STAT6 Gain-of-Function Disease (Hyper-IgE Syndrome 6, HIES6): A Comprehensive Disease Characterization Report

Summary

STAT6 gain-of-function (GOF) disease is a rare, recently described (2023) autosomal-dominant **primary atopic disorder (PAD)**—one of a growing group of inborn errors of immunity (IEIs) in which a single germline gene defect produces severe, early-onset allergic disease. It is caused by germline heterozygous **activating (gain-of-function) missense variants in *STAT6*** (Signal Transducer and Activator of Transcription 6; chromosome 12q13.3; HGNC:11364; NCBI Gene 6778; OMIM 601512). Pathogenic variants cluster in the **DNA-binding domain**, with a recurrent hotspot at codon **Asp419 (D419H/Y/G/N)** and additional recurrent variants including E372K, E377K, E382Q, and D519H/N. These variants produce **constitutive and/or ligand-hypersensitive IL-4/IL-13–JAK–STAT6 signaling**, with sustained STAT6 phosphorylation, enhanced nuclear translocation (in some cases even without phosphorylation), increased STAT6 target-gene expression, and pathological **TH2 skewing** of the adaptive immune system.

Clinically, the disease presents in **infancy (100% of the founding cohort)** with a profound, multi-system allergic phenotype: **widespread treatment-resistant atopic dermatitis (94%)**, **hypereosinophilia and markedly elevated serum IgE (94%)**, **IgE-mediated food allergy (94%)**, **asthma (69%)**, **eosinophilic gastrointestinal disease (63%)**, and **anaphylaxis (56%)**. Variable features include recurrent skin/respiratory/viral infections, short stature, osteoporosis, and a small but important risk of **B-cell/follicular lymphoma (~6%)**, mechanistically linked to the same DNA-binding-domain residues that are recurrently mutated somatically in follicular lymphoma. The disorder is catalogued as **OMIM #620532** ("Hyper-IgE syndrome 6, autosomal dominant, with recurrent infections; HIES6") and **MONDO:0957807**.

The disease is **highly actionable**: because the driver is a hyperactive, druggable signaling axis, **pathway-targeted therapy is transformative**. The anti–IL-4Rα monoclonal antibody **dupilumab** and **JAK inhibitors (e.g., ruxolitinib)** improve both clinical manifestations and immunological biomarkers. Diagnosis relies on exome/genome sequencing with functional

confirmation of STAT6 hyperactivation. Two constitutively active mouse models (Stat6VT transgenic and patient-derived D419N knock-in) recapitulate the human TH2/allergic phenotype and validate the causal mechanism. This report synthesizes 9 confirmed findings drawn from 11 reviewed papers into a full disease knowledge-base entry organized along the 15 requested characteristic domains, followed by a mechanistic model, evidence base, limitations, and proposed follow-up actions.

Key Findings

Finding 1 — STAT6 GOF disease is a novel autosomal-dominant primary atopic disorder caused by germline heterozygous gain-of-function *STAT6* variants

The defining evidence comes from a landmark international cohort of **16 patients from 10 families across three continents** (Sharma et al., 2023). **All patients carried monoallelic (heterozygous) rare variants in *STAT6***, and functional studies established a gain-of-function phenotype. As the authors state verbatim: *"All patients carried monoallelic rare variants in STAT6 and functional studies established their gain-of-function (GOF) phenotype with sustained STAT6 phosphorylation, increased STAT6 target gene expression, and TH2 skewing"* and *"This study identifies heterozygous GOF variants in STAT6 as a novel autosomal dominant allergic disorder"* (PMID: 36884218). Inheritance was **sporadic (de novo) in 7 kindreds and autosomal dominant in 3 kindreds**, consistent with a dominant, GOF (not loss-of-function/haploinsufficiency) mechanism.

Evidence source: human clinical/genetic (multi-family cohort with functional validation).

Finding 2 — Core clinical phenotype: early-onset treatment-resistant atopic dermatitis, hypereosinophilia, eosinophilic GI disease, asthma, elevated IgE, food allergy and anaphylaxis

The founding cohort described *"a profound phenotype of early-life onset allergic immune dysregulation, widespread treatment-resistant atopic dermatitis, hypereosinophilia with esosinophilic gastrointestinal disease, asthma, elevated serum IgE, IgE-mediated food allergies, and anaphylaxis"* (PMID: 36884218). This multi-system atopic constellation is the diagnostic

signature and is independently replicated in single-case/kindred reports: Baris et al. (E372K), Suratannon/independent (E377K), Minskaia (D419H), and Samra (D519N) each describe severe atopic dermatitis, eosinophilia, elevated IgE, and food allergy.

