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REVIEW

Unravelling the complex genetic background of atopic dermatitis: from genetic association results towards novel therapeutic strategies

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Abstract Atopic dermatitis (AD) is a chronic inflammatory skin disease arising from complex interaction between genetic and environmental factors. As the starting point of the so-called "atopic march", e.g. the progression towards allergic asthma in some but not all affected children, AD has come into focus for potential disease-modifying strategies. To elucidate the genetic factors influencing AD development, linkage, association as well as genome-wide association studies have been performed over the last two decades. The results suggest that besides variation in immune-mediated pathways, an intact skin barrier function plays a key role in AD development. Mutations in the gene encoding filaggrin, a major structural protein in the epidermis, have been consistently associated with AD, especially the early-onset persistent form of disease, and are regarded as the most significant known risk factor for AD development to date. Additionally, variation in some other genes involved in skin integrity and barrier function have shown association with AD. However, the known genetic risk factors can only explain a small part of the heritability at the moment. Whole-exome or whole-genome sequencing studies have not been reported yet, but will probably soon evaluate the influence of rare variations for AD development. Additionally, large multi-centre studies comprehensively incorporating gene–gene and gene–environment interactions as well as epigenetic mechanisms might further elucidate the genetic factors underlying AD pathogenesis and, thus, open the way for a more individualized treatment in the future.

Keywords Atopic dermatitis · Eczema · Association · GWAS · Filaggrin · Personalized therapy

Abbreviations

AD	Atopic dermatitis
EDC	Epidermal differentiation complex
FLG	Filaggrin
GWAS	Genome-wide association study
IgE	Immunoglobulin E
IV	Ichthyosis vulgaris
MHC	Major histocompatibility complex
NLR	NOD-like receptor
PRR	Pattern recognition receptor
RLR	RIG-I-like receptor
SNP	Single nucleotide polymorphism
Th	T helper lymphocyte
TLR	Toll-like receptor

Introduction

Atopic dermatitis (AD, also called atopic eczema) is a chronic inflammatory skin disease characterized by relapsing eczematous lesions, dry skin and strong pruritus. It affects up to 25 % of children and 1–3 % of adults worldwide [60], thus representing a major social and economic burden. Together with food allergies, allergic rhinitis and atopic asthma, AD belongs to the group of atopic (e.g. allergic) disorders, characterized by the development of immunoglobulin (Ig) E antibodies against

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common allergens. However, only about 70–80 % of AD patients exhibit elevated total or specific IgE levels (also termed "extrinsic AD"), while the rest do not show sensitization (named "intrinsic AD") [8]. AD mostly occurs in early childhood and has a tendency to improve or vanish during adolescence in the majority of patients; on the other hand, more than 60 % of affected children go on to develop allergic rhinitis and asthma over time [72]. This latter phenomenon has been called the "atopic march" [94], suggesting that AD may be the starting point for the subsequent development of asthma in a subgroup of (for example, genetically) predisposed individuals. Therefore, targeting AD pathogenesis to prevent or modify this march has been proposed as a promising therapeutic strategy in the future [6]. However, to reach this goal substantial knowledge has to be gained about the complex pathogenic mechanisms underlying AD development. In this review, we will summarize the current knowledge about the genetic factors for AD, with an emphasis on recent genome-wide analytic approaches and discuss how these results may be of relevance for potential future therapeutic and diagnostic strategies.

AD pathogenesis

AD belongs to a group of multifactorial diseases that are believed to arise from complex interactions between genetic and environmental factors [91]. In contrast to monogenic Mendelian disorders, complex diseases are probably influenced by variations in many different genes, each contributing only a small fraction to the overall disease risk. Twin studies have revealed concordance rates for monozygotic twins between 0.23 and 0.86 compared to 0.15–0.18 for dizygotic twins [74, 85], suggesting a rather high heritability for AD. However, the observed increase in AD prevalence over the past decades [10] cannot be explained by genetic factors alone and indicates that environmental factors also play an important role. Risk factors associated with increased prevalence include higher socioeconomic status, smaller family size, higher level of family education and urban environment [16], suggesting that a lack of childhood infections in our modern society may influence the immune system towards atopic diseases. This theory has been called the "hygiene hypothesis" [25]; however, the complex interactions between genes and environment are not yet conclusively uncovered.

