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Leveraging Genomic Databases to Identify Missense Variants and Therapeutic Targets for Atopic Dermatitis

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ABSTRACT

OBJECTIVE Atopic dermatitis (AD) is a complex inflammatory skin disorder with a strong genetic component. Identifying missense variants with functional relevance is essential for understanding disease mechanisms and informing therapeutic development. This study identified functionally relevant SNPs for AD using integrated genomic and bioinformatics analyses.

METHODS We screened 180 AD-associated SNPs from the GWAS Catalog and filtered missense variants with genome-wide significance. Functional impact was assessed using PolyPhen-2 and Sorting Intolerant From Tolerant (SIFT). Population allele frequencies were extracted from the 1000 Genomes Project, tissue expression profiles from the GTEx Portal, and drug–gene interactions from DGIdb.

RESULTS Two prioritized missense variants were identified: rs2228145 in *IL6R*, a common benign variant that modulates IL-6 signaling, and rs183884396 in *TESPA1*, a rare variant predicted to be damaging and enriched in European populations. *TESPA1* showed minimal expression in healthy skin but substantial expression in immune-relevant tissues, suggesting an indirect immunoregulatory role in AD. *IL6R* demonstrated broad immune-tissue expression and multiple interactions with approved anti-inflammatory drugs, underscoring its therapeutic relevance.

CONCLUSION By integrating genomic, functional, and pharmacological data, this study highlighted *TESPA1* as a biologically plausible yet understudied immunoregulatory gene and *IL6R* as a clinically actionable target in AD. These computational findings are hypothesis-generating and warrant experimental validation to elucidate variant-specific mechanisms. Importantly, the identification of *IL6R*-targeting drugs and the ancestry-specific nature of *TESPA1* variation provides a foundation for future precision-medicine approaches in AD.

KEYWORDS atopic dermatitis, bioinformatics, GWAS, *IL6R*, *TESPA1*

INTRODUCTION

Atopic dermatitis (AD), commonly known as eczema, is a chronic inflammatory skin disorder characterized by recurrent episodes of pruritus, erythema, and xerosis (1). It affects both pediatric and adult populations and imposes a substantial burden on quality of life, with significant psychosocial, economic, and healthcare impacts worldwide (1-4). The global prevalence of AD continues to rise, making it a major public health concern.

In addition to environmental and immunological factors, genetic predisposition plays a central role in determining an individual's susceptibility to AD (5-7). Numerous studies have demonstrated that heritable components contribute significantly to disease onset and severity, underscoring the importance of identifying functional genetic variants that may influence AD pathogenesis.

Advances in genomic technologies have facilitated the identification of numerous genetic variants associated with AD, including single-nucleotide polymorphisms (SNPs) that lead to missense mutations. These mutations result in amino acid substitutions that may alter the structure, function, or stability of proteins, potentially contributing to the dysregulated immune responses and impaired skin barrier functions observed in AD (8, 9). Despite these findings, the precise molecular mechanisms underlying the contribution of missense mutations to AD pathophysiology remain poorly understood, necessitating further investigation.

Bioinformatics tools and genomic databases provide powerful platforms to explore the functional implications of missense variants in AD. Integrating data from resources such as the 1000 Genomes Project (10), SNPnexus (11, 12), and GTEx (13), allows for comprehensive analyses of variant frequency, regulatory element overlap, and tissue-specific gene expression patterns across populations. Integrating these datasets can facilitate the identification of potentially pathogenic variants and their associated biological pathways, thereby advancing our understanding of disease mechanisms.

In this study, we applied a bioinformatics-driven approach to systematically investigate missense variants implicated in AD. By integrating multiple genomic databases and functional prediction tools, we aimed to elucidate the potential roles of these variants in disease pathogenesis, with a particular focus on their impact on protein function and regulatory networks. This strategy not only enhances insight into the genetic basis of AD but also lays the foundation for identifying novel therapeutic targets and precision medicine strategies for managing this complex disorder.

METHODS

Detection of AD-associated SNPs

The GWAS Catalogue Database from the National Human Genome Research Institute (NHGRI) (https://www.ebi.ac.uk/gwas/) was utilized to identify AD-associated SNPs (14). Using the search term "atopic dermatitis," all available association data were retrieved on January 22, 2025, yielding 180 variant and risk alleles. The dataset was then refined by focusing on missense variants with an odds ratio (OR) greater than 1 and a p-value < 1×10^{-8}. Missense variants are genetic changes that alter the amino acid sequence of proteins, and pathogenic missense variants can disrupt protein function, thereby influencing phenotypic outcomes. In contrast, benign missense variants typically have minimal effect on protein function (15). Therefore, prioritizing missense variants that are likely to alter protein function is crucial.

Functional impact prediction of GWAS-derived SNPs

The AD-associated SNPs obtained from the GWAS Catalog database were subsequently analyzed using the SNPnexus platform. This platform utilizes a range of prediction algorithms, including PolyPhen-2 (16) and Sorting Intolerant From Tolerant (SIFT) (17), to evaluate the potential effects of genetic variants on protein function (12). PolyPhen-2 (Polymorphism Phenotyping v2) is a widely used tool that predicts the possible impact of amino acid substitutions on the structure and function of proteins. It incorporates multiple sequence-based and structural features to estimate whether a specific mutation might be benign or damaging to the protein. PolyPhen-2 generates scores that suggest the likelihood of a variant affecting protein function, categorizing it as "probably damaging," "possibly damaging," or "benign" (11, 12, 16).

