



# Identifying Atopic Dermatitis Risk Loci in 1,094,060 Individuals with Subanalysis of Disease Severity and Onset

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Atopic dermatitis (AD) is a common inflammatory skin disease highly attributable to genetic factors. In this study, we report results from a genome-wide meta-analysis of AD in 37,541 cases and 1,056,519 controls with data from the FinnGen project, the Estonian Biobank, the UK Biobank, the EAGLE Consortium, and the BioBank Japan. We detected 77 independent AD-associated loci, of which 10 were, to our knowledge, previously unreported. The associated loci showed enrichment in various immune regulatory processes. We further performed subgroup analyses of mild and severe AD and of early- and late-onset AD, with data from the FinnGen project. Fifty-five of the 79 tested variants in the associated loci showed larger effect estimates for severe than for mild AD as determined through administered treatment. The age of onset, as determined by the first hospital visit with AD diagnosis, was lower in patients with particular AD-risk alleles. Our findings add to the knowledge of the genetic background of AD and may underlie the development of new therapeutic strategies.

**Keywords:** Atopic dermatitis, Genetics, GWAS

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## INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a lifetime prevalence of approximately 10–20%. AD can manifest at any age, but in most cases, AD symptoms start during the first year of life. In 70% of cases, AD onset occurs by the age of 5 years (Løset et al, 2019; Weidinger and Novak, 2016). AD is characterized by dry, itchy skin and periodically occurring eczematous lesions. The pathophysiology of AD involves skin barrier dysfunction and impaired immune regulation of the innate and adaptive immune responses. Basic treatment of AD includes the use of emollients to protect and restore the skin barrier (Lee et al, 2016). Medical therapies consist of topical corticosteroids or calcineurin inhibitors for patients with mild-to-moderate AD and systemic approaches, including cyclosporin, dupilumab, or Jak inhibitors targeting the immune system in cases of severe AD (Patrick et al, 2021). Causes of AD are multifactorial, including an interplay of genetic, epigenetic, and

environmental factors (Kantor and Silverberg, 2017; Liang et al, 2016).

Genetic variation has a high contribution to AD susceptibility, with heritability estimates of approximately 75% based on twin studies (Løset et al, 2019). Previous GWASs have identified approximately 80 genetic risk loci that explain about 30% of the variation in AD susceptibility (Brown, 2021; Budu-Aggrey et al, 2023; Paternoster et al, 2015). The major predisposing genetic factors include loss-of-function variants in *FLG* gene encoding FLG protein. FLG is essential in maintaining epidermal homeostasis, and *FLG* loss-of-function variants lead to skin barrier dysfunction that can lead to loss of hydration and make the skin prone to allergen and microbial entry (Liang et al, 2016). Further risk loci contributing to epidermal strength and integrity include variants in *DSC1* and *SERPINB7* (Sliz et al, 2022). Variants in multiple immune regulatory genes, such as *IL13* and *IL6R*, have been linked to immune dysregulation of AD (Liang et al, 2016).

The occurrence of AD symptoms displays high heterogeneity during the course of the disease, which is reflected in specific aspects of the disease, including the age of onset, disease severity, and longitudinal trajectories of disease progression (Irvine and Mina-Osorio, 2019). Previous studies have investigated some genetic variants in relation to AD severity, including variations in *FLG* and *KRT6A* (Martin et al, 2020; Zhu et al, 2022). *FLG* variants were associated with AD severity and early-onset AD in different populations (Martin et al, 2020). Altogether, little is known about the associated variants in the context of AD severity or the age of onset.

In this study, we aimed to identify further genetic factors of AD in a meta-analysis of 1,094,060 individuals with data from FinnGen, UK Biobank, Estonian Biobank, EAGLE Consortium, and BioBank Japan (BBJ). Another goal was to

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Abbreviations: AD, atopic dermatitis; BBJ, BioBank Japan; MMP, matrix metalloproteinase; PRS, polygenic risk score; Treg, regulatory T cell

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characterize the genetic background of AD disease subgroups that were classified as mild or severe on the basis of the administered medical treatment and as early or late onset according to age during the first hospital treatment period with AD diagnosis. We further aimed to investigate whether particular risk genotypes were associated with the age of onset.

## RESULTS

### Overview of the meta-analysis of AD

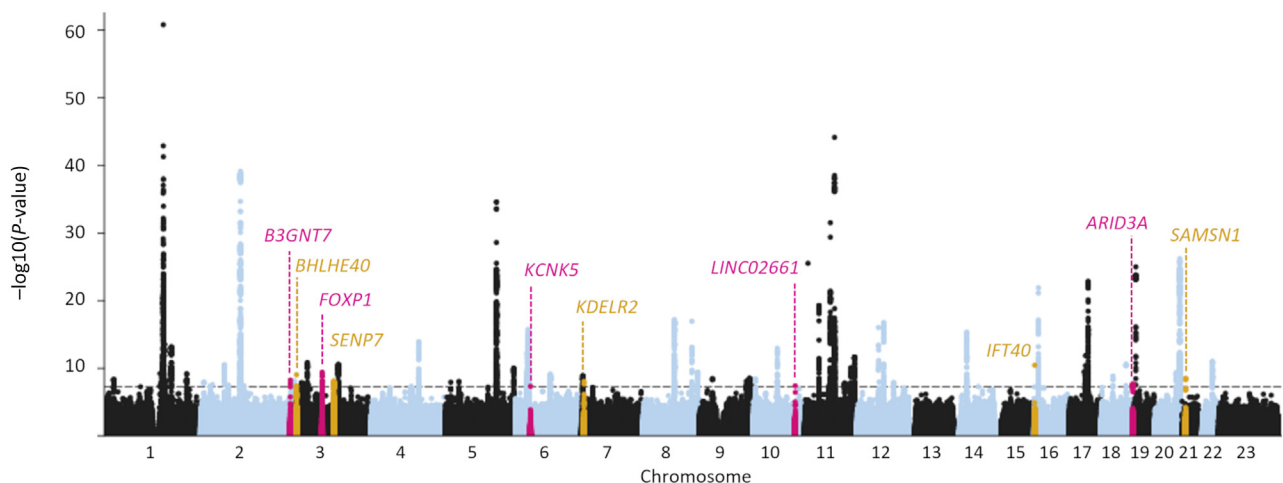
Meta-analysis of 1,094,060 individuals (37,541 cases; 1,056,519 controls) detected 77 associated loci (Figure 1, Table 1, and Supplementary Table S1). Majority of the identified associations were in intronic or intergenic genomic regions, and annotations were enriched in many categories (Supplementary Figure S1). The distance between the associated loci was at least 1 Mb, with the exception of an association signal in chromosome 1 due to variants in the *FLG* locus that are known to span several megabases and *DSC1* in chromosome 18 that was annotated as a causal gene in 2 loci. Our previous work indicates that the association signal linked to *DSC1* was driven by the missense variant rs200047736 (Sliz et al, 2022). Of the identified genome-wide significant loci, 10 were not previously associated with AD, as investigated in the NHGRI-EBI GWAS catalog (MacArthur et al, 2017) or in a recent meta-analysis of AD (Budu-Aggrey et al, 2023) with a  $\pm 1$  Mb window around the meta-analysis lead variants (Table 1, Supplementary Table S2, and Supplementary Figure S2). Conditional association analysis did not reveal secondary association signals (Supplementary Figure S3).