Since AD is a chronic relapsing inflammatory disease of the skin, the cytokine milieu in the epidermis has been extensively examined. As for the other atopic diseases, a predominance of T helper (Th)-2 cells producing interleukin (IL)-4, IL5 and IL13 has been found in the early phase of the disease, while chronic AD tends to show a Th1-related cytokine profile characterized by the production of interferon γ [38]. Under the influence of IL4 and IL13, plasma cells are stimulated to produce IgE. More recently, the role of additional T helper cell subsets such as Th17 and Th22 cells have come into focus for AD pathogenesis [23].

Genetic studies for AD

Three different approaches have been performed in genetic studies for AD to date. *Linkage studies* originally identified some chromosomal regions showing evidence for linkage to AD (including 1q, 3q, 3p, 17q and 18q), but conventional fine-mapping has only led to the identification of a single AD susceptibility gene in one of these regions, namely the *COL29A1* gene on chromosome 3q21 [76]. However, replication of this result in additional cohorts has failed so far ([27, 55] see below). In *association studies*, genotypic and allelic frequencies of polymorphisms in candidate genes, chosen because of their known or suspected functional relevance for AD development, are compared between cohorts of unrelated patients and healthy control subjects. In a comprehensive review in 2009, 81 genes were retrieved that had demonstrated significant association with AD in at least one study up to that time [3] and since then many more have been added. However, because of statistical issues including correction for multiple testing, small sample sizes and population stratification [5], results of association studies need to be replicated in independent cohorts to avoid false-positive findings. Of the many genes that have shown association in the literature, only some have been replicated, especially the gene encoding filaggrin (see below) which has been consistently associated with AD in >20 studies [3].

One shortcoming of single-gene association studies is that they rely on the selection of candidate genes and, thus, cannot identify completely new pathophysiological pathways. Since a few years, though, *genome-wide association studies* (*GWAS*) analysing >1,000,000 SNPs simultaneously with chip-based methods have become possible for complex diseases. For AD, six GWAS or related approaches have been reported to date (summarized in Table 1). The first GWAS, performed in a German cohort, was published in 2009 and identified a novel risk locus on chromosome 11q13.5 (close to the *C11orf30* gene) [22]. This locus has since then been replicated in additional GWAS [21] as well as in case–control studies [43, 62], strongly implicating this locus in AD pathogenesis. Further, it also showed association with atopic asthma [47]. *C11orf30* encodes the nuclear protein EMSY that is involved in DNA repair and transcriptional regulation [22] and was recently shown to regulate interferon response