Evidence source: human clinical.

Finding 3 — Recurrent pathogenic variants cluster in the STAT6 DNA-binding domain and cause constitutive/enhanced IL-4/JAK/STAT6 signaling

Reported germline missense variants include **p.E372K (c.1114G>A), p.E377K (c.1129G>A), p.E382Q (c.1144G>C), p.D419H (c.1255G>C), p.D419Y (c.1255G>T), p.D419G (c.1256A>G), p.D419N (c.1255G>A), and p.D519H/N (c.1555G>C)**—several within the **DNA-binding domain (DBD)**. Direct quotes anchor the mechanism: - *"a missense mutation in the DNA binding domain of STAT6 (c.1114G>A, p.E372K)"* (PMID: 36758835). - *"a novel heterozygous germline mutation STAT6 c.1255G > C, p.D419H leading to overactivity of IL-4 JAK/STAT signalling pathway"* (PMID: 37316763). - Ligand independence was shown for D419N: *"even in the absence of IL-4 stimulation, we observed the translocation of mutant STAT6 in its unphosphorylated state, which activated gene expression"* (PMID: 40603028).

Thus, some variants confer **hypersensitivity to IL-4** (elevated total/phospho-STAT6 at baseline and after IL-4, e.g., D419H) while others confer **constitutive, phosphorylation-independent nuclear translocation and transcription** (D419N).

Evidence source: human genetic + in vitro functional (HEK293T, patient PBMC, gastric organoids).

Finding 4 — Targeted therapy: dupilumab and JAK inhibitors are effective; disease is associated with follicular lymphoma risk

Because the disease is driven by a hyperactive IL-4/IL-13–JAK–STAT6 axis, **blocking that axis is therapeutic**. *"Precision treatment with the anti-IL-4Rα antibody, dupilumab, was highly effective improving both clinical manifestations and immunological biomarkers"* (PMID: 36884218); dupilumab was also effective for the D519N variant (Samra 2025, PMID: 40502541). JAK inhibition targets the upstream kinases: *"The selective JAK1/JAK2 inhibitor ruxolitinib reduced pSTAT6 levels in D419H HEK293T cells and patient PBMC"* (PMID: 37316763). Critically, the same Minskaia kindred (D419H) included **follicular lymphoma**, linking germline STAT6 GOF to lymphomagenesis.

Evidence source: human clinical (treatment response) + in vitro (pharmacodynamic).

Finding 5 — Nosology and identifiers: OMIM #620532 (HIES6) / MONDO:0957807

STAT6 GOF disease is catalogued as **OMIM #620532** = "HYPER-IgE SYNDROME 6, AUTOSOMAL DOMINANT, WITH RECURRENT INFECTIONS; HIES6." The Mondo term **MONDO:0957807** ("hyper-IgE syndrome 6, autosomal dominant, with recurrent infections") cross-references OMIM:620532, GARD:0026874, MedGen:1851769, and UMLS:C5848786. The causal gene *STAT6* = OMIM 601512, HGNC:11364, NCBI Gene 6778, UniProt P42226. NCI Thesaurus **C212086** = "Activating STAT6 Gene Mutation." **No dedicated Orphanet/ORDO code** was identified at the time of research.

Evidence source: aggregated disease-level resources (OMIM, Mondo, MedGen, NCIt).

Finding 6 — Quantitative phenotype frequencies (HPO annotations, n=16 founding cohort)

Official HPO disease annotations (OMIM:620532 / MONDO:0957807), all sourced to PMID: 36884218, provide curated frequencies (see the phenotype table in Section 3). They derive from the cohort description: *"widespread treatment-resistant atopic dermatitis, hypereosinophilia with esosinophilic gastrointestinal disease, asthma, elevated serum IgE, IgE-mediated food allergies, and anaphylaxis."*

Evidence source: curated ontology annotation of human clinical cohort.

