

Atopy as Immune Dysregulation: Offender Genes and Targets



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Allergic diseases are a heterogeneous group of disorders resulting from exaggerated type 2 inflammation. Although typically viewed as polygenic multifactorial disorders caused by the interaction of several genes with the environment, we have come to appreciate that allergic diseases can also be caused by monogenic variants affecting the immune system and the skin epithelial barrier. Through a myriad of genetic association studies and high-throughput sequencing tools, many monogenic and polygenic culprits of allergic diseases have been described. Identifying the genetic causes of atopy has shaped our understanding of how these conditions occur and how they may be treated and even prevented. Precision diagnostic tools and therapies that address the specific molecular pathways

implicated in allergic inflammation provide exciting opportunities to improve our care for patients across the field of allergy and immunology. Here, we highlight offender genes implicated in polygenic and monogenic allergic diseases and list targeted therapeutic approaches that address these disrupted pathways. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:1737-56)

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INTRODUCTION

Atopy is defined as the genetic tendency to develop allergic diseases,^{1,2} a group of conditions characterized by pathogenic type 2 inflammation.^{2,3} Often described as reaching epidemic proportions,²⁻⁴ allergic diseases are estimated to affect approximately 20% to 30% of the global population.^{5,6} These are chronic conditions that disproportionately affect youths⁴ resulting in reduced quality of life, increased morbidity and mortality, and considerable socioeconomic burden on the affected individuals and their families.⁶ Whereas allergic conditions are typically multifactorial and influenced by genetic susceptibility, allergic immune dysregulation can also be a manifestation of an underlying inborn error of immunity (IEI) caused by a damaging variant in a single gene. Therefore, providers in both allergy and clinical immunology face allergic inflammation in their practice and seek to understand, prevent, and treat it.

To design targeted therapeutics, in-depth knowledge of the defective immune pathways in allergy is required.⁷ Remarkable and ongoing advances in genetic sequencing tools have facilitated the identification of polygenic susceptibility loci^{8,9} and monogenic variants^{7,10} for allergic diseases, helping us to discover targetable cellular and molecular pathways (Figure 1).¹¹ This has led to an exciting era of precision-based approaches for both monogenic atopic disorders and common allergic conditions. In this review, we highlight several offender genes implicated in polygenic (Table I) and monogenic (Table II) allergic diseases, categorized by mechanism of pathogenicity, and list targeted therapeutic approaches that address disrupted pathways.

Epithelial barrier disruption

Atopic dermatitis (AD) is an itchy inflammatory skin disorder that waxes and wanes, is often diagnosed in early childhood, and is associated with atopic comorbidities such as asthma and allergic rhinitis. The sequential progression to asthma, allergic rhinitis, and other allergic illnesses such as food allergies and

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Abbreviations used

AD- Atopic dermatitis
ADGRE2- adhesion G protein-coupled receptor E2
Arp2/3- Actin-related protein 2/3
ASCT2- Alanine serine cysteine-preferring transporter 2
BCL10- B-cell CLL/lymphoma 10
CADINS- CARD11-associated atopy with dominant interference of NF- κ B signaling
CARD- Caspase recruitment domain
CBM- CARD11–BCL10–MALT1
CDC42- Cell division cycle 42
DHR- Drug hypersensitivity reaction
DN- Dominant negative
DOCK8- Dedicator of cytokinesis 8
FLG- Filaggrin
GlcNAc- N-Acetylglucosamine
GLUT1- Glucose transporter 1
GOF- Gain of function
GPCR- G protein-coupled receptor
GWAS- Genome-wide association studies
HLA- Human leukocyte antigen
HSCT- Hematopoietic stem cell transplantation
IEI- Inborn error of immunity
JAK- Janus kinase
JNK- c-Jun N-terminal kinase
KIR- Killer immunoglobulin-like receptors
LOF- Loss of function
MALT1- Mucosa-associated lymphoid tissue lymphoma translocation gene 1
MHC- Major histocompatibility complex
MRGPRX2- Mas-related G protein-coupled receptor-X2
mTORC1- Mammalian target of rapamycin complex 1
NF- κ B- Nuclear factor- κ B
NGS- Next-generation sequencing
PGM3- phosphoglucomutase 3
SCID- Severe combined immune deficiency
SNP- Single nucleotide polymorphism
STAT- Signal transducer and activator of transcription
TCR- T cell receptor
TSLP- Thymic stromal lymphopoietin
WAS- Wiskott-Aldrich syndrome
WASp- Wiskott–Aldrich Syndrome protein
WIP- WASp-interacting protein

eosinophilic esophagitis from AD describes the atopic march.^{164,165} Atopic dermatitis pathophysiology is strongly linked to epithelial barrier defects, genetic predisposition, and other environmental and immunologic factors.^{165,166} All contribute to an individual's susceptibility to systemic allergen sensitization and atopic march trajectory.^{166–168} This positions AD as a paradigm of barrier dysfunction and atopy.

Several studies demonstrated a genetic risk associated with AD, with heritability estimated to be about 84%.^{169–171} The most commonly reported genetic variants associated with skin barrier dysfunction are loss-of-function (LOF) variants in filaggrin (*FLG*) (Table II).¹⁷⁰ *FLG* encodes a critical skin barrier protein, and *FLG* LOF has been associated with the increased prevalence and persistence of AD.^{45,172–174,175–177} *FLG* is translated as profilaggrin, a 400-kDa polypeptide that is posttranslationally cleaved into FLG monomers. The FLG protein is expressed by keratinocytes during the late stages of terminal differentiation, where it has a multifunctional role in skin barrier

function: FLG monomers aggregate and align keratin bundles, strengthening the stratum corneum, and FLG breakdown products contribute to epidermal hydration and barrier function.¹⁷⁸

Approximately 500 *FLG* LOF variants have been identified by the gnomAD (genome aggregation database), an international aggregate database of exome and genome sequencing data supported by the Broad Institute.¹⁷⁹ Several studies have shown that the prevalence of *FLG* LOF variants vary by ethnicity, as do the frequency of variation of the *FLG* gene.^{45,172,173,180–182} In addition to FLG, variants in other molecules comprising the skin epithelial barrier have been associated with AD.^{180,183–185} Finally, type 2 cytokines such as IL-4, IL-13, thymic stromal lymphopoietin, and IL-33 can have a direct effect on diminishing FLG production such that genetic variation in these cytokines could have a profound effect on skin barrier function as well.^{168,186–189} All *FLG* LOF mutations do not cause a complete loss of profilaggrin protein; therefore, a complete absence of FLG does not occur in the skin barrier.¹⁹⁰ It is therefore likely that diminished FLG, caused either by genetic variation or by more common processes such as elevated type 2 cytokines, may be a culprit in barrier dysfunction and allergic disease.

Further emphasizing the critical role of an intact skin barrier is that barrier defects can also occur in monogenic IEIs, as seen in Netherton syndrome, caused by biallelic LOF variants in *SPINK5*.^{41,191} Clinical manifestations include ichthyosiform erythroderma, trichorrhexis invaginata (or bamboo hair), and allergic immune dysregulation (Table II).⁴¹ Similarly, LOF variants in genes encoding desmosomal proteins cause monogenic disorders of ichthyosis and atopy.¹⁰ Desmosomes mediate cell–cell adhesion between keratinocytes and are crucial for epithelial barrier integrity.¹⁹² Loss of desmoglein-1¹⁹³ and desmoplakin³⁰ causes severe dermatitis, multiple allergies, and metabolic wasting (SAM syndrome).

