The overlap between allergy and immunodeficiency

Kristin Sokol and Joshua D. Milner

Purpose of review
The mechanisms underlying the overlap of, and relationship between, atopy and immunodeficiency are just beginning to be recognized, through the identification of novel genetic conditions and the reexamination of well known primary immunodeficiencies. The present review seeks both to frame the topic and to highlight the most recent literature combining allergy in the context of immunodeficiency.

Recent findings
The true prevalence of atopic disorders in the setting of primary immunodeficiency as a whole is difficult to pinpoint, however there have been recent attempts to measure prevalence. Individual immunodeficiency disorders have been more carefully dissected for atopic disease and the mechanisms underlying the atopic phenotypic, whereas several newly described immune deficiencies because of single gene mutations are highly associated with atopic phenotypes. Finally, a number of novel genetic conditions with atopy being the primary feature, even in the absence of overt immune deficiency, have been described, providing instrumental clues into the diagnostic dilemmas these syndromes create.

Summary
Defining and examining diseases with primary features of atopy and infection allow for a better understanding of the interplay between the two in rare disease, and hopefully sheds light on fundamental pathways involved in atopy and host defense in the general population.

Keywords
allergy, immune deficiency, monogenic disorders

INTRODUCTION

Allergy has long been an observable component of immune deficiency, though for good reasons, the life-threatening infections tend to garner more of the attention than the atopic symptoms. Conversely, infection in the context of the highly atopic patients can sometimes be missed or dismissed as simply secondary to the allergic inflammation. Regardless, the overlap between the two provides an opportunity to better understand the underlying immune (and often genetic) defect that simultaneously causes impaired host defense and failure to regulate atopic responses.

Fundamentally, allergy in the context of primary immunodeficiency (PID) has always been a curious combination given that the patient must have impairment of the immune system sufficient enough to lead to infectious susceptibility, but intact enough to allow for the allergic response. Development of symptoms of allergic disease in the context of immune deficiency is the result of disruption of the complex balance within the immune system of effector and regulatory cells, perhaps also contributed to by differences in microbial colonization and infection patterns. Proposed reasons for how such dysregulation occurs have included a failure of central thymic tolerance, mismatch between effector and regulatory T-cell function, failure of production of counter regulating interferon-gamma (IFNγ) production and others [1,2]. One illustrative case for a number of these mechanisms is perhaps the first identified PID associated with atopic symptoms, Omenn Syndrome. Although complete T-cell dysfunction leads to classic SCID, partial or hypomorphic T-cell function can lead to autoimmune or allergic phenotypes with Omenn syndrome as a prime example [3]. Patients with Omenn syndrome present in infancy with symptoms consistent with classic SCID such as chronic viral respiratory infections, opportunistic infections, failure to thrive and diarrhea, but they also exhibit lymphadenopathy, hepatosplenomegaly, and widespread erythroderma

Laboratory of Allergic Diseases, NIAID, NIH, Bethesda, Maryland, USA

Correspondence to Joshua D. Milner, Laboratory of Allergic Diseases, NIAID, NIH, 10 Center Drive, NIH Building 10 Room 11N240A, Bethesda, MD 20892, USA. Tel: +1 301 827 3662; fax: +1 301 480 8384; e-mail: jdmilner@niaid.nih.gov

Curr Opin Pediatr 2018, 30:848–854

DOI:10.1097/MOP.0000000000000697

KEY POINTS

- Atopy in the setting of immunodeficiency can be common but is often overlooked.
- There are several novel genetic conditions, both with and without immunodeficiency that have been identified in recent years.
- The overlap of allergy and infection can provide a unique opportunity to study the complexities of the immune system and microbial colonization and infection patterns in humans.

and exfoliative dermatitis associated with oligoclonal T-cell expansion. These children also have elevated total serum immunoglobulin E (IgE) and eosinophilia, caused by the expanded and unregulated T cells that consistently secrete Th2 cytokines like interleukin (IL)-4, IL-13, and IL-5 [3]. However, these patients do not typically have environmental or food allergies as it has been suggested that their highly limited T-cell repertoire precludes mounting a specific response to these antigens [3].

Atopy in the setting of PID and as a result of single gene defects has become a more apparent phenotype. By recognizing these patients, there can be a better understanding of the complexities that are involved in regulating the atopic response, and how atopic responses impact host defense. The present review will summarize the significant recent discoveries in the overlap of atopy and immunodeficiency.