Effect estimates for the genome-wide significant loci in individual study cohorts were largely concordant (Supplementary Figure S4). Only 5 relatively well-established AD-risk loci—*IL18RAP*, *IL13*, *BACH2*, *ARRDC1*, and *ZNF652*—showed heterogeneity ( $P_{\text{adjusted}} < .05$ ) (Supplementary Table S1). In BBJ, the effect estimates were remarkably similar to those in the

European populations (Supplementary Figure S4). *IL7R* was the only locus that showed a clear directional effect size difference between BBJ and the European cohorts. The association for the *IL7R* variant was not significant in BBJ ( $P = .32$ ).

Sixty-five of the 77 associated loci were genome-wide significant in the European-only meta-analysis (ie, excluding BBJ) (Supplementary Table S3). Of the previously unreported AD associations, loci near *ARIDA3* and *KDELR2* had suggestive  $P$ -values in the European-only meta-analysis and reached genome-wide significance with the addition of BBJ. The associations at these loci showed nominal associations in at least 2 of the 5 meta-analysis cohorts (internal replication). Of the previously known associations, 7 showed suggestive or borderline significant associations in the European-only meta-analysis. Loci near *NLRP10*, *GLB1*, and *INPP5D*, originally discovered in Asian populations, were not associated in the meta-analysis with only European samples, suggesting population-specific associations at these loci (Hirota et al, 2012; Ishigaki et al, 2020; Sakaue et al, 2021; Tanaka et al, 2021).

Genome-wide inflation factor of the meta-analysis, calculated with linkage disequilibrium score regression, indicated that the slightly inflated value of the factor ( $\lambda_{\text{GC}} = 1.143$ ) was mostly accounted by polygenic signal with the intercept being close to 1 (1.047) (Bulik-Sullivan et al, 2015; Finucane et al, 2015). Linkage disequilibrium score regression—derived SNP heritability on a liability scale was 7.8% for the meta-analysis and 19.0% for the FinnGen sample. The heritability estimate based on the European-only meta-analysis was similar (7.8%) compared with that based on the whole meta-analysis. The estimates were in line with previous reports in which SNP heritabilities were estimated on the basis of GWAS data. Compared with our previous study (Sliz et al, 2022), heritability estimates increased approximately 2.4 and 4.7 percentage points in the meta-analysis and in the FinnGen sample, respectively.



**Figure 1.** Manhattan plot of the loci associated with AD in the meta-analysis of 1,094,060 individuals (37,541 cases; 1,056,519 controls) from FinnGen, Estonian Biobank, UK Biobank, BioBank Japan, and European individuals of the EAGLE Consortium. Variants are plotted on the x-axis according to their chromosomal positions, and the y-axis shows the corresponding association  $P$ -values at the  $-\log_{10}$  scale. Dashed line denotes the threshold of genome-wide significance ( $P < 5 \times 10^{-8}$ ). The loci highlighted in pink or gold illustrate the 10 previously unreported AD-associated loci, defined as loci without previous AD associations within a  $\pm 1$  Mb window around the meta-analysis lead variant in the GWAS Catalog or in a recent meta-analysis of AD (Budu-Aggrey et al, 2023). AD, atopic dermatitis.

**Table 1. Previously Unreported Loci Associated with Atopic Dermatitis in the Meta-Analysis of 1,094,060 Individuals from FinnGen, Estonian Biobank, UK Biobank, EAGLE Consortium, and Biobank Japan**

Chr:Pos	Rsid	EA	OA	Maf	Effect	SE	P-Value	Gene(s)	HetPVal
2:231404640	rs529979470	A	G	0.002	0.6579	0.1129	5.67E-09	<i>B3GNT7</i>	0.7705
3:4984323	rs11130215	A	G	0.225	0.0602	0.0098	8.99E-10	<i>BHLHE40</i>	0.1423
3:71331371	rs368546772	C	G	0.056	0.208	0.0332	3.76E-10	<i>FOXP1</i>	0.2863
3:101539934	rs4580527	A	C	0.390	-0.0485	0.0084	8.35E-09	<i>TRMT10C, SENP7</i>	0.4067
6:39232036	rs1172342321	T	C	8e-04	1.1316	0.2068	4.46E-08	<i>KCNK5</i>	0.0525
7:6485212	rs2347784	C	G	0.309	0.0511	0.0089	8.76E-09	<i>KDEL2, DAGLB</i>	0.0081
10:108842561	rs182341709	A	G	0.002	-0.7685	0.1398	3.90E-08	<i>LINC02661</i>	0.4977
16:1603218	rs933905994	A	G	6e-04	1.2259	0.1851	3.48E-11	<i>IFT140</i>	0.9485
19:928073	rs350143	T	C	0.273	-0.0552	0.0098	1.93E-08	<i>ARID3A</i>	0.0056
21:14590333	rs465340	A	G	0.462	-0.0498	0.0084	3.14E-09	<i>SAMS1-AS1, SAMS1</i>	0.5653

Abbreviations: Chr:Pos, chromosome:position; EA, effect allele; HetPVal, *P*-value for heterogeneity; Maf, minor allele frequency; OA, other allele; Rsid, reference SNP cluster ID; SE, standard error.  
Effect denotes beta coefficient. Variants represent individual associated loci with at least 1 Mb distance to one another, and each locus has at least 1 variant with a genome-wide significant ( $P < 5 \times 10^{-8}$ ) association. The most proximal genes to the index variants are shown.

