



What is new in HIES? Recent insights from the interface of primary immune deficiency and atopy

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Purpose of review

Understanding the pathophysiology of monogenic primary immunodeficiency (PID) with atopic presentation has pivotal implications for intervention strategies and potentially wider polygenic atopic-related traits. This review will discuss advances in gene discovery arising from monogenic defects at the interface between PID and atopy, notably the hyper-IgE syndromes.

Recent findings

Key molecular pathways underlying development of primary atopic diseases have recently been proposed. We test this classification through reviewing novel genes reported in the last 2 years and compare insights from pathway-analysis of genome-wide association studies (GWAS) of atopic-related traits.

Growing access to next-generation sequencing (NGS) has resulted in a surge in gene discovery, highlighting the utility and some pitfalls of this approach in clinical practice. The variability of presenting phenotypes reveals important gene-dosage effects. This has important implications for therapeutic strategies such as protein stabilization and modulators of JAK-STAT or T_H2-cytokine signalling. We also consider the therapeutic implications raised by CARD11 deficiency, and wider applications of NGS including polygenic risk score in atopy.

Summary

Disorders presenting at the interface between PID and allergy are often difficult to diagnose, with serious consequences if missed. Application of NGS has already provided critical insights to pathways enabling targeted therapeutic interventions, and potential wider translation to polygenic disorders.

Keywords

genome-wide association study, next-generation sequencing, primary atopic disease, primary immunodeficiency

INTRODUCTION

Hyper immunoglobulin E (HIES) syndromes are rare genetic immunodeficiency disorders characterized by recurrent infections, allergic symptoms, and systemic abnormalities that are associated with excessive T_H2 responses and often impaired T_H17 immunity. The introduction of next generation sequencing has contributed significantly to the pace of gene discovery, allowing both identification of novel defects where STAT3 sequencing has been normal in suspected hyper-IgE syndrome patients, and recognition of wider pathways linking primary immunodeficiency to atopy and allergy (Fig. 1).

Lyons and Milner have been major contributors to this field, and classify molecular pathways underlying such 'primary atopic diseases' within the broad categories of impaired T-cell receptor (TCR) signalling and cytoskeletal remodelling, altered cytokine signalling, T-cell repertoire restriction, tolerance failure, metabolic disturbance, mast cell

deregulation, or epithelial barrier disruption [1[■]]. It is important to note disorders may compromise multiple pathways leading to immune dysregulation syndromes with infection-susceptibility. For instance, the pleiotropic effects of DOCK8 deficiency are emerging beyond regulation of the actin cytoskeleton. These include modulation of STAT3

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KEY POINTS

- Monogenic and polygenic variation within immunological and barrier pathways link atopy, infection-susceptibility, and auto-immunity.
- Description of ZNF341 and STAT3 haploinsufficiency expand the phenotype of HIES syndromes and provide critical insights for gene dosage requirements in future therapies such as protein stabilization or gene therapy.
- SPINK7 identified as critical inhibitor of EoE, with description of germline deficiency cases awaited.
- ERBIN deficiency, JAK1-GOF, and CARD11-LOF mutations suggest the possibility of specific targeted therapies, with potential wider translation to polygenic disease.
- Polygenic risk scores may present additional benefits to clinical NGS beyond identification of Mendelian disorders.

and MyD88-dependent Toll-like receptor signalling [2] and extension of phenotype to include an IPEX-like disorder [3]. Truncating mutations in CARMIL2 (*RLTPR*) were reported in 2018 in three consanguineous Gulf families, presenting with recurrent skin abscesses, dermatitis, chest infections, and variable elevation of IgE [4]. This extends the previously reported phenotype from combined immunodeficiency with blunting of CD28-responses in T cells and B-cell receptor-signalling associated with pulmonary and cutaneous allergies [5].

What's New in HIES?

We will focus on genes associated with primary atopy and immune deficiency described since 2017, including those described subsequent to the development of this classification (Fig. 2).

