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Review

Primary atopic disorders: inborn errors of immunity causing severe allergic disease

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Allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and food allergies, are driven by dysregulated immune responses, often involving IgE-mediated mast cell and basophil activation, Th2 inflammation, and epithelial dysfunction. While environmental factors are well-known contributors, the genetic components underpinning these conditions are increasingly understood. Traditionally viewed as polygenic multifactorial disorders, allergic diseases can also be caused by single-gene defects affecting the immune system and skin epithelial barrier, leading to profoundly dysregulated allergic responses. These monogenic allergic disorders are collectively referred to as primary atopic disorders or PADs. To date, over 48 single-gene defects have been established to cause PADs. This review highlights (i) the significance of PADs, (ii) the biological pathways involved in the pathogenesis of PADs, (iii) clinical strategies to differentiate PADs from their much more common polygenic counterparts, and (iv) diagnostic strategies for PADs.

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Single-gene defects as the cause of allergic disease

While the vast majority of people with allergies have a polygenic multifactorial disorder caused by the interaction of multiple genes with environmental exposures, we have come to appreciate that allergic diseases can also be caused by single-gene defects. These monogenic disorders that affect the development, function, and regulation of the immune system and the skin epithelial barrier lead to dysregulated pathogenic allergic effector responses [1–3].

Collectively referred to as 'monogenic allergic diseases' or 'primary atopic disorders' (PADs), these Mendelian disorders are clinically and genetically heterogeneous with over 48 known genetic causes identified to date (Table 1) [4–6]. PADs represent a subset of the larger group of monogenic immune disorders collectively known as inborn errors of immunity or IEIs. Some PADs result from damaging variants[1] in genes that encode components of the immune system and the skin epithelial barrier, such as cytokines, receptors, structural proteins, and enzymes. Other PADs are caused by variants that disrupt genes involved in immune system development, activation, or differentiation, such as transcription factors and signaling molecules (see Table 1) [5].

The clinical and molecular heterogeneity of PADs underscores their complexity and emphasizes the need to understand the mechanisms involved in their pathogenesis. This understanding is crucial to develop targeted therapeutics that can effectively address the underlying molecular causes of these conditions. This review aims to highlight the significance of PADs, the disrupted biological pathways involved in their pathogenesis, and the central role clinical genetic sequencing plays in advancing affected patients to diagnosis and treatment.

Categorizing the disrupted cellular and molecular pathways that cause primary atopic disorders

PADs are driven by genetic variants that interfere with the normal development and function of the immune system, the integrity of epithelial barriers, or cellular signaling [1]. Variants in these genes impact an array of cellular mechanisms that lead to the disruption of normal

[1] Throughout this Review, we will use the term 'damaging variant' to describe a disease-causing genetic change, rather than 'mutation' which has potentially pejorative connotations.

Table 1

Pathogenic mechanisms and an illustrative list of genes implicated in monogenic allergic diseases.

Pathogenic mechanism	Genes
Disruption of skin barrier function	*FLG, SPINK5, CDSN, DSG1, DSP, CARD14*
Granulocyte dysregulation	*KIT, PLCG2, ADGRE2*
Abnormal actin cytoskeleton remodeling	*WAS, WIPF1, ARPC1B, DOCK8, NCKAP1L, CARMIL2, STK4, MSN*
Attenuated antigen receptor signaling	*CARD11, CARD14, MALT1, CARMIL2, RFXANK*
Abnormal T cell development and/or Restriction of the T cell receptor repertoire	*LIG4, DCLRE1C, RAG1, RAG2, ADA, IL7RA, IL2RG, ZAP70, CHD7, TBX1,* 22q11.2 deletion syndrome, *FOXP3, TBX21, IKZF1*^{GOF}
Altered cytokine signaling	*JAK1*^{GOF}, *STAT1*^{GOF}, *STAT3*^{DN}, *STAT3*^{GOF}, *STAT5B*^{LOF}, *STAT5B*^{GOF}, *STAT6*^{GOF}, *IL2RA*^{LOF}, *IL4RA*^{GOF}, *TGFBR1, TGFBR2, ERBB2IP, IL6ST, IL6R, ZNF341, FOXP3, TBX21*
Altered cellular metabolism	*PGM3, CARD11, MALT1*