### Gene set enrichment tests

FUMA (Functional Mapping and Annotation of GWASs)'s MAGMA gene analysis uses gene-based *P*-values assigned on the basis of the full distribution of SNP *P*-values. SNPs were mapped to protein coding genes from MgiDB, version 7, comprising 5500 curated genes sets and 9996 Gene Ontology terms with a window size of 0 kb for the genes to assign SNPs. The MAGMA gene set enrichment analysis indicated involvement of several immune processes known to be important in AD pathophysiology (Supplementary Table S4). As an example, pathways related to the regulation of lymphocyte activation, leukocyte-mediated immunity, and IL signaling were well-represented. Pathways with fewer occurrences included calcineurin-regulated NFAT (nuclear factor of activated T cells)-dependent transcription in lymphocytes, allograft rejection, and genes whose promoters are bound by FOXP3. Topical calcineurins are used for AD; systemic calcineurin inhibitors such as cyclosporin are used to treat severe AD and also to prevent allograft rejection after organ transplantation (Shah and Ginat, 2022). MAGMA tissue expression analysis detected an enrichment of AD-associated genes for the differentially expressed gene sets in tissues, including the spleen, the blood, and the skin among the 53 Genotype-Tissue Expression (version 8) tissues (Supplementary Figure S5). The genes mapped to AD-associated loci (variants in high linkage disequilibrium [ $r^2 > 0.6$ ] with independent [ $r^2 < 0.1$ ] significant SNPs mapped to genes within 10 kb) were most over-represented among the gene sets related to cancer modules and immunologic signatures, tested against a background of all genes with FUMA's GENE2FUNC process (Watanabe et al, 2017). Among the traits in the GWAS catalog category, the previously unreported AD associations were most over-represented in leukocyte proportions and inflammatory bowel disease (Supplementary Table S5).

### Colocalization analysis

We performed colocalization analysis to investigate whether the risk variants may influence AD by regulating gene or protein expression (Supplementary Table S6). Colocalization analysis suggested that *MMP12* affects AD susceptibility through the regulation of MMP levels (posterior probability =

0.999) in the blood, and the AD-risk variants were associated with upregulated *MMP12* level. Colocalization analysis at the level of gene expression suggested that many of the loci contribute to AD disease process through gene expression. As an example, an AD-associated variant in the *AQP3* locus colocalized with expression of *AQP7* and *AQP3* in the skin tissue. AD-risk alleles were associated with increased expression of *AQP7*. Of the previously unreported loci, we detected colocalization for *KDEL2* and *SENP7* in tissues, including blood, CD4 T cells, CD8 T cells, and monocytes.

### Survival analysis

Survival analysis detected a pattern of additive genetic effects, in which disease risk is proportional to the number of predisposing alleles in an individual, for the majority of the AD-risk loci. Besides or in addition to additive genetic variance, allelic interactions within locus (dominance variance) and gene-gene interaction (epistasis) may contribute to the phenotypic variance of complex traits (Zhu et al, 2015). We detected evidence for nonadditive genetic variance within the meta-analysis loci, including *ZNF652*, *HLA-DQA1*, *PGLYR*, and *PRR5L*. (Supplementary Figure S6 and Supplementary Table S7). The *HLA-DQA1* locus showed the clearest deviation from the additive pattern. *HLA* genes encode cell surface proteins involved in various regulatory functions of the immune response. In line with our result, previous studies have found nonadditive effects in several *HLA* genes in the context of immune system diseases that are closely related to AD, such as rheumatoid arthritis, psoriasis, and celiac disease (Lenz et al, 2015).

### Previous associations and potential functionality of previously unreported risk loci

We screened the previously unreported meta-analysis lead variants for trait associations (phenome-wide association study) in the FinnGen R7 data, in which genome-wide significant associations were only detected for AD (*ARID3A*, *BHLHE40*) (Supplementary Figure S7). The number of suggestively associated traits ( $P < 1e-05$ ) was highest in diseases of the skin and subcutaneous tissue category, followed by diseases of the musculoskeletal system and connective tissue category and endocrine, nutritional, and metabolic diseases

category. In the GWAS catalog, variants in the previously unreported AD-risk loci were associated with multiple traits, including blood cell counts or percentages for all loci except for *LINC02661* (Supplementary Table S2).

To assess the regulatory potential of the previously unreported AD-risk variants, we searched RegulomeDB (Boyle et al, 2012) for overlapping regulatory elements of the non-coding genome. Sixty percent of the loci had at least 1 genome-wide significant variant that was ranked as potentially regulatory with probability  $>0.8$  (Supplementary Table S8). RegulomeDB also ranks variants with scores 1–6 with most to least support of binding and expression of a target gene. Of the meta-analysis lead variants, the index variants in *BHLHE40*, *ARID3A*, and *SAMSN1* had the strongest evidence for regulatory potential when we looked at the combination of both probability ( $>0.8$ ) and ranking ( $\geq 2$ ) measures.

#### Subgroup analysis of early-onset and late-onset AD

To analyze the potential genetic differences related to the age of onset, we conducted FinnGen data-based analyses, in which we divided individuals into early-onset ( $<5$  years,  $n = 728$ ) and late-onset ( $>5$  years,  $n = 7765$ ) groups on the basis of the age during the first hospital visit with AD diagnosis. We detected a nominal effect size difference ( $P < .05$ ) for 6 of the AD meta-analysis risk loci; however, the effects were not consistently larger or smaller in either group (Supplementary Table S9). Kaplan–Meier plots of time-to-AD onset stratified by genotype showed that some variants in the *FLG* locus—most clearly, the deletion allele of the frameshift variant rs558269137—predispose to AD starting from early life (Figure 2). Other loci that were associated with high AD risk from childhood were *SERPINB7* and *TESPA1*, whereas for some of the AD-risk loci, including *B3GNT7* and *LINC02661*, results suggested that the risk of AD starts to rise later in life (Figure 2). For *B3GNT7*, 18% of the cases with the AD risk-increasing genotypes (rs529979470 AA or AB) were classified as severe on the basis of the medical treatment data (next paragraph), which was no different from 16% of severe AD cases within the nonrisk genotype group (Fisher's  $P = .696$ ). For *LINC02661*, the majority ( $>90\%$ ) of the cases with the AD risk-increasing genotypes (rs182341709 G/G or A/G) were classified as mild.

#### Subgroup analysis of mild and severe AD

To investigate the genetic background of AD severity, we classified AD cases as mild or severe on the basis of medical treatment information in the FinnGen data (Supplementary Table S10). Seventy percent of the effect sizes were larger in severe than in mild AD, and we detected consistently larger effect sizes for 6 of the AD-risk loci in severe than in mild AD ( $P < .05$ ) (Figure 3 and Supplementary Table S11). We further calculated polygenic risk score (PRS) on the basis of the AD-associated meta-analysis loci and observed a noticeable tendency toward larger effect sizes within severe than in mild AD (Supplementary Figure S8). Conclusions from the PRS analysis are suggestive because the base and target populations had overlapping samples.

