltration has also been observed. Some patients also presented with recurrent skin, respiratory, and viral infections, but no fatal infections were noted. Some extra-hematopoietic features shared with STAT3-loss-of-function (LOF) diseases were also documented, including short stature, pathological fractures, and generalized hypermobility. Other notable features included B cell lymphoma in one patient and a fatal cerebral aneurysm in another. Percentages denote the number of patients affected with each feature from the 21 patients with STAT6-GOF disease reported to date [14–18]. Figure created using BioRender ([biorender.com](https://www.biorender.com)).

Management

Disease-modifying therapies proven to be effective in the small numbers of patients with STAT6-GOF disease reported to date currently include dupilumab and the JAK inhibitors, ruxolitinib and tofacitinib (see Table 1 and Figure 4 in the main text) [14,16]. Since STAT6-GOF disease was only first described in 2022 and a total of 21 patients has been reported, the treatment recommendations available to date for this rare disease are based on case reports and expert clinical opinion; formal clinical trials have yet to be undertaken. We acknowledge that, at this stage, no treatments have been specifically approved for STAT6-GOF disease; however, our approach has been to use medication approved for specific allergic manifestations. Corticosteroids have been the mainstay of treatment for most patients with STAT6-GOF disease identified to date, resulting in many of the side effects known to be caused by long-term corticosteroid exposure. Mepolizumab (an anti-IL-5 monoclonal antibody), and various other immunosuppressive drugs have proven relatively ineffective in patients with STAT6-GOF disease, likely because they do not specifically target the dysregulated IL-4R/JAK/STAT6 pathway. Theoretically, other JAK inhibitors approved for atopic conditions might also be effective in patients with STAT6-GOF disease [107]. We strongly recommend using prospective objective measures to monitor treatment efficacy in patients with STAT6-GOF disease, including serial height and weight measurements as well as the SCORing Atopic Dermatitis (SCORAD) Index^{III} or Eczema Area and Severity Index (EASI)^{IV} to monitor skin conditions (see Table 1 in the main text). Prenatal or cascade genetic screening may be needed to inform family planning decisions and to diagnose other affected family members so that targeted therapy can be initiated. Monitoring should also address non-allergic complications that have been reported in patients with STAT6-GOF disease, notably lymphoma, cerebral aneurysm, and kidney failure [14,18].

resulting in higher T_H2 lineage commitment compared with WT naive $CD4^+$ T cells [90]. This suggested a central role for IL-6 signaling in restricting T_H2 polarization, which is an impairment that might explain allergic phenotypes in patients with IL-6/gp130/STAT3 signaling pathway variants. Consistent with this model, single-cell RNA sequencing of peripheral blood showed high *SOCS3* mRNA expression in both myeloid and lymphoid subsets in a single patient presenting with STAT6-GOF disease [14]; this implied potential overlap in pathways shared between the two diseases leading to allergic phenotypes. We posit that future investigations should be informative in providing clues regarding the non-allergic manifestations of STAT6-GOF disease that might be shared with patients bearing a defective STAT3 signaling pathway; these may include **coarse facies**, osteoporosis, pathological fractures, hypermobile joints, and vascular anomalies, such as aneurysms [91,92] (Table 1). We argue that it is possible that STAT6 GOF might interfere with STAT3-dependent pathways, such as by upregulating *SOCS3*, but this hypothesis remains to be rigorously explored. In addition, such explorations may pave the way for testing emerging therapeutic targeting approaches in STAT6-GOF disease (Box 2, Figure 4, Table 1, and Clinician's corner).

Concluding remarks

STAT6-GOF disease is a newfound PAD that causes severe, early-onset multi-system allergic pathology and that responds well to treatment with dupilumab (anti-IL-4R α monoclonal antibodies) or **JAK inhibitors** [14,16]. It is noteworthy that this newly discovered condition was recently reported in five independent reports from across the globe, beginning in 2022 [14–18]. Although many questions remain, particularly around the mechanisms of disease and best treatment

Box 2. Potential emerging therapeutic targets for STAT6-GOF activity

Some patients with STAT6-GOF disease described to date have responded favorably to dupilumab and JAK inhibitor treatment [14,16]. Future treatment approaches for patients with STAT6-GOF disease will evolve as more research in the field of STAT6 brings forth precise therapeutics to target the STAT6 signaling cascade (see Figure 4 in the main text).