SIFT is another algorithm that predicts the effect of amino acid substitutions on protein function based on sequence homology and the physical properties of the amino acids involved. SIFT uses the evolutionary conservation of amino acid residues across different species to assess whether a mutation is likely to affect the protein's function. Variants predicted to be "intolerant" are more likely to disrupt protein function, while those predicted to be "tolerant" are less likely to cause damage (12, 17). Together, these tools provide a comprehensive analysis of genetic variants by predicting their possible effects on protein function, helping researchers understand the biological significance of genetic changes and their potential role in disease mechanisms.

Population frequency analysis using 1000 genomes data

The SNPnexus v4 tool was employed to analyze the population data of the selected SNPs, utilizing information from the 1000 Genomes Database. This database categorizes human populations into five primary geographic regions: Africa, the Americas, Europe, East Asia, and South Asia. The 1000 Genomes Database provides comprehensive details on genetic variation across diverse human populations, offering a valuable resource for understanding allele distribution. As a result, it enabled the estimation of allele frequencies specific to each continental population, facilitating a deeper insight into global genetic diversity (18, 19).

Tissue-specific gene expression analysis using GTEx

The genes associated with the identified SNPs were analyzed for tissue-specific expression using the Genotype-Tissue Expression (GTEx) Portal v10 (http://www.gtexportal.org/home/). GTEx provides normalized transcript-level expression data (TPM) across a broad range of human tissues, enabling the evaluation of baseline gene expression patterns and supporting the functional interpretation of GWAS-implicated loci (13).

Drug candidates targeting AD-associated genes using DGIdb

To identify potential therapeutic agents for AD, we conducted an in silico drug-repurposing analysis by evaluating the interaction landscape between known AD-associated risk genes and pharmacological compounds using the Drug–Gene Interaction Database (DGIdb; https://www.dgidb.org/search_interactions) v5 accessed on January 22, 2025. DGIdb aggregates and curates drug-gene interaction data from multiple sources, including peer-reviewed publications, specialized databases, and other biomedical resources. The database standardizes and integrates information on druggable genes and their corresponding pharmacological agents into unified interaction categories (20). For this study, candidate compounds were shortlisted based on specific interaction types indicative of direct or functional modulation of the target gene. Additionally, only interactions with a DGIdb interaction score ≥ 1 were considered, ensuring the inclusion of drug-gene pairs with sufficient supporting evidence and predicted mechanistic relevance.

RESULTS

Functional prediction of missense variants in *IL6R* and *TESPA1*

Data downloaded from the GWAS Catalog (https://www.ebi.ac.uk/gwas) identified 180 SNPs associated with AD. After filtering for missense variants and a significance threshold of $p < 10^{-8}$ three SNPs were directly linked to increased AD risk (Table 1). In addition to these criteria, further analysis was performed using the SNPnexus platform, which integrates multiple predictive algorithms, including PolyPhen-2 and SIFT, to assess the potential impact of genetic variants on protein function (11, 12).

PolyPhen-2 evaluates amino acid substitutions based on evolutionary conservation and structural/functional features, while SIFT assesses the likelihood of functional disruption based on sequence homology and conservation (21). Table 2 summarizes the PolyPhen-2 analysis results. For SNP rs2228145 in the *IL6R* gene (chromosome 1),

Table 1. Missense variant of AD-associated risk SNPs

SNPs	*p*-value	Odds ratio
rs2228145	5×10^{-10}	1.08
rs183884396	2×10^{-10}	1.86
rs909341	8×10^{-10}	1.316

SNPs, single-nucleotide polymorphisms

Table 2. PolyPhen-2 analysis of AD-associated missense variants and predicted effects on protein function

SNPs	Chromosome	Position	Variant	Gene	AA Position	Score	Prediction
rs2228145	chr1	154454494	A/C	*IL6R*	358	0.02	Benign
rs2228145	chr1	154454494	A/T	*IL6R*	358	0.03	Benign
rs2228145	chr1	154454494	A/C	*IL6R*	161	0.029	Benign
rs2228145	chr1	154454494	A/T	*IL6R*	161	0.049	Benign
rs183884396	chr12	54963054	G/A	*TESPA1*	282	1	Probably damaging
rs183884396	chr12	54963054	G/A	*TESPA1*	282	1	Probably damaging
rs183884396	chr12	54963054	G/A	*TESPA1*	144	1	Probably damaging
rs183884396	chr12	54963054	G/A	*TESPA1*	144	1	Probably damaging
rs183884396	chr12	54963054	G/A	*TESPA1*	144	1	Probably damaging

Table 3. SIFT analysis of AD-associated missense variants and predicted effects on protein function

SNPs	Chromosome	Position	Variant	Gene	AA Position	Score	Prediction
rs2228145	chr1	154454494	A/C	*IL6R*	358	0.08	Tolerated
rs2228145	chr1	154454494	A/T	*IL6R*	358	0.12	Tolerated
rs2228145	chr1	154454494	A/C	*IL6R*	161	0.07	Tolerated
rs2228145	chr1	154454494	A/T	*IL6R*	161	0.06	Tolerated
rs183884396	chr12	54963054	G/A	*TESPA1*	282	0.00	Deleterious
rs183884396	chr12	54963054	G/A	*TESPA1*	282	0.00	Deleterious
rs183884396	chr12	54963054	G/A	*TESPA1*	144	0.00	Deleterious
rs183884396	chr12	54963054	G/A	*TESPA1*	144	0.00	Deleterious
rs183884396	chr12	54963054	G/A	*TESPA1*	144	0.00	Deleterious

SIFT, Sorting Intolerant From Tolerant

Table 4. Allele frequencies of AD-associated SNPs across global populations

SNPs	REF Allele	ALT Allele	Allele frequency				
			Africa	America	East Asia	Europe	South Asia
rs2228145	A	C	0.087	0.536	0.3234	0.3598	0.2996
rs183884396	G	A	None	None	None	0.005	None

multiple transcript variants showed amino acid substitutions at positions 358 and 161 due to A/C and A/T changes. These substitutions yielded low PolyPhen-2 scores (0.02–0.049), classifying them as benign and suggesting minimal impact on *IL6R* function. In contrast, rs183884396 in the *TESPA1* gene (chromosome 12) showed consistently high PolyPhen-2 scores of 1.0 for amino acid changes at positions 282 and 144, indicating probable functional disruption.

