Published in final edited form as:

Curr Opin Immunol. 2015 October ; 36: 115–126. doi:10.1016/j.coi.2015.08.002.

Genetics of allergy and allergic sensitization: common variants, rare mutations

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Abstract

Our understanding of the specific genetic lesions in allergy has improved in recent years due to identification of common risk variants from genome-wide association studies (GWAS) and studies of rare, monogenic diseases. Large-scale GWAS have identified novel susceptibility loci and provided information about shared genetics between allergy, related phenotypes and autoimmunity. Studies of monogenic diseases have elucidated critical cellular pathways and protein functions responsible for allergy. These complementary approaches imply genetic mechanisms involved in Th2 immunity, T-cell differentiation, TGF β signaling, regulatory T-cell function and skin/mucosal function as well as yet unknown mechanisms associated with newly identified genes. Future studies, in combination with data on gene expression and epigenetics, are expected to increase our understanding of the pathogenesis of allergy.

Introduction

Allergy and related diseases are highly heritable, and our understanding of the specific genetic background has improved in recent years due to identification of common risk variants from genome-wide association studies (GWAS) and increased understanding of rare, allergy-related monogenic diseases. Here, we review these two different approaches and their contribution to the field of allergy genetics.

Genome-wide association studies on allergy and allergic sensitization

The identification of susceptibility genes was accelerated by the introduction of microarrays that can determine hundreds of thousands of genetic variants, typically single nucleotide polymorphisms (SNPs), thereby assessing genetic variation across the entire genome. This allowed conduction of GWAS for identification of susceptibility loci without a priori

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Conflicts of interest

The authors report no conflict of interests of relevance to this paper.

hypotheses about disease mechanisms. The large number of variants tested requires a high level of statistical evidence for positive identification of a risk variant, and typically GWAS findings are based upon association p -values below 5×10^{-8} , so-called ‘genome-wide significance’, as well as replication of disease association in an independent population. For allergy-related diseases this has resulted in identification of relatively few, but robust, loci with more consistency between studies compared to previous candidate gene studies.

Related traits

Most allergy-related GWAS have investigated asthma with more than 35 studies registered to date [1]. A large, consortium-based study identified 6 genome-wide significant loci, all of which have been confirmed in independent studies [2]. The strongest associated asthma locus in this and other GWAS is located on chromosome 17q21. The disease-associated gene at this locus is still unclear with the earliest study pointing toward *ORMDL3* [3] while a later study using expression data from lung tissue pointed toward *GSDMA* [4]. Proposed mechanisms of *ORMDL3* include a role in sphingolipid synthesis [5•] and regulation of eosinophils [6•]. Two loci spanning *IL33* and *IL1RL1* (encoding an IL-33 receptor) respectively, imply an important role of IL-33-related airway inflammation in the pathogenesis of asthma [7•,8]. Other loci identified included the *HLA* region, *SMAD3* and *IL2RB*, and more have been proposed from other GWAS on asthma and other allergy-related diseases, such as eczema (atopic dermatitis) and eosinophilic esophagitis [1]. These highlight a number of potential pathogenetic mechanisms and pathways, mainly related to immune mechanisms and skin/mucosal barrier function (Figure 1).

Allergy and allergic sensitization

Asthma and eczema are associated with allergy but still many patients have these diseases without concurrent allergy, the so-called ‘non-atopic’ phenotypes. Therefore susceptibility loci for these diseases are not necessarily associated with allergic mechanisms. Only a few GWAS have specifically addressed allergy or allergic sensitization. The first large-scale study on allergic sensitization, the hallmark of allergic disease, was performed in 2013 by meta-analysis of data from 16 different studies [9••]. Allergic sensitization was assessed objectively and defined by elevated levels of allergen-specific IgE and/or a positive skin prick test. This study identified 10 loci associated with allergic sensitization at the genome-wide significant level and with robust replication. Simultaneously, a large GWAS was performed on allergic symptoms identifying 16 genome-wide significant loci [10••]. This study was based upon self-reported symptoms and a combination of allergic symptoms from different organ systems, including rhinitis, asthma and skin reactions. In spite of these phenotype differences, there was high agreement of results between the two studies (Table 1). Previous GWAS findings on allergic rhinitis and sensitization were confirmed [11] and together these studies increased the number of loci associated with allergy or allergic sensitization to 18. One of the strongest associated loci in both GWAS was on chromosome 11q13. The underlying mechanism is unclear, but this locus was associated with expression of the two nearby genes [9••]: *C11orf30*, a potential regulator of interferon-stimulated genes and viral immunity [12], and *LRRC32*, involved in TGF β signaling in regulatory T-cells (Tregs) [13]. The associated loci imply the importance of Th2 promoting/Th2 dominated immune mechanisms (*STAT6*, *TSLP*, *BCL6*, *IL1RL1*, *IL33*, *GATA3*), innate immunity

(*TLR1/6/10*), TGF β -signaling (*LRRC32*, *SMAD3*), T-cell (*IL2*, *PTGER4*) and Treg (*LRRC32*, *IL2*, *NFATC2*, *FOXA1*) differentiation and function in the pathogenesis of allergy.