STAT3 DOSAGE EFFECT

The molecular basis for the prototypic hyper IgE syndrome, Job's syndrome, was revealed in 2007 using functional characterization of cytokine signalling defects with linkage analysis to highlight STAT3 as the candidate gene [6,7]. Dominant-negative loss-of-function mutations in STAT3 are present in ~75% of sporadic or autosomal dominantly inherited HIES cases [8[■]]. Biallelic *DOCK8* mutations, found in 2016 by Keles *et al.* [9[■]] to have a role in regulation of STAT3, account for ~80% of patients with AR-HIES. The International Union of Immunological Societies (IUIS) classification [10] also recognizes autosomal recessive defects in glycosylation because of *PGM3* or the epithelial *SPINK5* as causes of HIES with distinctive clinical features (see [11[■]]).

Within the last year, two groups have reported another autosomal recessive form of hyper-IgE syndrome, caused by disruption of ZNF341-dependent STAT3 transcription and activity [8[■],12[■]]. These individuals displayed the clinical triad of HIES consisting of recurrent pneumonias, elevated serum IgE, and eczema with 'cold' skin abscesses. Mycotic infection risk was associated with marked reduction of T_H17 CD4⁺ T cells and enhanced T_H2 bias under conditions normally favouring T_H17 polarization

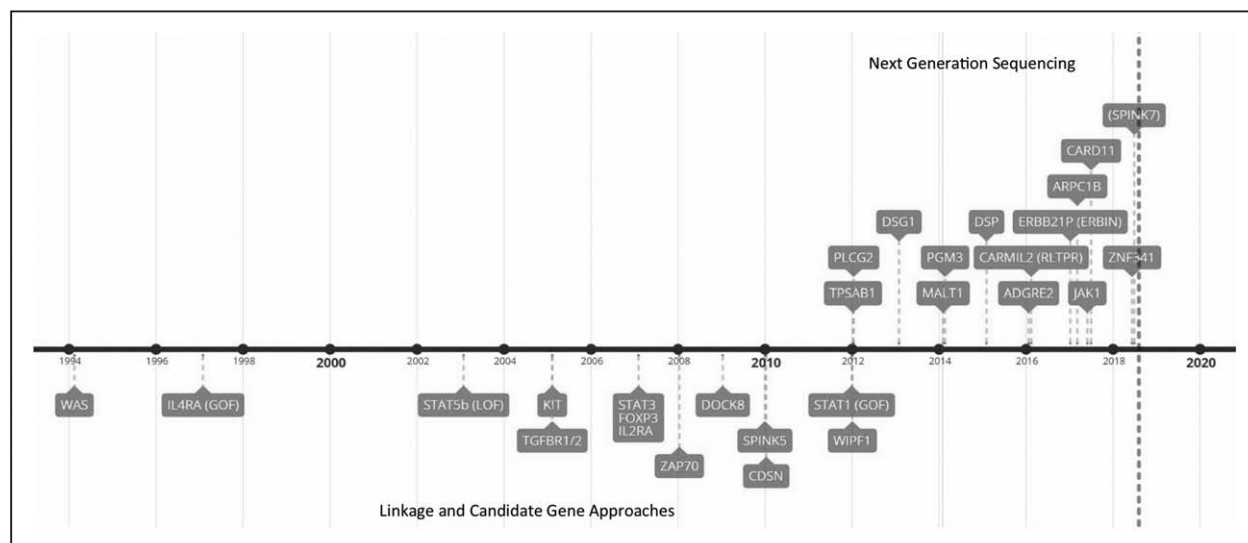


FIGURE 1. Impact of NGS on rate of gene discovery in primary atopic diseases, from [1[■]]. Genes associated with TCR repertoire restriction are not included as their initial descriptions were not associated with atopic or allergic manifestations; however, access to NGS has been instrumental in revealing hypomorphic mutations revealing these extended phenotypes [1[■]]. NGS, next-generation sequencing; TCR, T-cell receptor.

