



Shared genetic determinants between eczema and other immune-related diseases

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Purpose of review

Eczema and other allergic disorders are complex diseases caused by multiple genetic and environmental factors. Here, we review recent success in the identification of novel susceptibility loci for eczema.

Recent findings

Genome-wide association studies led to marked progress in unraveling the genetic determinants of allergic disorders. In the past 4 years, a total of 14 new eczema susceptibility loci have been identified and nearly all of them were successfully replicated. Seven additional eczema loci were recently identified by alternative strategies utilizing the remarkable overlap in the genetic cause of diverse immune-related traits. Apart from underlining the importance of the skin barrier in eczema, these studies point to specific immunological functions altered in eczema pathogenesis.

Summary

The new findings demonstrate that common pathways are involved in the development of eczema and other immune-related traits. Moreover, the genetic determinants shared between eczema, asthma, and allergic rhinitis should aid in resolving the molecular mechanisms triggering disease progression along the atopic march. The identification of the underlying genes and causal variants will be the major challenge for upcoming studies.

Keywords

atopic march, eczema, genome-wide association study, immunochip

INTRODUCTION

Eczema (atopic dermatitis) is a chronic skin disease, characterized by inflamed, itchy skin lesions. A clinical hallmark of eczema is cutaneous barrier dysfunction, which is associated with marked dryness of the skin and the propensity to bacterial and viral skin infections. Like asthma, allergic rhinitis, and food allergy, eczema is often associated with atopy, a hyperreactivity of the immune system resulting in the production of immunoglobulin E (IgE) antibodies against common environmental allergens [1].

Eczema is usually the earliest clinical manifestation of allergic disease affecting infants and young children. This suggests that early childhood is the phase during which the maturing skin barrier and immune system are particularly vulnerable to the development of eczema and atopy. Children with infantile eczema often develop asthma and allergic rhinitis later in life, which is referred to as the atopic march [2]. These observations indicate that allergic diseases may have partially overlapping etiological factors.

Allergic diseases are complex multigenic disorders; the importance of the environment is evidenced by the rapid increase in eczema prevalence observed over the past decades in industrialized countries, which cannot be explained by genetic changes in the population. However, familial aggregation and twin studies [3–5] clearly indicate that genetic factors are major determinants of allergic risk. During the past 20 years, multiple candidate-gene association studies have been performed aiming to identify the genetic determinants of eczema [6]. Unfortunately, this approach has been plagued

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KEY POINTS

- GWASs have led to marked progress in unraveling the genetic determinants of eczema and have highlighted important functional pathways.
- Recent genetic studies have identified key players in the transition from eczema to allergic airways disease along the atopic march, as well as shared etiological mechanisms among diverse inflammatory disorders.
- Functional characterization of the new susceptibility loci remains a challenge, but will provide important clues for the understanding of the mechanisms underlying disease progression and may help in the development of improved therapeutic strategies.

by lack of replication due to small sample sizes, clinical heterogeneity, insufficient marker coverage of the loci, and its restriction to selected candidate genes; only a few loci have been found associated with eczema in multiple independent studies.

Recent progress in high-throughput genotyping with microarrays and the increasing amount of publicly available sequencing and polymorphism data have allowed the investigation of the whole genome with millions of genetic markers, in order to search for disease variants. Here we review the new susceptibility loci for eczema identified in recent genome-wide association studies (GWASs) and related approaches. These studies were remarkably robust to replication and revealed a significant overlap in the genetic determinants of different allergic and other immune-related traits.

NEW ECZEMA RISK VARIANTS FROM GENOME-WIDE ASSOCIATION STUDIES

Four GWASs on eczema have been performed since 2009 (Table 1) [7,8,9[■]–12[■]], leading to the identification of 14 new susceptibility loci. However, in most cases, such studies identify an association with a common genetic marker that is not itself the culprit variant. Instead, they pinpoint a

chromosomal region containing genetic polymorphisms that are correlated or in linkage disequilibrium and include the functional variant. Here, we describe the genes reported for each locus and explain the function of the most likely candidate from each region, referring to its potential function in eczema (Table 2) [7,8,9[■]–12[■],13–15].