Phenotype-specific and shared loci

GWAS studies on different phenotypes allow investigation of shared mechanisms. The relationship between asthma and allergy was investigated in the large GWAS on asthma from the GABRIEL consortium by comparing association results for asthma and total IgE levels [2]. This showed surprisingly little overlap of associated loci indicating that allergy has little relevance in the pathogenesis of asthma. However, the later GWAS on allergic sensitization reached a different conclusion [9••]. This study showed that 9 of the ten loci associated with allergic sensitization were also associated with asthma in the GABRIEL study, in agreement with a potential causal role of allergy in asthma pathogenesis. These results also indicate different genetic backgrounds of total IgE and allergen-specific IgE levels, which is supported by the observation that loci such as *FCERIA* and *HLA-A* have been strongly and consistently associated with total IgE levels in GWAS but were weakly associated with allergic sensitization [9••].

Some susceptibility loci might be phenotype-specific. Age at onset seems to be an important genetic characteristic as demonstrated in the GABRIEL asthma GWAS where most loci were more strongly associated with the childhood onset phenotype [2]. Particularly, the 17q21 locus seems strongly associated with an asthma phenotype characterized by onset in early childhood [14] and recurrent, severe exacerbations [15••] and was more strongly associated with asthma than allergic rhinitis [10••]. Other loci have been associated with multiple allergy-related phenotypes, for example the chromosome 11q13 locus associated with allergic sensitization [9••], allergic symptoms [10••], eczema [16] and asthma [17], suggesting involvement in a central allergy mechanism. The overlap of susceptibility loci for allergy/allergic sensitization, asthma and eczema based upon findings from the largest GWAS are illustrated in Figure 2.

Overlapping susceptibility loci from GWAS should be interpreted with caution, due to potential issues such as diagnostic bias and limited statistical power, but might help understanding the pathogenetic relationship between allergy-related phenotypes and the mechanisms associated with individual loci.

Allergy and autoimmunity

Allergy and autoimmune diseases are classically considered representatives of Th2 and Th1/Th17 driven immune responses, respectively, with counteracting immune mechanisms. Overlapping mechanisms are suggested by some studies of comorbidity suggesting inverse as well as direct relationships [18] and by the parallel epidemic observed for allergy and autoimmune diseases in the last decades [19]. The two recent GWAS on allergy and allergic sensitization demonstrated a large overlap between susceptibility loci for allergy and autoimmune diseases with 12 of the 18 genome-wide significant loci for allergy also encompassing variants associated with autoimmune diseases (Table 1) [9••,10••]. Shared genetics are supported by a recent study showing that ~90% of variants associated to autoimmune diseases are non-coding, mapping to regulatory regions specifically active in

immune cells, and that these clustered closely together with asthma and allergy [20••]. Two examples of shared loci are the 11q13 locus, which showed strong association with several allergy-related diseases and was also among the strongest loci for inflammatory bowel disease [21], and the 17q21 asthma locus also associated with several autoimmune diseases, including type 1 diabetes and inflammatory bowel disease. Interestingly, the direction of effect was the same for allergy and autoimmune disease at the 11q13 locus [9••,10••] but opposite at the 17q21 locus [10••]. Further understanding of these shared susceptibility loci may help elucidate the complex relationship and pathogenesis of allergy and autoimmune diseases.

Clinical and research implications

The susceptibility variants identified in GWAS are mainly common variants with relatively small effect sizes (often with odds ratios around 1.1 per risk allele). Such variants have no clinical relevance in terms of predictive capacity, even in combination, as shown for both asthma [2] and allergic sensitization [9••]. On the other hand, the estimated population attributable risk fraction of hay fever for the 10 strongest sensitization loci was estimated to be more than 25% [9••] suggesting that targeting the mechanisms associated with these 10 loci would have a significant impact on disease burden on the population level.