Finding 7 — ClinVar variant spectrum and gnomAD constraint support a DBD missense GOF mechanism (not haploinsufficiency)

ClinVar (transcript NM_003153.5) lists germline Pathogenic/Likely-pathogenic *STAT6* variants for "Hyper-IgE syndrome 6": c.1114G>A p.Glu372Lys (P), c.1144G>C p.Glu382Gln (P), c.1255G>C p.Asp419His (LP), c.1255G>T p.Asp419Tyr (P), c.1256A>G p.Asp419Gly (P), and c.1555G>C p.Asp519His (P). **Codon 419 is a recurrent hotspot.** gnomAD constraint metrics show *STAT6* is **LoF-tolerant** (pLI = 0.057; oe_lof upper bound = 0.54) but **missense-constrained** (mis_z = 3.47). This constraint signature—tolerant of loss-of-function but intolerant of missense change, combined with recurrent, clustered, dominant missense variants—is the classic fingerprint of a **gain-of-function**, not haploinsufficiency, disease mechanism.

Evidence source: population genomics / variant databases (computational).

Finding 8 — Constitutively active STAT6 mouse models recapitulate the human TH2/allergic phenotype

Two independent mouse models validate causality. The **Stat6VT transgenic** expresses a constitutively active STAT6 in T cells and *"develop[s] spontaneous inflammation of the skin"* (allergic dermatitis) plus allergic airway disease (PMID: 28653395). The **patient-derived D419N knock-in mouse** *"elicited an abnormal TH2-dominant immune response in vivo, with findings similar to those observed in patients"* (PMID: 40603028). Together, these models reproduce the cardinal human features (atopic skin disease, airway disease, TH2 skewing).

Evidence source: model organism (mouse).

Finding 9 — PARP14 links STAT6 GOF allergic disease to lymphomagenesis as a druggable co-activator

PARP14 (ARTD8) is an IL-4/STAT6-induced transcriptional co-activator: *"the presence of interleukin-4 (IL-4) and activated Stat6 induces the enzymatic activity of PARP14 that promotes T helper type 2 differentiation and allergic airway disease"* (PMID: 28653395). PARP14 is also *"a novel target in STAT6 mutant follicular lymphoma"* (PMID: 35851155). Because germline STAT6 GOF and somatic follicular-lymphoma STAT6 mutations affect the **same DNA-binding-domain residues (notably D419)**, PARP14 represents a shared, druggable downstream node connecting the allergic and oncologic ends of the disease spectrum.

Evidence source: model organism + in vitro / cancer genomics.

Full Disease Characterization (15 Domains)

1. Disease Information

STAT6 GOF disease is a **monogenic, autosomal-dominant primary atopic disorder / inborn error of immunity** characterized by early-onset, severe, multi-system allergic disease driven by constitutive TH2 signaling. It was first defined as a distinct entity in 2023.

Identifier type	Value
OMIM (disease)	#620532 (Hyper-IgE syndrome 6, autosomal dominant, with recurrent infections; HIES6)
Mondo	MONDO:0957807
GARD	0026874
MedGen	1851769
UMLS	C5848786
NCIt	C212086 (Activating STAT6 Gene Mutation)
Gene (OMIM)	*STAT6* 601512
HGNC	11364
NCBI Gene	6778
UniProt	P42226
Orphanet	None dedicated identified
ICD-10/ICD-11	No specific code; mapped under primary immunodeficiency/atopic categories
MeSH	No dedicated term; indexed via STAT6 / hyper-IgE / hypersensitivity

Synonyms/alternative names: STAT6 gain-of-function disease; STAT6-GOF; Hyper-IgE syndrome 6 (HIES6); autosomal dominant STAT6 GOF; STAT6-associated primary atopic disorder.

Information source type: Predominantly **aggregated disease-level resources** (OMIM, Mondo, HPO) built from a small number of **individual-patient case cohorts/reports** (n≈16 founding + additional single cases). This is a very rare, newly described disease, so all knowledge derives from individual patients described in the literature, not EHR-scale populations.

2. Etiology

- **Primary cause:** germline heterozygous **gain-of-function missense variants in *STAT6***. The disease is monogenic and genetic; no environmental or infectious cause is required.