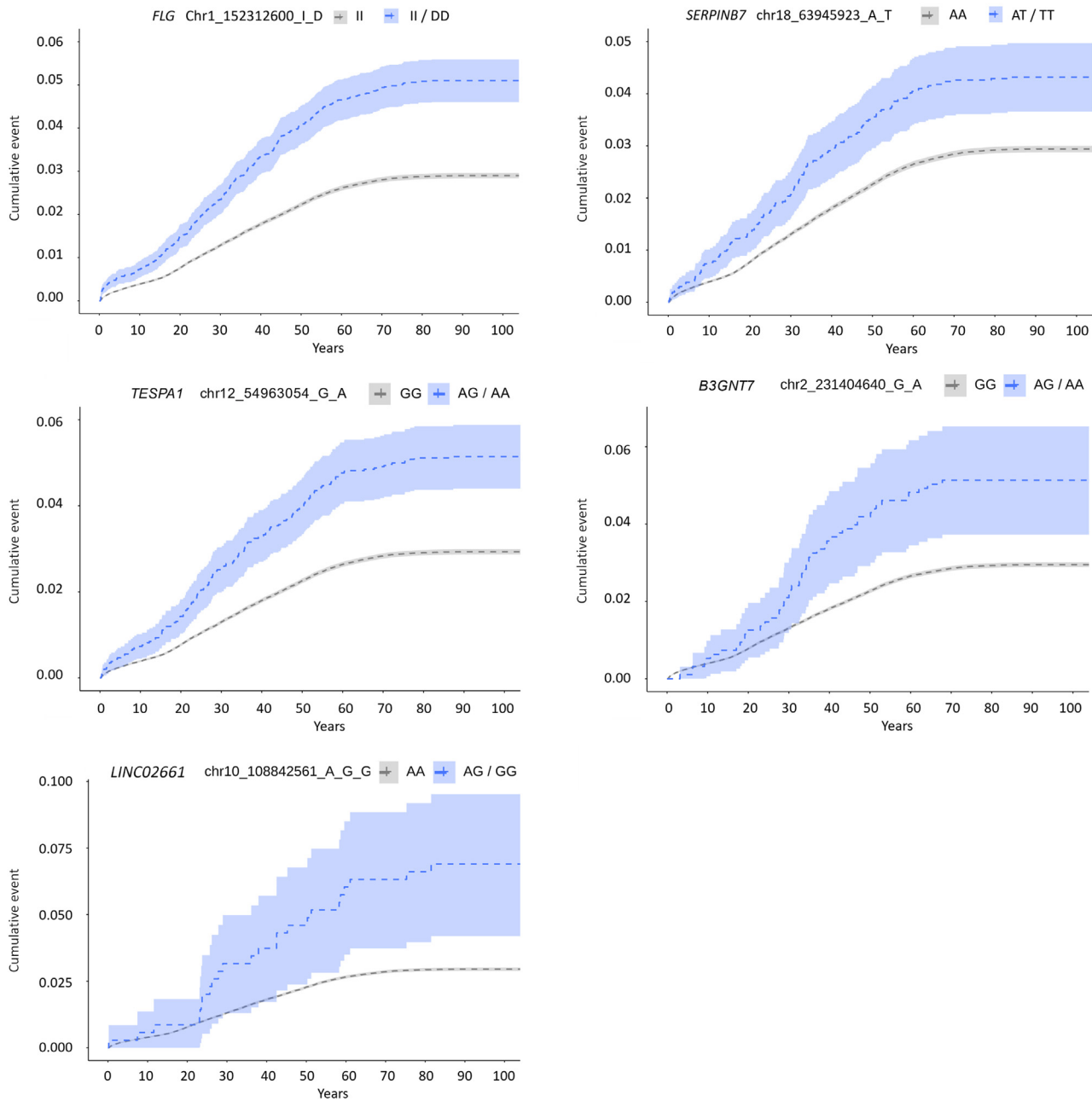
## DISCUSSION

The current genome-wide meta-analysis of AD detected 77 associated loci. Analyses with the genome-wide association landscape highlighted an involvement of T-cell-mediated and various other immunological pathways in AD pathophysiology, accentuated the close connection among AD and other inflammatory diseases, and emphasized the importance of the skin and inflammatory cells as the most relevant tissue and cell types in AD disease processes.

The heritability estimates of this analysis were small compared with those obtained from family studies but in line with previous studies reporting SNP-based heritability for AD (Budu-Aggrey et al, 2023; Løset et al, 2019; Sliz et al, 2022). SNP-based heritability estimates rely on genetic variation that is captured by the GWAS genotyping chip and are thus unlikely to completely capture the underlying causal genetic variation. There may be other causal genetic factors that have not reached the genome-wide significance, including rare genetic variants, yet to be discovered (Yang et al, 2017). It has been suggested that AD heritability estimates could improve with the use of more specific AD phenotypes; however, our previous work did not support this (Sliz et al, 2022). The heritability estimate for the FinnGen-based AD GWAS was higher than the estimate obtained from the meta-analysis. This could be due to a differing genetic architecture in the Finnish cohort as well as the smaller sample size of a single cohort that may lead to inflated effect estimates.

Besides the previously known pathways of AD, the pathway analysis indicated the involvement of genes whose promoters are bound by FOXP3. *FOXP3* encodes a transcription factor FOXP3 expressed in regulatory T cells (Tregs), where FOXP3 can regulate transcription of the bound genes. Tregs play important roles in immune responses and homeostasis of the skin, and FOXP3 is vital to Treg function. Variants in *FOXP3* have been associated with immune dysfunction and eczematous dermatitis that resembles severe AD (Kalekar and Rosenblum, 2019; Li et al, 2019; Roesner et al, 2015). Our results suggest that FOXP3-mediated signaling of the AD-associated genes leads to altered function of Tregs in the skin of patients with AD. However, the exact role of FOXP3-regulated AD-risk genes and their relationship to Treg function in the skin tissue of patients with AD warrant further study.