It can be argued that, until now, GWAS findings have contributed little to the basic understanding of disease mechanisms. One limitation is that they often merely identify a susceptibility locus without any clear relationship to a specific gene or functional mechanism. Examples of this are the 17q21 and 11q13 loci, where the associated mechanisms are still poorly understood several years after their discovery, even though these loci are strong and probably central to the pathogenesis of asthma and allergy. One example of a GWAS finding where the functional mechanism might have been identified is *CDHR3*, a susceptibility locus for childhood asthma with severe exacerbations [15••]. A recent follow-up study suggests that this gene is a rhinovirus C receptor, potentially explaining the underlying mechanism and identifying a target for future asthma and virology research [22•].

Currently, GWAS on allergy and related traits have identified novel and robust susceptibility loci, which need to be followed up in further functional studies. These are likely to increase our understanding of disease mechanisms and may ultimately help identify novel targets for treatment and prevention of disease.

Future GWAS

Larger, consortium-based, studies on allergy-related phenotypes are currently being conducted and are expected to identify many novel susceptibility loci. The resultant more complete picture of the genetic background will increase the possibilities for pathway-based analysis of functionally related loci and also increase the knowledge on shared genetic mechanisms between phenotypes.

An alternative approach to increasing sample size is to perform GWAS on more specific phenotypes. Such phenotypes are likely more closely associated with specific mechanisms

and the genetic substrate and might increase study power. This was demonstrated by a GWAS on early childhood asthma with severe exacerbations resulting in similar power for gene identification as previous much larger asthma GWAS, and showing very high effect sizes in the children with the highest number of exacerbations [15••].

The majority of GWAS, including those discussed above, have only included individuals of European descent. Ethnic differences have been demonstrated in allergy-related GWAS [23] and will be the focus of future studies including larger non-European populations. Also, future larger GWAS will have increased power to target gene by environment interactions and directly clinically relevant phenotypes, such as response to medication [24•].

Markers assayed by common GWAS array platforms do not typically include rare variants. For this purpose, approaches using custom arrays and sequencing-based efforts are being used and might uncover some of the genetic variation of allergy and related traits not detected in GWAS. However, a recent study indicated that for asthma, low-frequency variants are not likely to explain the ‘missing heritability’ [25••].

The advent of the era of inexpensive genome-wide nucleotide sequencing applied to gene expression-profiling and epigenome-profiling has brought new possibilities of marrying GWAS data with data from large public ‘omics repositories, inferring additional layers of functionality, regulation and tissue context from associated SNPs. These data will increase the usefulness of GWAS data by providing a shorter path to understanding functional effects of susceptibility loci [26•]. Often, these approaches consider the full range of SNPs, and not just single, genome-wide significant hits. For complex traits, like allergy, such approaches may better estimate the summarized variant burden on cellular regulatory and transcriptional networks, and produce additional mechanistic insight [20••,27]. Future GWAS on allergy (whether chip or sequence-based) will be a part of integrated approaches to discover how other molecular layers, including epigenetics and the immune–microbiome interface, modulate the genetic effect on disease, and will thereby be a central component in the attempt to tailor and improve medical treatment [28].

Monogenic diseases

The molecular complexity of allergic disease is nowhere more apparent than in the diverse group of monogenic diseases that present with a spectrum of atopic phenotypes such as asthma, food allergy, and eczema. Discovery of the underlying genetic defect often leads to better characterization of cellular mechanisms. Remarkably, aberrations in seemingly unrelated pathways can result in similar clinical pictures (Table 2).

Disorders of lymphocyte repertoire

The emergence of oligoclonal T-cell populations in a background of nearly complete immunodeficiency underlies much of the pathology seen in both atypical complete DiGeorge syndrome and Omenn syndrome. Atypical complete DiGeorge syndrome (which occurs in <1% of those with DiGeorge syndrome) and Omenn syndrome are both characterized by lymphadenopathy, elevated IgE and a severe eczematous skin eruption [29–31]. These patients have very few recent thymic emigrants, consistent with the diagnosis of SCID or athymia; however, they develop an oligoclonal T-cell population with

an activated phenotype that infiltrates the skin [29,31]. Omenn syndrome is frequently due to hypomorphic mutations in SCID-causing genes that result in a combination of immunodeficiency and autoimmunity [31]. Patients typically present early in life with infections, diarrhea, and erythroderma. There is decreased or absent humoral immunity with elevated IgE and activated, oligoclonal T-cell populations in the skin and gut [31,32]. Increased IgE in the absence of a severe Omenn-like phenotype is also seen in patients with SCID due to absent adenosine deaminase (ADA), a key enzyme in purine metabolism. Interestingly, patients with both delayed-onset ADA-SCID and treated early-onset disease often have elevated serum IgE, and the latter have increased risk of atopy [33,34]. Whether elevated IgE in ADA-SCID and Omenn syndrome are due to a shared pathway of immune dysregulation is not clear, however disruption of lymphocyte repertoires and cellular tolerance mechanisms are characteristic of both [35–38].