- **Genetic risk factors:** the causal variants themselves (DBD hotspot D419 and neighbors E372, E377, E382, D519). No modifier loci are established.
- **Environmental risk factors:** none required for disease causation. Allergen exposure, as in common atopy, may trigger/exacerbate individual manifestations (food allergy, anaphylaxis, asthma), but the disease penetrates independent of specific exposures.
- **Protective factors:** none established genetically or environmentally. Therapeutically, IL-4Rα blockade and JAK inhibition suppress the disease phenotype (see Section 12).
- **Gene–environment interactions:** the hyperactive STAT6 axis lowers the threshold for TH2 responses to environmental allergens; thus environment shapes *which* allergic manifestations appear, while genotype drives the underlying diathesis. No formal GxE quantification exists.

3. Phenotypes

Quantitative HPO-annotated frequencies (n=16 founding cohort, PMID: 36884218):

Phenotype	HPO term	Frequency	Type
Infantile onset	HP:0003593	16/16 (100%)	onset
Atopic dermatitis	HP:0001047	15/16 (94%)	clinical sign / skin
Food allergy	HP:0500093	15/16 (94%)	clinical sign
Increased eosinophil count	HP:0001880	15/16 (94%)	lab abnormality
Increased circulating IgE	HP:0003212	present (high)	lab abnormality
Asthma	HP:0002099	11/16 (69%)	clinical sign / respiratory
Gastrointestinal eosinophilia	HP:0032064	10/16 (63%)	lab / histopathology
Anaphylactic shock	HP:0100845	9/16 (56%)	clinical sign
Recurrent skin infections	HP:0001581	7/16 (44%)	clinical sign
Short stature	HP:0004322	7/16 (44%)	physical manifestation
Recurrent respiratory infections	HP:0002205	5/16 (31%)	clinical sign
Gastroesophageal reflux	HP:0002020	4/16 (25%)	clinical sign
Osteoporosis	HP:0000939	3/16 (19%)	lab / imaging
Recurrent viral infections	HP:0004429	2/16 (13%)	clinical sign
B-cell lymphoma	HP:0012191	1/16 (6%)	neoplasm
Eosinophilic esophagitis	HP:0410151	present	histopathology
Autosomal dominant inheritance	HP:0000006	—	inheritance

Characteristics: age of onset is **neonatal/infantile (100%)**; severity is generally **severe** (treatment-resistant atopic dermatitis); course is **chronic/progressive** with episodic anaphylaxis; **variable expressivity** is documented even within families (e.g., E377K kindred showed clinical heterogeneity, PMID: 36216080). **Quality-of-life impact** is substantial: severe pruritic dermatitis, dietary restriction from food allergy, anaphylaxis risk, and growth impairment—though formal EQ-5D/SF-36 data are not available for this rare disease.