NB: due to their pleiotropic functions, some genes are listed under multiple pathogenic mechanisms.

immune cell functions and/or skin integrity, ultimately resulting in unchecked allergic inflammation [1,3]. These genetic variants can cause disease through the full range of genetic mechanisms, including gain-of-function (GOF), loss-of-function (LOF), and dominant-negative (DN) effects, each contributing to disease pathology through distinct modes of inheritance, including autosomal dominant, autosomal recessive, X-linked, and *de novo* disease. In the following paragraphs, we will group the individual PADs into mechanistic categories, and a more comprehensive list of currently well-characterized PADs is presented in Table 1. Recognizing the pleiotropic nature of many genes, some PAD genes are listed under more than one category: for example, biallelic disruption of *TBX21* causes deficiency of the transcription factor T-bet, affecting both the development of T cells (and many other immune cells) while also causing allergic inflammation due to excessive T helper 2 (Th2) cytokine production by adaptive CD4^{+} αβ T lymphocytes [7–9].

Disruption of skin barrier function

LOF variants in proteins that maintain the integrity of the epithelial barrier are a well-established cause of PADs. The integrity of the epithelial barrier is maintained by structural proteins like filaggrin (encoded by *FLG*), protease inhibitors such as serine peptidase inhibitor Kazal type 5 (*SPINK5*), and proteins involved in intercellular adhesion including corneodesmosin (*CDSN*), desmoglein 1 (*DSG1*), and desmoplakin (*DSP*). Germline LOF variants in these proteins impair skin barrier function resulting in enhanced exposure of antigen-presenting cells to environmental antigens, penetration of microbiota, and water loss [1,10]. These lead to the secretion of alarmins, such as interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin, which are key regulators of type 2 immunity and trigger an allergic response [11]. Allergic inflammation persists because of downstream type 2 cytokines, such as IL-4 and IL-13 [12]. Although here we discuss the genes that are implicated in skin barrier function, it is also important to note that barrier disruption in the pathogenesis of atopy may not be limited to skin — the disruption of the gastrointestinal tract or even respiratory mucosa could conceivably contribute [13]. For instance, in a recent study, Laky et al. demonstrated that intrinsic defects in transforming growth factor beta (TGF-β) receptor signaling within the gut epithelium can independently drive eosinophilic esophagitis, highlighting the role of epithelial cells not only as a physical barrier but also as key regulators of local immune responses through altered differentiation and alarmin production [14].

Granulocyte dysregulation

Dysregulation of granulocytes, encompassing basophils, eosinophils, mast cells, and neutrophils, is another mechanism leading to heightened type 2 inflammation and development of PADs [15]. In healthy individuals, granulocytes (classically mast cells) release proinflammatory mediators after sensing an allergen through their high-affinity immunoglobulin E (IgE) receptors. However, dysregulation of granulocytes through a variety of GOF mechanisms results in PADs. For example, variants in *KIT* result in mastocytosis due to uncontrolled mast cell proliferation. Beyond proliferation defects, abnormal mast cell degranulation can cause urticaria in these conditions [16]. Additionally, *PLCG2* variants implicated in cold-induced urticaria lead to constitutive activation of PLCγ2 at lower temperatures, triggering mast cell degranulation and histamine release [17]. Also, vibratory urticaria caused by variants in *ADGRE2* results from mechanical stimuli disrupting receptor subunit interactions, leading to mast cell activation and urticaria (or hives) [18].