Disorders of antigen or cytokine receptor signaling

Aberrant antigen or cytokine signaling in leukocytes can disrupt homeostasis in a variety of ways leading to allergic phenotypes. Gain-of-function mutations in *PLCG2* in PLAID causes paradoxically decreased receptor-mediated intracellular signaling in NK cells and B-cells at physiologic temperatures, leading to autoimmunity and humoral immune deficiency. [39] However, at subphysiologic temperatures, B-cells, neutrophils, monocytes and mast cells have increased cellular activity, even in the absence of receptor crosslinking, leading to granulomatous skin lesions [40], and a form of cold urticaria [39,40]. A tendency toward a Th2 phenotype is also seen in patients with Loeys–Dietz syndrome (LDS), a connective tissue disorder commonly caused by mutations in *TGFBR1* or *TGFBR2* that result in upregulation of TGF β signaling [41•,42]; this increased signaling alone appears sufficient to drive naïve T-cells toward a Th2 phenotype [41•]. Interestingly, Tregs in LDS patients have been shown to produce IL-13, which may also contribute to the increased risk of atopic disease [41•]. Signaling abnormalities due to dominant negative mutations in the *STAT3* gene lead to autosomal dominant hyper-IgE syndrome (AD-HIES; Job's syndrome) [43]. The classic presentation is recurrent bacterial lung infections, early-onset eczema, skeletal and connective tissue abnormalities, and significantly elevated serum IgE [43,44]. Despite elevated allergen-specific IgE, patients with AD-HIES are at decreased risk of associated food allergies or food-related anaphylaxis compared to atopic individuals without *STAT3* mutations [45,46•]. The latter is likely due to altered *STAT3*-mediated signaling in IgE-dependent mast cell degranulation, which has recently been proposed to occur through a mitochondria-dependent mechanism [46•,47].

Disorders of glycosylation

Several families with hypomorphic mutations in *PGM3* have been described [48•,49•, 50•]. Common clinical features include atopic dermatitis, recurrent infections, and neurologic abnormalities possibly related to abnormal myelination. The enzyme phosphoglucomutase 3 is a member of the hexose phosphate mutase family and is necessary for production of a key substrate in several glycosylation pathways [48•]. Likely related to the high frequency of atopy in these patients, *in vitro* stimulation of CD4⁺ T-cells results in robust production of Th2 cytokines [48•]. The underlying mechanism is not known, but a

myriad of immune-related molecules are dependent upon normal glycosylation for function and tolerance [51].

Disorders of cytoskeletal function

The critical role of cytoskeletal rearrangement in lymphocyte function is demonstrated by mutations in *DOCK8* and *WAS*. *DOCK8* is part of a family of atypical guanine exchange factors necessary for proper cytoskeletal function. Lack of functional *DOCK8* protein results in a hyper-IgE syndrome with early-onset atopic dermatitis, cutaneous viral infections, recurrent bacterial infections, eosinophilia and neoplastic disease [52•,53]. Death from complications typically occurs by early adulthood unless treated with bone marrow transplantation [52•]. *WAS* protein (WASP) acts in a pathway similar to that of *DOCK8*; accordingly the two conditions share many clinical characteristics, to include atopic dermatitis with elevated IgE, autoimmunity, and lymphoma risk, while *WAS* also results in thrombocytopenia [52•,54–56]. Consistent with a shared role in regulating the actin cytoskeleton, *DOCK8* or *WASP* deficiency affects a broad range of cell types, to include T-cells, B-cells, NK cells, and Tregs [55,57]. Although the mechanism by which *DOCK8* deficiency results in atopy is not yet clear, it has been demonstrated that WASP can function in the nucleus to participate in transcription of master Th1 transcription factor T-bet [58] which might normally oppose Th2 phenotypes.