Colocalization analysis revealed that many of the AD-risk loci may contribute to AD by regulating gene or protein expression. At protein level, *MMP12* likely contributes to AD disease process by regulating *MMP12* expression. *MMP12* is a member of the MMP cluster involved in the degrading of the extracellular matrix under normal physiological conditions and in disease processes. *MMP12* was previously associated with diseases, including emphysema and chronic obstructive pulmonary disease, and the meta-analysis lead variant showed associations with similar phenotypes in the GWAS catalog. Elevated levels of *MMP12* were previously associated with UVA1-induced damage of the skin (Tewari et al, 2014), and molecular biological studies have linked *MMP12* with T-cell-mediated immune response in the skin and the gut of patients with dermatitis herpetiformis (Salmela et al, 2001) and as a molecule of the blood signature of AD



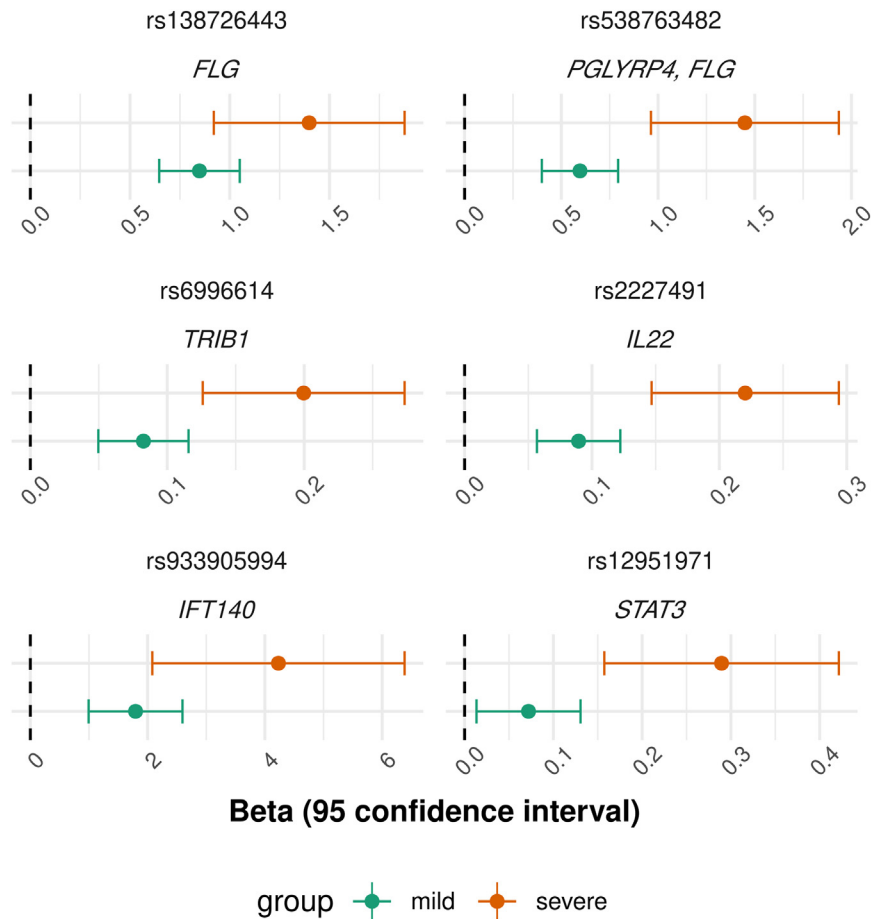
**Figure 2. Kaplan–Meier plots of the survival analysis of AD onset per genotype in the FinnGen data.** Disease onset is based on the first hospital visit with AD diagnosis. The y-axis shows cumulative AD incidence over time. The maximum follow-up period is set to 100 years (x-axis). The risk loci associated with early-onset AD included *FLG*, *SERPINB7*, and *TESPA1* (survdiff *P*-values for differences in survival curves =  $<2 \times 10^{-16}$ ,  $7 \times 10^{-7}$ , and  $2 \times 10^{-14}$ , respectively). The loci associated with late-onset AD included *B3GNT7* and *LINC02661* (survdiff *P*-value =  $6 \times 10^{-5}$  and  $1 \times 10^{-5}$ , respectively). To protect individual data, the rarer homozygous genotypes were combined with the heterozygous genotypes. AD, atopic dermatitis.

(Renert-Yuval et al, 2021). Our results suggest that the *MMP12* locus affects AD through elevated *MMP12* levels under inflammatory conditions.

Variants in loci, including *AQP3*, *SEN7*, and *KDELR2*, were associated with gene expression. *AQP3* locus was only recently found associated with AD (Budú-Aggrey et al, 2023), and associations for *SEN7* and *KDELR2* were discovered in this study. AD-associated variant in the *AQP3* locus colocalized with the expression of *AQP7* in the skin tissue. *AQP3* and *AQP7* are broadly expressed water and glycerol channels in cell membranes, and both molecules were linked to

keratinocyte function and inflammatory skin disease in previous molecular biological investigations (Olsson et al, 2006; Salman et al, 2022; Sonntag et al, 2019; Wagner et al, 2022). The AD-associated allele was linked with increased expression of *AQP7*, whereas increased expression of *AQP3* was previously detected in eczema compared with that in healthy skin (Olsson et al, 2006). It was further indicated that increased *AQP3* expression leads to loss of hydration, a process that could compromise epithelial integrity and barrier function in patients with AD. Thus, both *AQP3* and *AQP7* represent fascinating candidates for further molecular biological

**Figure 3. Effect size comparison of mild with severe AD.** Effect estimates of the associated loci were compared between mild and severe disease. Loci with  $P(Z_{diff}) < .05$  are shown. AD, atopic dermatitis; STAT3, signal transducer and activator of transcription 3.



investigations related to AD. *SENP7* and *KDELR2* variants colocalized with expression of the respective genes in, for example, lymphoblastoid cell lines and T cells, respectively. Interestingly, *SENP7* was previously linked to allergic disease (Ferreira et al, 2017), whereas *KDELR2* plays a role in protein trafficking in endoplasmic reticulum.