Given the critical physiologic role of a healthy skin barrier, restoring barrier function through the use of emollients and moisturizers is important for managing both monogenic skin barrier defects and AD in the general population.⁴¹ Treatments targeting type 2 cytokines such as dupilumab have also been found to reverse AD-associated epidermal abnormalities.¹⁹⁴ Recent studies have implicated the T_H17 axis in ichthyosis; therapies blocking IL-17A and IL-12/IL-23 showed benefit in case reports of patients with Netherton syndrome and desmosomal deficiencies.^{26,31,195}

Cytokines and cytokine signaling defects

Cytokines and their corresponding signaling pathways are central to the initiation and perpetuation of allergic inflammation.¹⁹⁶ A plethora of genome-wide association studies (GWAS) and candidate gene studies over the years have identified single nucleotide polymorphisms (SNPs) in the genes encoding multiple cytokines (IL-4, IL-5, IL-13, IL-6, thymic stromal lymphopoietin, IL-10, and TGF- β), and cytokine receptors (IL-4 receptor α chain, IL-13 receptor α 1 chain, and IL-31 receptor α) as associated with a host of allergic diseases such as allergic rhinitis,^{197–202} allergic asthma,^{200,203–206} and AD,^{207–209} as well as elevated IgE levels.^{203,210} Leveraging this biological understanding, several therapeutics in the form of monoclonal antibodies have been developed to target these cytokines and their receptors (Table I). One example is IL-4 receptor α blocking antibody, dupilumab, which is used to treat several common allergic diseases such as allergic asthma²¹¹ and AD.²¹²

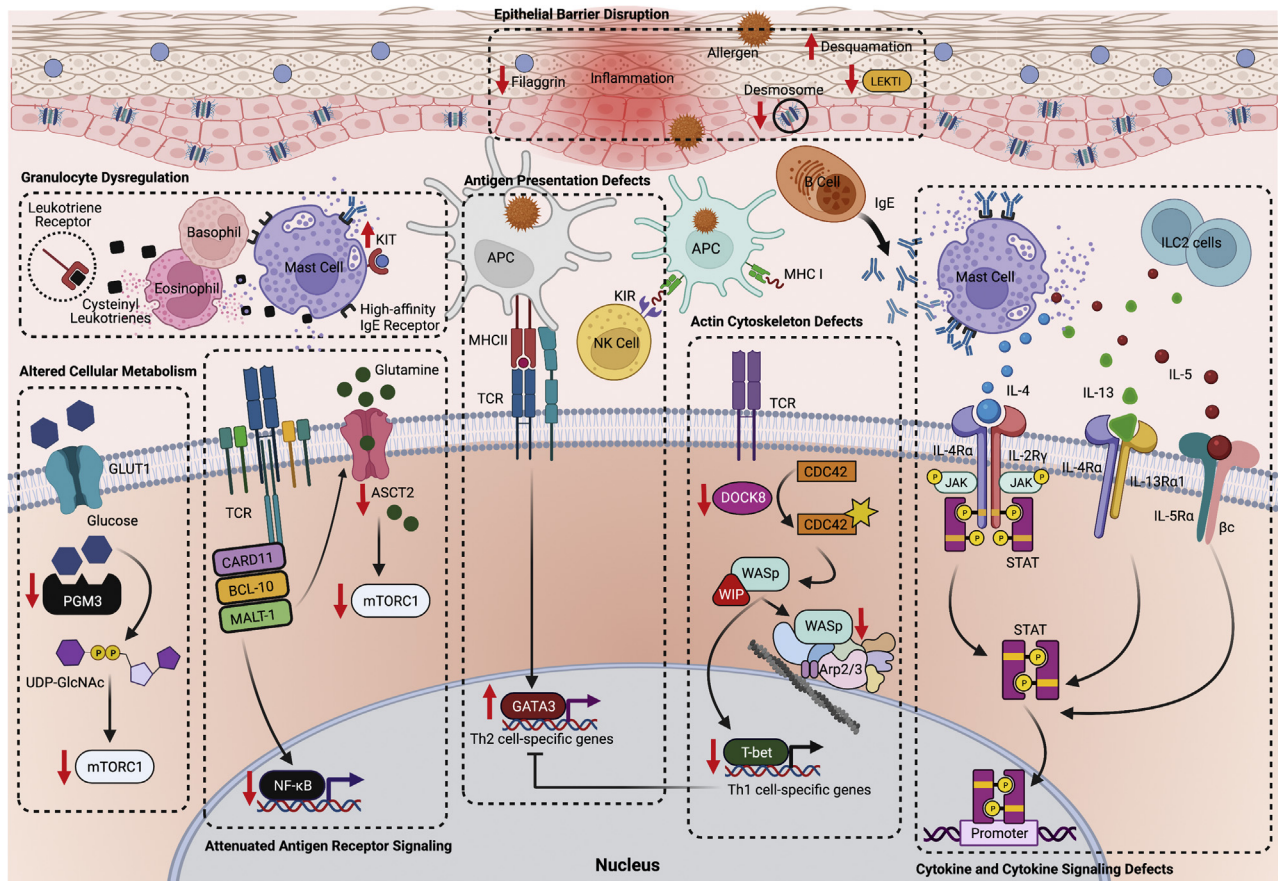


FIGURE 1. Schematic representation of key pathways and molecules involved in monogenic and polygenic allergic diseases. (The figure was created with BioRender.com [Shiz Aoki, Katya Shteyn, Ryan Marien], [Toronto, Ontario]). *Arp2/3*, actin-related protein 2/3; *ASCT2*, alanine, serine, cysteine-preferring transporter 2; *BCL10*, B-cell CLL/lymphoma 10; *CARD*, caspase recruitment domain; *CDC42*, cell division cycle 42; *DOCK8*, dedicator of cytokinesis 8; *GlcNAc*, N-acetylglucosamine; *GLUT1*, glucose transporter 1; *IL-13RA1*, IL-13 receptor α 1 chain; *JAK*, Janus kinase; *KIR*, killer immunoglobulin-like receptor; *MALT-1*, mucosa-associated lymphoid tissue lymphoma translocation gene 1; *MHC*, major histocompatibility complex; *mTORC1*, mammalian target of rapamycin complex 1; *NF- κ B*, nuclear factor- κ B; *NK*, natural killer; *PGM3*, phosphoglucomutase 3; *STAT*, signal transducer and activator of transcription; *TCR*, T cell receptor; *WASp*, Wiskott–Aldrich syndrome protein; *WIP*, WASp-interacting protein.