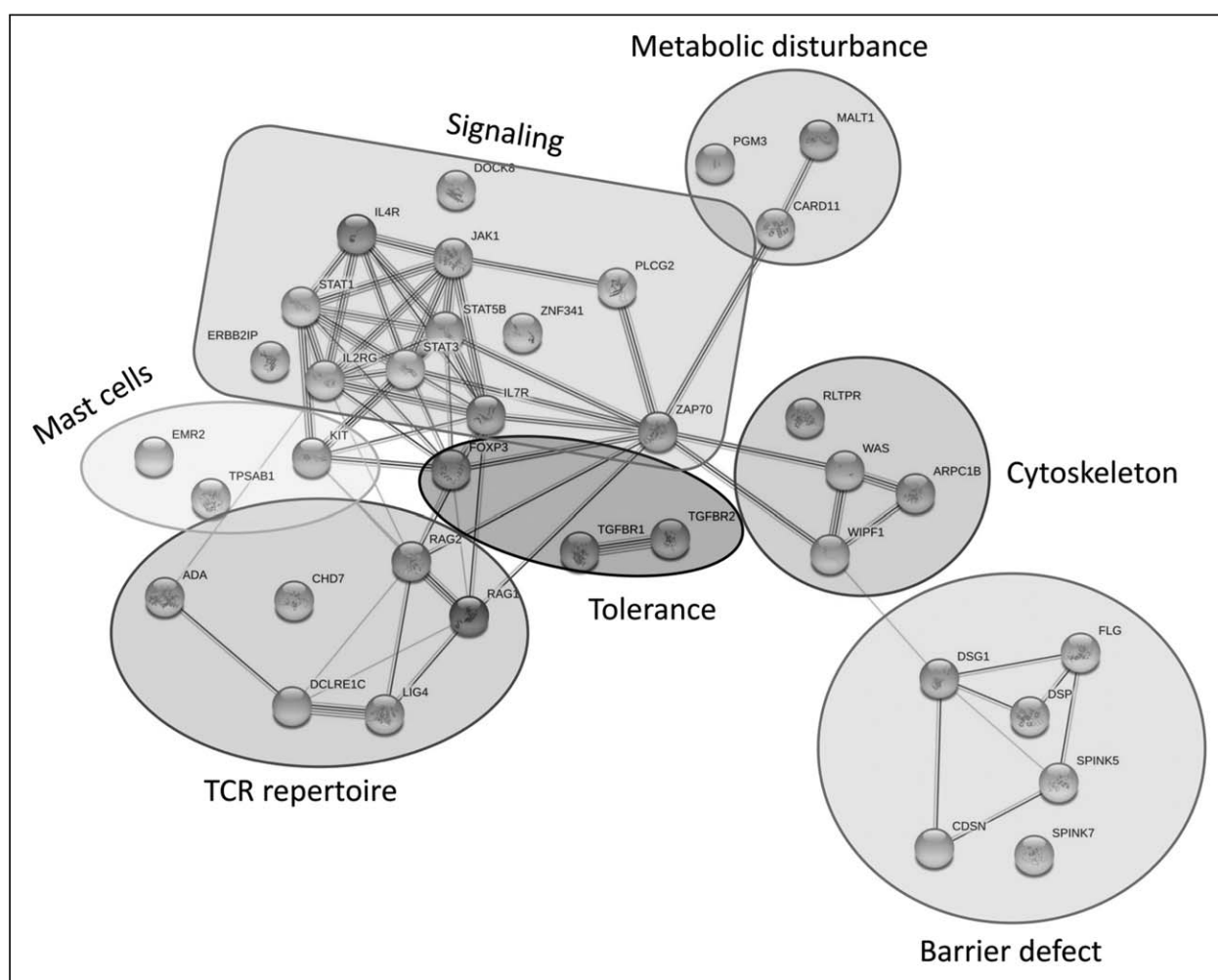


FIGURE 2. STRING protein–protein interaction network of currently published genes causing ‘primary atopic disease’ [1[■]]. Overlaid are proposed clusters of genes with similar pathophysiology, whilst links signify known or proposed interactions. Created using STRING version 10.5 (string-db.org/). Interactive figure with additional annotations available online at <https://version-10-5.string-db.org/cgi/network.pl?networkId=neudHitQfzGd>.