Loss of skin barrier

Proper epidermal function is critical for defense against pathogens, maintenance of homeostasis, and as a barrier against foreign substances. Desmosomes are specialized, multi-protein structures that connect keratinocytes; desmogleins are one group of desmosome proteins critical for intercellular adhesion [61]. Desmosomes transform to corneodesmosomes as keratinocytes cornify in the upper stratum granulosum. Both desmoglein-1 (*DSG1*) and corneodesmosin are two component corneodesmosome proteins. Loss-of-function mutations in the gene encoding *DSG1* (*DSG1*) have been described in two families with SAM syndrome, which presents as a severe, congenital dermatitis with food allergies and recurrent infections [59••]; a third family was recently described with a milder phenotype [60]. Degradation of corneodesmosomes in the stratum corneum causes keratinocyte desquamation, a process facilitated by proteases (kallikreins and cathepsins) in balance with inhibitor proteins, including *LEKTI* [61]. Netherton syndrome (NS) is an autosomal recessive disease caused by loss-of-function mutations in the gene for *LEKTI*, *SPINK5* [62]. The classic triad of NS is ichthyosis, trichorrhexis invaginata ('bamboo hair'), and atopy [62,63]. The *SPINK5* E420K variant has been implicated in atopic dermatitis in patients without NS [64]. Peeling skin disease is phenotypically similar to NS, with peeling skin, atopy, and recurrent cutaneous infections [61,65]; it is caused by loss-of-function mutations in the corneodesmosin gene, *CDSN* [61,65]. The fact that multiple different skin barrier protein disruptions lead to atopic inflammation suggests a common pathway by which a Th2 milieu develops after loss of skin integrity [66]. In addition to the structural barrier molecule defects, it is possible that primary genetic lesions causing increased local Th2 cytokine production may impair anti-microbial peptide upregulation [67]. Similarly, in the case of AD-HIES, a failure of STAT3-mediated AMP-upregulation could contribute to

the failure to maintain the type of normal skin flora necessary for protection against dermatitis [68].

Impaired Treg function

Treg cells (CD4+CD25+FOXP3+) play a critical role in the maintenance of immune tolerance to self-antigen. Failure to maintain adequate numbers of functional Treg cells results in autoimmunity and inflammation, but quite strikingly and reproducibly, atopic inflammation is a hallmark of the loss of Tregs. The most classic example of this is IPEX syndrome caused by mutations in *FOXP3* [69]. These patients have early-onset severe diarrhea, endocrinopathy, and dermatitis. Immune dysregulation with generation of reactive T-cells typically progresses with development of subsequent autoimmune phenomena and food allergy. Other genetic mutations that affect Treg cells and result in an IPEX-like phenotype include loss-of-function (*CD25*, *STAT5b*, *ITCH*, *LRBA*) and gain-of-function (*STAT1* and *STAT3*) mutations [70–72]. The autoimmune phenomena seen in patients with Omenn syndrome, WAS, and DOCK8 deficiency have also been linked to abnormal Treg function [37,55,73].

Conclusion

GWAS and studies of monogenic diseases have identified a number of susceptibility loci and genes associated with allergy, and more are expected to be identified in the future. These complementary approaches imply genetic mechanisms involved in Th2 immunity, T-cell differentiation, TGF β signaling, Treg function and skin/mucosal function (Figure 1), and mechanisms shared between allergy and autoimmune diseases. Further studies of the underlying mechanisms, including other omics-based approaches, will increase our understanding of the pathogenesis of allergy, and the hope is that this will provide the basis for improved treatment and prevention of disease.

Acknowledgements

We gratefully express our gratitude to the children and families of the COPSAC studies for all their support and commitment. We acknowledge and appreciate the unique efforts of the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) research team.

COPSAC is funded by private and public research funds all listed on www.copsac.com. The Lundbeck Foundation; The Danish Ministry of Health; Danish Council for Strategic Research; The Danish Council for Independent Research and The Capital Region Research Foundation have provided core support for COPSAC.

This research was further supported in part by the Intramural Research Program of the NIH, National Institute of Allergy and Infectious Diseases.

The funding agencies had no role in the study design; the conduct of the study; data collection and management; data analysis; or the preparation, review, or approval of the manuscript.

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Figure 1.

Genes and pathways identified from GWAS and/or studies of monogenic allergy-related diseases. Genes identified from GWAS are in bold while genes identified from studies of monogenic diseases are in normal font. A generic cell as well as the skin/mucosal barrier are depicted in order to illustrate the cellular location of gene products. For loci with multiple associated genes where one or more genes have a demonstrated function relevant for atopic disease, only these well-established genes are shown for clarity. It should be noted that the genes and pathways named in this figure might not represent the true causal gene or pathway associated with a given locus since these have not been definitively established for many GWAS findings.