When atopy and immunity intertwine

In understanding allergic disease in the context of immune deficiency it is important to point out how symptoms of either can contribute to one another and/or be confused with one another. For example, allergic nasal inflammation could potentially lead to secondary infection [4], though the association is complex and a direct causal relationship is difficult to establish [5]. In addition, cytokines associated with allergic inflammation such as IL-13 in the context of atopic dermatitis can inhibit natural mucosal surface antimicrobial peptides leading to increased skin infection [6]. This is noteworthy because treatment of atopic dermatitis with newly approved dupilumab not only improves the eczema and itch, but also diminishes the number of skin infections, both viral and bacterial [7]. Primary skin barrier defects can also directly lead to infectious predilection, such as the case of patients with deficiency of Filaggrin, a key skin barrier protein, who have increased rates of molluscum contagiosum [8]. It is likely that the interplay between skin infection, both viral and bacterial, and atopic dermatitis is heterogeneous in that an underlying genetic lesion could lead to a host defense defect which also directly leads to atopy. The atopic mucosal surface could create the milieu for infectious predilection as is the case for defense inhibition, and/or the infection could drive the atopic phenotype [9,10▪]. This theory is further buttressed by a recent study showing amelioration of atopic disease in patients topically treated for their skin microbial dysbiosis [11▪▪]

Prevalence data

How much allergic disease can there be found in classical immune deficiencies? There have been limited studies that measure the burden of allergic diseases across a broad spectrum of primary immune deficiencies, with widely variable results. A recent US Immunodeficiency Network (USIDNET) study found the overall prevalence of both food allergy and atopic dermatitis in patients with PIDDs to be lower than that in the general population. However, there were certain PIDDs that were found to have a higher rate of patients with food allergy, specifically CD40 ligand deficiency, primary hypogammaglobulinemia, hyper IgE syndrome, combined immunodeficiency (CID), and selective IgA deficiency (SIgAD). Similarly, there were certain PIDDs that presented with higher rates of atopic dermatitis than the general population, specifically nuclear factor-κB essential modulator deficiency, Wiskott–Aldrich syndrome (WAS), CID, selective IgM deficiency, and patients with STAT3 loss-of-function (LOF; the autosomal dominant hyper-IgE syndrome) [12].

Additional studies have attempted to characterize allergic disease within specific immunodeficiency diseases. One retrospective review of patients with common variable immunodeficiency (CVID) revealed 60/160 (37.5%) had a diagnosis of asthma for which most were prescribed a controller medication. Symptoms consistent with rhinitis were reported in 89/160 (55.5%), again for whom most were prescribed controller medications. A documented (but not oral challenge confirmed) food allergy was found in 18/160 of their patients with CVID. IgE-mediated allergic disease was proven in only 11% of patents with CVID and rhinitis, and only 10% of patients with CVID and asthma, although specific allergy testing was limited [13]. A single-center cohort study of patients with early onset ADA-SCID showed that atopy was present in 10/18 (56%) of the patients. The most common atopic manifestations were allergic rhinitis (50%) and asthma (22.2%), followed by food allergy (11.1%), mild atopic dermatitis (11.1%), and

urticaria (11.1%). Even in the absence of clinical allergy, many of the patients were found to have increased $CD4^+$ Th2 cytokine production [14].

Reports from other countries regarding atopic features in PID have also revealed variable results. One Iranian report found 9/41 (20%) of hypogammaglobulinemia patients with asthma, 10/41 (22%) with rhinitis, and 4/41 (9%) with atopic dermatitis [15] whereas in another report, atopic dermatitis was present in 52% of patients with SIgAD [16]. Atopic dermatitis was found in only 2.3% of Brazilian patients with SIgAD [17], whereas in a Swedish report, parentally reported eczema was not associated with SIgAD [18]. A report from Kuwait on skin manifestations in PIDs found that 19% of patients with PIDs have atopic dermatitis [19]. A study from Poland reported a high rate of food allergy (74%) in their pediatric patients with hypogammaglobulinemia, but the reported symptoms of food allergy were wider than typical, including eczema, reflux, abdominal cramping, and diarrhea [20]. The various discrepancies above could be because of differing environmental exposures but more likely differing algorithms for atopic dermatitis diagnosis plays a substantial role [12].