The first GWAS on eczema was published in 2009 and identified a novel common susceptibility locus on chromosome 11q13.5 [7]. Importantly, this finding was replicated in all GWASs on eczema performed afterwards and in three additional studies, confirming the involvement of the locus in eczema susceptibility and the robustness of the GWAS approach [8,9[■],10[■],11[■],16,17[■],18]. The risk variant is located in the intergenic region between *C11orf30* (chromosome 11 open reading frame 30) and *LRRC32* (leucine-rich repeat containing 32) and both genes are candidates for eczema. *LRRC32* encoding the protein GARP is important for the immunosuppressive function of regulatory T (T_{reg}) cells [19], and *C11orf30* encodes the protein EMSY that represses the interferon-mediated response against viral infection [20].

A GWAS on eczema in the Chinese Han population identified two new susceptibility loci on chromosomes 5 and 20 [8]. On chromosome 5q22.1, the associated region includes *TMEM232* (transmembrane protein 232) and *SLC25A46* (solute carrier family 25, member 46), the functions of which are unknown. However, nearby *TSLP* (thymic stromal lymphopoietin) is an important player in epithelial Th2 immune responses and in the pathogenesis of allergic diseases [21]. On chromosome 20q13.33, the risk locus comprises eight genes with tumor necrosis factor receptor superfamily, member 6b, decoy (*TNFRSF6B*) being the best candidate. *TNFRSF6B* encodes decoy receptor 3 (Dcr3), a secreted protein with various functions in adaptive immunity, including the response to *Staphylococcus aureus* infections that are characteristic of eczema [22]. Interestingly, individuals with eczema had increased Dcr3 plasma levels [23], supporting a potential role in disease etiology.

Table 1. Study characteristics

Reference	Study type	Discovery number of cases/ number of controls	Follow-up number of cases/number of controls	Ethnicity
[7]	GWAS (case-control and family-based)	939/975 + 270 families	2637/3957	European
[8]	GWAS (case-control)	1012/1362	3624/12 197	Han Chinese
[9 [■]]	Meta GWAS (case-control)	5606/20 565	5419/19 833	European
[10 [■]]	GWAS (case-control)	1472/7971	1856/7021	Japanese
[11 [■]]	ImmunoChip (case-control)	2425/5449	1951/4599	European
[12 [■]]	Candidates from GWASs (case-control)	2895/2448	4235/6805	European