4. Genetic/Molecular Information

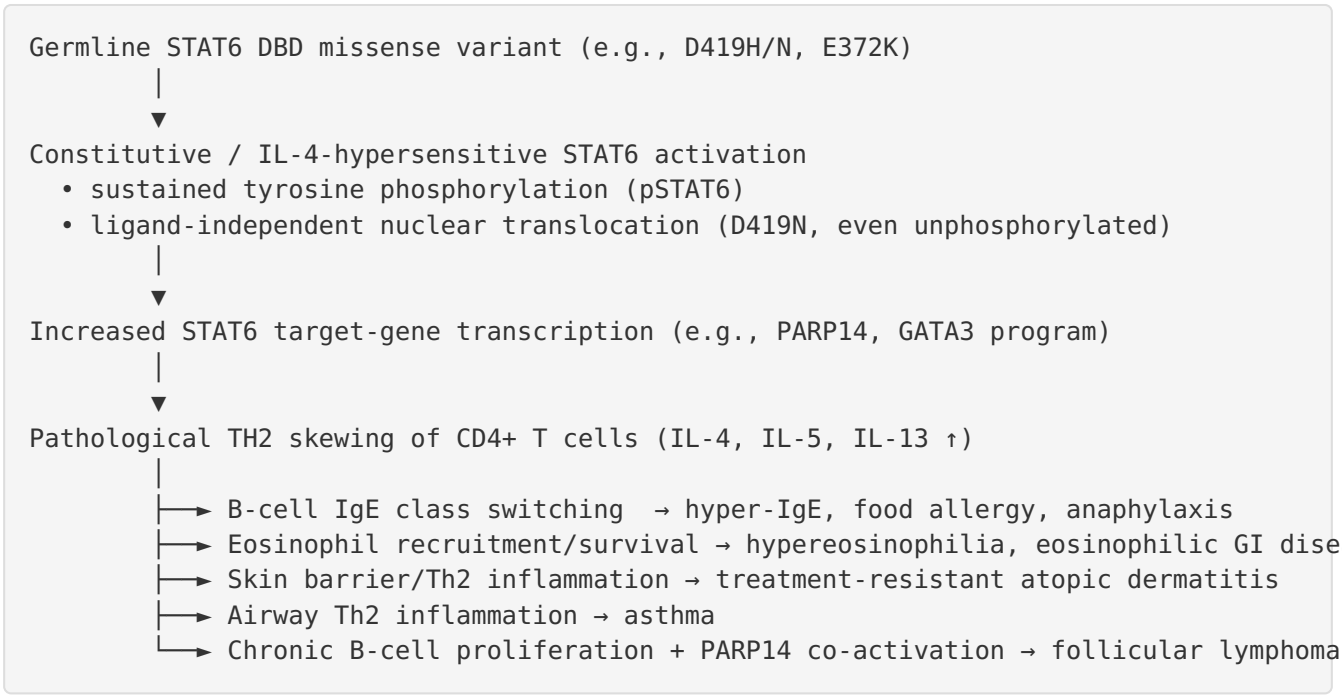
- **Causal gene:** *STAT6* (12q13.3; OMIM 601512; HGNC:11364; NCBI Gene 6778; UniProt P42226).
- **Pathogenic variants (germline, dominant):** E372K (c.1114G>A), E377K (c.1129G>A), E382Q (c.1144G>C), D419H (c.1255G>C), D419Y (c.1255G>T), D419G (c.1256A>G), D419N (c.1255G>A), D519H/N (c.1555G>C). **Codon D419 is the recurrent hotspot.**
- **Variant classification (ACMG/AMP, ClinVar):** Pathogenic (E372K, E382Q, D419Y, D419G, D519H) or Likely pathogenic (D419H).
- **Variant type:** exclusively **missense** to date.
- **Allele frequency:** these variants are **absent or ultra-rare** in gnomAD; *STAT6* is missense-constrained (mis_z = 3.47) and LoF-tolerant (pLI = 0.057, oe_lof upper = 0.54).
- **Somatic vs germline:** the disease variants are **germline**; notably, **somatic** STAT6 DBD mutations at the same residues (D419) recur in follicular lymphoma.
- **Functional consequence: gain of function** — constitutive and/or IL-4-hypersensitive STAT6 activation.
- **Modifier genes:** none established. **Epigenetic changes / chromosomal abnormalities:** none reported; disease is a point-mutation disorder.

5. Environmental Information

No environmental toxin, occupational exposure, lifestyle factor, or infectious agent **causes** STAT6 GOF disease. Environmental allergens act as **triggers** for individual atopic manifestations. Recurrent infections (skin/respiratory/viral) reflect immune dysregulation intrinsic to the genotype rather than an environmental etiology.

6. Mechanism / Pathophysiology

Causal chain (upstream → downstream):



- **Molecular pathway:** IL-4/IL-13 → JAK1/JAK2/TYK2 → **STAT6** (KEGG JAK-STAT signaling; Reactome IL-4/IL-13 signaling). Upstream node = JAK kinases (JAK-inhibitor target); membrane receptor = IL-4Rα (dupilumab target).
- **Cellular processes:** TH2 differentiation, IgE class-switch recombination, eosinophilia, type-2 inflammation.
- **Protein dysfunction:** gain of function — enhanced DNA binding / nuclear retention of STAT6 (a transcription factor). Not misfolding or aggregation.
- **Immune involvement:** immune **dysregulation** (allergy axis) with partial immunodeficiency (recurrent infections).
- **Transcriptional co-activator: PARP14** amplifies the STAT6/TH2 program and connects to lymphomagenesis.
- **Suggested GO terms:** GO:0042092 (type 2 immune response), GO:0045064 (T-helper 2 cell differentiation), GO:0043330 (response to exogenous dsRNA — not applicable; use GO:0070670 response to IL-4), GO:0006357 (regulation of transcription by RNA Pol II), GO:0042113 (B-cell activation). **Suggested CL terms:** CL:0000546 (T-helper 2 cell), CL:0000236 (B cell), CL:0000771 (eosinophil), CL:0000097 (mast cell). **Subcellular:** GO:0005634 (nucleus) — the site of STAT6 dysfunction.