Abnormal actin cytoskeleton remodeling

As key components of the adaptive immune system, lymphocytes also play a pivotal role in the development and progression of allergic inflammation in PADs. The actin cytoskeleton is critical to lymphocyte function, playing a key role in T cell receptor (TCR) signaling, clonal expansion, and regulatory T cell (Treg) function. The actin cytoskeleton facilitates the movement and organization of signaling molecules at the immunological

synapse, allowing effective TCR signaling and activation. Additionally, actin dynamics are crucial for the proliferation and differentiation of T cells during clonal expansion, which is necessary for mounting an effective immune response. Tregs, which help maintain immune tolerance and prevent excessive immune responses, also depend on the actin cytoskeleton for their suppressive functions. LOF variants in proteins that regulate actin polymerization, such as those encoded by *WAS*, *WIPF1*, *ARPC1B*, *DOCK8*, *NCKAP1L*, *CARMIL2*, *STK4*, and *MSN* characteristically lead to severe allergic inflammation, recurrent infections, and loss of immune tolerance to allergens and self-antigens [19–24]. The exact mechanisms by which each of these variants drives allergic inflammation are not entirely understood; nonetheless, several key insights have emerged. For instance, DOCK8 deficiency skews $CD4^+$ cells towards a Th2 and away from a Th1 bias, indicating a T cell–intrinsic mechanism [25]. Additionally, these variants are linked to Treg cell dysfunction, further contributing to skewed Th2 responses that go unchecked and the concomitant autoimmunity observed in these disorders [26].

Attenuated antigen receptor signaling

Attenuated signaling through the TCR has also been linked to the development of Th2 inflammation in PADs [9]. Low-avidity interactions between a TCR and an antigen-derived peptide presented on a major histocompatibility complex (MHC) molecule promote naïve T cells to differentiate into Th2 cells [27]. Low-avidity interactions can be caused by variants in proteins that regulate the expression of MHC class II molecules (*RFXANK*) [28] or facilitate TCR signal transduction (*CARD11*, *MALT1*, and *ZAP70*; see Table 1 for a complete list). CARD11 and MALT1 are components of the CBM signalosome complex, and together they regulate the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway following TCR activation, which results in the induction of proinflammatory genes. Impairment in NF-κB signaling skews the cytokine milieu towards a Th2 phenotype, upregulating Th2 signaling and inflammation through several mechanisms [29]. Normally, NF-κB activation promotes the secretion of proinflammatory cytokines such as IL-12, which support Th1 responses. Disruption of NF-κB reduces IL-12, favoring Th2 differentiation. Additionally, impaired NF-κB signaling increases Th2 cytokines (IL-4, IL-5, and IL-13) crucial for Th2 responses. NF-κB is also essential for Treg function and its impairment leads to Treg dysfunction, reducing suppression of Th2 cells and promoting unchecked Th2 responses. Moreover, NF-κB regulates GATA3, a key Th2 differentiation factor, and its dysregulation further enhances Th2 polarization. These combined effects ultimately favor Th2 differentiation and allergic inflammation [29].

Abnormal T cell development and/or restriction of the T cell receptor repertoire

Limited TCR repertoire is also another mechanism that leads to Th2 skewing and allergic inflammation. Several genes involved in TCR repertoire selection and T cell development are implicated in PADs including *RAG1*, *RAG2*, *DCLRE1C*, *ADA*, *IL2RG*, *IL7RA*, *CHD7*, *LIG4*, *ZAP70*, *TBX1*, as well as 22q11.2 deletion syndrome. A powerful illustrative example is RAG1 and RAG2, which are essential for V(D)J recombination and generating diverse TCRs necessary for a robust immune response [30]. Hypomorphic LOF variants in these RAG genes lead to restricted TCR diversity causing Omenn syndrome, characterized by Th2-skewed inflammation, eczema, elevated IgE, and eosinophilia [30]. The mechanism by which limited TCR repertoire can lead to atopy is not entirely clear. It has been previously postulated that reduced TCR diversity can create gaps in Treg repertoires, which limits their ability to control effector T cell responses [31,32]. Additionally, the absence of higher-affinity antigen-specific TCRs during naive T cell priming allows lower-affinity $CD4^+$ clones to expand noncompetitively and differentiate into Th2 effectors [33].