Mirroring these population-based insights into allergic disease, monogenic immune defects involving cytokine signaling pathways can result in severe allergic inflammation. This is elegantly demonstrated by single gene defects affecting Janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins.^{7,10,213} Binding of cytokines such as IL-4 and IL-13 to their receptors activates JAK proteins to phosphorylate and activate the STAT family of transcription factors. Both LOF and gain-of-function (GOF) variants in *STAT5* and *STAT3*, and GOF variants in *JAK1* and *STAT1* cause IEs with allergic features. One of the best described monogenic atopic disorders is autosomal dominant hyper-IgE syndrome (AD-HIES) or Job syndrome, caused by heterozygous dominant negative (DN) LOF of *STAT3*. Loss-of-function variants in *STAT3* and the upstream and downstream players in the *STAT3* pathway (eg, *ZNF341*, *DOCK8*, *IL6ST*, *IL6R*, and *ERBIN*) result in severe allergic diseases, eosinophilia, and markedly elevated IgE levels, together with other immunodeficiency features.⁷

More recently, Ma et al²¹⁴ described two cases of somatic heterozygous GOF variants in *STAT5B* within multiple hematopoietic lineages, with neonatal hypereosinophilia, AD, urticaria, and diarrhea. Because JAK1 is upstream of *STAT5B* in the signaling pathway, the oral JAK1/2 inhibitor ruxolitinib was used successfully to treat two patients with somatic GOF *STAT5B* variants as well as patients with JAK1 GOF⁸⁶ who were unresponsive to conventional treatment with oral corticosteroids, resulting in marked improvement of clinical symptoms and hypereosinophilia.⁸⁸

Interestingly, several GWAS studies have reported SNPs in *STAT5B* to be associated with risk of developing polygenic forms of allergic disease.^{215–221} As the JAK/STAT pathway's role in allergic inflammation becomes more evident, clinical trials have started testing JAK inhibitors to treat common allergic diseases in the hope of achieving higher efficacy and fewer side effects compared with corticosteroids. In 2019, a phase II study reported that topical ruxolitinib cream may serve as a preferred treatment for AD over topical corticosteroids, and certain JAK

TABLE I. Genes implicated in common allergic conditions that have a targeted therapy

Offender gene	Protein function ¹²	Associated allergic conditions ^{13,14}	Targeted therapy	Mechanism	Indications
<i>IL4R</i> (interleukin 4 receptor α)	Regulates IgE production and promotes differentiation of T _H 2 cells	Eosinophil counts, IgE levels, asthma, AR, AD ¹³	Dupilumab	Anti-IL-4 receptor α	(C): Moderate-severe eosinophilic asthma, moderate to severe AD, CRSwNP, EoE
<i>IL5</i> (interleukin 5)	Growth and differentiation factor for B cells and eosinophils Regulates eosinophil formation, maturation, recruitment, and survival	Eosinophil counts, asthma ¹³	Mepolizumab	Anti-IL-5	(C): Severe eosinophilic asthma, CRSwNP, EGPA, HES (CT): EoE ¹⁵
			Reslizumab	Anti-IL-5	(C): Severe eosinophilic asthma (CT): EoE ¹⁵
<i>IL5RA</i> (interleukin 5 receptor α)	Alpha chain of IL-5 receptor that binds IL-5	Eosinophil and basophil counts, HES ¹³	Benralizumab	Anti-IL-5 receptor α	(C): Severe eosinophilic asthma
<i>IL13</i> (interleukin 13)	Upregulates CD23 and major histocompatibility complex class II expression and promotes IgE isotype switching of B cells. Produced primarily by activated T _H 2 cells	IgE levels, asthma, AD, AR ¹³	Dupilumab	Anti-IL-4 receptor α	(C): Moderate-severe eosinophilic asthma, moderate-severe AD, CRSwNP, EoE
			Lebrikizumab	Anti-IL-13	(CT): Moderate-severe AD ¹⁶
			Tralokinumab	Anti-IL-13	(C): Moderate-severe AD
<i>TSLP</i> (thymic stromal lymphopoietin)	Promotes T _H 2 cell responses Contributes to pruritus in AD by activating cutaneous sensory neurons Induces release of T cell —attracting chemokines from monocytes and enhances maturation of CD11c(+) dendritic cells	Eosinophil and basophil counts, asthma, AD, EoE, CRSwNP, AR, EGPA ¹³	Tezepelumab	Anti-TSLP	(CT): Asthma, AD ¹⁴
<i>IL31RA</i> (interleukin 31 receptor α)	Involved in IL-31 signaling via activation of STAT3 and STAT5 Has a role in pruritus via overexpression of IL-31 receptors on sensory nerves	AD ¹⁷	Nemolizumab	Anti-IL-31 receptor α	(CT): Moderate-severe AD ¹⁴
<i>FCER1A</i> (high-affinity IgE receptor)	IgE receptor is initiator of allergic response. Binding of allergen to receptor-bound IgE leads to cell activation and release of mediators such as histamine	IgE levels ¹³	Omalizumab	Anti-IgE	(C): Moderate-severe allergic asthma, CSU, CRSwNP (CT): EoE ¹⁵

<i>JAK1/JAK2</i> (Janus kinase 1 and 2)	Protein-tyrosine kinases are involved in JAK-STAT pathway Key role in inflammatory response via IFN-alpha/beta, IFN-gamma, and cytokine signal transduction	JAK1: Eosinophil counts, AD ¹⁸ JAK2: Eosinophil counts, AD, AR, asthma, EoE ¹⁸	Ruxolitinib (topical)	JAK1,2 inhibitor	(C): AD
			Upadacitinib (oral)	JAK1 inhibitor	(C): Moderate-severe AD
			Baricitinib (oral)	JAK1,2 inhibitor	(CT): Severe AD ¹⁴
			Abrocitinib (oral)	JAK1 inhibitor	(CT): Severe AD ¹⁴
<i>PDE4D</i> (phosphodiesterase 4D)	Metabolizes cyclic adenosine monophosphate inside inflammatory cells Regulates smooth muscle contractility and inflammation ¹⁹	Asthma ²⁰	Crisaborole (topical)	PDE4 inhibitor	(C) AD
<i>CYSLTR1</i> (cysteinyl leukotriene 1 receptor)	Receptor for cysteinyl leukotrienes Activation of receptor results in contraction and proliferation of bronchial smooth muscle cells, eosinophil migration, and damage to pulmonary mucus layer in lung	Asthma, ²¹ AD ²²	CHF 6001 (inhaled)	PDE4 inhibitor	(CT): Asthma ¹⁹
			Montelukast	Leukotriene Receptor Antagonist	(C): Asthma, AR (CT): AD, CSU ^{23,24}
			Zafirlukast	Leukotriene Receptor Antagonist	(C): Asthma (CT): CSU ²⁴
			Pranlukast	Leukotriene Receptor Antagonist	(C): Asthma, AR

AD, atopic dermatitis; AR, allergic rhinitis; C, approved clinical indication; *CRSwNP* = chronic rhinosinusitis with nasal polyposis; CSU, chronic spontaneous urticaria; CT, clinical trial; *EGPA*, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; HES, hypereosinophilic syndrome; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