Table 1 Genome-wide association studies for atopic dermatitis

ID	References	Study population	Gene chip	Original sample	Replication sample	Region	Gene(s)	Most significant associations
1	Esparza-Gordillo et al. [22]	German	Affymetrix 5.0 (500K)	939 cases, 975 controls, 270 complete nuclear families	2,637 cases, 3,957 controls	11q13.5	*C11orf30*	rs7927894: $p = 7.6 \times 10^{-10}$
						1q21	*FLG*	rs6661961: $p = 1.2 \times 10^{-9}$
2	Sun et al. [80]	Han Chinese	IlluminaBeadChips	1,012 cases, 1,362 controls	3,624 cases, 12,197 controls	5q22.1	*TMEM232/SLC25A46*	rs7701890: $p = 3.15 \times 10^{-9}$
						20q13.33	*TNFRSF6B/ZGPAT*	rs6010620: $p = 3.0 \times 10^{-8}$
						1q21.3	*FLG*	rs3126085: $p = 5.9 \times 10^{-12}$
3	Hirota et al. [29]	Japanese	IlluminaBeadChips	1,472 cases, 7,971 controls	1,856 cases, 7,021 controls	2q12	*IL1RL1-IL18R1-IL18RAP*	rs13015714: $p = 8.35 \times 10^{-18}$
						6p21.3	*GPSM3* (*MHC*)	rs176095: $p = 8.38 \times 10^{-20}$
						11p15.4	*OR10A3-NLRP10*	rs878860: $p = 1.54 \times 10^{-22}$
						3p21.33	*GLB1*	rs6780220: $p = 2.77 \times 10^{-16}$
						3q13.2	*CCDC80*	rs12634229: $p = 1.56 \times 10^{-19}$
						7p22	*CARD11*	rs4722404: $p = 7.83 \times 10^{-9}$
						10q21.2	*ZNF365*	rs10995251: $p = 5.58 \times 10^{-20}$
						20q13	*CYP24A1-PFDN4*	rs16999165: $p = 1.65 \times 10^{-8}$
4	Paternoster et al. [67]	16 populations of European descent (meta-analysis)	n.s.	5,606 cases, 20,565 controls	5,419 cases, 19,833 controls	11q13.1	*OVOL1*	rs479844: $p = 1.1 \times 10^{-13}$
						19p13.2	*ACTL9*	rs2164983: $p = 7.1 \times 10^{-9}$
						5q31	*KIF3A*	rs2897442: $p = 3.8 \times 10^{-8}$
5	Weidinger et al. [90]	Northern European	IlluminaBeadChips	1,562 cases, 4,054 controls	2,286 cases, 3,160 controls	1q21	*FLG*	rs11205006: $p = 1.02 \times 10^{-15}$
						5q31	*RAD50/IL13*	rs2158177: $p = 2.65 \times 10^{-10}$
						6q21	*MHC*	rs6474: $p = 1.61 \times 10^{-9}$
						11q13	*LRRC32*	rs2155219: $p = 8.17 \times 10^{-9}$
6	Ellinghaus et al. [21]	German, Japanese, Chinese, Irish	Immuno-chip (Illumina iSelect HD)	2,425 cases, 5,449 controls	7,196 cases, 15,480 controls	4q27	*IL2/IL21*	rs17389644: $p = 1.30 \times 10^{-8}$
						11p13	*PRR5L*	rs12295535: $p = 7.96 \times 10^{-13}$
						16p13.13	*CLEC16A*	rs2041733: $p = 3.44 \times 10^{-15}$
						17q21.32	*ZNF652*	rs16948048: $p = 2.92 \times 10^{-9}$
						1q21.3	*LCE3A*	rs72702813: $p = 1.49 \times 10^{-33}$
						2q12.1	*SLC9A4*	rs759382: $p = 6.01 \times 10^{-11}$
						5q31.1	*KIF3A/IL13*	rs848: $p = 8.22 \times 10^{-28}$
						11q13.5	*C11orf30*	rs7110818: $p = 3.33 \times 10^{-16}$
						20q13.33	*TNFRSF6B*	rs909341: $p = 7.77 \times 10^{-16}$

[24]. In a subsequent GWAS in the Chinese Han cohort, novel susceptibility loci on chromosomes 5q22.1 (containing the *TMEM* and *SLC25A46* genes) and 20q13.33 (*TNFRSF6B* and *ZGPAT*) were reported as well as the known *FLG* locus replicated [80]. A GWAS in the Japanese population added eight other new susceptibility loci, including among others the major histocompatibility complex (MHC) region on chromosome 6p21 and the *IL1RL1–IL18R1–IL18RAP* locus on chromosome 2q12 [29]. Since large sample sizes are needed to reach sufficient statistical power for the analysis of complex disorders, a meta-analysis including 5,606 AD cases and 20,565 controls from 16 European cohorts was performed that discovered three SNPs meeting genome-wide level of significance [67]. These are located in the vicinity of the *OVOL1* (11q13) and *ACTL9* (19p13) genes, both of which presumably play a role in epidermal proliferation and differentiation [67], as well as the *KIF3A* gene (within the cytokine gene cluster on chromosome 5q31.1). A European GWAS for childhood-onset AD further confirmed the *FLG* and MHC loci as well as the regions on chromosomes 11 and 5 (although here, the highest association was found near *RAD50/IL13* on chromosome 5q13) [90].

Overall, there has been a rather high degree of replication between the different GWAS, suggesting that the discovered susceptibility regions appear robust. However, replication hardly ever includes exactly the same SNPs, but rather SNPs within the same chromosomal regions. Ellinghaus et al. [21] recently used the so-called ImmunoChip (Illumina), a custom genotyping array that contains all known variants from 188 loci involved in chronic inflammatory disorders [15]. Even though this approach does not qualify as a genome-wide association study, the results are included in our overview because it also makes use of the new chip-based genotyping technologies that have dominated research for complex disorders in recent years. Besides replication of the most important regions identified before, four new loci were discovered in this analysis (*IL2-Il21*, *PRR5L*, *CLEC16A* and *ZNF652*; see Table 1).