[12[■]]. ZNF341 acts as a transcription factor with highly specific sequence-binding capacity to regulate both STAT3 and STAT1 expression [12[■]], highlighting it as an important modulator controlling the balance of these key signalling molecules.

Dominant loss-of-function mutations in STAT3 result in a ~75% reduction in protein expression. STAT3 haploinsufficiency has been described this year presenting with adult-onset allergic rhinitis, eosinophilic esophagitis, but without classical features such as recurrent cutaneous ‘cold’ abscesses and with preserved T_H17 counts [13[■]]. The patient followed a relatively benign clinical course until development of rhino-orbital *Aspergillus* sinusitis with fatal cerebral invasion aged 37. This was a de novo splice site mutation, preventing further pedigree characterization. Extra-immunological syndromic features of STAT3-HIES were not clearly present, including bone fragility, abnormal facies,

and life-threatening vascular abnormalities such as vascular ectasia and aneurysmal tendency. It is relevant, that such extra-haematopoietic complications were reported in patients with ZNF341 (although not universally), further highlighting the sensitive gene dosage effects of STAT3 [12[■]].

Another molecular partner of STAT3 has been revealed by ERBIN deficiency [14[■]], connecting STAT3 to the TGF- β signalling pathway. ERBIN expression is induced by IL-6, forming a cytoplasmic complex sequestering SMAD2/3 and STAT3 in the cytoplasm, favouring induction of IL-4/IL-4R α /GATA3 axis *in vitro*.

Together, these observations add further weight to the central role of dysregulated STAT3 signalling at the interface between allergy and immune deficiency and support a change from the step-wise approach to genetic diagnosis towards target gene panels or whole exome or genome sequencing (WES or WGS).

BARRIER DEFECTS LINK ATOPY, ALLERGIC-SENSITIZATION, AND INFECTION SUSCEPTIBILITY

The importance of skin and mucosal barrier function for development of allergic reaction has been newly reinforced by Azouz *et al.* [15[¶]] who identify a critical role for serine protease inhibitor SPINK7 (5q32) in the development of eosinophilic esophagitis (EoE). EoE has similarly been recognized in a range of other HIES syndromes in relation to other barrier defects (SPINK5 deficiency in Comel Netherton Syndrome, CNS) [16] and in STAT3-HIES [17[¶]]. The inclusion of CNS within the IUIS classification of PID highlights the close overlap between immune dysregulation and the physical barrier and prompting multicentre immunological profiling of other severe barrier defects. Patients with CNS meet commonly used criteria alerting to the presence of PID including failure to thrive with recurrent multisystem infections requiring repeated hospitalization and impairment of innate and adaptive immune arms [18,19]. Beyond direct barrier compromise, epithelial genes associated with atopy in genome-wide association studies (GWAS) studies are also expressed within the thymus – leading to speculation that this may affect T-cell maturation. Intrathymic SPINK5 expression is primarily within Hassall's corpuscles of the thymic medulla, which express high levels of thymic stromal lymphopoietin (TSLP) and are involved in generation of regulatory T cells in humans [20]. The significance of this remains unclear, with apparent preservation of T_{REG} numbers in CNS patients and absence of autoimmunity [19]. It remains possible some of the immunological findings in disorders with severe barrier defects are confounding sequelae of malabsorption or because of absorption of topical treatments [18].