TABLE II. Monogenic allergic disorders and their targeted treatments

Gene	Protein function	Inheritance	Allergic and other key manifestations	Treatment strategies†
Epithelial barrier disruption				
<i>DSG1</i>	Desmosomal protein mainly expressed in epidermis and mucosa ²⁵	Autosomal recessive, LOF	Severe dermatitis, FA, ↑IgE level, metabolic wasting	Secukinumab ^{26,27}
<i>CDSN</i>	Component of corneodesmosomes in epidermis and hair follicles, which helps to maintain epidermal barrier ²⁸	Autosomal recessive, LOF	Erythroderma, FA, ↑IgE level, diffuse ichthyosis, peeling skin	Supportive treatment
<i>DSP</i>	Desmosomal protein, anchors intermediate filaments to desmosomal plaques ²⁹	Autosomal dominant, LOF	Severe dermatitis, erythroderma, FA, eosinophilia, ↑IgE level, metabolic wasting ³⁰	IVIG plus systemic acitretin ³⁰ Ustekinumab ³¹
<i>SPINK5</i>	Protease inhibitor crucial to epithelial tissue homeostasis and epidermal differentiation ³²	Autosomal recessive, LOF	Erythroderma, AR, asthma, FA, angioedema, EGID, eosinophilia, ↑IgE level, trichorrhexis invaginatam, ichthyosis ³³	IVIG ³⁴ Dupilumab ³⁵⁻³⁹ Omalizumab ⁴⁰ Ustekinumab ⁴¹ Secukinumab ⁴² Ixekezumab ⁴³ Infliximab ⁴⁴
<i>FLG</i>	Keratin-aggregating protein in stratum corneum of epidermis, crucial for epidermal structure and skin barrier function ⁴⁵	Autosomal dominant, or autosomal recessive, LOF	AD, ichthyosis vulgaris ⁴⁶	Oral L-histidine (pilot clinical studies) ^{47,48}
Cytokines and cytokine signaling defects				
<i>STAT3 (LOF)</i>	Acts as signal transducer for many cytokines and growth factors through cytoplasm and as transcription factor for many inflammatory, cell growth, ⁴⁹ and cancer-related genes in nucleus ⁵⁰	Autosomal dominant, DN LOF	Eczema, EGID, FA, eosinophilia, ↑IgE level, infections, connective tissue abnormalities, lymphomas ⁵¹	HSCT ^{52,53} Omalizumab ^{54,55} Dupilumab ⁵⁶ Reslizumab Benralizumab Mepolizumab ³¹⁴
<i>ERBB2IP</i>	Negative regulator of transforming growth factor (TGF)-β through interaction with SMAD proteins, which are important signal transducers for TGF-β receptors ⁵⁷	Autosomal dominant, LOF	Eczema, FA, EGID, eosinophilia, ↑IgE level, connective tissue abnormalities	Dupilumab ³¹⁵
<i>IL6ST</i>	Signal transducer of IL-6 receptor complex, important in JAK/STAT signaling pathway Binds to IL-6Rα and other receptor complexes including OSM receptor, LIF receptor, CNTF receptor, and IL-11Rα ⁵⁸	Autosomal recessive, LOF or autosomal dominant, DN LOF	Eczema, FA, eosinophilia, ↑IgE level, infections, connective tissue abnormalities ⁵⁹	Supportive treatment ⁵⁸
<i>ZNF341</i>	Transcription factor that promotes STAT3 transcription by binding STAT promoter ⁶⁰	Autosomal recessive, LOF	Eczema, eosinophilia, ↑IgE level, infections, connective tissue abnormalities ⁶⁰	Supportive treatment ⁶⁰ Dupilumab ⁵⁶
<i>TGFBR1</i>	Receptor for TGF-β cytokines, which have roles in immune tolerance, cell cycle arrest, and wound healing ⁶¹	Autosomal dominant	Eczema, asthma, AR, EGID, FA eosinophilia, ↑IgE level, vascular and connective tissue abnormalities ⁶²	Supportive treatment
<i>TGFBR2</i>	Receptor for TGF-β cytokines, which have roles in immune tolerance, cell cycle arrest, and wound healing ⁶¹	Autosomal dominant	Eczema, asthma, AR, EGID, FA eosinophilia, ↑IgE level, vascular and connective tissue abnormalities ⁶²	Supportive treatment

<i>IL6R</i>	Component the receptor for IL-6, a cytokine that regulates a multitude of immune functions including hemopoiesis, inflammation, and acute phase response ⁶³	Autosomal recessive, LOF	Eczema, eosinophilia, ↑IgE level, infections ⁶⁴	Supportive treatment ⁶⁴
<i>STAT5B (LOF)</i>	Acts as a signal transducer for many cytokines and growth factors through cytoplasm ⁶⁵ and as a transcription factor for expression of genes such as <i>FOXP3</i> , <i>CD25</i> , and <i>IGF1</i> ⁶⁶	Autosomal dominant or autosomal recessive, LOF	Eczema, ↑IgE level, growth failure, autoimmunity	Supportive treatment Cyclosporine therapy for eczema ⁶⁷
<i>IL2RA</i>	Component of IL-2 receptor, also known as CD25 CD25 expression on regulatory T cells is crucial for sequestering IL-2 and maintaining immune tolerance ⁶⁸	Autosomal recessive, LOF	Eczema, severe autoimmune enteritis, viral infections, lymphoproliferation	Rapamycin ⁶⁹
<i>FOXP3</i>	Main transcription factor for differentiation of regulatory T cells that maintain immune tolerance ⁷⁰	X-linked, LOF	AD, asthma, EGID, FA, eosinophilia, ↑IgE level, infections, autoimmunity, enteropathy	Rapamycin HSCT ⁷¹⁻⁷³
<i>STAT3 (GOF)</i>	Acts as signal transducer for many cytokines and growth factors through cytoplasm, and as transcription factor for many inflammatory, cell growth ⁴⁹ and cancer-related genes in nucleus ⁵⁰	Autosomal dominant, GOF	Eczema, lymphadenopathy, multiorgan autoimmunity, infections, short stature	Tocilizumab ± JAK inhibitors (ruxolitinib) ⁷⁴⁻⁷⁷ HSCT ⁷⁸
<i>STAT1</i>	Acts as signal transducer for many cytokines and growth factors through cytoplasm, and as both transcription activator and suppressor for many interferon genes in nucleus ⁷⁹	Autosomal dominant, GOF	Eczema, infections, autoimmunity, enteropathy, short stature, vascular abnormalities	JAK inhibitors (ruxolitinib) ⁸⁰⁻⁸² HSCT ^{83,84}
<i>JAK1</i>	Tyrosine kinase, associates with a variety of cytokine and growth factor receptors to transmit signals via phosphorylation of STAT proteins ⁸⁵	Autosomal dominant, GOF	AD, AR, asthma, FA, eosinophilia, poor growth	JAK inhibitors (ruxolitinib ⁸⁶ and tofacitinib ⁸⁷)
<i>STAT5B (GOF)</i>	Acts as signal transducer for many cytokines and growth factors through cytoplasm ⁶⁵ and as transcription factor for expression of genes such as <i>FOXP3</i> , <i>CD25</i> , and <i>IGF1</i> ⁶⁶	Somatic, GOF	AD, FA, urticaria, eosinophilia, diarrhea	JAK inhibitors (ruxolitinib) ⁸⁸
<i>TBX21</i>	Important transcription factor for differentiation of T _H 1 cells and production of IFN-γ, and in turn, the attenuation of T _H 2 cell development ⁸⁹	Autosomal recessive, LOF	Upper airway hyperresponsiveness, eosinophilia, mycobacterial disease	Supportive treatment ⁹⁰
Actin cytoskeleton defects				
<i>WAS</i>	Initiates actin polymerization in hematopoietic cells by binding to Arp2/3 complex subunit 1B Actin cytoskeleton remodeling is crucial for several immune functions such as signal transduction, cell adhesion/migration/proliferation, and phagocytosis ⁹¹	X-linked, LOF	Eczema, eosinophilia, ↑IgE level, infections, thrombocytopenia, autoimmunity, malignancy	HSCT ⁹² Gene therapy ^{93,94}

(continued)

TABLE II. (Continued)