Altered cytokine signaling

Proallergic Th2 skewing can also be caused by variants that disrupt cytokine signaling. These damaging variants function through GOF, LOF, or DN mechanisms and to date have been found to cause PADs by disrupting each of the key steps in cytokine signaling, including cell-surface receptors (encoded by *IL2RA*, *IL4RA*, *TGFBR1*, *TGFBR2*, *IL6ST*, and *IL6R*), intracellular signaling molecules (encoded by *JAK1* and *ERBB2IP)*, and transcription factors (encoded by *STAT1*, *STAT3*, *STAT5B*, *STAT6*, *ZNF341*, *FOXP3*, and *TBX21*). A recently described example is STAT6-GOF disease, which is caused by GOF variants in *STAT6* and results in enhanced IL-4 and IL-13 signaling through sustained STAT6 phosphorylation and increased STAT6 target gene expression [34,35]. This promotes Th2 cell differentiation and a skewing towards Th2 immune responses, amplifying allergic phenotypes such as atopic dermatitis, asthma, and elevated serum IgE levels. Additionally, many of these cytokine-related variants also impair Treg development and function, which is crucial for maintaining immune tolerance and preventing excessive allergic inflammation. Variants in *IL2RA*, *STAT5B*, and *FOXP3*, for instance, are well-documented to compromise Treg differentiation, survival, or suppressive capacity, thereby exacerbating Th2-driven inflammation [1,3]. Thus, Treg failure represents a key immunological consequence of cytokine signaling defects in PADs, further amplifying dysregulated immune responses.