This raises wider questions regarding how clinicians approach and treat barrier dysfunction: a cohort study of over three million UK adults reported that in addition to cutaneous infection prevalence, the rate of pneumonia among individuals with atopic dermatitis is also elevated relative to nonatopic controls [21]. This cohort was genetically undefined and did not distinguish between individual and population risk. The risk of infections was further enriched in adults with additional diagnoses of asthma or seasonal rhinitis, and again this effect maybe compounded by treatment. It is also possible novel causes of atopic dermatitis associated with variable infections beyond the skin such as dominant-negative CARD11 mutations [22^{¶¶}] were included; however, these have only been described as rare variants to date.

PATHWAY ANALYSIS SHOWS OVERLAP BETWEEN GENOME-WIDE ASSOCIATION STUDIES AND MONOGENIC PRIMARY ATOPIC DISEASES

Atopy affects a significant proportion of the general population, with atopic dermatitis affects up to 20% of paediatric populations and 3% of adults from developed countries [23]. GWAS are designed and powered to detect common variants (typically with a minor allele frequency, MAF, of >5%) associated with the disease being studied and to further understanding of the biological pathways. GWAS of allergy and atopy have identified common genetic loci, which map genes, which should have marked overlap with monogenic causes of primary atopic disease [24]. To test this hypothesis, we reviewed the National Center for Biotechnology Information European Bioinformatics Institute GWAS catalogue using the search term 'allergy OR atopy' for loci from GWAS that met genome-wide significance ($P < 1 \times 10^{-8}$). From this search, we excluded studies that did not report either B-coefficients or odds ratios for the loci, or those that did not map to any known gene or characterized noncoding RNA, which resulted in over 200 loci, including CARD11 and STAT3. We then used Reactome pathway analysis to study enrichment of these genes within biological pathways. The results of this (Supplementary table 1, <http://links.lww.com/COAI/A16>) showed significant enrichment of multiple immunological pathways, similar to those of the 'primary atopic diseases,' including of antigen processing and MHC 1 presentation ($P = 1.11 \times 10^{-16}$), antigen cross presentation ($P = 1.11 \times 10^{-16}$), cytokine signalling ($P = 1.11 \times 10^{-16}$) immunoregulatory reactions between lymphoid and nonlymphoid cells ($P = 1.11 \times 10^{-16}$), and TCR stimulation (1.92×10^{-7}). These results suggest that genetic polymorphisms within similar immune pathways confer a polygenic atopic risk, albeit at a far lower clinical penetrance than in patients with rare monogenic defects. This is also consistent with overlaps between monogenic causes of atopy and wider immune dysregulation manifesting with infective and autoimmune susceptibilities [25].

OPPORTUNITIES AND PITFALLS OF NEXT-GENERATION SEQUENCING

Wide-scale genomic investigation, via whole exome or genome sequencing, of individuals with severe atopic phenotypes is now possible in clinical care [26]. The identification of a monogenic cause for atopy can have clinically important impacts on patients and their families allowing both precision medical interventions and family counselling