Gene	Protein function	Inheritance	Allergic and other key manifestations	Treatment strategies†
<i>WIPF1</i>	Key regulator of actin cytoskeleton remodeling, which is crucial to immune synapse formation, signal transduction, cytokine secretion and the survival and migration of T cells, and generation of immune memory in CD8 T cells ⁹⁵	Autosomal recessive, LOF	Eczema, ↑IgE level, diarrhea, infections, thrombocytopenia	HSCT ⁹⁶
<i>ARPC1B</i>	Component of Arp2/3 complex Roles in actin polymerization ⁹⁷ and T cell and thrombocyte development ⁹⁸ Downstream of and regulated by Wiskott–Aldrich syndrome protein family ⁹⁹	Autosomal recessive, LOF	Eczema, asthma, FA, eosinophilia, ↑IgE level, vasculitis, infections, bleeding	HSCT ¹⁰⁰
<i>DOCK8</i>	Guanine nucleotide exchange factor (GEF) Roles in immune cell migration, phagocytosis and adhesion, actin cytoskeleton regulation, ¹⁰¹ Toll-like receptor signaling, and STAT3 activation ¹⁰²	Autosomal recessive, LOF	AD, AR, asthma, EGID, FA, eosinophilia, ↑IgE level, infections, autoimmunity, malignancy ¹⁰²	HSCT ¹⁰³⁻¹⁰⁷ Dupilumab for AD ¹⁰⁸
<i>NCKAP1L</i>	Subunit of WAVE regulatory complex Regulator of actin polymerization in hematopoietic cells through Arp2/3 complex, crucial to cell migration, adhesion, phagocytosis, and proliferation ¹⁰⁹	Autosomal recessive, LOF	Eczema, FA, urticaria, elevated IgE, infections, hepatosplenomegaly, lymphadenopathy, autoimmunity ¹¹⁰	Supportive treatment
Antigen presentation defects				
<i>RFXANK</i>	Subunit of regulatory factor X (RFX) complex, which assembles on promoters of MHC II genes and regulates their transcription ¹¹¹	Autosomal recessive, LOF	Eczema, allergic cutaneous reaction to antibiotics, eosinophilia, infections, failure to thrive, autoimmunity ^{112,113}	HSCT ¹¹³
Attenuated antigen receptor signaling				
<i>CARD11</i>	T and B cell-specific scaffold protein that interacts with BCL10 and MALT1 in a complex upon engagement of B cell receptor (BCR) and T cell receptor (TCR) with antigens Mediates NF-κB activation in T and B cells ¹¹⁴	Autosomal dominant, DN	AD, asthma, AR, EGID, FA, eosinophilia, ↑IgE level, infections, autoimmunity, lymphoma ¹¹⁵	Dupilumab ¹¹⁶ Omalizumab ¹¹⁷ Glutamine supplementation (preclinical) ¹⁵⁵
<i>CARD14</i>	Scaffold protein that promotes activation of NF-κB pathway by recruiting BCL10 and MALT1, ultimately resulting in the production of proinflammatory genes and antimicrobial peptides ¹¹⁸	Autosomal dominant, LOF	AD, AR, asthma, FA, ↑IgE level	Supportive treatment ¹¹⁹
<i>MALT1</i>	Protease and scaffold protein Regulates NF-κB signaling in various immune cells Important for cellular activation, proliferation and survival ¹²⁰	Autosomal recessive, LOF	Eczema, ↑IgE level, poor growth, infections ¹²¹	HSCT ¹²²⁻¹²⁴
<i>CARMIL2</i>	Regulator of actin polymerization in T cells, also required for CD28-mediated costimulation of NF-κB signaling in T cells ¹²⁵	Autosomal recessive, LOF	AD, asthma, FA, cold urticaria, ↑IgE level, infections	HSCT ¹²⁶

<i>LIG4</i>	DNA ligase involved in double-stranded DNA (dsDNA) break repair during V(D)J recombination Important for generating TCR and BCR diversity during T and B cell development ¹²⁷	Autosomal recessive, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ¹²⁷
<i>DCLRE1C</i>	Endonuclease involved in nonhomologous end-joining of DNA segments during V(D)J recombination Important for generating TCR and BCR diversity during T and B cell development ¹²⁸	Autosomal recessive, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ¹²⁹ Gene therapy (clinical trial)
<i>RAG1</i>	Catalytic component of RAG complex involved in introducing dsDNA breaks during V(D)J recombination Important for generating TCR and BCR diversity during T and B cell development ¹³⁰	Autosomal recessive, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ¹³¹
<i>RAG2</i>	Core component of RAG complex involved in introducing dsDNA breaks during V(D)J recombination Important for generating TCR and BCR diversity during T and B cell development ^{130,132}	Autosomal recessive, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ¹³¹
<i>ADA</i>	Deaminating enzyme involved in purine metabolism that has a key role in T and B cell development ¹³³	Autosomal recessive, LOF	AD, AR, asthma, FA, urticaria, eosinophilia, ↑IgE level, ¹³⁴ diarrhea, infections, multiorgan abnormalities	HSCT ¹³⁵ Enzyme replacement therapy ¹³⁶ Gene therapy ^{137,138}
<i>IL7RA</i>	Alpha chain of IL-7 receptor, important for T cell development and homeostasis ¹³⁹	Autosomal recessive, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ^{140,141}
<i>IL2RG</i>	Gamma chain of receptor of many cytokines including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, ¹⁴² which is required for full ligand binding for these cytokines ¹⁴³	X-linked, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ¹⁴⁴ Gene therapy ¹⁴⁵
<i>ZAP70</i>	Tyrosine kinase, associates with TCR complex upon engagement with antigen presenting cells Roles in T cell proliferation and differentiation, cytoskeleton rearrangement, and positive selection ¹⁴⁶	Autosomal recessive, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ¹⁴⁷
<i>CHD7</i>	Chromatin remodeler that regulates gene expression during thymic development in the developing fetus ¹⁴⁸	Autosomal dominant, LOF*	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT ¹⁴⁹ Thymus transplantation ¹⁵⁰
<i>TBX1</i>	Crucial transcription factor for thymus formation during fetal development, important for T cell development and function ¹⁵¹	Haploinsufficiency	Erythroderma, eosinophilia, ↑IgE level, enteropathy, infections*	HSCT Thymus transplantation ¹⁵⁰
Altered cellular metabolism				
<i>PGM3</i>	Carbohydrate-modifying enzyme involved in glycosylation of proteins, ¹⁵² which is critical for various immune system processes including leukocyte trafficking and T and B cell development ¹⁵³	Autosomal recessive, LOF	Eczema, asthma, FA, eosinophilia, ↑IgE level, bronchiectasis, infections, developmental delay, autoimmunity, malignancy, connective tissue abnormalities ⁵¹	HSCT ¹⁵⁴

(continued)

TABLE II. (Continued)

Gene	Protein function	Inheritance	Allergic and other key manifestations	Treatment strategies†
<i>CARD11</i>	See earlier description. Also required for TCR-induced mTORC1 activation by facilitating glutamine uptake through ASCT2	Autosomal dominant, DN	AD, asthma, AR, EGID, FA, eosinophilia, ↑IgE level, infections, autoimmunity, lymphoma ¹¹⁵	Dupilumab ¹¹⁶ Omalizumab ¹¹⁷ Glutamine supplementation (preclinical) ¹⁵⁵
Granulocyte dysregulation				
<i>KIT</i>	Involved in differentiation of myeloid and lymphoid progenitors Important for proper mast cell functioning including survival, differentiation, and chemotaxis ¹⁵⁶	Autosomal dominant, GOF	Systemic mastocytosis	Imatinib ¹⁵⁷ Avapritinib (phase II trial) ¹⁵⁸
<i>PLCG2</i>	Important enzyme for activation and function of B cells, natural killer cells, mast cells, and macrophages Upon BCR activation, allows calcium entry into B cell ¹⁵⁹	Autosomal dominant, GOF	Cold urticaria, infections, autoimmunity, skin granulomas	Supportive treatment ¹⁶⁰
<i>ADGRE2</i>	Member of epidermal growth factor 7 transmembrane subfamily of GPCRs that acts as a cell surface receptor and promotes cell adhesion in neutrophils, macrophages, and mast cells ¹⁸	Autosomal dominant, GOF	Vibratory urticaria ¹⁸	Avoiding stimulus Antihistamines
<i>NLRP3</i>	Intracellular receptor involved in recognition of pathogen- and danger-associated molecular patterns, leading to caspase 1 activation and IL-1β production ¹⁶¹	Autosomal dominant, GOF	Urticarial rash, eosinophilia, central nervous system involvement, arthropathy ¹⁶²	Canakinumab Anakinra Riloncept ¹⁶³

AD, atopic dermatitis; AR, allergic rhinitis; CARD, caspase recruitment domain; DN, dominant-negative; EGID, eosinophilic gastrointestinal disease; FA, food allergy; GOF, gain of function; GPCR, G protein-coupled receptor; HSCT, hematopoietic stem cell transplantation; JAK, Janus kinase; LOF, loss of function; STAT, signal transducer and activator of transcription.