The SIFT algorithm predicts mutation impact based on the evolutionary conservation of amino acid positions across species (17). Mutations at highly conserved positions are considered more likely to impair protein function. Table 3 presents SIFT analysis results. For rs2228145, SIFT scores ranged from 0.06 to 0.12, suggesting these variants are likely tolerated. Conversely, rs183884396, involving a G/A substitution in *TESPA1*, produced SIFT scores of 0 at both tested positions, indicating a high probability of functional disruption. These findings reinforce the hypothesis that *TESPA1* variants may contribute more significantly to AD pathogenesis than *IL6R* variants.

Global distribution of allele frequencies for AD-associated SNPs

Table 4 presents the allele frequencies of two AD-associated SNPs across five global regions, based on data from the 1000 Genomes Project. The SNP rs2228145, with the reference (REF) allele A and alternate (ALT) allele C, exhibits variable frequencies: 0.087 in Africa, 0.536 in America, 0.3234 in East Asia, 0.3598 in Europe, and 0.2996 in South Asia. In contrast, SNP rs183884396, with the REF allele G and ALT allele A, is only observed in Europe, with a frequency of 0.005, and no data is available for other regions. These findings highlight the global variation in the distribution of AD-associated alleles.

Tissue expression of *TESPA1* and *IL6R* in AD

The GTEx Portal was utilized to examine the expression patterns of *TESPA1* and *IL6R* across a range of human tissues, as illustrated in Figure 1 and Figure 2. To investigate the potential roles of these candidate genes in the pathogenesis of AD, we analyzed their tissue-specific expression profiles using bulk RNA-seq data. *TESPA1* is highly expressed in brain regions (cortex, BA9, BA24) and moderately in whole blood and EBV-transformed lymphocytes, suggesting its involvement in both neuroimmune regulation and T-cell–mediated immune responses in AD. *IL6R* exhibits strong expression in whole blood and skeletal muscle, with moderate levels in liver, lung, and adipose tissue, reflecting its role in systemic inflammation and Th2/Th17 immune activation associated with AD. These expression patterns highlight *TESPA1* and *IL6R* as key candidates in the immune and neuroimmune pathogenesis of AD.

Drug-gene interactions of *IL6R* and *TESPA1* in AD

Using the DGIdb, we evaluated the druggability of the *IL6R* and *TESPA1* genes, both of which are implicated in the molecular mechanisms of AD. Notably, only *IL6R* was identified as a druggable target, interacting with four clinically approved drugs: sarilumab, satralizumab, bazedoxifene, and tocilizumab (Figure 3). These drugs are primarily indicated for inflammatory and autoimmune conditions, including rheumatoid arthritis, neuromyelitis optica spectrum disorder, osteoporosis, and other inflammatory disorders, respectively. In contrast, no approved drugs currently target *TESPA1*, although its potential biological significance warrants further investigation.

DISCUSSION

This study aimed to prioritize functionally relevant missense variants associated with AD by

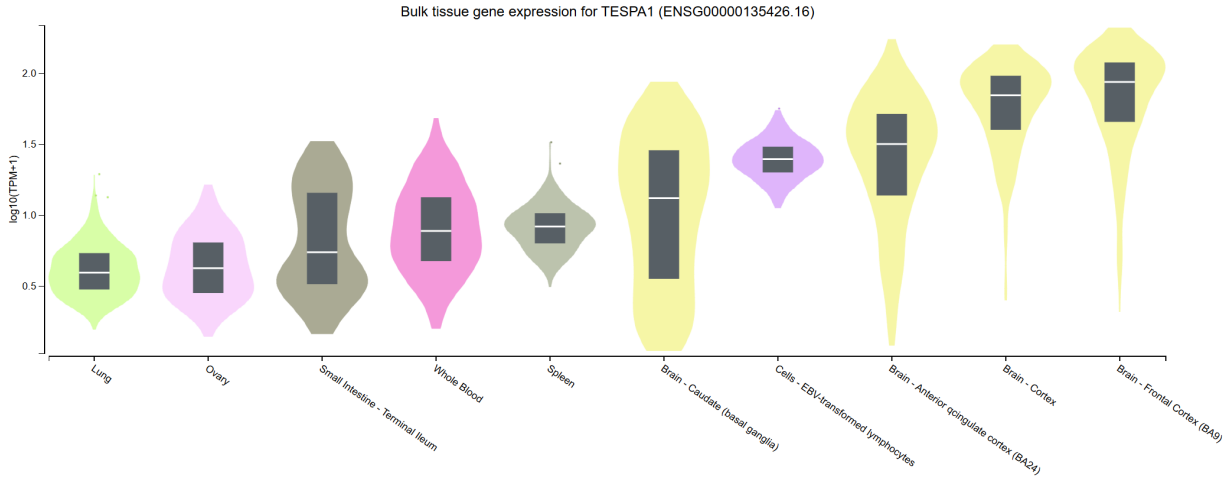


Figure 1. *TESPA1* gene expression associated with AD across human tissues based on GTEx Portal analysis