Table 2. Eczema susceptibility loci identified by GWASs and related approaches

Reference	Chromosome	Variant (allele)	Frequency in controls	Odds ratio (confidence interval)	Reported genes ^a	Potential function ^b	Replication ^c	Additional traits ^d
[13]	1q21.3	R501X and 2282del combined (mut)	0.04	2.48 ^f (2.06–2.99)	FLG^g	Epidermal differentiation and skin barrier function	[7,8, ^h 9, ^h 10, ^h 11, ^h 12]	Ichthyosis vulgaris, eczema-associated asthma, peanut allergy
[7]	11q13.5	rs7927894(A)	0.36	1.22 (1.15–1.30)	C10orf30, LRRC32	Interferon response, regulatory T-cells	rs7936562 ^k [8] rs7927894 ^h [9, ^h 10, ^h 11, ^h 12] rs11236809 ^k [10, ^h 11, ^h 12] rs7110818 ^h [11, ^h 12]	Allergic rhinitis, allergic sensitization to grass, asthma, inflammatory bowel disease
[8]	5q22.1	rs7701890(G)	0.13	1.24 (n.a.)	TMEM232, SIC25A46, TSLP	Epithelial Th2 response	rs7701890 ^h [10, ^h 11, ^h 12]	Asthma, eosinophil counts, allergic sensitization to grass, eosinophilic esophagitis
[8]	20q13.33	rs6010620(G)	0.26	1.17 (n.a.)	GMEB2, STMN3, RTEL1, TNFRSF6B, ARFRP1, ZGPAT, LIME1, SIC2A4RG, ZBTB46	Adaptive immune response	rs6010620 ^h [9, ^h 10, ^h 11, ^h 12] rs909341 ^h [11, ^h 12]	Glioma, inflammatory bowel disease
[9 ^h]	5q31.1	rs2897442(C)	0.29	1.11 (1.07–1.15)	RAD50, IL13, IL4, KIF3A	Th2 response	rs1295686 ^k [10, ^h 11, ^h 12] rs848 ^k [11, ^h 12]	Asthma, eosinophil counts, Hodgkin lymphoma, psoriasis, total IgE
[9 ^h]	11q13.1	rs479844(A)	0.44	0.88 (0.85–0.91)	OVL1	Epidermal differentiation	rs479844 ^h [10, ^h 11, ^h 12] rs11820062 ^k [11, ^h 12]	–
[9 ^h]	19p13.2	rs2164983(A)	0.15	1.16 (1.10–1.22)	ACTL9	Unknown	rs4804075 ^h [10, ^h 11, ^h 12]	–
[10 ^h]	2q12.1	rs13015714(G)	0.41	1.27 (1.20–1.34)	IL1RL1, IL18R1, IL18RAP	Th2 response	rs13015714 ^h [11, ^h 12]	Asthma, celiac disease, eosinophil counts
[10 ^h]	3p21.33	rs6780220(G)	0.53	1.25 (1.19–1.32)	GLI1, CCR4	T-cell recruitment to skin	–	Celiac disease
[10 ^h]	3q13.2	rs12634229(G)	0.33	1.29 (1.22–1.37)	CCDC80	Skin differentiation and immunity	–	–
[10 ^h]	6p21.33	rs176095(T)	0.81	1.40 (1.30–1.51)	MHC region	Antigen presentation	rs176095 ^h [11, ^h 12]	Many autoimmune diseases
[10 ^h]	7p22.2	rs4722404(G)	0.33	1.18 (1.12–1.25)	CARD11	Th17 differentiation	rs6978200 ^h [11, ^h 12]	–
[10 ^h]	10q21.2	rs10995251(C)	0.51	1.28 (1.22–1.36)	ZNF365, EGR2	T-cell anergy	rs2393903 ^h [8]	Crohn's disease
[10 ^h]	11p15.4	rs878860(G)	0.54	1.31 (1.24–1.38)	OR10A3, NLRP10	Skin immune response	–	–
[10 ^h]	20q13.2	rs16999165(T)	0.69	1.19 (1.12–1.26)	CYP24A1, PFDN4	Vitamin D metabolism	–	Multiple sclerosis
[11 ^h]	4q27	rs17389644(A)	0.24	1.19 (1.12–1.26)	KIAA1109, ADAD1, IL2, IL21	T-cell proliferation, regulatory T-cell homeostasis	–	Alopecia areata, celiac disease, inflammatory bowel disease, type 1 diabetes
[11 ^h]	11p13	rs12295535(A)	0.02	1.68 (1.46–1.93)	PRR5L	Cell migration and apoptosis	–	–
[11 ^h]	16p13.13	rs2041733(A)	0.45	1.23 (1.17–1.29)	CLEC16A, DEXI	Endosomal maturation and trafficking	–	Multiple sclerosis, primary biliary cirrhosis, type 1 diabetes
[11 ^h]	17q21.32	rs16948048(G)	0.38	1.17 (1.11–1.23)	AB13, PHOSPHO1, FLJ40194, ZNF652, PHB, NGFR	Repressor of invasion and metastasis	–	Prostate cancer

[12 ^{***}]	1p36.11	rs10903122(G)	0.47	1.11 (1.05–1.16)	RUNX3	Development of dendritic epidermal T-cells	-	Ankylosing spondylitis, celiac disease, psoriasis
[12 ^{***}]	1q21.3	rs2228145(C)	0.38	1.15 (1.09–1.21)	IL6R	Acute and chronic inflammation	-	Asthma, C-reactive protein levels, fibrinogen levels, rheumatoid arthritis, myocardial infarction
[12 ^{***}]	12q13.2	rs2292239(A)	0.31	1.11 (1.05–1.17)	RAB5B, SUOX, IKZF4, RPS26, ERBB3	Epithelial cell growth and survival	-	Alopecia areata, asthma, type 1 diabetes, vitiligo

n.a., not available.

^aGenes located in the associated region (best candidate genes according to the potential biological relevance in eczema in bold).

^bFunctions of the best candidate genes.

^cAdditional GWASs replicating the reported association of the region with eczema (V_{LD} , or R indicates that the same variant, a variant in linkage disequilibrium ($r^2 > 0.3$), or another variant from the associated region was reported in the replication study).