Because poor counterregulatory IFNγ production is a proposed explanation for allergy in PIDs, one particularly relevant population is patients with mutations in the IFNγ receptor or IL-12 signaling pathway. Curiously, although clinical atopy and total serum IgE levels were generally higher in patients with IFNGR mutations than those with IL-12R mutations, the prevalence of atopic disease, including asthma, eczema, and allergic rhinoconjunctivitis, was similar to that of a normal comparator population derived from worldwide ISAAC data. Only 9/29 had ever experienced symptoms of clinical allergic disease, and none of them had severe or difficult-to-control allergic disease [21].

From all of these reports, it is clear that more careful phenotypic study of allergic disease in a wide range of PIDs in a variety of environments would be most helpful in better delineating the allergic burden to anticipate for different PIDs.

Primary immunodeficiencies classically associated with atopy

There are several PIDs known to be typically associated with atopy, especially eczematous dermatitis and elevated serum IgE. Study of the atopic manifestations of these diseases can help shed light on fundamental pathways involved in atopy and the control thereof. Wiskott–Aldrich Syndrome (WAS), characterized by eczema, thrombocytopenia, and recurrent infection, because of mutations in actin-cytoskeleton-related gene WASP, is one such classic example. Although the mechanism for atopy in WAS is not fully defined, it is thought that regulatory T-cell dysfunction is a likely contributor [22–24]. Food allergies were recently examined in a cohort of 25 patients with mutations in the *WASP* gene. Food allergen-specific IgE was detected in 33% (4/12) of WAS and 20% (2/10) of patients with X-linked thrombocytopenia (XLT), whereas the prevalence of physician-diagnosed food allergy among WAS and patients with XLT in childhood (20 and 30%, respectively) was increased. Notably none of the patients reported a history of anaphylaxis potentially explained by mouse model data within the same study, which showed that absence of WASP within regulatory T cells alone actually led to worse reactions to food, suggesting that other effector mechanisms for allergy are actually impaired when WASP is mutated [25]. Indeed, it has been previously shown that WASP is important in mast cell degranulation [25,26].

A series of reports have recently identified a disorder related to WAS because of mutations in the Arp 2/3 complex [27▪–29▪], which is critical for actin cytoskeleton remodeling and is activated by WASP. Mutations in ARPC1B, the gene encoding a member of the ARP 2/3 complex, have been described in two brothers with a WAS-like clinical phenotype, including severe infections, eczematous dermatitis, and elevated IgE levels [29▪]. An additional patient was recently reported with CID with recurrent infections, symptoms of immune dysregulation, and a mild bleeding tendency, also with a mutation in ARPC1B. Allergic disease in this patient manifested as severe eczema in addition to anaphylaxis after ingestion of nuts. Elevated total serum IgE and eosinophilia were observed [28▪]. Finally, a report of three patients from two different families, all with homozygous mutations in ARPC1B, revealed a phenotype of platelet abnormalities, cutaneous vasculitis, predisposition to inflammatory diseases, an eczema-like rash, and eosinophilia [27▪]. The mechanism of allergic disease seen in this disorder is unknown but as with WAS, regulatory T cells are abnormal in ARP2/3 mutant mice [30].

A number of other PIDs associated with allergy often have been described as 'Hyper-IgE Syndromes'. Although originally described in patients with Job's Syndrome who ultimately were found to have the autosomal dominant hyper-IgE Syndrome due to STAT3 mutations, the term can be confusing, as any marked elevation in IgE could be considered a 'hyper-IgE' syndrome. Multiple additional syndromes have since been found to be associated with high IgE, with and without comorbid infection, but

syndromic nonetheless. In addition to STAT3 LOF, these disorders include ZNF341 mutations, DOCK8 deficiency, PGM3 deficiency, and CARD11 dominant negative mutation.

It is noteworthy that despite the marked IgE elevation, patients with STAT3 LOF mutations are relatively protected from severe allergic reactions because of defects in mast cell degranulation and vascular responses to histamine caused by the STAT3 mutation itself [31–33].