Despite these promising results, the identified genetic risk factors can only explain a small part (~14.4 %) of AD heritability at the moment [3, 21]. One reason for this phenomenon may be that the three approaches accomplished so far only evaluate common variation, but cannot judge the relevance of rare variants which might also play a role in disease pathogenesis [3]. The SNPs included in GWAS for example are usually chosen to have a minor allele frequency of >1 %. More recently, next-generation sequencing techniques have been developed that allow analysing all exonic sequences (so-called whole exome sequencing) or the total genomic sequence (whole-genome sequencing) of an individual simultaneously. While initial reports of whole-exome sequencing have been presented for other complex diseases including asthma [20] and multiple sclerosis [70], no such comprehensive study has been published for AD to date. However, these studies will surely be accomplished in the near future and might shed some light on the question whether rare variants may contribute to the observed "missing heritability". Another reason why GWAS results cannot fully explain AD heritability is given by their limited power to detect common variants with only a small effect [46]. Further, investigation of the role of copy number variations, gene–gene as well as gene–environment analyses have not yet been incorporated in large scale.

Combining the results of linkage, association and GWAS analyses for AD accomplished so far, evidence has been accumulating that the genes involved in disease pathogenesis mainly fall into two pathophysiologic groups: immune-mediated pathways (including innate and adaptive immunity) on the one hand and skin barrier functions on the other. For both groups, we will summarize the most important findings.

Immune-related pathways

Adaptive immune system

For a long time, candidate gene studies for AD mainly have focused on immunological pathophysiology, especially the Th2-dominated cytokine milieu typical for allergic diseases as well as the development of IgE antibodies. Therefore, among the genes most consistently (studied and) replicated in association studies before the era of GWAS are the genes encoding IL13, IL4 and the IL4 receptor [3]. In the *IL13* gene, both a promoter polymorphism (−1112C/T) and a coding variation (Arg130Gln) have been associated with AD in several populations [33, 44, 54]. In *IL4*, the −590 C/T promoter SNP conveyed risk for AD or related atopic phenotypes in some studies [18, 28, 39]. The gene encoding the alpha chain of the IL4 receptor (*IL4RA*), which is also part of the IL13 receptor, was also associated with AD risk in several studies [32, 52, 64]. Additionally, variation in *STAT6*, acting downstream of the IL4 receptor as well as in the alpha and beta chains of the high-affinity IgE receptor (*FCER1A/B*), have been implicated in AD pathogenesis in some studies [12, 57, 81, 82, 95].

Innate immune system

In contrast to the specific, but rather slow adaptive immune reaction mediated by T and B cells, the innate immune system builds up a rapid, but unspecific defence against invading pathogens. To reach this goal, pattern recognition receptors (PRRs) recognize certain molecules of bacteria,

viruses or fungi (so-called pathogen-associated molecular patterns, PAMPs) and initiate a rapid innate immune response [41]. The known PRRs include the Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs). Interestingly, genetic variation in PRR genes has been implicated in the pathogenesis of many different autoimmune and inflammatory diseases, including AD [69]. For example, a significant association was seen between variation in the *TLR2* gene and severe AD in some populations [1, 63, 68]. Additionally, a polymorphism in the *TLR9* gene was associated with extrinsic AD [61]. Further, a promoter SNP in the gene encoding the toll-interacting protein (*TOLLIP*) showed association with AD in a German cohort [73] and variation in the adaptor protein MYD88 adapor-like (Mal) was associated with AD in Japanese patients [2]. In the group of NLRs, polymorphisms in the *NOD1* gene were associated with AD and serum IgE levels [88]. Further, a study evaluating variation in seven selected NLR genes showed evidence for an association of SNPs in the *NOD2* (*CARD15*) and *NALP12* genes with AD [45]. Association studies of RLR genes with AD have not been reported yet.