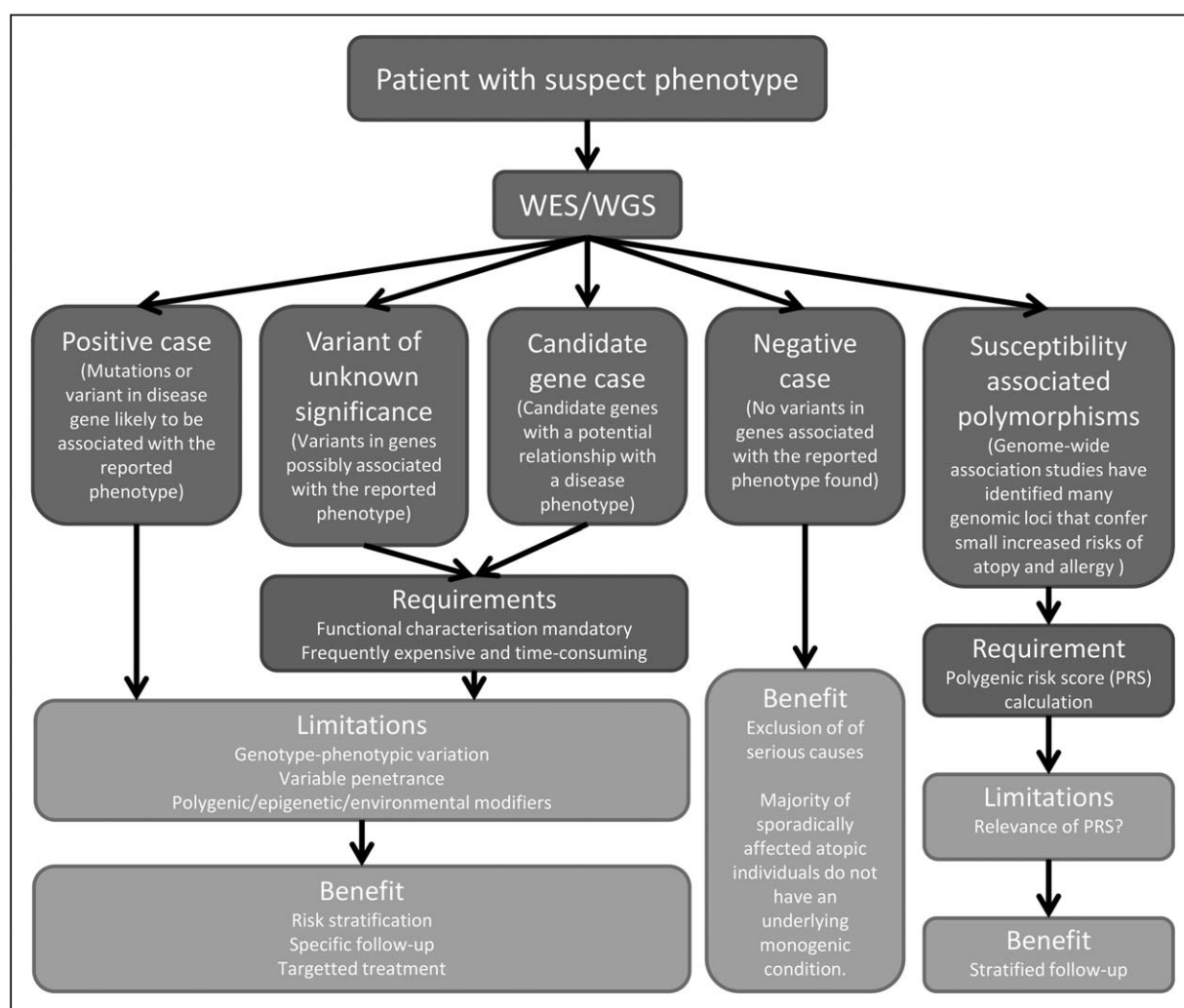


FIGURE 3. Utility of next-generation sequencing in clinical practice.

(Fig. 3). GWAS of atopy and allergy have identified many associated genomic loci and pathways that confer small increased risks of disease. Applying this to targeted gene panels or through analysis of WES/WGS from individuals can now be applied to individuals by calculation of a polygenic risk score (PRS) [27]. Such PRS are in use for conditions such as type 1 diabetes [28]. This may be of use in future risk stratification of atopy and disease severity prediction for individuals where NGS does not reveal a likely pathogenic monogenic variant. Harnessing the full potential of WES/WGS, including for PRS, requires detailed clinical characterization of large cohorts, bioinformatics, and facilities for functional validation.

The benefit of close collaboration between clinicians and bioinformaticians is apparent from several recent reports. Kuijpers *et al.* [29] described the first human genetic defect of the actin-related protein complex-1 (ARCP1B), resulting in a combined immunodeficiency with immune dysregulation

and a mild bleeding tendency. Here exome sequencing initially failed to detect this mutation because of the 'variant caller' parameters used and required subsequent platelet proteomics analysis to prompt re-examination based on the complete lack of ARCP1B. Somatic mosaicism [30], reversion or deep intronic variants can add to bioinformatic challenges.