Ten of the identified loci were not previously associated with AD. The previously unreported associations point to several promising candidate genes that were prioritized on the basis of known biology, functional annotations, and quantitative trait locus colocalization analysis. Previous associations of the previously unreported AD-risk loci included inflammatory diseases and cell-type counts or proportions of the inflammatory cell types. Interestingly, some of the genes had associations with diseases of the digestive system, such as inflammatory bowel disease, and the new AD candidate genes together were enriched for inflammatory bowel disease associations. AD and inflammatory bowel disease have been shown to correlate (Huang et al, 2012; Shi et al, 2020), and our findings provide genetic links between the 2 clinically different diseases. Many of the previously unreported AD-associated loci had putative regulatory functions that may play a role in AD pathophysiology. The meta-analysis lead variants in *BHLHE40*, *ARID3A*, and *SAMSN1* showed high likelihood of being regulatory. *BHLHE40* was recently recognized as a central regulator of inflammation (Cook et al, 2020; Yu et al, 2018). The adjacent lead SNP rs11130215 in

the *BHLHE40* 3' untranslated region binds to multiple transcription factors in the blood, including *RUNX3* that was associated with AD in previous GWASs. The lead variant rs350143 in *ARID3A* had binding sites to several transcription factors, including *AGO2* that was only recently discovered to be associated with AD (Budu-Aggrey et al, 2023). *ARID3A* is a B-cell–restricted transcription regulator of Ig heavy chain, and the locus had recent associations with AD-related traits, including autoimmune and inflammatory disease and immune dysregulation preceding asthma (Chang et al, 2020; Qiu et al, 2017), whereas *AGO2* has a central role in the biogenesis of microRNAs. *AGO2* has been shown to participate in inflammation-related wound healing and was recently found to be upregulated in keratinocytes of patients with psoriasis (Domingo et al, 2020; Mori et al, 2018). *SAMSN1* is a negative regulator of B-cell activation that is upregulated in peripheral blood B cells by IL-4 and IL-13 and by CD40 stimulation. Interestingly, differential expression of *SAMSN1* was previously detected in the transcriptomic signatures of patients with AD (Badi et al, 2022).

In the subanalysis of the age of AD onset, we detected loci that confer a high AD risk starting from childhood and loci that were associated with AD later in life. We speculate that rather than some risk loci predisposing to late-onset AD, it is more likely that the observed patterns were driven by a low and delayed need for specialist care due to mild AD. The view of the genetic risk loci and AD onset will likely become

more accurate in the future, if big datasets with genotype data can be more accurately phenotyped.

We further found support for differing genetic architecture in mild versus severe AD, when we assigned patients with AD into severity groups on the basis of administered treatments. We found consistently larger effect sizes and PRS estimates for severe than for mild AD, implying that the risk of severe AD is likely more extensively affected by genetic factors and more accurately predicted by the PRS. Interestingly, a recent study found that PRS estimates correlated with AD severity defined by, for example, Rajka Langeland score and Eczema Area and Severity Index (Arehart et al, 2022). Unfortunately, in this study based on nationwide health registries, it was not possible to obtain more detailed clinical data.

One of the limitations of this study was that we had no replication population available. However, 7 of the index variants in the 10 previously unreported loci showed nominal associations in at least 2 meta-analysis cohorts. *B3GNT7*, *FOXP1*, and *IFT140* did not show internal replication; thus, associations for these loci should be viewed critically until replicated in independent populations. Of note, *FOXP1* and *IFT140* were associated in the FinnGen data alone. Furthermore, the results from the subpopulation analysis of AD severity and the age of onset should be replicated in independent studies.

Altogether, the genome-wide findings of the meta-analysis fit well with the current understanding of AD and strengthen the view of relevant tissues, cell types, and pathways involved in AD pathophysiology. Through gene set analysis, genomic annotations, and colocalization, this study highlighted additional biological routes that connect genetic variants to AD pathophysiology. These in silico functional analyses all implicated immune cells and the skin as tissue types of interest and emphasized the role of immunological processes, providing genetic support to the current understanding of AD pathophysiology. Our study suggests that some of the AD risk genotypes may predispose to early onset of AD. Furthermore, our findings suggest a more prominent genetic contribution in severe than in mild AD. The discovery of new loci and candidate genes enhances our understanding of AD risk and provides previously unreported opportunities to gain insight into AD etiology and develop new treatments.

## MATERIALS AND METHODS

The meta-analysis was conducted with data from 37,541 cases and 1,056,519 controls originating from FinnGen (10,277 cases; 278,795 controls), Estonian Biobank (11,187 cases; 125,537 controls), UK Biobank (2,904 cases; 412,489 controls), EAGLE Consortium (10,788 cases; 30,047 controls), and BBJ (2,385 cases; 209,651 controls). Patients and control subjects in FinnGen provided written informed consent for biobank research on the basis of the Finnish Biobank Act. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa statement number for the FinnGen study is Nr HUS/990/2017. For more details, see [Supplementary Materials and Methods](#). The study cohorts included in this analysis represent certain time points when data were acquired from biobanks with ongoing sample collections or from publicly available summary statistics that were accessible at the time of the analysis.

FinnGen samples were genotyped with Illumina and Affymetrix chip arrays (Illumina and Thermo Fisher Scientific). Samples with ambiguous sex, non-Finnish ancestry, high missingness (>5%), and excess heterozygosity ( $\pm 4$  SD) were excluded. Variant quality control entailed excluding variants with high missingness (>2%), minor allele count <3, and deviation from Hardy-Weinberg equilibrium ( $P < 1e-6$ ). Genotypes were imputed against a Finnish population-specific SISu reference panel with Beagle, followed by exclusion of variants with imputation INFO < 0.7 (<https://github.com/FINNGEN/finngen-documentation>).

FinnGen GWAS was done with REGENIE 2-step regression model implemented in an automated pipeline at FinnGen environment. Age, sex, genotyping batch, and 10 top principal components were used as covariates. Minor allele count was set to 5 for cases and controls to be retained in the analysis. Information of genotyping methods, quality control, and GWAS of the other cohorts can be found in the [Supplementary Materials and Methods](#).

METAL (Willer et al, 2010) was used to conduct fixed-effect inverse variance-weighted meta-analysis to estimate the combined genetic effect with the presumption of no influence from environmental or life-style factors. We implemented an additional evaluation of heterogeneity to test the assumption that all cohorts share the same causal alleles. We report associating loci on the basis of at least 2 of the meta-analysis populations. Genome-wide inflation factor of the meta-analysis was calculated with linkage disequilibrium score regression (Bulik-Sullivan et al, 2015). We further performed conditional association tests with Genome-wide Complex Trait Analysis software package (Yang et al, 2011) to dissect the risk loci for secondary association signals in the previously unreported loci ([Supplementary Materials and Methods](#) provides the details).