Taken together, evidence is accumulating that genetic variation in innate immune receptor genes may play a role in AD pathogenesis, building up another promising starting point for future therapeutic strategies [19]. However, most of the associations described here were in rather small cohorts, and many still await replication in independent larger populations.

Skin barrier function

Additional to innate and adaptive immune dysregulation, a defective epidermal barrier has been discovered as an essential factor for AD development over the last 7 years. The most important function of the human epidermis is to establish and maintain an effective barrier that protects against dehydration as well as percutaneous absorption of exogenous substances [40]. During a complex differentiation process, epidermal cells develop from mitotically active cells in the basal layer into dead, flattened squames in the outermost layer, the stratum corneum. There, they are tightly connected to each other and further surrounded by lipids, building the so-called cornified envelope [30] (Fig. 1). Genetically determined defects in this complex barrier function have been shown to increase risk for AD, especially mutations in the gene encoding filaggrin which constitute the most significant known risk factor for AD development discovered to date [51].

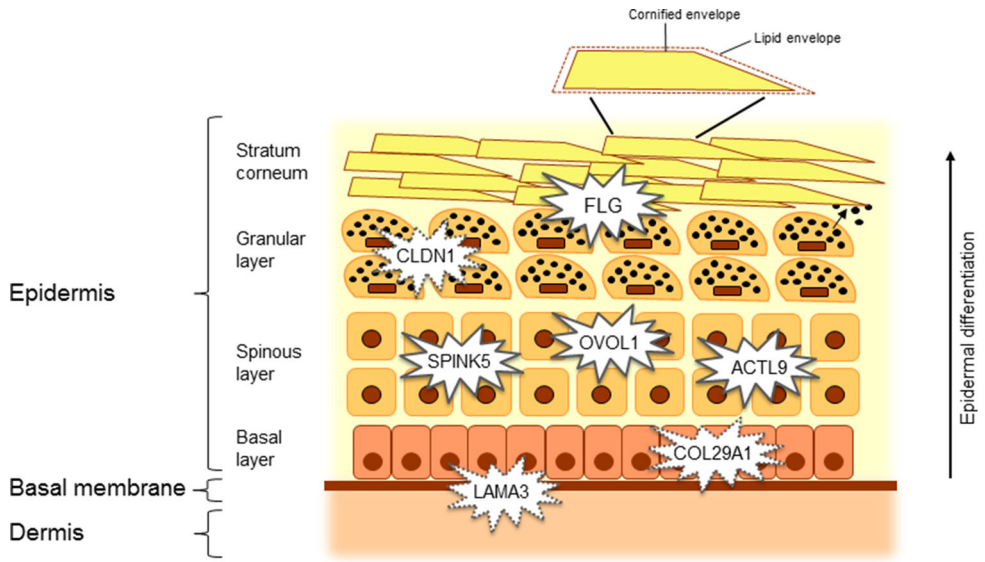

Fig. 1 Epidermal differentiation and localization of proteins in which mutations have been proposed to contribute to epidermal barrier defects in AD (adapted from [30]). While moving from the basal layer through the spinous and the granular layer towards the stratum corneum, corneocytes develop from mitotically active cells into dead, flattened squames. They are stabilized by both the cornified envelope, a thick peripheral protein envelope built through cross-linking of epidermal proteins, and the lipid envelope, established by lipids extruded into the extracellular space. Additional to mutations in filaggrin (FLG) that plays a major role in the integrity of the cornified envelope, variation in the protease inhibitor SPINK5/LEKTI-1 has been associated with AD in several association studies. Further, variation near the *OVOL1* and *ACTL9* genes, both presumably playing a role in epidermal regulation and differentiation, gave highly significant association with AD in a large meta-analysis of GWAS studies, but not much is known about their specific function in the epidermis yet. Variation in the tight junction protein claudin 1 (CLDN1), the epidermal collagen COL29A1 and the alpha chain of laminin 5 (LAMA3), expressed in the basal layer of the epidermis, have also been implicated in AD pathogenesis, but replication has not yet been reported (preliminary results indicated by *dotted lines*)