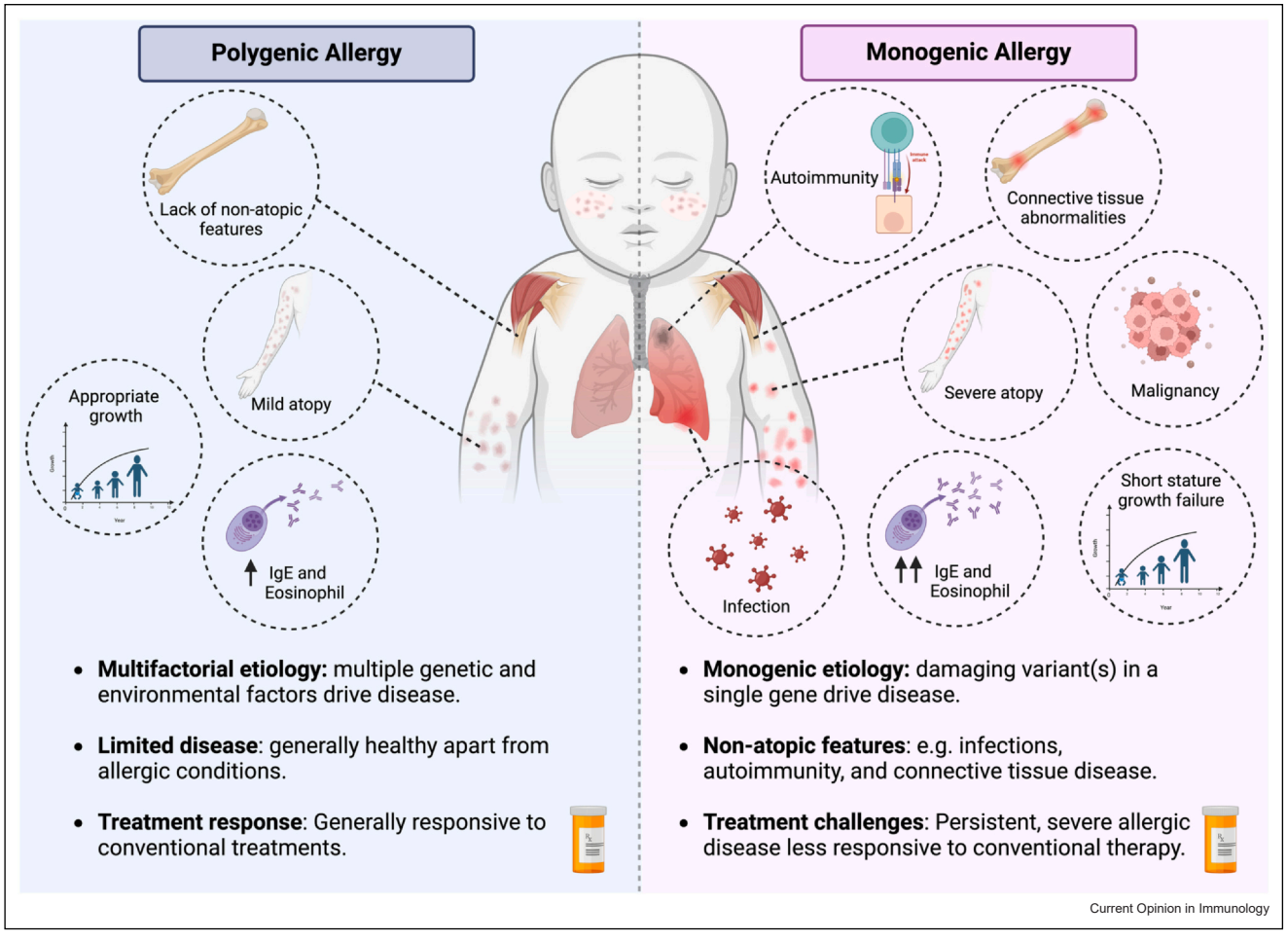
Altered cellular metabolism

Finally, disruption of cellular metabolism is an emerging mechanism leading to the development of PADs. For example, LOF and DN variants in *CARD11* result in Th2 skewing through the disruption of the mechanistic target of rapamycin (mTOR) pathway, which is crucial for cell growth, proliferation, and metabolism [36]. Specifically, *CARD11* variants impair mTOR signaling by disrupting the expression of the amino acid transporter ASCT2, leading to decreased cellular glutamine uptake. This reduction in glutamine uptake impairs mTORC1 activation, subsequently reducing tricarboxylic acid cycle activity and glycolysis [36]. Th2 cells rely less on glycolysis than Th1 and Th17 cells; as such, disruptions in metabolic pathways that impact glycolysis can preferentially support Th2 cell survival and proliferation, supporting a milieu conducive to allergic inflammation.

Clinical features of primary atopic disorders

Although differentiating PADs from common polygenic allergic diseases poses a challenge for clinicians, the nature and severity of symptoms can provide a clue (Figure 1). Common allergic diseases typically present with isolated conditions such as atopic dermatitis, asthma, and allergic rhinitis, or may follow the classic childhood chronological progression referred to as the 'atopic march' that begins with atopic dermatitis [37]. Polygenic versions of atopic disease typically begin in early childhood but can develop at any age, often follow

Figure 1



Differentiating factors between polygenic and monogenic allergy. This figure illustrates the clinical and diagnostic distinctions between common polygenic allergic disease and monogenic allergic disease (also known as primary atopic disorders). Individuals with polygenic allergy generally present with a disease that is limited to allergic manifestations and that follows a typical childhood progression known as the 'atopic march'. Primary atopic disorders frequently involve additional nonatopic features, such as increased susceptibility to infections, autoimmunity, malignancy, growth impairment, and connective tissue disease. Atopic manifestations often develop early in life, are severe, and are resistant to conventional treatments. The figure was created using Biorender (www.biorender.com).

a waxing and waning disease course, and generally respond well to conventional therapies. In contrast, PADs manifest with more severe, persistent symptoms that typically emerge in the first months or year of life and often show an inadequate response to first-line therapies that are effective for common polygenic disease. Another key warning sign for PADs is the finding of additional nonatopic disease manifestations, such as increased susceptibility to infections, autoimmunity, and systemic features including failure to thrive, connective tissue abnormalities, and gastrointestinal inflammation [4].