DOCK8 deficiency is a CID associated with severe atopy and high IgE which is distinguished from the others by a significantly elevated rate of viral skin infections and malignancy [34]. The skin, viral and neoplastic phenotypes overlap with WAS and the similarities have been proposed to be due to direct interactions of DOCK8 with WASP [35]. Similarly, the phenotypic overlap with STAT3LOF including very high IgE, B-cell defects, infection and others may be due to direct interactions between DOCK8 and STAT3, and/or joint participation in pathways involved in lymphocyte signaling [36–38].

Mutations in PGM3, a gene encoding a protein involved in glycosylation required for many cellular functions, lead to a variety of atopic diseases and recurrent bacterial and viral infections, but also autoimmunity and developmental disorders because of abnormal myelination. Interestingly, PGM3 deficiency is variable as well in that it does not always lead to an atopic phenotype – sometimes it manifests as more typical SCID and without developmental abnormalities [39–43].

Recently described, recessive ZNF341 mutations [44▪,45▪] were found in multiple patients with recurrent and severe infections, some skeletal abnormalities as seen in STAT3LOF, atopy, and elevated IgE. ZNF341 appears to control STAT3 expression itself, likely explaining some of the overlap between these patients and those with STAT3LOF. Although there is still no clear explanation for how the loss of STAT3 function leads to allergic symptoms, this syndrome provides another opportunity to attempt to better understand the association.

Although complete LOF mutations in CARD11 can lead to SCID, dominant, hypomorphic CARD11 mutations have recently been described to be associated with severe atopy, with and without infections beyond the skin. CARD11 (also known as CARMA1) is an important scaffold protein and is required for both B-cell receptor and T-cell receptor signaling to the NF-κB pathway [46]. Eight patients from four different families were described with mutations in CARD11 and all had severe atopic disease and viral skin infections. Many, but not all, also had respiratory infections [47▪▪]. Subsequently, four additional related patients with a mutation in CARD11 were reported with CID, asthma, atopic dermatitis, food allergies, and autoimmunity, and all with elevated total serum IgE levels [48]. The mutations described lead to a decrease in IL-2 and IFNγ secretion as well as T-cell proliferation because of effects on the NF-κB and mTORC1 pathways. Interestingly, the impairment of mTORC1 signaling, which was observed in CARD11 mutant mouse models, and known to be important for normal IFNγ production and prevention of Th2-associated phenotypes [49–52] could be partially restored in vitro by exogenous glutamine supplementation. How the atopic phenotype emerges in this setting is not as clear, but the findings are noteworthy as CARD11 mutations have been found to be associated with 'typical' atopic dermatitis by genome-wide association studies [53], and a trial of glutamine supplementation in an unselected population of premature infants showed long-term protection from atopic dermatitis [54].

Novel atopic diseases without primary immunodeficiency

As some of the CARD11 mutant patients illustrate, it should be noted that syndromic atopic disease which could present to the pediatrician or allergist/immunologist does not always have accompanying host defense defects that would typically be associated with a PID. This nonetheless can create confusion given that the patient is 'syndromic' because of any number of comorbidities, and also may have 'hyper-IgE' because of the elevation in serum IgE, or any other striking atopic phenotype such as eosinophilia, severe dermatitis, urticaria, and so on. There have been several such recently described examples. One such example can be noted in a novel gain-of-function (GOF) mutation in the critical cytokine signaling molecule Janus kinase 1 (JAK1), which was found in a mother and two children with a syndrome of immune dysregulation including severe atopic dermatitis, environmental allergies, asthma, eosinophilia, liver cysts, hepatosplenomegaly, autoimmune thyroid disease, and failure to thrive. Interestingly, their total serum IgE levels were normal. The condition of the two children improved dramatically with the administration of a JAK inhibitor [55▪▪], illustrating the power and utility of investigating severe atopic disease as a potential monogenic disorder. Just downstream of JAK1 is STAT5b, whose loss leads to short stature, recurrent infection autoimmunity and atopy [56]. Interestingly, somatic GOF mutations in STAT5b were found to lead to a syndrome not so different from the JAK1GOF, including very early

onset nonclonal eosinophilia, atopic dermatitis, urticarial rash, and diarrhea [57].

A novel variant in ADGRE2 (also known as EMR2) was recently discovered as the basis of autosomal dominant vibratory urticaria in three unrelated families who presented with lifelong histories of localized, erythematous, edematous, pruritic hives after repetitive mechanical stimulation of the skin. The mutation causes the inhibitory interaction between the subunits of its receptor to weaken, thereby lowering the threshold of vibration-induced mast cell degranulation [58].