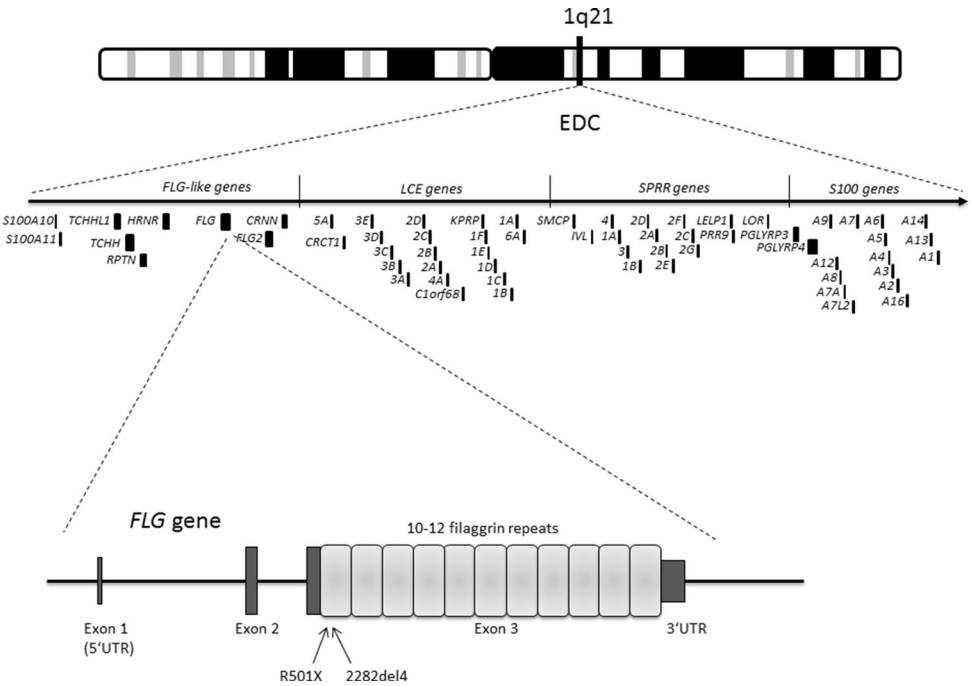

Fig. 2 Localization of the epidermal differentiation complex (EDC) on chromosome 1q21 and structure of the filaggrin (FLG) gene. The EDC contains a cluster of genes involved in epidermal differentiation, including for example loricrin, involucrin, small proline-rich proteins (SPRRs), calcium-binding proteins of the S100A family and late cornified envelope (LCE) proteins. The *FLG* gene comprises three exons of which the first exon is non-coding. The large third exon is composed of nearly identical tandem repeats, each ~972 bp in length, of which allelic variants of 10, 11 or 12 repeats exist. The two loss-of-function mutations most commonly associated with AD in European populations are R501X and 2282del4

Filaggrin and the epidermal differentiation complex (EDC)

Profilaggrin, the precursor of filaggrin, is located in the keratohyalin granules of the stratum granulosum (Fig. 1). Upon activation by proteolytic cleavage, the filaggrin peptides aggregate the keratin filaments into tight bundles, leading to a collapse of the cells into flattened squames [11]. Thus, filaggrin plays a major role for the integrity of the cornified envelope. In 2006, null-mutations in the filaggrin gene (*FLG*) were identified as causative for ichthyosis vulgaris (IV), another chronic skin disease characterized by fine scaling that is most prominent over the lower abdomen, arms and legs [75]. Because several members of the IV families also exhibited AD, *FLG* mutations were subsequently evaluated in AD patients and found to be strongly associated with this disease [66]. Since this initial report, numerous replication studies have been performed that uniformly confirmed association of *FLG* variation with AD. The two most common mutations in European populations are R501X and 2282del4, both resulting in formation of a premature stop codon and complete loss of filaggrin peptide production [36]. In Asian populations, different loss-of-function mutations were identified in the *FLG* gene that also showed significant association with AD [58, 59]. Overall, the reported frequencies of *FLG* mutations lie between 18 and 48 % in AD patients [35]. *FLG* mutations have also been associated with food allergy [86] and with asthma, but only in the presence of AD [89]. Further, they were consistently implicated in a more severe phenotype of AD, including onset in early childhood and persistence into adulthood, suggesting that *FLG* mutations may serve as biomarkers for early-onset severe AD that is likely to progress into allergic sensitization and asthma [6]. In African populations, however, *FLG* mutations seem to play a less important role [50, 84, 92].