^dAdditional phenotypes associated with the region according to the NIH GWAS Catalog (accessed 20 April 2013) [14].

^eDisease associations of loss-of-function mutations in *FLG* (R501X and 2282del) were identified in a candidate gene study/ frequency of the combined mutations (R501X and 2282del) are reported from [13].

^fOdds ratio of the combined *FLG* mutations was calculated from the largest population-based study, the ALSPAC, the Avon Longitudinal Study of Parents and Children cohort [15].

The third GWAS on eczema meta-analyzed 30 study populations of European ancestry and included more than 10 000 cases and 40 000 controls [9^{***}]. This largest genetic study on eczema to date, identified three new eczema susceptibility loci. The risk variant on chromosome 11q13.1 points to *OVOL1* (ovo-like 1), which encodes a transcription factor important for differentiation of epidermal keratinocytes [24]. On chromosome 19p13.2, the function of the candidate gene *ACTL9* (actin-like 9) is still unknown. Finally, this study confirmed the Th2 cytokine gene cluster on chromosome 5q31.1 as a susceptibility locus for eczema including *IL13* (interleukin 13) and *IL4* (interleukin 4). A previous study [25] had provided evidence that a common arginine to glutamine exchange in IL-13 (rs20541) enhances the Th2 effector functions of IL-13. Interestingly, dense genotyping at this locus demonstrated that apart from the functional polymorphism in *IL13*, an additional association with eczema exists in the *IL4* region.

A recent GWAS on eczema in the Japanese population confirmed all previously reported GWAS hits and identified eight new susceptibility loci for eczema (Table 2) [10^{***}]. The associated region on chromosome 2q12 contains the family of IL-1-receptor genes, *IL1RL1* (IL-1 receptor-like 1), *IL18R1* (IL-18 receptor 1), and *IL18RAP* (IL-18 receptor accessory protein). Members of this family are abundantly expressed in the skin, and *IL1RL1* is involved in Th2 responses and is important for the pathogenesis of eczema [26,27]. Strong association was also found at the major histocompatibility complex (MHC) on chromosome 6p21.33 that represents a major locus for many autoimmune diseases. This finding supports the hypothesis that autoreactivity found in eczema patients could play a role in disease [28^{*}]. On chromosome 11p15.4, the risk locus includes *NLRP10* (NLR family, pyrin domain containing 10), which is important for the regulation of inflammatory, antimicrobial, and adaptive immune responses in the skin [29]. The 3p21.33 region contains *CCR4* [chemokine (C–C motif) receptor 4] that encodes a receptor for the thymus and activation regulated chemokine TARC, mediating recruitment of T-cells to affected skin in eczema patients [30]. On chromosome 3q13.2, the candidate gene *CCDC80* (coiled-coil domain containing 80) is involved in the induction of CCAAT/enhancer-binding protein alpha (C/EBP α) and peroxisome proliferator-activated receptor gamma (PPAR γ) [31], which are important in epidermal differentiation and in the regulation of the immune response, respectively. The associated region on chromosome 7p22.2 contains *CARD11* (caspase recruitment domain family, member 11)

encoding CARMA1, a protein critical for differentiation of Th17 cells, which are involved in immunity against extracellular bacteria [32]. Interestingly, mice carrying a functional mutation in *CARD11* develop eczema with elevated IgE levels [33]. An additional risk variant was identified on chromosome 10q21.2, within *ZNF365* (zinc finger protein 365) and near *EGR2* (early growth response 2), which is important for the inhibition of T-cell function or T-cell anergy [34]. Finally, association with eczema was found on chromosome 20q13.2, between *CYP24A1* (cytochrome P450, family 24, subfamily A, polypeptide 1) and *PFDN4* (prefoldin subunit 4). *CYP24A1* encodes a mitochondrial protein involved in the degradation of vitamin D, a modulator of innate and adaptive immune suspected to play a role in allergic disorders [35].

On chromosome 1q21.3, genetic variants in linkage disequilibrium with loss-of-function mutations in *FLG* (filaggrin) were highly significantly associated with eczema in all GWASs performed. *FLG* mutations were initially identified as a risk factor for eczema in a candidate gene study [13]. Filaggrin is a major structural protein of the skin and its deficiency leads to an impaired epidermal barrier. A detailed description of filaggrin's role in the disease process is provided below.