WIDER APPLICATIONS OF NEXT-GENERATION SEQUENCING

NGS has also provided insights into the human skin microbiome, revealing a disrupted landscape in patients with primary immunodeficiencies [31]. Diversity in STAT3-HIES individuals appeared reduced to healthy controls, with enrichment of *Staphylococcus epidermidis* in the STAT3-HIES group. *Staphylococcus aureus* was also significantly enriched at skin sites but less prevalent than in atopic dermatitis controls [31]. *S. aureus* in atopic dermatitis has

been linked with T_H2 lymphocyte skewing and wider immune dysfunction, leading to novel therapeutic approaches including transfer of bacterial species with selective antimicrobial-peptide activity against *S. aureus* [32[■]]. Changes to the microbiome during targeted biologic therapies can also be studied [33].

The advent of high-throughput deep sequencing of peripheral lymphocytes offers a powerful clinicoresearch tool, for instance in quantifying variation of somatic mosaicism between cell lineages [13[■]]. Such analysis of individual B-cell immunoglobulin gene rearrangements can also enable efficient discrimination of routes to IgE class switching and inference of antibody affinity. This remains an uncharted area in hyper-IgE syndromes despite current knowledge that generation of follicular helper T cells contributing to germinal centre-formation is compromised in STAT3-HIES [34], and the discordance between atopy and allergic-manifestations [35]. Investigation of this discordance has already revealed multiple mechanistic insights including impaired mast cell degranulation [35] and barrier preservation [36]. We suggest skewing towards low-affinity IgE generation may also contribute to the discrepancy of atopy and observed allergic symptoms in STAT3-HIES and DOCK8. The demonstration that defects in lymphocyte apoptosis in the FAS pathway linked early escape of 'rogue' germinal centre B cells with elevation of serum IgE but without allergic symptoms [37] would be consistent with this hypothesis. Remarkably, FAS-deficient mice also showed progressive accumulation of low-affinity germinal centre IgG B-cells with a paradoxical reversal of the normal affinity maturation process [37]. This may be relevant to impaired durability of vaccine responses observed clinically [38].

IMPACT OF NEXT-GENERATION SEQUENCING ON TREATMENT

Whilst atopic traits may represent relatively minor clinical sequelae relative to life-threatening infection or autoimmune manifestations, allergic disease is the most frequent comorbidity of PID patients in general [39], across the IUIS groups [11[■]], and enriched within specific patient groups relative to the general population [40]. In a multinational survey of 136 DOCK8-deficiency cases, over 70% had clinical symptoms of allergy, including 16% with reported food-related anaphylaxis. Asthma, rhinitis, and drug allergy were also common [41]. Furthermore, food allergy can persist in such patients despite myeloablative bone marrow transplantation [42]. Multiple allergies are reported in WAS patients, with physician-diagnosed allergy in 20–30% of

cases [43] and conservative estimates of food allergy prevalence in Loeys-Dietz Syndrome of 31% [44].

GWAS and NGS of selected patients aim to identify new targets of scientific and therapeutic interest. A recent review highlighted the impact of GWAS in asthma over the last decade, which has identified 39 genetic susceptibility loci, but with limited novel pathway discovery and therapeutic translation. One trial of IL6-antagonist therapy in asthmatics is currently in progress, based on genotype and predicted soluble IL-6R levels [45]. In contrast, a number of molecularly targeted therapies have been revealed by NGS in monogenic primary immunodeficiency or atopic disorders. These include germline Janus kinase (JAK)2-gain-of-function mutations causing a systemic immune dysregulatory condition presenting with severe atopic dermatitis, environmental allergies, eosinophilia with autoimmunity, and failure to thrive [46[■]]. JAK inhibition with ruxolitinib proved transformative in the steroid-resistant atopic dermatitis, although the effects of long-term therapy remain unclear. Topical JAK inhibitors also ameliorate eczema via STAT3-mediated suppression and enhancement of filaggrin expression [47].