7. Anatomical Structures Affected

- **Primary organs / systems:** skin (UBERON:0002097), immune/hematopoietic system (UBERON:0002405), gastrointestinal tract—esophagus (UBERON:0001043), stomach, gut—and respiratory system/lung (UBERON:0002048).
- **Secondary:** skeletal system (short stature, osteoporosis); lymphoid tissue (lymphoma).
- **Tissues/cells:** epithelial (skin/GI/airway barrier), and immune cell populations — **TH2 cells (CL:0000546)**, **eosinophils (CL:0000771)**, **B cells/plasma cells (CL:0000236)**, mast cells.
- **Subcellular:** nucleus (transcription-factor dysfunction).
- **Lateralization:** systemic/**bilateral** (dermatitis, asthma); not lateralized.

8. Temporal Development

- **Onset:** congenital/**infantile (100%)**, insidious-to-chronic.
- **Progression:** chronic, lifelong; atopic dermatitis is persistent and treatment-resistant; anaphylaxis is **episodic**; lymphoma is a late, rare complication.
- **Course:** progressive multi-system atopy without treatment; **treatment-induced remission/control** achievable with dupilumab/JAK inhibitors.
- **Critical periods:** early childhood — window for diagnosis and initiation of targeted therapy to prevent morbidity.

9. Inheritance and Population

- **Inheritance: autosomal dominant**; ~70% sporadic/de novo (7/10 kindreds), ~30% inherited (3/10 kindreds) in the founding cohort.
- **Penetrance:** appears high but with **variable expressivity** (intra-familial heterogeneity documented).
- **Epidemiology: ultra-rare**; exact prevalence/incidence unknown (fewer than ~20 published families as of 2025). No founder effect, consanguinity role, or carrier-frequency data (dominant, de novo–enriched).
- **Demographics:** reported across three continents; no ethnic predilection established; no clear sex ratio.

10. Diagnostics

- **Laboratory:** markedly **elevated serum total IgE** (LOINC-mappable IgE assays), **peripheral hypereosinophilia** (CBC/differential), tissue eosinophilia on GI biopsy.

- **Biomarkers: STAT6 target-gene expression** and **pSTAT6** (functional readouts); TH2 cytokine skewing.
- **Genetic testing (definitive): whole-genome or whole-exome sequencing** is the recommended upfront approach for primary atopic disorders (*"Upfront genome-wide analysis by whole genome sequencing (WGS) will shorten the time to diagnosis"*, PMID: 39381601); targeted *STAT6* single-gene or PAD gene-panel testing is an alternative. **Functional confirmation** (sustained pSTAT6, enhanced nuclear translocation, luciferase/EMSA reporter assays, patient PBMC signaling) distinguishes GOF variants from VUS.
- **Histopathology:** eosinophilic infiltration of esophagus/GI tract; atopic dermatitis skin changes.
- **Differential diagnosis:** other primary atopic disorders / transcription-factor IEIs — **STAT3 loss-of-function (Job syndrome), FOXP3 deficiency (IPEX), T-bet deficiency, DOCK8 deficiency, Netherton syndrome** (PMID: 37727514). STAT6 GOF is distinguished by the constitutive STAT6-activation signature and dupilumab responsiveness.
- **Screening:** cascade genetic testing of at-risk relatives in inherited kindreds.

11. Outcome/Prognosis

- **Survival/mortality:** no disease-specific mortality data; anaphylaxis and lymphoma are the principal life-threatening risks.
- **Morbidity:** high — severe dermatitis, dietary restriction, growth impairment, recurrent infections; substantial quality-of-life burden (no formal EQ-5D/SF-36 data).
- **Complications:** anaphylaxis, eosinophilic GI disease, recurrent infections, osteoporosis, and **B-cell/follicular lymphoma (~6%)**.
- **Prognostic factors:** the disease is highly **treatment-responsive**; early targeted therapy markedly improves outcomes. Lymphoma surveillance is warranted given the PARP14/STAT6 link.