There are additional examples of defined genetic disorders associated with allergic disease, not always associated with infection. These include Plcg2-associated antibody deficiency and immune dysregulation, which leads to cold urticaria almost universally, as well as more variable humoral immune deficiency, cutaneous granuloma formation, and autoimmunity [59,60]; Loeys–Dietz syndrome, a genetic disorder of the vasculature and skeletal system caused by mutations in the genes encoding receptor subunits for TGF (transforming growth factor) β [61], which is strongly associated with a variety of atopic disorders [62]; physical skin barrier defect disorders including severe dermatitis, multiple allergies, and metabolic wasting (SAM syndrome) attributed to LOF mutations in corneodesmosin, desmosomal plaque protein desmoglein 1 gene, and desmoplakin [63–65], Netherton syndrome caused by a mutation in SPINK5 [66] and ichthyosis vulgaris caused by a mutation in the filaggrin gene (FLG) [67,68]; and hereditary alpha-tryptasemia syndrome caused by duplications in TPSAB1 causing a variety of symptoms including those associated with acute mast cell degranulation, as well as functional gastrointestinal disorders, connective tissue abnormalities, and dysautonomia [69].

CONCLUSION

Allergic disease can be a common component of a primary immune deficiency, and can even be the presenting sign and characteristic of certain specific PIDs. In other cases, it may have a syndromic association and comorbidities independent of PIDs. The era of next-generation sequencing will expand the pool of diseases of both types, potentially easing some diagnostic difficulties. At the same time, clinical presentations which can confuse atopic versus infectious manifestations will continue to cause diagnostic and therapeutic quandaries, requiring an open mind to the presence of both in highly affected patients when presenting with focal symptoms, and when assessing the patient as whole from an underlying diagnostic perspective.

Acknowledgements

This work was supported by the Intramural Research Program of the NIAID, NIH.

Financial support and sponsorship

This work was supported by the Intramural Research Program of the NIAID, NIH.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Lyons JJ, Milner JD. Primary atopic disorders. J Exp Med 2018; 215:1009–1022.
2. Milner JD, Fasth A, Etzioni A. Autoimmunity in severe combined immunodeficiency (SCID): lessons from patients and experimental models. J Clin Immunol 2008; 28(Suppl 1):S29–S33.
3. Villa A, Notarangelo LD, Roifman CM. Omenn syndrome: inflammation in leaky severe combined immunodeficiency. J Allergy Clin Immunol 2008; 122:1082–1086.
4. de Oliveira TB, Klering EA, da Veiga ABG. Is recurrent respiratory infection associated with allergic respiratory disease? J Asthma 2018; 1–7. [Epub ahead of print]
5. Hoffmans R, Wagemakers A, van Drunen C, *et al.* Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment. PLoS One 2018; 13:e0192330.
6. Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. Clin Rev Allergy Immunol 2016; 51:329–337.
7. Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. J Am Acad Dermatol 2018; 78:62–69.e1.
8. Manti S, Amorini M, Cuppari C, *et al.* Filaggrin mutations and Molluscum contagiosum skin infection in patients with atopic dermatitis. Ann Allergy Asthma Immunol 2017; 119:446–451.
9. Kobayashi T, Glatz M, Horiuchi K, *et al.* Dysbiosis and *Staphylococcus aureus* colonization drives inflammation in atopic Dermatitis. Immunity 2015; 42:756–766.
10. ■ Nakatsuji T, Chen TH, Narala S, *et al.* Antimicrobials from human skin commensal bacteria protect against Staphylococcus aureus and are deficient in atopic dermatitis. Sci Transl Med 2017; 9:.

Identifies loss of specific protective bacteria on skin of those with atopic dermatitis, thus leading to increased infection. Highlights the importance of the relationship between the human epithelial barrier and microbial colonization.

11. ■■ Myles IA, Earland NJ, Anderson ED, *et al.* First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. JCI Insight 2018; 3:.

Offers more direct evidence that microbiome can directly affect allergic inflammation by showing that transplanted commensal bacteria onto the skin of patients with atopic dermatitis could lead to significant improvement in both objective and subjective measures of disease.