GWAS results have been aggregated from the most powerful GWAS (>3 genome-wide significant loci) on allergy/allergic sensitization, eczema, asthma, and eosinophilic esophagitis: Allergy/allergic sensitization: Ramasamy A, 2011, J Allergy Clin Immunol; Hinds DA, 2013, Nat Genet; Ferreira MA, 2013, J Allergy Clin Immunol; Bønnelykke K, 2013, Nat Genet. Eczema: Paternoster L, 2011, Nat Genet; Hirota T, 2012, Nat Genet; Weidinger S, 2013, Hum Mol Genet; Ellinghaus D, 2013, Nat Genet. Asthma: Moffatt MF, 2010, N Engl J Med; Hirota T, 2011, Nat Genet; Torgerson DG, 2011, Nat Genet; Wan YI,

2012, Thorax; Ferreira MA, 2013, J Allergy Clin Immunol. Eosinophilic esophagitis: Rothenberg ME, 2010, Nat Genet; Kottyan LC, 2014, Nat Genet; Sleiman PM, 2014, Nat Commun.

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Figure 2.

Overlap of susceptibility genes associated with allergy/allergic sensitization, asthma and/or eczema in GWAS.

GWAS results have been aggregated from the most powerful GWAS (>3 genome-wide significant loci) on allergy/allergic sensitization, eczema, and asthma: Allergy/allergic sensitization: Ramasamy A, 2011, J Allergy Clin Immunol; Hinds DA, 2013, Nat Genet; Ferreira MA, 2013, J Allergy Clin Immunol; Bønnelykke K, 2013, Nat Genet. Eczema: Paternoster L, 2011, Nat Genet; Hirota T, 2012, Nat Genet; Weidinger S, 2013, Hum Mol Genet; Ellinghaus D, 2013, Nat Genet. Asthma: Moffatt MF, 2010, N Engl J Med; Hirota T, 2011, Nat Genet; Torgerson DG, 2011, Nat Genet; Wan YI, 2012, Thorax; Ferreira MA, 2013, J Allergy Clin Immunol. For loci with multiple associated genes where one or more genes have a demonstrated a function relevant for atopic disease, only these genes with relevant function are shown for clarity.

Table 1

Genetic loci associated with allergy and/or allergic sensitization in recent GWAS

Locus	Nearby genes [*]	Allergic sensitization(1) ^{\$}	Allergic symptoms(2) ^{\$}	Potential function	Other traits associated with locus ^{\$,§}		
					Asthma	Eczema	Total IgE Autoimmune
2q12.1	<i>IL1RL1/IL18R1</i>	GWS	GWS	Interleukin receptors, IL33-signaling, Th2-response (IL1RL1); pleiotropic immune responses (IL18R1)	●	●	●
2q33.1	<i>PLCL1</i>	NS	GWS	Phospholipase, intracellular signaling			●
3q28	<i>LPP/BCL6</i>	GWS	GWS	Transcription factor, Th2-differentiation (BCL6); cell-cell adhesion (LPP)			●
4p14	<i>TLR1/6/10</i>	GWS	GWS	Pattern recognition receptor, innate immunity	●		
4q27	<i>IL2/ADAD1</i>	GWS	GWS	Interleukin, T-cell differentiation, Treg maturation			●
5p13.1	<i>PTGER4</i>	+	GWS	Prostaglandin receptor, T-cell signaling, skin immunity			●
5q22.1	<i>SLC25A46/TSPL</i>	GWS	GWS	Cytokine, Th2 immune responses	●		
6p21.32	<i>HLA-DQB1</i>	GWS	GWS	Antigen presenting protein, self tolerance	●	●	●
6p21.33	<i>HLA-B/MICA</i>	GWS	GWS	Antigen presenting protein, self tolerance			●
8q24.21	<i>MYC/PVT1</i>	GWS	++	Transcription factor, B-cell proliferation and differentiation			●
9p24.1	<i>RANBP6/IL33</i>	NS	GWS	Interleukin, Th2-signaling, Th2 cytokine production	●		
10p14	<i>GATA3</i>	+	GWS	Transcription factor, Th2-differentiation.			
11q13.5	<i>C11orf30/LRRC32</i>	GWS	GWS	Treg expressed, TGFβ signaling	●	●	●
12q13.3	<i>STAT6</i>	GWS	++	Transcription factor, Th2-differentiation, IL4-response		●	●
14q21.1	<i>FOXA1/ITC6</i>	NS	GWS	Transcription factor, Treg differentiation			
15q22.33	<i>SMAD3</i>	NS	GWS	Transcriptional factor, TGFβ signaling	●		●

Locus	Nearby genes [*]	Allergic sensitization(1) [§]	Allergic symptoms(2) [§]	Potential function	Other traits associated with locus [§]		
					Asthma	Eczema	Total IgE Autoimmune
17q12	<i>GSDMB</i> / <i>GSDMA</i> / <i>ORMDL3</i>	NS	GWS	ER [†] Ca ²⁺ homeostasis and unfolded protein response, sphingolipid metabolism, eosinophil trafficking (ORMDL3); Modulator of mitochondrial oxidative stress (GSDMA)	●		●
20q13.2	<i>NFATC2</i>	NS	GWS	Transcription factor, activated T-cell gene transcription			

(1) : Bønnelykke et al. Nat Genet. 2013 Aug;45(8):902–6., (2): Hinds et al. Nat Genet. 2013 Aug;45(8):907–11.