Independent replication of GWAS loci is critical in order to detect false positive results, which may arise as a result of multiple testing, genotyping errors, or population stratification. Replication of GWAS results has some complexities that need to be considered when analyzing the data. The best level of replication is achieved when the same allele from the same genetic variant is reported as a risk factor in an independent study (replication at the variant level). However, each GWAS analyzes a different set of SNPs depending on the genotyping platform used. As a consequence, different studies may report different correlated variants from a region (variants in linkage disequilibrium). Additionally, disease variants as well as linkage disequilibrium between variants may be population-specific and GWASs performed on samples from different ethnic backgrounds may report different uncorrelated variants from the same region (replication at the locus level). Importantly, different GWASs have provided independent evidence of association with eczema for many of the new risk loci (Table 2), confirming their role in disease susceptibility.

OVERLAP WITH IMMUNE-RELATED DISEASES

An exaggerated immune response is a hallmark of eczema, but it also plays a major role in other

allergic, chronic inflammatory, and autoimmune disorders, in which inappropriate inflammatory responses to environmental, microbial or self-antigens contribute to dysfunction and destruction of target organs. Epidemiological studies have revealed prevalence increases that are similar among diverse immune-mediated diseases [36]. This has led to the concept that their causes, including environmental influences and genetic factors, may also be shared. Indeed, GWASs revealed common genetic susceptibility loci for different immune-related disorders [37], suggesting shared molecular pathways involved in their etiology. Notably, some of the new eczema susceptibility loci were also identified in GWASs for chronic inflammatory diseases. In the *C11orf30* region on chromosome 11, the same allele not only conferred risk for eczema and the closely associated disorders asthma and allergic rhinitis [17[¶]], but also predisposed to Crohn's disease [38]. Similarly, within the cytokine gene cluster on chromosome 5q31.1, the same susceptibility allele was identified in eczema and asthma [39], whereas the opposite allele was a risk factor for psoriasis [40].

A recent study conducted by Ellinghaus *et al.* [11^{¶¶}] took advantage of the shared genetic determinants of different immune-related traits in order to identify new genetic risk factors for eczema (Table 1). The Immunochip (Illumina, San Diego, CA, USA), a custom genotyping array containing all known variants from 188 loci involved in chronic inflammatory disorders [41], was used to perform an association study on eczema. In this study, four new susceptibility loci were identified (Table 2), and the most likely candidate gene from each region is described here. The locus on chromosome 4q27 includes the cytokine genes *IL2* (interleukin 2) and *IL21* (interleukin 21). Both, IL-2 and IL-21, can induce proliferation of T-cells, but IL-21 counteracts IL-2-induced T_{reg} cell expansion [42,43]. In the absence of IL-2, a disturbed balance between Th17 cells and T_{reg} cells leads to enhanced susceptibility to inflammatory disorders [44]. On chromosome 11p13, *PRR5L* (proline-rich protein 5 like) is involved in cell migration [45] and apoptosis [46]. Little is known about the function of *CLEC16A* (C-type lectin domain family 16, member A) on chromosome 16p13.13. A study [47] on *Drosophila* spp. suggested a role in endosomal regulation of immune receptor signaling pathways. Genetic variants in *CLEC16A* also regulate expression of the neighbouring gene *DEXI* [48], a dexamethasone induced gene of unknown function. An additional locus on chromosome 17q21.32 contains *ZNF652* (zinc finger protein 652), which encodes a transcriptional repressor of genes involved in invasion and metastasis of breast cancer [49].