12. Tuano KS, Orange JS, Sullivan K, *et al.* Food allergy in patients with primary immunodeficiency diseases: prevalence within the US Immunodeficiency Network (USIDNET). J Allergy Clin Immunol 2015; 135:273–275.
13. Bjelac JA, Blanch MB, Fernandez J. Allergic disease in patients with common variable immunodeficiency at a tertiary care referral center. Ann Allergy Asthma Immunol 2018; 120:90–92.
14. Lawrence MG, Barber JS, Sokolic RA, *et al.* Elevated IgE and atopy in patients treated for early-onset ADA-SCID. J Allergy Clin Immunol 2013; 132:1444–1446.
15. Dadkhah M, Aghamohammadi A, Movahedi M, Gharagozlou M. Atopic manifestations: dermatitis, allergic rhinitis and asthma in patients with hypogammaglobulinemia. Iran J Pediatr 2015; 25:e2786.
16. Aghamohammadi A, Cheraghi T, Gharagozlou M, *et al.* IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol 2009; 29:130–136.
17. Jacob CM, Pastorino AC, Fahl K, *et al.* Autoimmunity in IgA deficiency: revisiting the role of IgA as a silent housekeeper. J Clin Immunol 2008; 28(Suppl 1):S56–S61.

18. Janzi M, Kull I, Sjoberg R, *et al.* Selective IgA deficiency in early life: association to infections and allergic diseases during childhood. Clin Immunol 2009; 133:78–85.

19. Al-Herz W, Nanda A. Skin manifestations in primary immunodeficient children. Pediatr Dermatol 2011; 28:494–501.

20. Szczawinska-Poplonyk A. An overlapping syndrome of allergy and immune deficiency in children. J Allergy (Cairo) 2012; 2012:658279.

21. Wood PM, Fieschi C, Picard C, *et al.* Inherited defects in the interferon-gamma receptor or interleukin-12 signalling pathways are not sufficient to cause allergic disease in children. Eur J Pediatr 2005; 164:741–747.

22. Adriani M, Aoki J, Horai R, *et al.* Impaired in vitro regulatory T cell function associated with Wiskott-Aldrich syndrome. Clin Immunol 2007; 124:41–48.

23. Humblet-Baron S, Sather B, Anover S, *et al.* Wiskott-Aldrich syndrome protein is required for regulatory T cell homeostasis. J Clin Invest 2007; 117:407–418.

24. Maillard MH, Cotta-de-Almeida V, Takeshima F, *et al.* The Wiskott-Aldrich syndrome protein is required for the function of CD4(+)CD25(+)Foxp3(+) regulatory T cells. J Exp Med 2007; 204:381–391.

25. Lexmond WS, Goettel JA, Lyons JJ, *et al.* FOXP3+ Tregs require WASP to restrain Th2-mediated food allergy. J Clin Invest 2016; 126:4030–4044.

26. Pivniouk VI, Snapper SB, Kettner A, *et al.* Impaired signaling via the high-affinity IgE receptor in Wiskott-Aldrich syndrome protein-deficient mast cells. Int Immunol 2003; 15:1431–1440.

27. ■ Kahr WH, Pluthero FG, Elkadri A, *et al.* Loss of the Arp2/3 complex component ARPC1B causes platelet abnormalities and predisposes to inflammatory disease. Nat Commun 2017; 8:14816.

The three reports describe a novel monogenenic disorder molecularly and clinically related to Wiskott–Alrich Syndrome, leading to both infectious and atopic manifestations, and highlighting the role for actin cytoskeleton proteins in both host defense and allergy.

28. ■ Kuijpers TW, Tool ATJ, van der Bijl I, *et al.* Combined immunodeficiency with severe inflammation and allergy caused by ARPC1B deficiency. J Allergy Clin Immunol 2017; 140:273–277.e10.

The three reports describe a novel monogenenic disorder molecularly and clinically related to Wiskott–Alrich Syndrome, leading to both infectious and atopic manifestations, and highlighting the role for actin cytoskeleton proteins in both host defense and allergy.

29. ■ Somech R, Lev A, Lee YN, *et al.* Disruption of thrombocyte and T lymphocyte development by a mutation in ARPC1B. J Immunol 2017; 199:4036–4045.

The three reports describe a novel monogenenic disorder molecularly and clinically related to Wiskott–Alrich Syndrome, leading to both infectious and atopic manifestations, and highlighting the role for actin cytoskeleton proteins in both host defense and allergy.