^{*} Most plausible causal gene(s) in bold if more genes are listed.

[§] GWS: genome-wide significant association (p<5e-8) for the top variant at the locus.

⁺⁺ p<0.005 for the top variant in the companion paper

⁺ p<0.05, NS: not significantly associated (p>0.05).

[§] Based on NCBI GWAS Catalog SNPs in LD > 0.5 with locus.

[†] ER: Endoplasmic reticulum.

Table 2

Allergy-related monogenic diseases

Disease	Gene Protein product Type of mutation Inheritance	Abnormality	Common clinical features	Common laboratory features
PLAID PLC γ ₂ -associated antibody deficiency and immune dysregulation [39,40]	Gene: <i>PLCG2</i> Protein: PLC γ ₂ (phospholipase C γ ₂) Mutation: gain-of-function Inheritance: autosomal dominant	Decreased receptor-mediated activity in B-cells and NK cells at physiologic temperatures. Spontaneous activation in mast cells, B-cells, neutrophils, monocytes at subphysiologic temperatures.	Cold urticaria (positive by evaporative cooling test) Recurrent sinopulmonary infections Autoimmune disease Graulomatous skin lesions Allergen-specific atopy	Elevated IgE Low IgA, IgM Decreased B-cells, including class-switched memory B-cells Decreased NK cells
WAS Wiskott-Aldrich syndrome [55,56,74]	Gene: <i>WAS</i> Protein: WASP (WAS protein) Mutation: loss-of-function (WASP typically truncated or absent) Inheritance: X-linked	Cytoskeletal abnormalities that affect numerous cell types, including T-cells, B-cells, Treg cells	Moderate to severe eczema Easy bruising and bleeding Recurrent infections Autoimmunity (most commonly autoimmune cytopenias, vasculitis, arthritis) Lymphoma, often EBV-related	Thrombocytopenia with small platelets Abnormal T-cell and B-cell function with poor response to polysaccharide antigens Diminished T-cell responses to mitogens and anti-CD3 T-cell lymphopenia and oligoclonality that worsen with age Low IgM, elevated IgA & IgE Defective Treg function
Autosomal dominant hyper-IgE syndrome [43,75]	Gene: <i>STAT3</i> Protein: STAT3 (signal transducer and activator of transcription 3) Mutation: dominant negative Inheritance: autosomal dominant	Aberrant STAT3-dependent signaling	Staphylococcal infections (skin and lung); skin abscesses often “cold” without associated warmth, redness, pain Chronic eczema Musculoskeletal abnormalities (hyperextensibility, osteoporosis, scoliosis) Bacterial pneumonia with resulting pneumatoceles and fungal infection Craniofacial abnormalities (retained primary teeth, craniosynostosis, high-arched palate) Chronic mucocutaneous candidiasis Characteristic facial features (coarse skin, prominent forehead and chin, deep-set eyes, broad nasal bridge, bulbous nose)	Elevated IgE Eosinophilia Decreased Th17 cells Decreased central memory T-cells Decreased memory B-cells
PGM3 deficiency [48••,49••,50••]	Gene: <i>PGM3</i> Protein: PGM3 (phosphoglucomutase 3) Mutation: hypomorphic protein Inheritance: autosomal recessive	Aberrant glycosylation	Severe atopic dermatitis Allergen-specific atopy Recurrent viral and bacterial infections Motor and neurocognitive impairment	Elevated IgE Eosinophilia CD4 lymphopenia
DOCK8 deficiency [52•,73]	Gene: <i>DOCK8</i> Protein: DOCK8 (dedicator of cytokinesis 8) Mutation: loss-of-function Inheritance: autosomal recessive	Cytoskeletal and immune synapse abnormalities	Viral skin infections with associated malignancies Recurrent bacterial skin and lung infections Atopy (severe atopic dermatitis starting early in life, asthma, food allergy) Mucocutaneous candidiasis Autoimmunity	T-cell lymphopenia Eosinophilia Elevated IgE Low IgM that declines with age Decreased Treg cell number and function