The *FLG* gene comprises three exons of which the first exon is non-coding [30] (Fig. 2). The large exon three is composed of nearly identical tandem repeats, each ~972 bp in length, of which allelic variants of 10, 11 or 12 repeats exist [9]. After exclusion of the known rare loss-of-function mutations, analysis of an Irish case–control cohort recently demonstrated that the number of repeats was significantly lower in AD cases than controls, suggesting that common copy number variations in *FLG* also contribute to AD risk [9].

The filaggrin gene is located on chromosome 1q21, a region that contains a cluster of genes involved in epidermal differentiation, the so-called epidermal differentiation

complex (EDC; Fig. 2) [42]. Besides *FLG*, at least 45 genes are located within in the EDC, encoding for example loricrin, involucrin, small proline-rich proteins (SPRRs), calcium-binding proteins of the S100A family and late cornified envelope (LCE) proteins. The 1q21 region had already shown linkage to AD in a linkage screen in the British population [14]. However, even though *FLG* mutations are without any doubt a very strong genetic risk factor across populations in this linkage region, incorporating *FLG* variation did not entirely reduce the linkage peak in the 1q21 region, suggesting that additional EDC genes may be involved in AD pathogenesis [53]. Recently, a 24-bp deletion in the gene encoding small proline-rich protein 3 (*SPRR3*) was shown to be associated with AD in cohorts from Germany, Poland and the Czech Republic [48]. On the other hand, no association was seen for a deletion of the cornified envelope 3B and 3C genes in a European cohort [4], and a case–control study evaluating polymorphisms across 21 EDC genes in a German cohort did not find evidence for associations apart from *FLG* [77]. In contrast to European and Asian populations, *FLG* mutations have not commonly been found in African American subjects with AD. However, loss-of-function mutations in *FLG2*, also located within the EDC, have recently shown association with AD persistence in African American children in a similar magnitude as observed for *FLG* in European subjects [49]. Taken together, the role of additional EDC genes still cannot be sufficiently assessed yet.

Additional genes involved in epidermal differentiation and integrity

Besides the important role of the cornified envelope for epidermal barrier function, tight junctions in the granular layer of the epidermis have been proposed to build up a second line of defence, especially regulating transepidermal water loss [37]. Tight junctions are composed of several transmembrane proteins, including the claudin family [26]. It was recently demonstrated that expression of claudin-1 was reduced in the skin of AD patients and inversely correlated with Th2 biomarkers; further, haplotype-tagging SNPs in the *CLDN1* gene were found to be associated with AD in two small North American populations [17]. Additionally, association of AD with variation in the gene encoding the alpha chain of laminin 5 (*LAMA3*), expressed in the basal layer of the epidermis, was recently identified in a German case–control cohort [78]. However, the sample sizes of the investigated cohorts were only small to moderate and replication of these association results has not been accomplished so far. Two of the genes discovered in the meta-analysis of GWAS data, namely *OVOL1* and *ACTL9*, have also been suggested to play a role in epidermal regulation and differentiation [67], although not much is known about their actual function yet.

AD has further been associated with variation in the serine protease inhibitor of kazal type 5 (*SPINK5*) gene encoding lympho-epithelial kazal type-related inhibitor type 5 (LEKTI-1), a protease inhibitor effective in the epidermis [56, 87]. Loss-of-function mutations in this gene are known to cause Netherton syndrome, a severe autosomal recessive skin disease including AD and sensitization [13]. In 2007, Söderhall et al. [76] identified an epidermal collagen gene (*COL29A1*) as the AD susceptibility gene in the linkage region on chromosome 3q21 in their European population. However, neither a replication study in a German case–control cohort [27] nor a comprehensive analysis in five independent study populations [55] supported a role of variation in this gene for AD pathogenesis. Thus, even though COL29A1 may be an interesting functional candidate because of its epidermal localization, replication of the initial report is still awaiting and it remains to be seen whether variation in this gene influences AD.

Still, taken together, these results suggest that besides the strong influence of *FLG* mutations, genetic variation in more deeply located components of the epidermis may also—at least in part—contribute to AD pathogenesis (Fig. 1). Evaluation of gene–gene interactions in this group of genes involved in a common pathophysiological pathway appears an interesting approach to follow in the future.