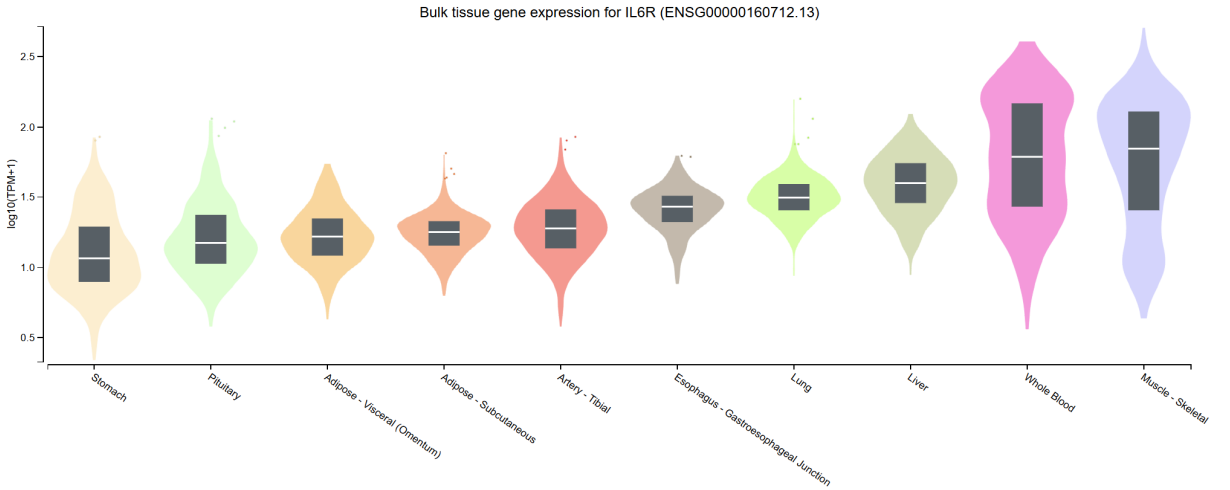


Figure 2. *IL6R* gene expression associated with AD across human tissues based on GTEx Portal analysis

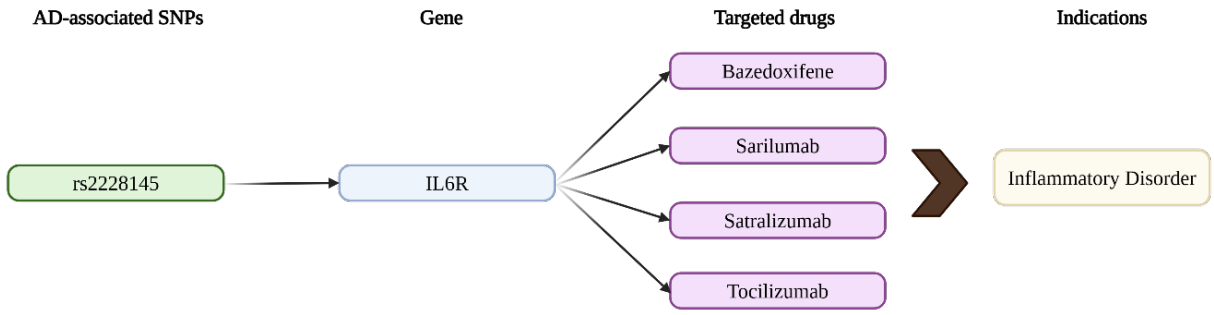


Figure 3. The connection of the AD risk gene to drug targets

integrating GWAS data, computational pathogenicity predictions, tissue-specific expression profiles, population allele frequencies, and drug-gene interaction analyses. Among the 180 AD-associated SNPs identified through the GWAS Catalog, we focused on two missense variants: rs2228145 in *IL6R* and rs183884396 in *TESPA1*, based on statistical significance, predicted functional impact, and potential therapeutic relevance.

The *IL6R* variant rs2228145 (Asp358Ala) was predicted to be benign by both PolyPhen-2 and SIFT (Table 2 and Table 3). Despite this, previous research has demonstrated that this variant increases the levels of soluble *IL-6* receptor (s*IL-6*R), thereby altering IL-6 classical versus trans-signaling without directly disrupting receptor structure (22, 23). It has been linked to persistent AD (24) and, in a recent Mendelian randomization study, shown to be causally associated with increased AD risk when used as a genetic proxy for *IL6R* inhibition (25). These findings suggest that while rs2228145 may be structurally tolerated, its regulatory effects on *IL-6* signaling pathways may still influence AD pathophysiology. Our analysis confirms *IL6R* expression in immune-related tissues and identifies four clinically approved *IL6R*-targeting drugs: sarilumab, satralizumab, bazedoxifene, and tocilizumab, highlighting potential for stratified therapeutic approaches in AD depending on genetic background (26).

The *TESPA1* variant rs183884396 was consistently predicted to be damaging by both PolyPhen-2 and SIFT. *TESPA1* plays essential roles in thymocyte positive selection and T-cell receptor (TCR) signaling, and previous work has linked *TESPA1* to immune regulation and early-onset AD (27-29). *TESPA1*-deficient mouse models show reduced T-cell numbers and impaired TCR signaling (29), highlighting its immunological importance. Although *TESPA1* shows low expression in healthy skin in GTEx (13), this does not exclude its relevance to AD because GTEx reflects non-inflamed tissue states and may not capture disease-induced changes. Importantly, *TESPA1* acts primarily in immune cells—guiding thymocyte selection, modulating T-cell activation, and regulating mast-cell responses (27-29), all of which contribute to AD's systemic immune dysregulation.