Disease	Gene Protein product Type of mutation Inheritance	Abnormality	Common clinical features	Common laboratory features
IPEX syndrome Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome [69,70]	Gene: <i>FOXP3</i> Protein: FOXP3 (forkhead box protein 3) Mutation: loss-of-function Inheritance: X-linked	Aberrant development or function of Treg cells	Autoimmune enteropathy (severe, early-onset diarrhea) Endocrinopathy (most commonly type I diabetes, thyroiditis) Dermatitis (eczematiform, ichthyosiform, or psoriasiform) Other autoimmune phenomena (autoimmune cytopenias, autoimmune renal and liver disease) Food allergy	Elevated IgE Eosinophilia
Omenn syndrome [31,32,37,76]	Most common genetic cause: hypomorphic mutations in <i>RAG1</i> , <i>RAG2</i> . Proteins: RAG1, RAG2 (recombination activating gene-1, recombination activating gene-2) Other causative genes include <i>DCLRE1C</i> , <i>ADA</i> , <i>RMRP</i> .	Impaired V(D)J recombination	Generalized erythroderma Recurrent infections Chronic diarrhea Autoimmunity (especially of skin and gut) Lymphadenopathy Hepatosplenomegaly Thymic dysplasia	Elevated IgE Eosinophilia Oligoclonal T-cells Decreased T-cell proliferation to antigen and mitogen B-cells low or absent in some forms Defective Treg function
Atypical complete DiGeorge syndrome [29,30]	Most commonly due to hemizygous deletion of 22q11.2	Oligoclonal T-cells	Abnormal facies Congenital heart disease Athymia Eczematous dermatitis with infiltrating T-cells Lymphadenopathy Hypoparathyroidism	Oligoclonal T-cells with activated phenotype Elevated IgE Eosinophilia Hypocalcemia
ADA-SCID Adenosine deaminase deficient severe combined immunodeficiency [33,34]	Gene: <i>ADA</i> Protein: ADA (adenosine deaminase) Mutation: loss-of- function Inheritance: autosomal recessive	Defect in purine metabolism	Early-onset & delayed- onset, pre-treatment: Recurrent infections Early-onset, post- treatment: Atopic dermatitis Allergen-specific atopy	Early-onset, pre-treatment: B- cell, T-cell, NK cell lymphopenia Delayed-onset, pre-treatment & early-onset, post-treatment: Elevated IgE
Loeys-Dietz syndrome [41••,42]	Genes: <i>TGFBR1</i> , <i>TGFBR2</i> Proteins: TGFBR1, TGFBR2 (transforming growth factor β receptor I, transforming growth factor β receptor II) Mutation: gain-of- function Inheritance: autosomal dominant Mutations in <i>SMAD3</i> are responsible for a minority of cases	Increased TGF β signaling skews lymphocytes to Th2 phenotype	Cardiovascular abnormalities Marfanoid habitus with skeletal and craniofacial abnormalities Atopic dermatitis Allergen-specific atopy Eosinophilic gastrointestinal disease	Elevated IgE Eosinophilia
Peeling skin disease (also called peeling skin syndrome type B) [61,65]	Gene: <i>CDSN</i> Protein CDSN (corneodesmosin) Mutation: loss-of- function Inheritance: autosomal recessive	Abnormal corneodesmosomes	Ichthyosiform erythroderma with peeling skin Severe pruritus Allergen-specific atopy Recurrent skin infections	Elevated IgE

Disease	Gene Protein product Type of mutation Inheritance	Abnormality	Common clinical features	Common laboratory features
SAM syndrome Severe dermatitis, multiple allergies, metabolic wasting syndrome [59,60]	Gene: <i>DSG1</i> Protein: DSG1 (desmoglein-1) Mutation: loss-of-function Inheritance: autosomal recessive Mutation in desmoplakin gene (<i>DSP</i>) reported in one patient [77]	Abnormal desmosomes in upper epidermis; acantholysis	Severe dermatitis Hypotrichosis Malabsorption Food allergy Recurrent skin and pulmonary infections Metabolic wasting	Elevated IgE Hypoalbuminemia
Netherton syndrome [62,63]	Gene: <i>SPINK5</i> Protein: LEKTI (lymphoepithelial Kazal-type related inhibitor type 5) Mutation: loss-of-function Inheritance: autosomal recessive	Defective serine protease inhibitor	Skin manifestations can include congenital ichthyosiform erythroderma and ichthyosis linearis circumflexa Trichorrhexis invaginata ("bamboo hair") Allergen-specific atopy Urticaria, angioedema Recurrent infections	Elevated IgE Eosinophilia