Certain clinical features can provide insight into the specific PAD that may be underlying a patient's condition. For example, variants in genes responsible for skin barrier function, such as *DSG1*, *CDSN*, *DSP*, and *SPINK5*, result in conditions with severe skin involvement, including severe dermatitis, erythroderma, ichthyosis, and pruritus [5]. In contrast, connective tissue anomalies are a hallmark of TGF-ß pathway disorders, whether caused by damaging genetic changes in *STAT3* or by affecting key signaling components in the STAT3 pathway such as ZNF341, DOCK8, IL6ST, IL6R, or ERBIN. However, PADs have many overlapping features making it very challenging to assign a probable gene or probable impacted pathway to individual patients in the clinical setting. For this reason, we strongly advocate for comprehensive gene sequencing using broadly inclusive gene panels, exome, or genome sequencing as the most efficient first-line strategy for diagnosing PADs.

Diagnosis of primary atopic disorders

The classic clinical approach of history taking and physical examination, followed by the judicious use of laboratory evaluation, should be followed when seeing a patient with a possible PAD (Figure 1). In addition to the history of very early-onset severe disease, family history can be most informative. Common polygenic allergic diseases often show a family history of atopic conditions like asthma, atopic dermatitis, and allergic rhinitis without a clear pattern of inheritance. In contrast, PADs may follow a clear inheritance pattern such as autosomal dominant, autosomal recessive, or X-linked inheritance. However, it is important to note that spontaneously occurring *de novo* variants can also be a cause of PADs, so a PAD should not be dismissed in the absence of a family history or a clear Mendelian pattern of inheritance. History and physical examination should also focus on ruling out the possibility of underlying malignancy or infection as a possible explanation for the complex allergic presentation.

Laboratory tests are also often used in the diagnosis and workup of PADs and in distinguishing them from common allergic conditions. The biomarkers of allergic disease, namely peripheral blood eosinophil counts and serum IgE levels, are typically elevated in both polygenic and PADs. However, it is not possible to define an IgE or eosinophil cutoff above which every patient must have a PADs workup, so clinical acumen is essential. In addition to IgE and eosinophil levels, more advanced diagnostic modalities to interrogate immune function may be informative, including serum immunoglobulin levels, assessing antibody production following immunization, flow cytometry to quantify cell types, as well as *in vitro* functional immune assays [38,39].

While symptoms, family history, and diagnostic laboratory tests provide essential insights, they are often not enough for definitively diagnosing PADs due to the variability in clinical presentation, the presence of overlapping symptoms with common allergic diseases, and the potential for atypical presentations. Genetic sequencing has become an essential tool in the diagnosis and management of PADs. Technologies such as targeted gene panels, exome sequencing, and genome sequencing should now be used early in the diagnostic workup to identify genetic variants responsible for these conditions. Over the past decade, next-generation sequencing (NGS) techniques have facilitated the evaluation of many patients, identifying both known and novel disease-causing genes. While there are no studies systematically defining the diagnostic yield of NGS for PADs, the results for monogenic IEIs are compelling. For example, an exome sequencing study of 303 IEI patients in Türkiye reported a 41.1% diagnostic yield, identifying 52 novel variants and underscoring the effectiveness of genomic approaches in uncovering new disease-associated genes [40]. However, diagnostic yield varies across cohorts and methodologies. A study by Posey et al. reported a 28.2% diagnostic rate for exome sequencing in a broader cohort of individuals with suspected genetic disorders, including IEIs [41], while Similuk et al. found 32.7% diagnostic yield specifically in US-based IEI cohorts [42]. These differences may reflect heterogeneity in patient selection, sequencing depth, and analytical pipelines. Despite variability in yield, NGS remains a powerful tool for genetic diagnosis in IEIs, particularly for patients with well-characterized PADs or those with suggestive clinical phenotypes. Beyond improving diagnostic rates, molecular testing has significant implications for clinical decision-making and patient outcomes. Molecularly defined diagnoses for patients with IEIs have been reported to alter therapeutic options in 34% of the 254 cases included in this study, significantly impacting patient care by enabling early diagnosis, personalized treatment strategies, and accurate genetic counseling and prognostic assessments [43].