Future options and novel therapeutic strategies

Even with the great improvements brought by the GWAS technology, association analyses for complex disorders have so far mainly focused on single-gene effects, while comprehensive analyses of gene–gene or gene–environment interactive effects have not been incorporated yet. As one of the few attempts to look at gene–environment interactions, Bisgaard et al. [7] reported an interaction between *FLG* genotype and cat (but not dog) exposure at birth in a high-risk Danish birth cohort. In this study, an increased risk for AD was found for children carrying *FLG* mutations, but this risk was further increased if children were exposed to cat allergen at birth [7]. More such investigations in larger populations and preferably on a genome-wide level are needed to elucidate the complex interactions between skin barrier defects and environmental risk factors. It is still an ongoing debate whether skin barrier defects in the first place lead to secondary sensitization through the impaired skin, or whether immune dysregulation is the first pathogenic mechanism (outside-in vs. inside-out hypothesis) [93].

Further, whole-exome/-genome sequencing strategies will probably soon shed some more light on the interesting

question to what extent rare variation contributes to AD and whether rare variation can explain the observed "missing heritability". For multiple sclerosis, for example, exome sequencing has successfully identified rare variants in a gene involved in vitamin D metabolism in families with several affected individuals [70]. Similarly, in a family segregating asthma, exome sequencing led to the identification of several potentially functional variants in interesting candidate genes [20]. For AD, however, only exome sequencing-based targeted analysis of a group of genes has been reported so far [50], but comprehensive whole-exome analyses are still awaiting. Besides heritable changes in DNA sequence, epigenetic mechanisms such as methylation or histone modification have also been implicated in allergic diseases. A recent pilot study comparing methylation differences between epidermal lesions from AD patients and healthy control epidermis revealed striking differences that partly correlated with altered transcript levels of genes involved in epidermal differentiation and innate immune response [71]. For *FLG*, two preliminary studies on methylation have been reported so far, but presented controversial results [83, 96]. Therefore, initial evidence suggests that epigenetic phenomena seem to play an important role for AD pathogenesis, but additional studies are needed to gain more specific insight into this complex field.

The growing knowledge about the role of filaggrin and additional epidermal proteins for AD development has prompted intriguing new therapeutic strategies recently [34]. In general, the concept of "barrier therapy", i.e. topical treatment to preserve or restore the disturbed epidermal barrier in AD, has led to the development of new moisturizers and emollients, out of which some have already shown therapeutic efficacy in clinical studies (reviewed in [31]). However, long-term studies are needed to evaluate whether improving barrier function may prevent progression of the atopic march. As a more specific approach, topical application of a recombinant partial filaggrin protein was shown to be internalized and appropriately processed by dermal cells [79]. Further, it could restore the normal phenotype in an AD mouse model, suggesting that topically delivered recombinant FLG may be an effective therapy for AD [79]. In another preliminary study, it was shown that up-regulating filaggrin expression was also beneficial to skin lesions in the mouse model of AD [65].Therefore, evidence is accumulating that FLG-targeted therapeutic approaches may provide a promising treatment option in the future. However, it will still take a while before these therapeutic approaches can become applicable for human AD patients, since a lot of issues will have to be addressed, including, e.g. safety, dosing and duration of the effect.

Unravelling the complex genetic architecture underlying AD is an important premise for future therapies, since AD—as the starting point of the so-called "atopic march"—has been proposed to be a good candidate for disease-modifying strategies [6]. To reach this goal, the large number of AD patients needs to be stratified into subgroups based on a set of biomarkers (genetic as well as non-genetic) of prognostic value. Filaggrin mutations have already been proposed as a reliable screening marker for early-onset severe AD with a higher risk to develop asthma [6]. For the other genetic variations associated with AD, such prognostic value has not been assessed yet. It is expected that not a single biomarker will be sufficient to stratify AD patients, but rather a combination of several biomarkers. Therefore, additional research on the genetic basis of AD, including comprehensive analyses of both gene–gene and gene–environment interactions as well as epigenetic mechanisms, is necessary to pave the way towards more personalized therapeutic options in the future.

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Conflict of interest The authors declare that they have no competing interests.

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