For example, allergic airway disease in mice was recently treated using the small-molecule peptide inhibitor, PM-431, targeted against the STAT5/6 SH2 domain [79,80]. The SH2 domain, crucial for STAT6 binding to phosphorylated cytoplasmic domains of activated receptors and subsequent dimerization, is necessary for STAT6 activity [57]. However, total STAT6, irrespective of phosphorylation, has also been found to be increased in the nucleus of cells derived from patients with STAT6-GOF disease, which might suggest increased STAT6 activity [15,17]. Nevertheless, the utility of PM-431 in STAT6-GOF disease remains to be validated.

Similarly, another small-molecule inhibitor, AS1517499, first described in 2007 as a potent inhibitor of STAT6 [99], and consequently used for the treatment of bronchial hypercontractility [100], was recently used to treat mice exhibiting atopic dermatitis [101]. The severity of induced atopic dermatitis in BALB/c mice was reduced with AS1517499 relative to controls, along with alleviated skin lesions and reduced serum IL-13 and IL-33 concentrations [101].

Another possibility may be to target STAT6 using antisense oligonucleotides that competitively inhibit the binding of STAT6 to promoter regions in target genes. Administering STAT6 decoy oligodeoxynucleotides (ODNs) in induced atopic dermatitis in mice inhibited STAT6 nuclear binding, attenuated the late-phase allergic response, and was accompanied by significant reduction in edema, neutrophil, and eosinophil infiltration [102]. In humans, a pilot study, in which ten subjects were treated with an ointment containing 2% decoy STAT6 ODNs, reported significantly improved skin condition [evaluated using the Eczema Area and Severity Index (EASI)] in patients with moderate to severe atopic dermatitis [103].

Finally, PARP14, a regulator of STAT6-mediated transcription [104], was recently implicated in a positive feedback loop enhancing STAT6 activity in lymphoma cells harboring STAT6-GOF variants [105]. OCI-Ly1 cells expressing STAT6 variants (p.D419G, p.D419N, or p.N421K) stimulated with IL-4 strongly upregulated *PARP14* mRNA expression as measured by RNA sequencing, compared with WT STAT6 [105]. The use of a PARP inhibitor, PJ34, blocked STAT6 GOF IL-4-induced expression of CD23 down to a level seen with WT STAT6, without impacting WT STAT6 activity [105]. Given this finding, the use of PARP inhibitors for future patients with germline STAT6-GOF disease may represent a promising treatment approach.

Ultimately, the effectiveness of these emerging treatment strategies in STAT6-GOF disease remains to be seen, because none have yet been tested clinically or even *in vitro* against germline STAT6-GOF variants.

Outstanding questions

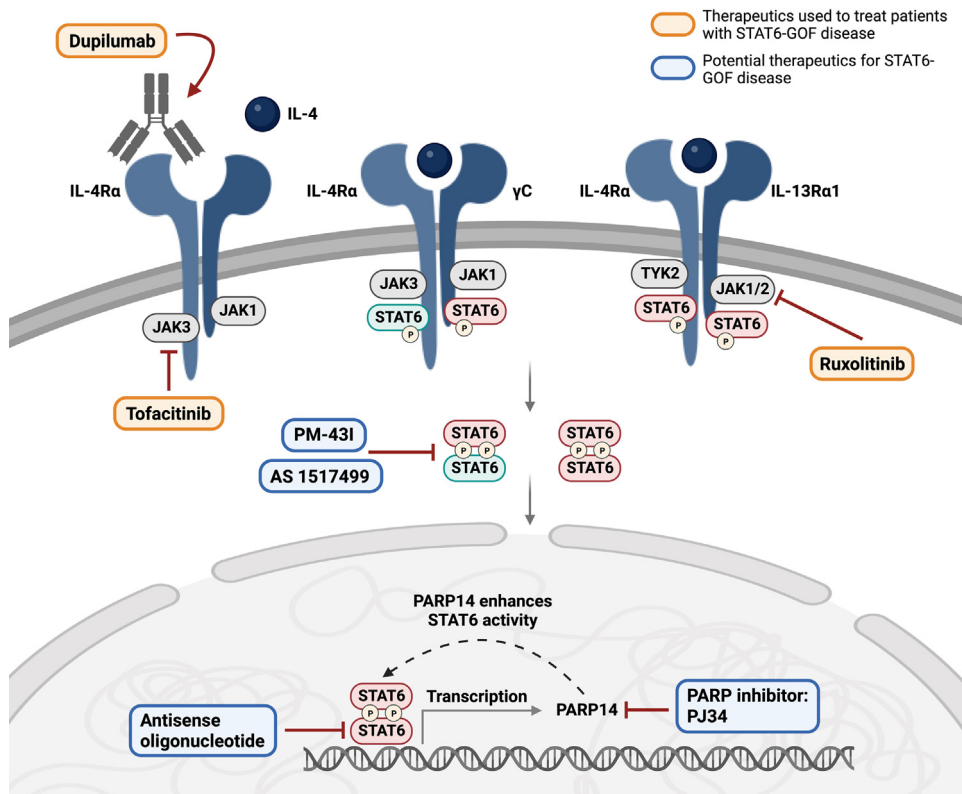
How common is STAT6-GOF disease in patients with severe, early-onset allergic disease? This information may help clinicians understand which patients should be treated for this newfound condition.