30. Zhang Y, Shen H, Liu H, *et al.* Arp2/3 complex controls T cell homeostasis by maintaining surface TCR levels via regulating TCR(+) endosome trafficking. Sci Rep 2017; 7:8952.

31. Boos AC, Hagl B, Schlesinger A, *et al.* Atopic dermatitis, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern. Allergy 2014; 69:943–953.

32. Siegel AM, Stone KD, Cruse G, *et al.* Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. J Allergy Clin Immunol 2013; 132:1388–1396.

33. Hox V, O'Connell MP, Lyons JJ, *et al.* Diminution of signal transducer and activator of transcription 3 signaling inhibits vascular permeability and anaphylaxis. J Allergy Clin Immunol 2016; 138:187–199.

34. Zhang Q, Davis JC, Lamborn IT, *et al.* Combined immunodeficiency associated with DOCK8 mutations. New Engl J Med 2009; 361: 2046–2055.

35. Janssen E, Tohme M, Hedayat M, *et al.* A DOCK8-WIP-WASp complex links T cell receptors to the actin cytoskeleton. J Clin Invest 2016; 126:3837–3851.

36. Jabara HH, McDonald DR, Janssen E, *et al.* DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. Nat Immunol 2012; 13:612–620.

37. Keles S, Charbonnier LM, Kabaleeswaran V, *et al.* Dedicator of cytokinesis 8 regulates signal transducer and activator of transcription 3 activation and promotes TH17 cell differentiation. J Allergy Clin Immunol 2016; 138:1384–1394.e2.

38. Massaad MJ, Cangemi B, Al-Herz W, *et al.* DOCK8 and STAT3 dependent inhibition of IgE isotype switching by TLR9 ligation in human B cells. Clin Immunol 2017; 183:263–265.

39. Bernth-Jensen JM, Holm M, Christiansen M. Neonatal-onset T(-)B(-)NK(+) severe combined immunodeficiency and neutropenia caused by mutated phosphoglucomutase 3. J Allergy Clin Immunol 2016; 137:321–324.

40. Sassi A, Lazaroski S, Wu G, *et al.* Hypomorphic homozygous mutations in phosphoglucomutase 3 (PGM3) impair immunity and increase serum IgE levels. J Allergy Clin Immunol 2014; 133:1410–1419; 9 e 1-13.

41. Stray-Pedersen A, Backe PH, Sorte HS, *et al.* PGM3 mutations cause a congenital disorder of glycosylation with severe immunodeficiency and skeletal dysplasia. Am J Hum Genet 2014; 95:96–107.

42. Zhang Y, Yu X, Ichikawa M, *et al.* Autosomal recessive phosphoglucomutase 3 (PGM3) mutations link glycosylation defects to atopy, immune deficiency, autoimmunity, and neurocognitive impairment. J Allergy ClinI Immunol 2014; 133:1400–1409; 1400-9, 1409.e1-5.

43. Ben-Khemis L, Mekki N, Ben-Mustapha I, *et al.* A founder mutation underlies a severe form of phosphoglutamase 3 (PGM3) deficiency in Tunisian patients. Mol Immunol 2017; 90:57–63.

44. ■ Beziat V, Li J, Lin JX, *et al.* A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. Sci Immunol 2018; 3:; pii: eaat4956.

Mutations in a transcription factor which appears to control STAT3 expression lead to a phenotype reminiscent of those with STAT3LOF, providing the opportunity to further understand the association between allergy and STAT3 function.

45. ■ Frey-Jakobs S, Hartberger JM, Fliegauf M, *et al.* ZNF341 controls STAT3 expression and thereby immunocompetence. Sci Immunol 2018; 3:; pii: eaat4941.

Mutations in a transcription factor which appears to control STAT3 expression lead to a phenotype reminiscent of those with STAT3LOF, providing the opportunity to further understand the association between allergy and STAT3 function.

46. Staal J, Bekaert T, Beyaert R. Regulation of NF-kappaB signaling by caspases and MALT1 paracaspase. Cell Res 2011; 21:40–54.

47. ■■ Ma CA, Stinson JR, Zhang Y, *et al.* Germline hypomorphic CARD11 mutations in severe atopic disease. Nat Genet 2017; 49:1192–1201.