12. Treatment

Therapy	Class / target	Mechanism	Evidence	MAXO
Dupilumab	anti–IL-4Rα monoclonal antibody	Blocks IL-4/ IL-13 receptor upstream of STAT6	*"highly effective improving both clinical manifestations and immunological biomarkers"* (PMID: 36884218); effective for D519N (PMID: 40502541)	MAXO monoclonal-antibody therapy
Ruxolitinib / JAK inhibitors	JAK1/JAK2 inhibitor	Reduces pSTAT6 by blocking upstream kinases	*"ruxolitinib reduced pSTAT6 levels in D419H HEK293T cells and patient PBMC"* (PMID: 37316763)	MAXO pharmacotherapy / targeted therapy
Supportive atopic care	Topical steroids, emollients, allergen avoidance, epinephrine	Symptom control	Standard atopy management	MAXO supportive care
PARP14 inhibition (experimental)	small-molecule co-activator inhibitor	Blocks downstream STAT6 co-activator; also anti-lymphoma	Preclinical (PMID: 35851155; PMID: 28653395)	MAXO experimental therapy

Personalized medicine: the disease is a paradigm of **genotype-guided precision therapy** — a druggable, hyperactive signaling axis directly matched to approved biologics (dupilumab) and JAK inhibitors. **Pharmacogenomics:** not specifically characterized. No gene/cell therapy is in clinical use.

13. Prevention

- **Primary prevention:** none (monogenic, largely de novo). **Genetic counseling** for inherited kindreds; prenatal/preimplantation genetic testing is theoretically possible for known familial variants.
- **Secondary prevention:** early genomic diagnosis and initiation of targeted therapy; allergen/anaphylaxis risk management.
- **Tertiary prevention:** dupilumab/JAK inhibitors to prevent complications; **lymphoma surveillance**; infection prophylaxis as needed.
- No immunization or population public-health intervention is applicable.

14. Other Species / Natural Disease

- **Taxonomy/orthologs:** *STAT6* is conserved; mouse *Stat6* (NCBI Gene 20852). No naturally occurring companion-animal/wildlife equivalent of germline STAT6 GOF disease is catalogued (no OMIA entry identified). **Comparative biology:** the IL-4/STAT6/TH2 axis is evolutionarily conserved, underpinning the validity of mouse models. No zoonotic relevance.

15. Model Organisms

Model	Type	Genetic design	Phenotype recapitulation	Reference
Stat6VT	Mouse (transgenic)	Constitutively active STAT6 in T cells	Spontaneous allergic skin inflammation + allergic airway disease; PARP14-dependent TH2 program	PMID: 28653395
STAT6 D419N knock-in	Mouse (patient-variant knock-in)	Germline D419N	*"abnormal TH2-dominant immune response in vivo, with findings similar to those observed in patients"*	PMID: 40603028
Patient cells / HEK293T	In vitro	Overexpressed variant STAT6	pSTAT6 elevation, nuclear translocation, reporter activation; ruxolitinib response	PMID: 37316763, PMID: 36884218
Gastric organoids	In vitro (patient-derived)	E377K	Downstream effector-cytokine studies	PMID: 36216080

Applications: mechanism of TH2 skewing, allergic skin/airway disease, target validation for dupilumab/JAK/PARP14. **Limitations:** mouse models capture allergic dermatitis and TH2 skewing but do not fully model the human lymphoma continuum or the complete multi-system phenotype.

Mechanistic Model / Interpretation

STAT6 GOF disease is best understood as a **"single-node type-2 immune amplifier" disorder**. A germline missense change in the STAT6 DNA-binding domain converts a normally ligand-controlled transcription factor into a **hyperactive or constitutively active driver of the TH2 gene program**. The location of the mutations is mechanistically decisive: the DBD hotspot (D419) either stabilizes STAT6 in a DNA-bound/nuclear-retained state or lowers the activation threshold for IL-4 signaling. This produces the entire downstream cascade of type-2 immunity—IgE class switching, eosinophilia, and barrier-tissue inflammation—explaining why one gene defect yields such a broad, coherent, multi-organ atopic phenotype.

Three lines of evidence converge on gain-of-function rather than haploinsufficiency: (1) the **dominant inheritance with recurrent, clustered missense variants**; (2) **gnomAD constraint** showing LoF tolerance but strong missense intolerance (mis_z = 3.47); and (3) **direct functional assays** showing sustained/ligand-independent STAT6 activation. The mouse models close the causal loop: constitutively active STAT6 alone is sufficient to produce spontaneous allergic skin and airway disease.