We also explored whether *IL6R* and *TESPA1* might be functionally linked through a shared protein-protein interaction (PPI) network. A PPI analysis was performed using STRING. However, *TESPA1* and *IL6R* did not display a direct interaction, nor did they share strong intermediary hub proteins under default confidence settings. This suggests that, based on current PPI databases, the relationship between these genes is likely indirect, occurring through broader immune-regulatory pathways rather than through a shared molecular complex. While this finding does not diminish their individual relevance to AD, it indicates that *TESPA1* and *IL6R* crosstalk may involve higher-order immune network interactions that remain to be elucidated experimentally.

The rarity of rs183884396 and its enrichment in European, particularly Finnish, populations suggests that its effect may be ancestry-specific. This interpretation aligns with multi-ancestry GWAS results showing that while *TESPA1* missense variants are prioritized in Europeans, distinct putatively causal variants such as those in NLRP10, appear in East Asian populations (28). These patterns underscore the population-dependent architecture of AD and imply that different ancestral groups may harbor distinct functional variants within shared immune pathways. Larger, ancestrally diverse AD cohorts will be crucial to determine whether *TESPA1* is a shared susceptibility locus with variant-level population differences or whether its impact is primarily European-specific.

TESPA1's immunological functions also highlight the need for experimental validation. *TESPA1* dysfunction may contribute to immune dysregulation through altered thymic selection, skewed T-cell subsets, impaired regulatory signaling, or enhanced FcεRI-mediated mast-cell activity, mechanisms consistent with the IgE-driven inflammatory profile of AD (29). Given the rarity of rs183884396, its effect may be modest yet meaningful in genetically predisposed individuals, but its precise biological consequences remain unresolved.

Although GTEx data provide a useful baseline expression profile for *IL6R* and *TESPA1* (13), they do not capture variant-specific or inflammation-induced gene expression differences. Future analyses incorporating transcriptomic data from AD lesions—including single-cell RNA-seq—and proteomic datasets could clarify *TESPA1* regulation in disease contexts. Targeted genotyping of rs2228145 and rs183884396 in diverse AD case–control cohorts may help confirm ancestry-specific associations and refine genotype–phenotype relationships.

This study is exploratory and computational in nature. While multiple high-confidence tools and publicly available datasets were employed to prioritize potentially relevant missense SNPs, the findings remain probabilistic. Definitive functional validation will require protein-level studies, CRISPR-based variant models, and immune-cell functional assays. Given its predicted damaging effect, immunological role, and support from multi-ancestry GWAS, the *TESPA1* variant warrants further investigation in future AD research.

CONCLUSIONS

This integrative computational analysis prioritized two missense variants in *IL6R* and *TESPA1* as candidates of interest in AD pathogenesis, reflecting distinct mechanistic and population-dependent characteristics. While the *IL6R* variant rs2228145 aligns with known *IL-6*–mediated inflammatory pathways and existing therapeutic targets, the *TESPA1* variant rs183884396 emerges as a potentially damaging, ancestry-enriched immune-regulatory variant warranting deeper investigation. Although our findings are hypothesis-generating and require experimental validation, they provide a focused set of genetic and molecular targets that can guide future functional studies, population-based analyses, and therapeutic exploration in AD.

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CONFLICTS OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

I.N.S.: conceptualization, formal analysis, visualization, writing — original draft preparation; L.M.I.: conceptualization, data curation, formal analysis, writing review & editing; S.P.: methodology, writing review & editing; F.F.: methodology, writing review & editing; Y.V.A.P: methodology, writing review & editing; R.A.: methodology, writing review & editing; R.D.S.: methodology, writing review & editing; W.A.: conceptualization, funding acquisition, data curation, formal analysis, writing review & editing.

All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data used in this study are available in the supplementary data.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

INFORMED CONSENT STATEMENT

Not applicable.