Associated loci were defined as genomic regions within  $\pm 1$  Mb window around the lead variant. The locus was defined as previously unreported if there were no significant AD associations reported in the NHGRI-EBI Catalog of human GWASs (MacArthur et al, 2017) or in a recent meta-analysis of AD (Buduy-Aggrey et al, 2023) within the locus. We investigated associated traits in the FinnGen R7 data. We used FUMA (Watanabe et al, 2017) to perform functional mapping, prioritize genes for gene-based enrichment test, and assess tissue specificity by testing enrichment of differentially expressed gene sets in Genotype-Tissue Expression (version 8) tissue types (GTEx Consortium, 2020). We performed colocalization analysis with HyprColoc (Foley et al, 2021), a Bayesian method for finding shared genetic associations among complex traits in a particular genomic region, to assess whether the loci (index variant  $\pm 500$  kb) contribute to AD risk by affecting gene or protein expression. We used *cis*-eQTLs from eQTLGen (Vösa et al, 2021) and eQTL Catalogue (Kerimov et al, 2021) and protein level data assayed in plasma (Sun et al, 2018). We report colocalization results with a posterior probability > 0.6. We performed survival analysis with R (R Core Team, 2020) survival package to assess inheritance models of the meta-analysis risk loci. For evidence of nonadditive genetic effects, we calculated a difference of observed and expected heterozygote effects. Observed effects were extracted with R survival package functions, and expected effects were considered a mean of the 2 homozygous effects. We further extracted confidence intervals of the effects to see whether the differences among genotypes were significant.

We estimated SNP-based heritability on a liability scale for the meta-analyzed sample and the FinnGen GWAS with linkage disequilibrium score regression (Bulik-Sullivan et al, 2015). We used

a population prevalence of 15% (Sliz et al, 2022) and sample prevalences of 3.40% for the whole meta-analysed sample, 3.99% for the meta-analyzed sample excluding BBJ, and 3.56% for the FinnGen sample.

To assess the genetic background of early-onset and late-onset AD, we used FinnGen data and Hospital Discharge Registry data that contain information about all visits in Finnish hospitals, including duration and diagnosis. We defined the early-onset and the late-onset AD on the basis of hospital treatment periods related to AD (main or side diagnosis) as a dichotomous outcome starting before or after 5 years of age and performed GWAS on both classifications with SAIGE using the population without AD as a control group. We used a cut off of age 5 years because the FinnGen data concerning AD are derived from tertiary care, and the time from symptom onset to a referral to specialized care and the diagnosis of AD diagnosis may be delayed. A similar cut off for early-onset AD has been used previously (Esaki et al, 2016). We then compared the effect size estimates of the AD-risk loci from the current meta-analysis in the early-onset group with those in the late-onset groups. We investigated the role of AD-risk loci in early- and late-onset AD with survival analysis of time to AD onset stratified by risk variant genotypes.

To investigate the genetic background of AD severity, we classified AD cases in the FinnGen data as mild or severe on the basis of the medical therapy they had received. Medication data were derived from the Social Insurance Institution of Finland, which includes data on all reimbursed drug purchases from 1995 onward. Classifications by Anatomical Therapeutic Chemical codes were used in the analysis (Supplementary Materials and Methods).

#### DATA AVAILABILITY STATEMENT

Summary statistics of the meta-analysis are made available in the NHGRI-EBI GWAS Catalog (<https://www.ebi.ac.uk/gwas/studies/>) with an accession number GCST90297795.

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#### CONFLICT OF INTEREST

The authors state no conflict of interest.

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Finnish biobank data can be accessed through Fingenius services (<https://site.fingenius.fi/en/>) managed by FINBB. CSC—IT Center for Science is acknowledged for computational resources. Estonian Biobank Research Team includes Mari Nelis, Lili Milani, Tõnu Esko, Andres Metspalu, and Georgi Hudjashov.

Contributors of FinnGen are listed in the Supplementary Table S12.

#### AUTHOR CONTRIBUTIONS

Conceptualization: LH, KT, JK; Formal Analysis: AP, ES; Project Administration: KT, JK; Resources: FinnGen, Estonian Biobank Research Team; Supervision: JK; Visualization: AP; Writing - Original Draft Preparation: AP; Writing - Review and Editing: ES, LH, ER, RM, TL, KT

#### SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at [www.jidonline.org](http://www.jidonline.org), and at <https://doi.org/10.1016/j.jid.2024.02.036>.

#### REFERENCES

- Arehart CH, Daya M, Campbell M, Boorgula MP, Rafaels N, Chavan S, et al. Polygenic prediction of atopic dermatitis improves with atopic training and filaggrin factors. *J Allergy Clin Immunol* 2022;149:145–55.
- Badi YE, Pavel AB, Pavlidis S, Riley JH, Bates S, Kermani NZ, et al. Mapping atopic dermatitis and anti-IL-22 response signatures to type 2-low severe neutrophilic asthma. *J Allergy Clin Immunol* 2022;149:89–101.
- Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, et al. Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res* 2012;22:1790–7.
- Brown SJ. What have we learned from GWAS for atopic dermatitis? *J Invest Dermatol* 2021;141:19–22.
- Budu-Aggrey A, Kilanowski A, Sobczyk MK, 23andMe Research Team, Shringarpure SS, Mitchell R, et al. European and multi-ancestry genome-wide association meta-analysis of atopic dermatitis highlights importance of systemic immune regulation. *Nat Commun* 2023;14:6172.
- Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015;47:291–5.
- Chang YS, Turturice B, Schott C, Finn P, Perkins D. Immune network dysregulation precedes clinical diagnosis of asthma. *Sci Rep* 2020;10:12784.
- Cook ME, Jarjour NN, Lin CC, Edelson BT. Transcription factor Bhlhe40 in immunity and autoimmunity. *Trends Immunol* 2020;41:1023–36.
- Domingo S, Solé C, Moliné T, Ferrer B, Cortés-Hernández J. MicroRNAs in several cutaneous autoimmune diseases: psoriasis, cutaneous lupus erythematosus and atopic dermatitis. *Cells* 2020;9:2656.
- Esaki H, Brunner PM, Renert-Yuval Y, Czarnowicki T, Huynh T, Tran G, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. *J Allergy Clin Immunol* 2016;138:1639–51.
- Ferreira MA, Vonk JM, Baurecht H, Marenholz I, Tian C, Hoffman JD, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet* 2017;49:1752–7.
- Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat Genet* 2015;47:1228–35.
- Foley CN, Staley JR, Breen PG, Sun BB, Kirk PDW, Burgess S, et al. A fast and efficient colocalization algorithm for identifying shared genetic risk factors across multiple traits. *Nat Commun* 2021;12:764.
- GTE Consortium. The GTE Consortium atlas of genetic regulatory effects across human tissues. *Science* 2020;369:1318–30.
- Hirota T, Takahashi A, Kubo M, Tsunoda T, Tomita K, Sakashita M, et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. *Nat Genet* 2012;44:1222–6.
- Huang BL, Chandra S, Shih DQ. Skin manifestations of inflammatory bowel disease. *Front Physiol* 2012;3:13.
- Irvine AD, Mina-Osorio P. Disease trajectories in childhood atopic dermatitis: an update and practitioner's guide. *Br J Dermatol* 2019;181:895–906.
- Ishigaki K, Akiyama M, Kanai M, Takahashi A, Kawakami E, Sugishita H, et al. Large-scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. *Nat Genet* 2020;52:669–79.