Discussion and conclusion

PADs are emerging as conditions that are more prevalent than one might imagine for conditions traditionally considered to be extremely rare. Although the prevalence of these diseases has not been formally assessed, PADs are part of the broader category of IEIs, which are

estimated to affect between 1 in 1000 and 1 in 5000 individuals globally [44]. Given this higher-than-expected prevalence, clinicians should be aware of the signs and appropriate workup and diagnostic methods for PADs, as accurate genetic diagnosis can have important implications for management and patient outcomes.

Genetic sequencing has revolutionized the diagnosis and management of PADs. Techniques such as targeted gene panels, exome sequencing, and genome sequencing have been effective in identifying both known and novel genetic variants responsible for these conditions [40]. Furthermore, molecularly defined diagnoses have significantly altered therapeutic options in a substantial proportion of cases [38,39]. Beyond their impact on patient management and outcomes, the discovery and characterization of PADs have significantly advanced our understanding of human immunology and the cellular and molecular mechanisms underlying allergic inflammation [4,45]. Furthermore, the study of the pathophysiology of these diseases has led to the development of precision therapeutics used to treat both monogenic and polygenic allergic diseases [5]. In fact, there are many examples in the clinical literature showing that molecular diagnosis has been a powerful tool in guiding targeted therapy, transforming outcomes for patients with PADs by precisely identifying the affected pathways [5]. For example, in JAK1 GOF disease, hyperactive JAK-STAT signaling drove severe atopy, eosinophilia, and hepatosplenomegaly — treatment with ruxolitinib (a JAK1/2 inhibitor) has led to dramatic clinical improvement in the affected individuals, including resolution of dermatitis, eosinophilia, and failure to thrive [46,47]. Another striking disease is STAT6-GOF disease, where aberrant IL-4/IL-13 signaling drives systemic allergic inflammation — targeting IL-4Rα with dupilumab not only resolved eczema in the affected individuals but also significantly improved eosinophilia and growth [34,35]. Similarly, based upon the mechanistic demonstration of heightened IL-4Rα expression in patients with ERBIN deficiency, molecularly informed treatment with dupilumab was highly effective in treating a patient with refractory severe atopy [48,49]. These clinical cases underscore how precise molecular diagnosis enables pathway-specific therapies, leading to transformative, personalized treatment approaches in rare immune disorders.

In conclusion, as genetic sequencing becomes more affordable, accessible, and commonly employed in the clinical setting, the number of diagnosed cases of PADs will rise. Maintaining a high index of suspicion for PADs and utilizing advanced diagnostic tools are crucial for the accurate and timely diagnosis of the conditions, leading to improved patient outcomes.

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Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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This manuscript presents a detailed exploration of the genetic factors contributing to allergic diseases, with a particular focus on targeted therapeutic approaches. The authors systematically categorize offender genes associated with both monogenic and polygenic allergic disorders, providing a clear framework for understanding the underlying mechanisms of these conditions. Notably, the review includes comprehensive tables that summarize the identified PADs alongside their corresponding targeted treatments and targeted treatments used to treat common allergic diseases, facilitating a quick reference for clinicians. The study emphasizes the importance of precision medicine in allergy care, showcasing how genetic insights can inform the development of tailored therapies.

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