SUPPLEMENTARY MATERIAL

Table S1. Summary of AD risk SNPs from GWAS Catalog

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	A	B	C	D	E	F	G	H	I
1	**Supplementary Table 1.** Summary of AD risk SNPs from GWAS Catalog								
2									
3	DISEASE/TRAIT	MAPPED_GENE	SNPS	CONTEXT	P-VALUE	OR or BETA	95% CI (TEXT)		
4	Paradoxical eczema in biologic-treated plaque psc	SGPL1 - UNC5B	rs192705221	intergenic_variant	1.00E-09	7.94	[4.09-15.43]		
5	Paradoxical eczema in biologic-treated plaque psc	SLC1A2	rs72925168	intron_variant	2.00E-09	4.98	[2.96-8.4]		
6	Recalcitrant atopic dermatitis	NBAS	rs13403179	intron_variant	8.00E-08	2.947	[1.989-4.386]		
7	Recalcitrant atopic dermatitis	LGMNP1 - STARP1	rs9540294	intergenic_variant	1.00E-08	2.655	[1.904-3.717]		
8	Atopic dermatitis	S100A11	rs78914480	intron_variant	8.00E-11	2.400272	[1.843869165-3.124573471]		
9	Atopic dermatitis	NBPF17P	rs188069315	intergenic_variant	5.00E-09	2.36	[1.77-3.15]		
10	Atopic dermatitis	CCDST	rs189163698	intergenic_variant	4.00E-20	2.23	[1.88-2.65]		
11	Atopic dermatitis	LCE3A - LCEP4	rs72702813	intergenic_variant	1.00E-33	2.06	[1.83â€“2.31]		
12	Atopic dermatitis	LINC00624	rs1035121917	intergenic_variant	4.00E-08	1.94	[1.53-2.45]		
13	Atopic dermatitis	TESPA1	rs183884396	missense_variant	2.00E-10	1.86	[1.54-2.26]		
14	Atopic dermatitis	EHMT1	rs3125788	intron_variant	1.00E-08	1.76	[1.45-2.14]		
15	Atopic dermatitis	EHMT1	rs3125788	intron_variant	2.00E-08	1.73	[1.43-2.1]		
16	Atopic dermatitis	PRR5L	rs12295535	intron_variant	8.00E-13	1.68	[1.46â€“1.93]		
17	Atopic dermatitis	CCDST - LCE5A	rs11205006	intergenic_variant	2.00E-25	1.615	[1.543-1.691]		
18	Atopic dermatitis	CRCT1 - LCE3E	rs61813875	intergenic_variant	6.00E-29	1.61	[1.48â€“1.75]		
19	Atopic dermatitis	TSBP1, TSBP1-AS1	rs9469099	intron_variant	5.00E-19	1.61	[1.44-1.80]		
20	Atopic march	CCDST - LCE5A	rs12081541	intergenic_variant	9.00E-11	1.61	[1.41-1.89]		
21	Atopic dermatitis	TNXB	rs12153855	intron_variant	3.00E-14	1.581	[1.405-1.779]		
22	Atopic march	RPL6P25 - SLC6A15	rs993226	intergenic_variant	5.00E-09	1.58	[1.35-1.84]		
23	Inflammatory skin disease	CCDST - LCE5A	rs12144049	intergenic_variant	3.00E-30	1.54	[1.37â€“1.73]		
24	Inflammatory skin disease	CCDST - LCE5A	rs471144	intergenic_variant	2.00E-12	1.54	[1.37â€“1.73]		
25	Atopic dermatitis	RNU6-408P - MIR302F	rs1361355315	intergenic_variant	4.00E-08	1.54	[1.32-1.79]		
26	Atopic dermatitis	SEMA6C	rs187325802	intron_variant	2.00E-10	1.51	[1.33-1.71]		
27	Inflammatory skin disease	CRCT1 - LCE3E	rs10888499	intergenic_variant	5.00E-25	1.49	[1.38â€“1.61]		
28	Atopic dermatitis	CCDST	rs61816766	intergenic_variant	1.00E-228	1.41	[1.39-1.43]		
29	Atopic dermatitis	TH2LCRR, IL13	rs848	3_prime_UTR_variant	8.00E-28	1.4	[1.32â€“1.49]		
30	Atopic dermatitis	PBX2 - GPSM3	rs176095	intergenic_variant	8.00E-20	1.4	[1.30-1.51]		
31	Atopic dermatitis	CCDST - LCE5A	rs12144049	intergenic_variant	1.00E-16	1.39	[NR]		
32	Atopic dermatitis	IL13, TH2LCRR	rs1295686	intron_variant	2.00E-17	1.383	[1.283-1.49]		
33	Atopic dermatitis	IVL - LINC01527	rs61815704	intergenic_variant	6.00E-212	1.36	[1.34-1.39]		
34	Atopic dermatitis	LINC02571 - HLA-B	rs9368677	intergenic_variant	1.00E-17	1.36	[1.27-1.46]		
35	Atopic dermatitis	IL13, TH2LCRR	rs1295686	intron_variant	5.00E-09	1.347	[1.28-1.418]		
36	Atopic march	EMSY - LINC02757	rs2155219	intergenic_variant	2.00E-15	1.33	[1.24-1.43]		
37	Atopic dermatitis	ITGB8	rs3757723	intron_variant	2.00E-08	1.33	[1.2-1.47]		
38	Atopic dermatitis (moderate to severe)	MSL3B - TRPM8	rs213549	intergenic_variant	1.00E-41	1.327	[1.135-1.519]	unit increase	
39	Atopic dermatitis	TNFRSF6B, RTEL1-TNFRSF6B	rs909341	missense_variant	8.00E-10	1.316	[1.205-1.429]		
40	Atopic dermatitis	OR10A3 - NLRP10	rs878860	intergenic_variant	2.00E-22	1.31	[1.24-1.38]		
41	Atopic dermatitis	TNFRSF6B, RTEL1-TNFRSF6B	rs909341	missense_variant	8.00E-17	1.2987013			