What is the best treatment approach for STAT6-GOF disease? Identifying the most effective long-term treatment strategies for STAT6-GOF disease is essential for establishing a standardized therapeutic regimen that optimizes patient outcomes following diagnosis.

How do STAT6-GOF variants interact with DNA differently from WT STAT6? Is affinity of STAT6 binding to the DNA backbone increased? Do STAT6-GOF variants redirect STAT6 away from the classical STAT6 TTCNNNGAA DNA-binding motif [112]? If so, what are the differentially expressed genes associated with this new binding activity? Investigating the differential DNA-binding properties and target gene modulation of STAT6-GOF variants may enable a deeper understanding of the molecular mechanisms underlying the disease and refine targeted therapeutic strategies.

Activated STAT6 can associate with STING [113], yet none of the patients identified exhibited a clinical phenotype of STING-associated vasculopathy with onset in infancy (SAVI) as would be expected in a GOF scenario in the STING pathway. How are the binding partners of STAT6 changed by STAT6-GOF variants? Answering this question can further enhance our understanding of the drivers of STAT6-GOF disease while also clarifying the mechanism involved in the regulation of STING activation.

How do STAT6-GOF and STAT3-DN variants interfere with STAT3 and STAT6 signaling, respectively? A better understanding of the crosstalk between these pathways may help explain phenotypes that are common between these two IELs, particularly the extra-hematopoietic features.



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Figure 4. Current and future putative therapeutic options for patients with signal transducer and activator of transcription 6 (STAT6)–gain-of-function (GOF) disease. Dupilumab, a monoclonal antibody against IL4Rα, has been used most often in patients with STAT6-GOF disease [14]. Downstream of the receptor, the inhibition of intracellular kinases (Janus kinases; JAKs) using ruxolitinib and tofacitinib has also been used in patients, with promising clinical resolution of the disease [14,16]. Other JAK inhibitors might be useful in the context of this disease. Specific STAT6 inhibitors are not currently approved but have shown promise in *in vitro* and mouse studies: AS1517499 (STAT6-specific small-molecule inhibitor) [101], PM-43I (STAT5/STAT6 SH2 domain-specific inhibitor) [79,80], STAT6 antisense oligonucleotides (to directly inhibit DNA binding) [102,103], and PJ34, (PARP inhibitor hypothesized to be specific for p.D419 GOF variants in lymphoma cell lines; may work as an inhibitor for alternative STAT6 activation) [105]. Currently used therapeutics are highlighted in orange, potential therapeutics not yet in clinical use are highlighted in blue. Figure created using BioRender ([biorender.com](https://www.biorender.com)).

approaches (see [Outstanding questions](#)), we anticipate that the description of STAT6-GOF disease will now empower not only the diagnosis and treatment of many more individuals, but also, through this effort, the characterization of the full phenotype of STAT6-GOF pathology.

The detailed phenotyping and molecular characterization of patients with monogenic IEs has a rich history of advancing fundamental knowledge of human immunity and in developing treatments that have applications far beyond IEs. We expect that the discovery of STAT6-GOF disease will similarly inform our understanding of human allergic inflammation and may accelerate the development of new therapies that can benefit patients with STAT6-GOF disease as well as other overlapping conditions, and, as a whole, the much larger population of people living with common, polygenic allergic diseases.

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Declaration of interests

The authors declare no conflicts of interest pertinent to this review.

Resources

ⁱ<https://gnomad.broadinstitute.org/>

ⁱⁱ<https://cancer.sanger.ac.uk/cosmic>

ⁱⁱⁱwww.scorad.corti.it/

^{iv}www.mdcalc.com/calc/10427/eczema-area-severity-index-easi

Supplemental information

Supplemental information associated with this article can be found online at <https://doi.org/10.1016/j.it.2023.12.003>.

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