A different approach, exploiting the overlap in the genetic etiology of allergic diseases and other immune-related and inflammatory traits, was used by Esparza *et al.* [12[¶]]. They selected all GWAS hits reported for any immune-related trait from a publicly available database and tested them for association with eczema (Table 1). Of 318 candidates, four genetic variants were significantly associated with eczema (Table 2). One of the associated variants is located in *RAD50*, near *IL13* and *IL4*, providing further support for the Th2 cytokine gene cluster on chromosome 5q31.1 [9[¶]]. On chromosome 12q13.2, a new risk variant was identified in *ERBB3* (v-erb-b2 erythroblastic leukemia viral oncogene homolog 3). *ErbB3* belongs to the epidermal growth factor receptor family and is involved in oncogenesis, in epithelial cell growth and survival, and in wound repair [50,51]. The risk variant on chromosome 1p36.11 points to *RUNX3* (runt-related transcription factor 3), encoding a member of the RUNT domain family of transcription factors. In a mouse model, *Runx3* was important for the development of dendritic epidermal T-cells and their migration to and retention in the epidermis [52,53]. Finally, a functional variant in *IL6R* (IL-6 receptor) on chromosome 1q21.3 was identified as a risk factor for eczema. The resulting amino acid exchange determines the balance between the two alternative IL-6 signaling pathways, involving either the membrane-bound IL-6 receptor (classical signaling) or the soluble form (trans-signaling) [54,55]. Classical signaling has been linked to the acute phase response in the liver, whereas trans-signaling plays an important role in transition from acute to chronic inflammation [54,56,57]. Interestingly, an antibody against the IL-6 receptor (tocilizumab) has already been approved for the treatment of rheumatoid arthritis [58[¶]]. A small open label study [59] of tocilizumab in eczema showed strong clinical efficacy but was interrupted due to bacterial infections. Specific blockade of the soluble IL-6 receptor could be a promising approach to protect from chronic inflammation without impairing the anti-bacterial immune response.

Overall, the new genetic susceptibility loci revealed a remarkable contribution of loci shared with other immune-related diseases in the development of eczema (Table 2). The identified candidate genes are involved in cytokine pathways and they encode transcription factors, both of which may shift the balance toward a Th2-mediated immune response. Interestingly, Th2 and Th17 cytokines decrease filaggrin expression [60[¶],61], suggesting that genetic factors influencing immunity may also affect eczema risk through their impact on skin barrier function.

OVERLAP WITH ALLERGIC DISEASES

Epidemiological studies have demonstrated that eczema is a major risk factor for the development of allergic rhinitis and allergic asthma [2]. Early onset, severe eczema and specific sensitization are important cofactors increasing the risk. However, the molecular mechanisms underlying the progression from eczema to asthma are largely unknown. Additionally, the disease course of eczema is very heterogeneous ranging from infants, who outgrow the disease by school age, to individuals with eczema that persists a lifetime [2]. Therefore, uncovering the mechanisms underlying eczema development is essential in order to identify and classify children at risk and to develop targeted treatment and prevention strategies.

Recent GWASs have revealed shared genetic determinants for eczema, asthma, and allergic rhinitis. However, the overlap is only partial. Some well established risk factors for asthma were not associated with eczema in the largest GWAS reported to date [9[¶]], suggesting that a combination of disease-specific and disease-overlapping genetic risk factors drive the manifestation and progression of allergic diseases. Among the new susceptibility loci for eczema, the IL-6 receptor gene (chromosome 1q21.3), the IL-1 receptor gene cluster (2q12.1), the *TSLP* locus (5q22.1), the Th2 cytokine gene cluster (*RAD50/IL13/IL4*, 5q31.1), the MHC region (6q21.33), the *C11orf30* locus (11q13.5), and the *ERBB3* locus (12q13.2) were also associated with asthma at genome-wide significance levels. A recent GWAS on allergic rhinitis and grass sensitization [62[¶]] identified three loci at genome-wide significance (*C11orf30*, MHC, and *TMEM232*). Intriguingly, all three loci have also been identified as risk factors for eczema, pointing to common pathways in different allergic diseases, which should aid in deciphering the molecular mechanisms involved in the atopic march.

The effect of filaggrin mutations on disease progression along the atopic march has been extensively analyzed in multiple study populations, including large longitudinal birth cohorts. The association with the combined phenotype eczema and asthma has been repeatedly demonstrated [13,15,63,64]. Indeed, children with eczema carrying a *FLG* mutation have a higher risk of developing asthma than noncarrier eczema children. Moreover, *FLG* mutations increase the risk of asthma only in individuals with a previous history of eczema. These observations suggest that *FLG* mutations play a major role in the transition from eczema to asthma characteristic of the atopic march [63].