	A	B	C	D	E	F	G	H	I
42	Atopic dermatitis	TNXB	rs41268896	intron_variant	4.00E-08	1.298	[1.238-1.361]		
43	Atopic dermatitis	GLB1	rs7613051	intron_variant	6.00E-21	1.29	[1.22-1.36]		
44	Atopic dermatitis	CCDC80 - MAT2AP1	rs12634229	intergenic_variant	2.00E-19	1.29	[1.22-1.37]		
45	Atopic dermatitis	EMSY - LINC02757	rs7130588	intergenic_variant	4.00E-13	1.29	[1.2-1.38]		
46	Inflammatory skin disease	EMSY - LINC02757	rs2212434	intergenic_variant	3.00E-12	1.29	[1.21â€“1.39]		
47	Atopic dermatitis	XIRP2, XIRP2-AS1	rs6720763	intron_variant	4.00E-08	1.29	[NR]		
48	Atopic dermatitis	LINC02929	rs10995251	intron_variant	6.00E-20	1.28	[1.22-1.36]		
49	Atopic dermatitis	EMSY - LINC02757	rs7110818	intergenic_variant	3.00E-16	1.28	[1.21â€“1.36]		
50	Atopic dermatitis	CCDC80 - MAT2AP1	rs75024669	intergenic_variant	2.00E-12	1.2705826	[1.188956631-1.357812297]		
51	Atopic dermatitis	CCDST	rs12123821	intergenic_variant	1.00E-228	1.27	[1.25-1.29]		
52	Atopic dermatitis	IL18R1	rs13015714	intergenic_variant	8.00E-18	1.27	[1.20-1.34]		
53	Atopic march	EFHC1	rs9357733	intron_variant	2.00E-08	1.27	[1.17-1.38]		
54	Atopic dermatitis	IL18RAP	rs368124191	intron_variant	4.00E-16	1.26	[1.19-1.33]		
55	Atopic dermatitis (moderate to severe)	LINC00603	rs10053502	intergenic_variant	5.00E-15	1.259	[0.944-1.574]	unit increase	
56	Atopic dermatitis	GABPB2	rs146527530	intron_variant	2.00E-88	1.25	[1.22-1.28]		
57	Atopic dermatitis	CCDC80 - MAT2AP1	rs72943976	intergenic_variant	3.00E-14	1.25	[1.18-1.32]		
58	Atopic march	AP5B1 - OVOL1	rs479844	regulatory_region_variant	4.00E-10	1.25	[1.24-1.43]		
59	Atopic dermatitis	GLB1	rs79497729	intron_variant	2.00E-11	1.2465895	[1.169118136-1.329194619]		
60	Atopic dermatitis	SNX27	rs149199808	intron_variant	3.00E-134	1.24	[1.22-1.26]		
61	Atopic dermatitis	AFF1	rs80199341	intron_variant	5.00E-08	1.24	[1.15-1.34]		
62	Atopic march	KIF3A	rs17690965	3_prime_UTR_variant	5.00E-08	1.24	[1.15-1.33]		
63	Atopic dermatitis	LCE1D - LCE1C	rs72702900	intergenic_variant	4.00E-163	1.23	[1.22-1.25]		
64	Inflammatory skin disease	LCE1F - LCE1E	rs77199844	intergenic_variant	2.00E-17	1.23	[1.15â€“1.32]		
65	Atopic dermatitis	CLEC16A	rs2041733	intron_variant	3.00E-15	1.23	[1.17â€“1.29]		
66	Atopic dermatitis	GLB1	rs79497729	intron_variant	1.00E-12	1.23	[1.16-1.3]		
67	Atopic dermatitis	CDKN2B-AS1 - DMRTA1	rs10738626	intergenic_variant	1.00E-08	1.23	[NR]		
68	Atopic dermatitis	IFT140	rs933905994	intron_variant	3.00E-11	1.2259	[0.86-1.59]	unit increase	
69	Atopic dermatitis	CCDST	rs3126085	intergenic_variant	6.00E-12	1.22	[NR]		
70	Atopic dermatitis	SLC9A4	rs759382	intron_variant	6.00E-11	1.22	[1.15â€“1.29]		
71	Atopic dermatitis	EMSY - LINC02757	rs7927894	intergenic_variant	8.00E-10	1.22	[1.15-1.30]		
72	Atopic march	IKZF3	rs10445308	intron_variant	5.00E-08	1.22	[1.14-1.30]		
73	Atopic dermatitis	GLB1	rs79497729	intron_variant	4.00E-12	1.21	[1.15-1.28]		
74	Atopic dermatitis	LINC02757	rs11236809	intergenic_variant	2.00E-09	1.21	[1.14-1.28]		
75	Atopic dermatitis	IL2 - IL21	rs17389644	intergenic_variant	1.00E-08	1.19	[1.12â€“1.26]		
76	Atopic dermatitis	CYP24A1 - PFDN4	rs16999165	intergenic_variant	2.00E-08	1.19	[1.12-1.26]		
77	Atopic dermatitis (moderate to severe)	GOLGA4 - APRG1	rs6799780	intergenic_variant	7.00E-24	1.188	[0.957-1.42]	unit increase	
78	Atopic dermatitis	PRR5L	rs28520436	intron_variant	5.00E-81	1.18	[1.16-1.2]		
79	Atopic dermatitis	PRR5L	rs11033603	intron_variant	1.00E-12	1.18	[1.13-1.23]		
80	Atopic dermatitis	CARD11 - SDK1-AS1	rs4722404	intergenic_variant	8.00E-09	1.18	[1.12-1.25]		
81	Atopic dermatitis (moderate to severe)	LINC02055	rs1841513	intergenic_variant	2.00E-28	1.171	[0.963-1.379]	unit decrease	
82	Atopic dermatitis	SNX27	rs71625130	intron_variant	2.00E-89	1.17	[1.16-1.19]		