In a different approach, recognition of the destabilising effect of AD-STAT3 mutations underlying HIES has directed approaches to restore STAT3-protein expression via induction of chaperones *in vitro* with patient cells [48[■]]. Furthermore, this approach could restore differentiation of naïve CD4⁺ splenocytes into IL-17-producing cells in a murine model of STAT3-HIES [48[■]]. It is important to note most (81%) but not all of AD-HIES mutations analyzed were predicted to destabilize the protein, and further exploration in light of gene dosage variation revealed by ZNF341 and STAT3-haploinsufficiency are required. The potential of protein stabilization therapy to ameliorate wider extraimmunological manifestations of STAT3 is of particular interest, but poorly dealt with by current murine models of STAT3-HIES [49]. Augmentation of ZNF341 function to enhance STAT3 expression is an alternative potential therapeutic avenue [8[■],12[■]]. Given the pleiotropic roles and delicate balance between STAT signalling pathways (for instance autoimmunity associated with STAT3-GOF mutations [50]) personalized monitoring of treatment will likely be vital and supported by tools such as gene expression profiling and flow-cytometric evaluation of phosphorylated STAT activity [51[■]].

The treatment and prevention of atopic-related traits has made significant advances including use of trans-epidermal water loss (TEWL) to risk-stratify and direct treatment in neonates at risk of future atopic dermatitis [52]. Biologic therapies include

anti-IgE, trials of anti-TSLP, and the recent landmark approval of dupilumab [53]. This targets the shared IL-4 α receptor subunit to block both IL-4 and IL-13 signalling with efficacy in moderate-to-severe atopic dermatitis [54]. Observations of IL4R α upregulation on CD4 $^{+}$ T cells in ERBIN or STAT3 deficiency [14 *] suggest a role for dupilumab in potentially averting T_H2 polarization – although access remains limited by cost and relative novelty [55].

Targeted therapeutic strategies for Comel-Netherton syndrome include genetic correction of patient keratinocytes to enable autologous grafting [56], whilst treatment of epithelia with a protease inhibitor alpha-1-antitrypsin alleviated pathologic features associated with SPINK7 deficiency [15 *]. If successful, these promise to reveal if restoration of barrier function can prevent development of the associated allergic and broader immunodeficiency phenotypes.

The discovery of hypomorphic dominant negative CARD11 mutations highlight the importance of adequate strength of TCR signalling to ensure correct Th differentiation, with in-vitro glutamine supplementation rescuing T-cell polarization from T_H2 bias, bypassing the CARD11-mediated and activating mTOR [22 **] during T-cell activation and TCR signal transduction. Glutamine supplementation has previously been reported to ameliorate allergic disease in low-birth-weight infants [57] and has also been associated with a reduction in infectious complication rates in surgical and critically ill patients [58]. Clinical trials have yet to commence in hypomorphic CARD11 or wider polygenic atopic dermatitis populations but would offer a significantly lower cost alternative to biological or small-molecule inhibitors.

CONCLUSION

Atopic and allergic manifestations are associated with monogenic defects across the IUIS classification. Application of NGS to disorders at this interface of atopy and immune deficiency continue to reveal a rich tapestry of interlinked molecular pathways and highlight STAT3's roles as a central regulator of immune function, epithelial integrity, and wider tissue patterning. These have directed current licensed therapies such as JAK inhibitors, suggest targeted anticytokine interventions, and direct novel innovations including protein stabilization and gene therapy. Targeted nutritional supplementation or even correction of disrupted microbiota offer translational impact to the wider polygenic disorders.

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Conflicts of interest

There are no conflicts of interest.

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