- Kalekar LA, Rosenblum MD. Regulatory T cells in inflammatory skin disease: from mice to humans. *Int Immunol* 2019;31:457–63.
- Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev Clin Immunol* 2017;13:15–26.
- Kerimov N, Hayhurst JD, Peikova K, Manning JR, Walter P, Kolberg L, et al. A compendium of uniformly processed human gene expression and splicing quantitative trait loci. *Nat Genet* 2021;53:1290–9.
- Lee JH, Son SW, Cho SH. A comprehensive review of the treatment of atopic eczema. *Allergy Asthma Immunol Res* 2016;8:181–90.
- Lenz TL, Deutsch AJ, Han B, Hu X, Okada Y, Eyre S, et al. Widespread non-additive and interaction effects within HLA loci modulate the risk of autoimmune diseases. *Nat Genet* 2015;47:1085–90.
- Li Y, Xu W, Yao J, Cheng H, Sun X, Li L. Correlation of blood FoxP3+ regulatory T cells and disease activity of atopic dermatitis. *J Immunol Res* 2019;2019:1820182.
- Liang Y, Chang C, Lu Q. The genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms. *Clin Rev Allergy Immunol* 2016;51:315–28.
- Løset M, Brown SJ, Saunes M, Hveem K. Genetics of atopic dermatitis: from DNA sequence to clinical relevance. *Dermatology* 2019;235:355–64.
- MacArthur J, Bowler E, Cerezo M, Gil L, Hall P, Hastings E, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* 2017;45:D896–901.
- Martin MJ, Estravís M, García-Sánchez A, Dávila I, Isidoro-García M, Sanz C. Genetics and epigenetics of atopic dermatitis: an updated systematic review. *Genes (Basel)* 2020;11:442.
- Mori R, Tanaka K, Shimokawa I. Identification and functional analysis of inflammation-related miRNAs in skin wound repair. *Dev Growth Differ* 2018;60:306–15.
- Olsson M, Broberg A, Jernås M, Carlsson L, Rudemo M, Suurküla M, et al. Increased expression of aquaporin 3 in atopic eczema. *Allergy* 2006;61:1132–7.
- Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet* 2015;47:1449–56.
- Patrick GJ, Archer NK, Miller LS. Which way do we go? Complex interactions in atopic dermatitis pathogenesis. *J Invest Dermatol* 2021;141:274–84.
- Qiu F, Tang R, Zuo X, Shi X, Wei Y, Zheng X, et al. A genome-wide association study identifies six novel risk loci for primary biliary cholangitis. *Nat Commun* 2017;8:14828.
- R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
- Renert-Yuval Y, Thyssen JP, Bissonnette R, Bieber T, Kabashima K, Hijnen DJ, et al. Biomarkers in atopic dermatitis—a review on behalf of the International Eczema Council. *J Allergy Clin Immunol* 2021;147:1174–1179.e1.
- Roesner LM, Floess S, Witte T, Olek S, Huehn J, Werfel T. Foxp3(+) regulatory T cells are expanded in severe atopic dermatitis patients. *Allergy* 2015;70:1656–60.
- Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshihara S, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet* 2021;53:1415–24.
- Salman MM, Kitchen P, Yool AJ, Bill RM. Recent breakthroughs and future directions in drugging aquaporins. *Trends Pharmacol Sci* 2022;43:30–42.
- Salmela MT, Pender SLF, Reunala T, Macdonald T, Saarialho-Kere U. Parallel expression of macrophage metalloelastase (MMP-12) in duodenal and skin lesions of patients with dermatitis herpetiformis. *Gut* 2001;48:496–502.
- Shah S, Ginat DT. Calcineurin inhibitors. *Neuroimaging Pharmacopoeia* 2022:177–87.
- Shi X, Chen Q, Wang F. The bidirectional association between inflammatory bowel disease and atopic dermatitis: a systematic review and meta-analysis. *Dermatology* 2020;236:546–53.
- Sliz E, Huilaja L, Pasanen A, Laisk T, Reimann E, Mägi R, et al. Uniting bio-bank resources reveals novel genetic pathways modulating susceptibility for atopic dermatitis. *J Allergy Clin Immunol* 2022;149:1105–12.e9.
- Sonntag Y, Gena P, Maggio A, Singh T, Artner I, Oklinski MK, et al. Identification and characterization of potent and selective aquaporin-3 and aquaporin-7 inhibitors. *J Biol Chem* 2019;294:7377–87.
- Sun BB, Maranville JC, Peters JE, Stacey D, Staley JR, Blackshaw J, et al. Genomic atlas of the human plasma proteome. *Nature* 2018;558:73–9.
- Tanaka N, Koido M, Suzuki A, Otomo N, Suetsugu H, Kochi Y, et al. Eight novel susceptibility loci and putative causal variants in atopic dermatitis. *J Allergy Clin Immunol* 2021;148:293–306.
- Tewari A, Grys K, Kollet J, Sarkany R, Young AR. Upregulation of MMP12 and its activity by UVA1 in human skin: potential implications for photoaging. *J Invest Dermatol* 2014;134:2598–609.
- Vösa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat Genet* 2021;53:1300–10.
- Wagner K, Unger L, Salman MM, Kitchen P, Bill RM, Yool AJ. Signaling mechanisms and pharmacological modulators governing diverse aquaporin functions in human health and disease. *Int J Mol Sci* 2022;23:1388.
- Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun* 2017;8:1826.
- Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016;387:1109–22.
- Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 2010;26:2190–1.
- Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet* 2011;88:76–82.
- Yang J, Zeng J, Goddard ME, Wray NR, Visscher PM. Concepts, estimation and interpretation of SNP-based heritability. *Nat Genet* 2017;49:1304–10.
- Yu F, Sharma S, Jankovic D, Gurrum RK, Su P, Hu G, et al. The transcription factor Bhlhe40 is a switch of inflammatory versus antiinflammatory Th1 cell fate determination. *J Exp Med* 2018;215:1813–21.
- Zhu AY, Mitra N, Margolis DJ. Longitudinal association of atopic dermatitis progression and keratin 6A. *Sci Rep* 2022;12:13629.
- Zhu Z, Bakshi A, Vinkhuyzen AAE, Hemani G, Lee SH, Nolte IM, et al. Dominance genetic variation contributes little to the missing heritability for human complex traits. *Am J Hum Genet* 2015;96:377–85.



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