Upward arrow indicates elevation.

*Omenn syndrome and/or Omenn syndrome-like presentations, resulting from hypomorphic LOF variants that retain residual function.

†Specific targeted therapies that address allergic inflammation are highlighted in the table. However, they are not meant to represent comprehensive or standardized management guidelines for these conditions.

inhibitors are now approved for treating AD (Table I).²²² This serves as an example of how studying monogenic atopic disorders can inform the treatment of more common allergic diseases in the general population.

Actin cytoskeleton defects

The actin cytoskeleton has a crucial role in immune cell function, particularly in lymphocytes.²²³ T-cell activation,²²⁴ propagation of T cell receptor (TCR) signaling,²²⁵ clonal expansion,²²⁶ and ultimately migration and adhesion²²⁷ all heavily rely on the repetitive cytoskeletal rearrangement of actin filaments.²²⁸ In fact, a host of predominantly hematopoietically expressed proteins including Wiskott-Aldrich syndrome protein (WASp),⁹³ WASp-interacting protein (WIP),²²⁹ dedicator of cytokinesis 8 (DOCK8),^{101,102} and hematopoietic protein 1 (HEM1), in addition to protein complexes such as actin-related protein 2/3 (Arp2/3) complex²³⁰ regulate the actin cytoskeleton in T cells. In the steady state, WASp is autoinhibited and stabilized by WIP, but after TCR stimulation, DOCK8 activates cell division cycle 42 (CDC42), which in turn activates WASp by releasing it from WIP. WASp is then able to associate with Arp2/3 complex, which allows downstream actin polymerization to commence, ultimately facilitating the propagation of various signaling cascades and cellular functions in the T cell.^{225,231} Arp 2/3-mediated filamentous actin nucleation is also controlled by the WAVE regulatory complex, which contains HEM1.

Deficiencies of WASp, WIP, DOCK8, HEM1 and Arp2/3 complex subunit 1B are collectively referred to as “immuno-actinopathies”²³¹ and cause a broad range of manifestations that include atopy. X-Linked WASp deficiency causes Wiskott-Aldrich syndrome (WAS), which presents with the characteristic triad of immunodeficiency, thrombocytopenia, and AD.²³² Deficiencies of WIP and Arp2/3 complex subunit 1B also present as phenocopies of WAS, with the same triad of symptoms. Biallelic loss of *DOCK8* causes severe allergic inflammation, significant eosinophilia as well as elevated IgE levels, chronic infections, and an increased risk for cancer and autoimmunity.^{102,233,234} Interestingly, SNPs in *DOCK8* have also been linked to elevated IgE levels in a recent case-control study of AD patients.²³⁵

Severe allergic inflammation in actinopathies may be partially explained by defects in T-cell polarization. For instance, WASp-deficient CD4 T cells exhibit diminished T_H1 cytokine secretion (IL-2, IFN- γ , and TNF- α), but near-normal T_H2 cytokine secretion (IL-4, IL-5, and IL-10).²³⁶ In addition, WASp has been shown to epigenetically regulate the transcription of T_H1 master gene *TBX21* (encoding T-bet), which could also explain the T_H1 – T_H2 imbalance seen in WASp-deficient patients.^{227,237} Similarly, CD4 T cells from DOCK8-deficient patients are preferentially polarized to T_H2 effector phenotype at the expense of T_H1 and T_H17 polarization, which can be explained by concomitant defective STAT3 signaling in these patients.²³⁸ As such, DOCK8 deficiency-related dermatitis and elevated IgE levels are successfully treated with dupilumab, which perhaps counteracts the elevated IL-4 production caused by a T_H2 -skewed immune system.¹⁰⁸ In terms of curative treatments for WASp, WIP, Arp2/3 complex, and DOCK8 actinopathies, because the expression of these proteins is predominantly limited to the hematopoietic compartment, hematopoietic stem cell transplantation has been successfully used to treat these conditions (Table II).^{92,96,100,103,239} HEM1 deficiency may also be

amenable to hematopoietic stem cell transplantation, although no cases reported thus far have undergone transplant, possibly because it is a newly recognized disease. In addition, stem cell gene therapy for WASp deficiency has shown promising results for treating atopic disease in affected patients.^{93,94}

Antigen presentation defects

T-cell recognition of antigens displayed on major histocompatibility complex (MHC) class I and II molecules is an essential component of human immunity and the maintenance of self-tolerance. Genes encoding MHC molecules are found on chromosome 6. In humans, they are called human leukocyte antigens (HLA).²⁴⁰ CD8 and CD4 T-cell receptors recognize peptides bound to class I and II MHC molecules, respectively; however, MHC class I ligands are also important regulators of natural killer cell activity.²⁴¹ Natural killer cells interact with MHC class I using killer Ig-like receptors (KIR).^{241,242} HLA genes are highly polymorphic. Multiple amino acid substitutions result in structural changes that alter peptide binding and antigen presentation for MHC molecules produced from different alleles.^{243,244} This dictates how antigens are presented to T cells and shapes the immune response that ensues, with certain HLA and KIR genetic variants skewing the resulting T-cell response toward an allergic phenotype.²⁴⁵

Previous studies, including GWAS and immunophenotyping techniques, found associations between HLA genes and the risk for AD, as well as other atopic diseases such as asthma, allergic rhinitis, and food allergies.^{8,246–250} Whereas GWAS has localized genetic variation to the HLA region, because GWAS assays are based on the analysis of SNPs, imputation of the actual HLA allele has been difficult and not always accurate compared with next-generation sequencing (NGS) high-resolution HLA typing.^{251,252} Because of similar technologic issues, most studies have reported only the presence or absence of KIR genes. As a result, studies that report both HLA and KIR variation using older technologies need to be carefully scrutinized. More recently, studies using NGS technologies have shown associations with AD susceptibility as well as AD persistence, in which specific HLA class I alleles and binding pocket epitopes as well as KIR genes are linked to either an increase or decrease in risk.^{253–256}

As an example of a monogenic immune disorder affecting antigen presentation, MHC class II deficiency is caused by pathogenic variants in genes regulating the transcription of MHC II genes (Table II).²⁵⁷ The clinical phenotype is primarily characterized by severe infections; however, features of type 2 inflammation, such as hypereosinophilia, AD, or cutaneous drug reactions, were reported in 10 of 35 patients with MHC II deficiency caused by a homozygous *RFXANK* deletion.¹¹³