Filaggrin is a major structural protein of the cornified layer of the epidermis with multiple

functions important for the skin barrier. Breakdown products of filaggrin serve as natural moisturizing factors and maintain the pH gradient in the epidermis, which is important for epidermal homeostasis and antimicrobial defense [65[¶]]. Filaggrin deficiency dose-dependently impairs the permeability barrier of the skin [66], which is critical for the development of eczema. Mouse models of filaggrin deficiency demonstrated that allergen exposure through a defective epidermal barrier increased the systemic allergen-specific antibody response, resulting in cutaneous inflammation [67,68[¶]]. Moreover, epicutaneous exposure to staphylococcal enterotoxin B, which is frequently found in eczema patients, enhanced lung inflammation and airway hyperresponsiveness via an IL-17A-dependent mechanism in mice [69[¶]], providing a potential mechanism triggering transition from eczema to asthma.

Subphenotype analyses were also performed for the *C11orf30* locus on chromosome 11q13.5, which was identified in the first GWAS on eczema. In a large birth cohort, the risk variant was associated with atopic eczema and atopic asthma, but not with the nonatopic forms of these diseases [17[¶]]. Interestingly, and as reported for the *FLG* mutations, larger effect sizes were identified in children with eczema and asthma or eczema and allergic rhinitis. In addition, among children with a history of eczema, the 11q13.5 risk variant provided a significant risk on asthma and allergic rhinitis, supporting a role in the progression from eczema to asthma. Associations with asthma and allergic rhinitis were further confirmed in GWASs [62[¶],70]. Although this is one of the best replicated risk loci in eczema, the functional link to disease has not yet been found.

The above results suggest a causative role for *FLG* mutations and the *C11orf30* locus in the development of eczema and the disease progression along the atopic march. Other susceptibility loci associated with eczema and with asthma are involved in Th2 responses, chronic inflammation, or antigen presentation, mechanisms that are important for the development of both, eczema and asthma. Further studies in longitudinal birth cohorts could dissect their role in allergic disease in more detail.

CONCLUSION

GWASs have rapidly increased our knowledge of the genetic factors involved in eczema and other allergic diseases. In the past 4 years, 21 new susceptibility loci for eczema were identified by GWASs and related approaches, and most of them were successfully replicated. The largest study on eczema, a meta-analysis of approximately 40 GWASs

worldwide, is currently being performed and is expected to reveal a comprehensive set of genetic risk factors by the end of this year. Although GWAS results point to candidate genes, they usually do not resolve the causative variant. They have limited power to detect rare variants that are emerging as important players in the susceptibility to common disease [71]. The field is therefore rapidly moving to fine-mapping studies using high-throughput sequencing technologies. They provide a complete picture of genetic variants within a region and should aid in identifying the disease causing variants and genes.

From the new genetic risk factors, a broader picture of pathways and biological processes altered in eczema is emerging. The critical role of an impaired skin barrier function is supported by the identification of various genes involved in skin differentiation and homeostasis, such as *FLG*, *OVOL1*, and *ERBB3*. Additionally, the identified candidate genes highlight the immunological processes involved in eczema pathogenesis, such as epithelial immunity (*TSLP*, *IL1R* cluster, *CCR4*), response against microbial infections (*NLRP10*, *CARD11*, *IL2/IL21*), T-cell differentiation (*RUNX3*, *IL2/IL21*), autoimmunity (MHC, *IL2/IL21*), and Th2 immunity (*IL13/IL4* cluster, *IL1R* cluster, *TSLP*).

A remarkable overlap among the genetic determinants of eczema and other inflammatory disorders points to shared pathogenic pathways. In particular, genes which are involved in different allergic phenotypes and in disease progression from eczema to asthma as shown for *FLG* and *C11orf30* could aid in resolving the mechanisms responsible for the atopic march.

In the case of *FLG* and *IL6R*, the identification of the causative variants has delineated key disease mechanisms in eczema, the impairment of the skin barrier and the shift from acute to chronic inflammation. Intriguingly, both disease mechanisms have already been targeted in treatment trials [58[¶],72], demonstrating that unraveling the genetic causes of eczema will improve our understanding of the disease and lead the way to prevention and personalized treatments based on the molecular defects present in each individual.

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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

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 579).

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