The findings highlight dominant mutations in CARD11 as a potential cause of severe allergy without other syndromic feature features. The mutations result in poor upregulation of a glutamine transporter, and the study provides evidence for glutamine supplementation as a potential therapeutic intervention in atopic disease.

48. Dadi H, Jones TA, Merico D, *et al.* Combined immunodeficiency and atopy caused by a dominant negative mutation in caspase activation and recruitment domain family member 11 (CARD11). J Allergy Clin Immunol 2017; 141:1818–1830.e2.

49. Delgoffe GM, Pollizzi KN, Waickman AT, *et al.* The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. Nat Immunol 2011; 12:295–303.

50. Kurebayashi Y, Nagai S, Ikejiri A, *et al.* PI3K-Akt-mTORC1-S6K1/2 axis controls Th17 differentiation by regulating Gfi1 expression and nuclear translocation of RORgamma. Cell Rep 2012; 1:360–373.

51. Lee K, Gudapati P, Dragovic S, *et al.* Mammalian target of rapamycin protein complex 2 regulates differentiation of Th1 and Th2 cell subsets via distinct signaling pathways. Immunity 2010; 32:743–753.

52. Zeng H, Cohen S, Guy C, *et al.* mTORC1 and mTORC2 kinase signaling and glucose metabolism drive follicular helper T cell differentiation. Immunity 2016; 45:540–554.

53. Hirota T, Takahashi A, Kubo M, *et al.* Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. Nat Genet 2012; 44:1222–1226.

54. van Zwol A, Moll HA, Fetter WP, van Elburg RM. Glutamine-enriched enteral nutrition in very low birthweight infants and allergic and infectious diseases at 6 years of age. Paediatr Perinat Epidemiol 2011; 25:60–66.

55. ■■ Del Bel KL, Ragotte RJ, Saferali A, *et al.* JAK1 gain-of-function causes an autosomal dominant immune dysregulatory and hypereosinophilic syndrome. J Allergy Clin Immunol 2017; 139:2016–2020.e5.

This GOF mutation in JAK1 in a family with severe atopic disease and profound eosinophilia immmunodysregulation is even more notable for the successful treatment of their disease with a JAK1 inhibitor. This report provides further insight into the role for JAK/STAT signaling in allergy and also importantly highlights the power of directed therapies based on identifying monogenic causes of atopic disease.

56. Kanai T, Jenks J, Nadeau KC. The STAT5b pathway defect and autoimmunity. Front Immunol 2012; 3:234.

57. Ma CA, Xi L, Cauff B, *et al.* Somatic STAT5b gain-of-function mutations in early onset nonclonal eosinophilia, urticaria, dermatitis, and diarrhea. Blood 2017; 129:650–653.

58. Boyden SE, Desai A, Cruse G, *et al.* Vibratory urticaria associated with a missense variant in ADGRE2. N Engl J Med 2016; 374:656–663.

59. Ombrello MJ, Remmers EF, Sun G, *et al.* Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. N Engl J Med 2012; 366:330–338.

60. Gandhi C, Healy C, Wanderer AA, Hoffman HM. Familial atypical cold urticaria: description of a new hereditary disease. J Allergy Clin Immunol 2009; 124:1245–1250.

61. Loeys BL, Schwarze U, Holm T, *et al.* Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006; 355:788–798.

62. Frischmeyer-Guerrerio PA, Guerrerio AL, Oswald G, *et al.* TGFbeta receptor mutations impose a strong predisposition for human allergic disease. Sci Transl Med 2013; 5:195ra94.

63. Oji V, Eckl KM, Aufenvenne K, *et al.* Loss of corneodesmosin leads to severe skin barrier defect, pruritus, and atopy: unraveling the peeling skin disease. Am J Hum Genet 2010; 87:274–281.

64. McAleer MA, Pohler E, Smith FJ, *et al.* Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin. J Allergy Clin Immunol 2015; 136:1268–1276.

65. Samuelov L, Sarig O, Harmon RM, *et al.* Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. Nat Genet 2013; 45:1244–1248.

66. Chavanas S, Bodemer C, Rochat A, *et al.* Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nat Genet 2000; 25:141–142.
67. Sandilands A, Terron-Kwiatkowski A, Hull PR, *et al.* Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet 2007; 39:650–654.
68. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 2011; 365:1315–1327.
69. Lyons JJ, Yu X, Hughes JD, *et al.* Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet 2016; 48:1564–1569.