Understanding the role of HLA genetics in allergic disease risk has brought targeted approaches to immune-mediated delayed drug hypersensitivity reactions (DHRs). Because of the strong association between the HLA-B*57:01 genotype and DHRs to the antiviral abacavir, screening patients before initiating treatment is now recommended.^{258–260} HLA associations with DHRs to allopurinol, carbamazepine, vancomycin, and anticytokine biologics, among others, have also been described.^{260–263} Evaluating how additional host or environmental factors (such as variations in T-cell receptor and KIR allelic repertoires, concurrent infections, and medications) contribute to a patient's risk for DHRs may further refine the ability to prevent and appropriately manage these life-threatening drug reactions.²⁶⁰

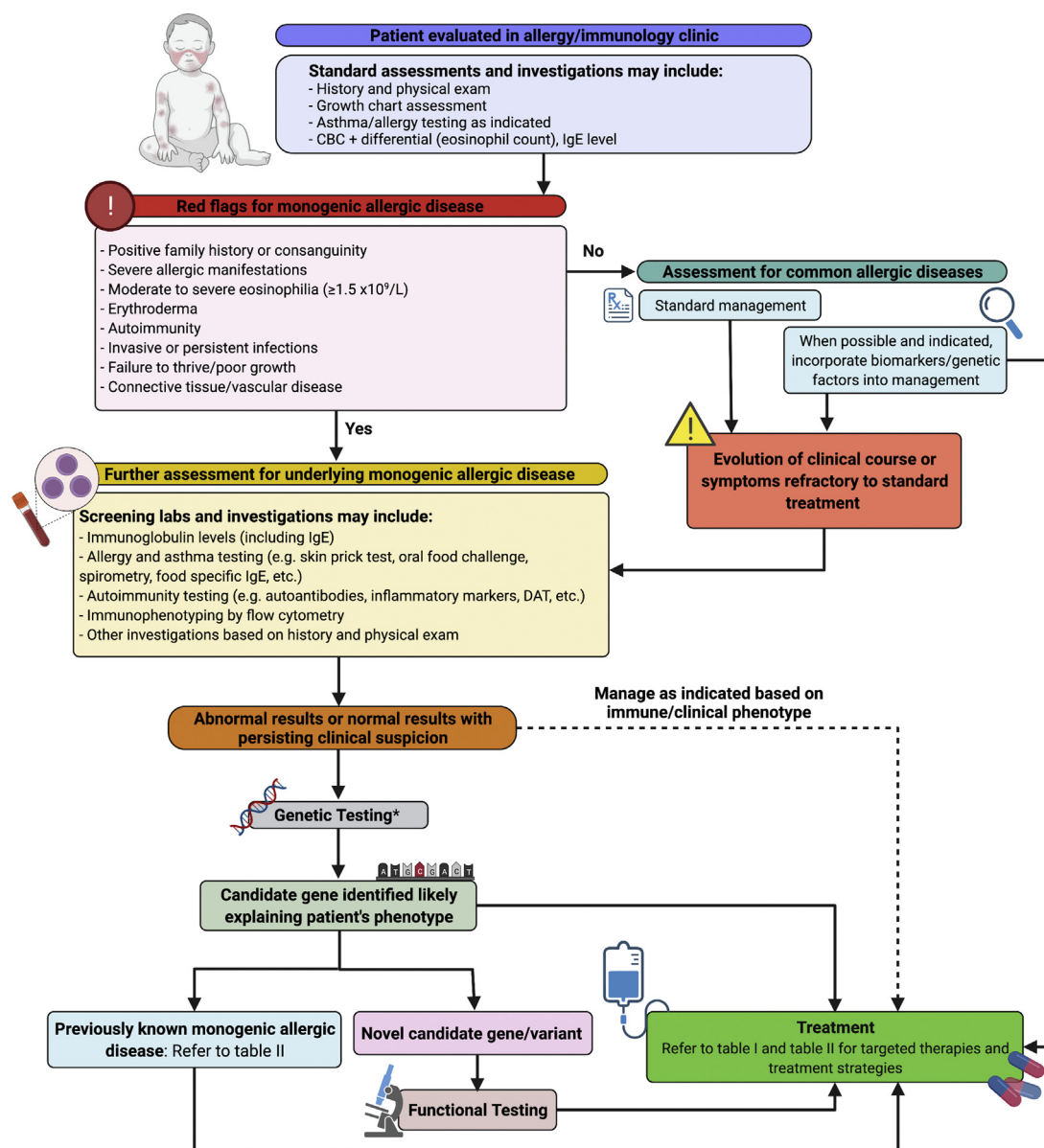


FIGURE 2. Road map for evaluating patients who present to the allergy and immunology clinic with symptoms of allergic disease. After standard assessments, screen for red flags of monogenic allergic disease. If the presentation is not concerning for a monogenic allergic disease, patients should receive standard management for the allergic condition, including the use of biomarkers or genetic testing as indicated for personalized management and/or targeted therapies (see [Table I](#)).^{310,311} Patients should be monitored periodically, and if red flags develop over time or they become refractory to treatment, reconsider the possibility of a monogenic condition. If the presentation suggests a possible monogenic allergic disease, patients should undergo an immune evaluation, and if laboratory values are abnormal or there is persistent clinical concern, genetic testing.^{312,313} Genetic testing may yield known or novel monogenic causes of allergic disease, informing management and the potential use of targeted therapies (see [Table II](#)). (The figure was created with BioRender.com.) CBC, complete blood count. *For detailed information on the diagnostic interpretation of genetic studies in patients with primary immunodeficiency diseases, please see the working group report from the Primary Immunodeficiency Diseases Committee of the American Academy of Allergy, Asthma & Immunology.³¹²

Attenuated antigen receptor signaling

Multiple lines of evidence suggest that CD4⁺ helper T-cell differentiation is influenced by the relative avidity of TCR peptide–MHC interactions. More specifically, several studies corroborated the concept that a weaker TCR signal can bias both murine and human CD4⁺ T cells to differentiate into T_H2 effector cells.^{264–267} T_H2-based atopic phenotypes are observed

in various murine models harboring germline mutations in specific molecules involved in TCR signal transduction, including *Zap70*, *Lat*, *Card11*, and *Malt1*.^{268–271} In humans, homozygous null mutations in homologous TCR signaling molecules naturally result in severe combined immunodeficiency (SCID), often linked to compromised thymocyte development and a complete loss of peripheral T cells.^{124,272–279} However,

heterozygous hypomorphic variants in these genes (eg, *ZAP70*) that preserve protein expression but attenuate TCR signaling (without blocking it entirely) expose a predisposition to T_H2 differentiation in human patients with moderate to severe atopic disease.^{272,274,275,280,281}

Over the past 10 years, the caspase recruitment domain (CARD)11–B-cell CLL/lymphoma 10 (BCL10)–mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) (CBM) complex has emerged as a particularly important site for hypomorphic mutations that result in primary atopic disorders in humans, featuring dysregulated allergic effector responses (ie, T_H2 skewing, IgE production, eosinophilia) irrespective of allergen-specific sensitization.^{119,213} Indeed, GWAS identified *CARD11* as a significant risk locus for AD in the Japanese population²⁴⁶ and mapped a peak association signal for peanut allergy in the *MALT1* locus in subjects who avoided peanuts in early life.²⁸² *CARD11* encodes an essential lymphocyte-specific scaffold protein that connects antigen receptor engagement with the activation of key downstream transcription factors, including nuclear factor- κ B (NF- κ B), c-Jun N-terminal kinase, and mammalian target of rapamycin complex 1 (mTORC1).^{283–287} Upon TCR-induced phosphorylation, CARD11 adopts an open conformation that recruits BCL10 and MALT1 in assembling a large, filamentous CBM signalosome best known for recruiting I κ B kinase (IKK) to foster I κ B degradation and nuclear translocation of NF- κ B heterodimers that transcribe multiple genes involved in lymphocyte proliferation, survival, and effector function.^{288,289} The CBM complex is also required for TCR-dependent activation of c-Jun N-terminal kinase and mTORC1,^{283,285} although molecular mechanisms governing these outputs remain only partly elucidated.