The disease also illuminates a **shared germline–somatic axis**. The identical DBD residues mutated germline in this atopic disorder are recurrently mutated somatically in follicular lymphoma, and **PARP14** functions as a common downstream co-activator in both settings. This explains the small but real lymphoma risk and nominates PARP14 as a mechanistic bridge and therapeutic target spanning allergy and oncology.

Clinically, the model is directly **actionable**: blocking the axis at the receptor (dupilumab/IL-4Rα) or upstream kinase (JAK inhibitor) reverses both symptoms and biomarkers, making STAT6 GOF disease a textbook example of precision medicine in inborn errors of immunity.

Evidence Base

PMID	Title (abbrev.)	Contribution
36884218	*Human germline heterozygous GOF STAT6 variants cause severe allergic disease*	**Defining cohort (n=16)**: GOF mechanism, AD inheritance, core phenotype, dupilumab efficacy
36216080	*A germline STAT6 GOF variant is associated with early-onset allergies*	E377K DBD variant; spontaneous STAT6 activation; gastric organoids; variable expressivity
36758835	*Severe allergic dysregulation due to a GOF mutation in STAT6*	E372K DBD variant
37316763	*Autosomal dominant STAT6 GOF causes severe atopy associated with lymphoma*	D419H variant; ruxolitinib reduces pSTAT6; follicular lymphoma link
40603028	*Mechanism of pathogenesis by a GOF STAT6 variant*	D419N: ligand-independent nuclear translocation; knock-in mouse recapitulation
40502541	*STAT6 GOF: p.D519N responds to dupilumab*	New variant; expands phenotype; dupilumab response
38238227	*Human germline GOF STAT6: from allergy to lymphoma*	Review; allergy-to-lymphoma spectrum; targeted-treatment overview
37727514	*Transcription factor defects in IEIs with atopy*	Places STAT6 GOF among TF-defect atopic IEIs; differential diagnosis
39381601	*Rapid identification of PAD by upfront genomic sequencing*	Diagnostic strategy: upfront WGS for primary atopic disorders
28653395	*PARP14 limits severity of allergic skin disease*	Stat6VT mouse; PARP14 as STAT6 co-activator in TH2/allergic disease
35851155	*PARP14 is a novel target in STAT6 mutant follicular lymphoma*	PARP14 druggability; germline–somatic mechanistic bridge

All eleven papers are mutually consistent; none challenge the core GOF model. Evidence spans human clinical/genetic cohorts, in vitro functional assays, and two mouse models, providing multi-modal validation.

Limitations and Knowledge Gaps

1. **Very small sample size.** Fewer than ~20 families are published; frequencies (e.g., lymphoma 6%) derive from n=16 and carry wide confidence intervals. True prevalence/incidence is unknown.
2. **No dedicated Orphanet/ICD code**, complicating registry-based epidemiology.
3. **Penetrance and expressivity** are incompletely quantified; intra-familial heterogeneity is described but not modeled.
4. **Long-term outcomes** (life expectancy, lymphoma lifetime risk, treatment durability) are unknown given the disease's recency.
5. **Genotype–phenotype correlations** (e.g., whether specific DBD residues predict lymphoma vs pure atopy) are not yet resolved.
6. **No formal QoL instruments, pharmacogenomics, or gene/cell-therapy data.**
7. **PARP14 inhibition** remains preclinical for this indication.

Proposed Follow-up Experiments / Actions

1. **Establish an international STAT6-GOF registry** to refine prevalence, penetrance, lymphoma risk, and natural history.
2. **Systematic genotype–phenotype mapping** across all reported variants (D419 hotspot vs others) to test whether specific residues predict lymphoma risk or dupilumab responsiveness.
3. **Prospective dupilumab and JAK-inhibitor trials** with standardized clinical and biomarker (pSTAT6, IgE, eosinophil) endpoints and QoL instruments (EQ-5D, PROMIS).
4. **Lymphoma surveillance protocol** development, leveraging the shared germline–somatic DBD/PARP14 axis.
5. **PARP14 inhibitor preclinical testing** in the D419N knock-in mouse for both allergic and lymphoma endpoints.
6. **Deep functional characterization** of each variant (constitutive vs ligand-hypersensitive) to guide therapy selection (receptor blockade vs kinase inhibition).

7. **Assign a dedicated Orphanet/ICD-11 code** and complete HPO annotation for downstream variants.