We and others recently described an expansive cohort of patients with CARD11-associated atopy with dominant interference of NF- κ B signaling (CADINS) disease.^{290–292} Although a sizable subset of CADINS patients present with immune dysregulation features including cutaneous viral infections, sinopulmonary infections, and autoimmune sequelae, severe atopic disease (eg, AD, asthma, food allergies, eosinophilic esophagitis) remains the cardinal clinical manifestation, which is consistent with T_H2 skewing and elevated IgE. As the name implies, CADINS is caused by heterozygous DN *CARD11* variants that universally impair the ability of wild-type CARD11 to stimulate NF- κ B after TCR/CD28 ligation, often accompanied by defective mTORC1 activation. Consistent with this observation, mice harboring hypomorphic or DN *Card11* or *Malt1* mutations develop increased serum IgE with age, often accompanied by AD, despite marked lymphocyte activation defects.^{268,270,293,294} Mechanisms of CADINS disease pathogenesis must be further clarified to resolve questions about variable penetrance and expressivity, potential genotype–phenotype correlations, and the importance of specific downstream signaling defects in both T and B cells. Nevertheless, both dupilumab and omalizumab have recently been shown to ameliorate AD symptoms in CADINS patients,^{116,117} which suggests that the blockade of atopic effector molecules may suffice as a treatment paradigm in the absence of appropriate therapeutic targets for restoring optimal antigen receptor signaling.

Altered cellular metabolism

Cellular metabolism is inextricably linked to immune function. For example, lipid metabolism produces bioactive mediators such as leukotrienes, which are important in allergic

disease development through their roles in bronchoconstriction and inflammation, with therapies targeting leukotrienes in clinical practice (Table I).²⁹⁵ We now appreciate that dynamic changes in metabolic programming shape the differentiation and function of effector and regulatory T cells. Newly activated T cells rapidly switch their metabolic balance from oxidative phosphorylation to aerobic glycolysis and glutaminolysis, which supplies macromolecules for rapid clonal expansion and regulates the synthesis of T_H effector cytokines such as IFN- γ .^{115,155,296} We can thus hypothesize that metabolic dysregulation contributes to the pathogenesis of common atopic disorders and certain IEs, including those with allergic manifestations. One illustrative example is triggered by recessive hypomorphic variants in phosphoglucosyltransferase 3 (*PGM3*), which result in a syndrome featuring both neurologic deficits and immune dysregulation in the form of infections, autoimmunity, and a remarkable array of allergic disease presentations.^{152,297,298} Phosphoglucosyltransferase 3 is an essential enzyme in the hexosamine biosynthesis pathway that is responsible for generating UDP-GlcNAc, a molecule required for complex N- and O-linked protein glycosylation. A huge increase in complex branched N-glycans on the plasma membrane accompanies the switch to aerobic glycolysis in healthy activated T cells.²⁹⁹ In fact, reduced N-glycan complexity on CD4 T cells can be used as a diagnostic hallmark of PGM3 deficiency using lectin-based flow cytometry.³⁰⁰ Whether this glycosylation defect underlies the skewed T_H2/T_H17 response observed in PGM3-deficient patients remains unclear.

Notably, both glucose and glutamine feed the hexosamine pathway for UDP-GlcNAc synthesis. Indeed, all three molecules are integral to activating mTORC1, a central governor of metabolic reprogramming and T_H differentiation.^{301,302} Dramatic increases in glucose and glutamine influx foster the switch to aerobic glycolysis and T_H1 differentiation, respectively facilitated by the upregulation of plasma membrane transporters glucose transporter 1 (GLUT1) and alanine, serine, cysteine-prefering transporter 2 (ASCT2).¹¹⁵ Here we see a striking parallel with CADINS disease, in which patient T cells harboring DN CARD11 variants show diminished ASCT2 expression, glutamine uptake, and S6 phosphorylation (a marker of mTORC1 signaling) upon activation.²⁹² Moreover, culturing CADINS patient T cells in excess glutamine (plus NF- κ B-activating cytokines) partially rescues proliferation and IFN- γ secretion,²⁹² ostensibly by overcoming limited ASCT2 expression. We do not yet know whether exogenous UDP-GlcNAc would produce similar effects. Nevertheless, these findings imply a shared atopic disease etiology in patients with defective CBM complex or PGM3 function, stemming from a related metabolic insufficiency that attenuates mTORC1 activity in T cells. This hypothesis introduces a compelling therapeutic possibility whereby allergic disease might be ameliorated in both disorders by metabolite supplementation (eg, glutamine, GlcNAc). Intriguingly, dietary glutamine supplementation during infancy was shown to reduce the incidence of atopic disease in early childhood dramatically, and topical glutamine can suppress contact dermatitis.^{303,304}

Granulocyte dysregulation

Granulocytes (eosinophils, basophils, neutrophils, and most notably, mast cells) are critical effectors in the pathogenesis of

allergic disease. Mast cells and basophils release mediators such as lipids, proteases, and histamine upon cross-linking of their high-affinity IgE receptor, which act on secondary effectors and tissues to elicit features of an allergic reaction.³⁰⁵ Genes encoding proteins involved in this cascade, from the Fc fragment of the IgE receptor to leukotrienes/leukotriene receptors and phosphodiesterases, have been linked to atopy and serve as therapeutic targets for allergic disease (Table I).^{13,20-22} Monogenic disorders affecting mast cell signaling lead to clinical manifestations of mast cell mediator release (Table II). Mastocytosis is caused by somatic or germline GOF variants in *KIT*, encoding for a tyrosine kinase receptor critical for mast cell survival.¹⁵⁶ Recently, early-phase clinical trials of a selective kinase inhibitor targeting the most common activating *KIT* variant found in systemic mastocytosis showed promising response rates.¹⁵⁸ Heterozygous GOF variants in the gene encoding adhesion G protein-coupled receptor E2 (ADGRE2) cause vibratory urticaria, owing to the degranulation of dermal mast cells activated through ADGRE2 by physical stimuli.¹⁸ Similarly, a link between Mas-related G protein-coupled receptor X2 (MRGPRX2) on cutaneous mast cells and AD was recently proposed.³⁰⁶⁻³⁰⁸ MRGPRX2 is activated and causes mast cell degranulation by a vast array of substances including host-defense peptides, neuropeptides, and cationic drugs.³⁰⁷ Although no studies to date link rare variants or SNPs in *MRGPRX2* to monogenic or common allergic disease in humans, studies have observed upregulation in *MRGPRX2* expression and its agonists in the skin transcriptome of patients with AD compared with healthy controls.³⁰⁸ This has led to MRGPRX2 being considered a potential therapeutic target for AD and other allergic-like diseases mediated by this receptor.^{306,309}

CONCLUSION

Uncovering the genetic basis of allergic immune dysregulation has been instrumental in discovering therapeutic targets for allergic disease. With increasing access to sophisticated genetic sequencing technologies, opportunities for personalized approaches in preventing and treating both common and rare forms of allergic inflammation will continue to grow. Indeed, the recognition of red flags for monogenic allergic disease is increasingly imperative as more clinicians are tasked with integrating clinical symptoms, immunologic and laboratory tests, and genetic sequencing results to arrive at definitive diagnoses and tailored treatments (Figure 2).

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