	A	B	C	D	E	F	G	H	I
83	Atopic dermatitis	ZNF652-AS1	rs16948048	intergenic_variant	3.00E-09	1.17	[1.11â€“1.23]		
84	Atopic dermatitis	NFILZ	rs2164983	3_prime_UTR_variant	7.00E-09	1.16	[1.10-1.22]		
85	Atopic dermatitis	RPRD2	rs187080438	intron_variant	2.00E-41	1.14	[1.12-1.16]		
86	Atopic dermatitis	SLC25A46 - BCLAF1P1	rs10073425	intergenic_variant	9.00E-24	1.14	[1.1-1.16]		
87	Atopic dermatitis	TH2LCRR	rs12188917	intergenic_variant	4.00E-17	1.14	[1.10â€“1.17]		
88	Atopic dermatitis	AP5B1 - OVOL1	rs479844	regulatory_region_variant	1.00E-13	1.14	[1.10-1.18]		
89	Atopic dermatitis	KCNK5 - KCNK17	rs1172342321	regulatory_region_variant	4.00E-08	1.1316	[0.73-1.54] unit increase		
90	Atopic dermatitis (moderate to severe)	KCTD8	rs983363	intron_variant	2.00E-08	1.126	[0.732-1.521] unit increase		
91	Atopic dermatitis (moderate to severe)	RCBTB1	rs61961401	intron_variant	8.00E-08	1.121	[0.712-1.53] unit increase		
92	Atopic dermatitis	OVOL1	rs10791824	intron_variant	2.00E-19	1.12	[1.09â€“1.15]		
93	Atopic dermatitis	NFILZ	rs2918307	3_prime_UTR_variant	5.00E-12	1.12	[1.08â€“1.16]		
94	Atopic dermatitis	NFILZ	rs2164983	3_prime_UTR_variant	2.00E-11	1.12	[1.08-1.15]		
95	Atopic dermatitis	IL18R1, IL1RL1	rs1861246	intron_variant	2.00E-10	1.12	[1.09-1.15]		
96	Atopic dermatitis	CTIF - SMAD7	rs28558565	regulatory_region_variant	4.00E-08	1.12	[1.07-1.16]		
97	Atopic dermatitis	AP5B1 - OVOL1	rs479844	regulatory_region_variant	2.00E-18	1.1111112	[1.09-1.14]		
98	Atopic dermatitis	RTEL1, RTEL1-TNFRSF6B	rs4809219	intron_variant	7.00E-13	1.1111112			
99	Atopic dermatitis	EMSY - LINC02757	rs11236791	intergenic_variant	2.00E-27	1.11	[1.09-1.13]		
100	Atopic dermatitis	RTEL1, RTEL1-TNFRSF6B	rs3848669	intron_variant	3.00E-15	1.11	[1.08-1.13]		
101	Atopic dermatitis	IL18R1 - SDR42E1P5	rs6419573	intergenic_variant	2.00E-13	1.11	[1.08â€“1.14]		
102	Atopic dermatitis	KIF3A	rs2897442	intron_variant	4.00E-08	1.11	[1.07-1.15]		
103	Atopic dermatitis	RPL32P23 - RBM17	rs12251307	intergenic_variant	5.00E-107	1.1	[1.09-1.11]		
104	Atopic dermatitis	CCR7 - SMARCE1	rs9911533	regulatory_region_variant	7.00E-19	1.1	[1.07-1.12]		
105	Atopic dermatitis	IL13, TH2LCRR	rs847	3_prime_UTR_variant	4.00E-17	1.1	[1.07-1.12]		
106	Atopic dermatitis	NFILZ - ACTL9	rs35358447	intergenic_variant	2.00E-12	1.1	[1.07-1.13]		
107	Atopic dermatitis	IL18R1	rs13015714	intergenic_variant	2.00E-12	1.1	[1.07-1.14]		
108	Atopic dermatitis	KIF3A	rs4705962	3_prime_UTR_variant	7.00E-12	1.1	[1.07-1.13]		
109	Atopic dermatitis	LINC02571 - HLA-B	rs28752924	intergenic_variant	5.00E-11	1.1	[1.07-1.14]		
110	Atopic dermatitis	HLA-DRB1 - HLA-DQA1	rs4713555	intergenic_variant	5.00E-09	1.098901			
111	Atopic dermatitis	GABPB2	rs115161931	intron_variant	2.00E-32	1.09	[1.08-1.11]		
112	Atopic dermatitis	EMSY - LINC02757	rs2212434	intergenic_variant	5.00E-13	1.09	[1.07â€“1.12]		
113	Atopic dermatitis	KIF3A	rs2897442	intron_variant	1.00E-10	1.09	[1.06-1.12]		
114	Atopic dermatitis	RTEL1-TNFRSF6B, RTEL1	rs6010620	intron_variant	2.00E-09	1.09	[1.06-1.13]		
115	Atopic dermatitis	LINC02098 - ETS1	rs533495047	intergenic_variant	4.00E-08	1.09	[1.06-1.13]		
116	Atopic dermatitis	PPP2R3C, FAM177A1	rs2143950	intron_variant	2.00E-15	1.08	[1.06-1.10]		
117	Atopic dermatitis	ZNF652	rs35073649	intron_variant	2.00E-14	1.08	[1.06-1.1]		
118	Atopic dermatitis	RTEL1, RTEL1-TNFRSF6B	rs3208007	synonymous_variant	3.00E-12	1.08	[1.06-1.11]		
119	Atopic dermatitis	CLEC16A	rs2041733	intron_variant	3.00E-11	1.08	[1.06-1.11]		
120	Atopic dermatitis	BLTP1	rs45605540	intron_variant	9.00E-11	1.08	[1.05-1.1]		
121	Atopic dermatitis	IL6R	rs2228145	missense_variant	5.00E-10	1.08	[1.05-1.11]		
122	Atopic dermatitis	EMSY - LINC02757	rs7927894	intergenic_variant	3.00E-09	1.08	[1.05-1.10]		
123	Atopic dermatitis	TRIB1AL - LINC02964	rs6996614	intergenic_variant	2.00E-08	1.08	[1.05-1.11]		

	A	B	C	D	E	F	G	H	I
124	Atopic dermatitis	EMSY - LINC02757	rs7936323	intergenic_variant	2.00E-133	1.07	[1.07-1.08]		
125	Atopic dermatitis	RTEL1, RTEL1-TNFRSF6B	rs6062486	intron_variant	5.00E-109	1.07	[1.07-1.08]		
126	Atopic dermatitis	OVOL1	rs10791824	intron_variant	1.00E-105	1.07	[1.06-1.07]		
127	Atopic dermatitis	STAT3	rs17881320	intron_variant	1.00E-38	1.07	[1.06-1.08]		
128	Atopic dermatitis	GATAD2B	rs12138773	intron_variant	4.00E-16	1.07	[1.05-1.09]		
129	Atopic dermatitis	LINC02929	rs10995245	intron_variant	5.00E-12	1.07	[1.05-1.1]		
130	Atopic dermatitis	IL22 - MDM1	rs3947727	intergenic_variant	1.00E-11	1.07	[1.05-1.1]		
131	Atopic dermatitis	RPL13AP18 - RNU6-1213P	rs11786685	intergenic_variant	2.00E-11	1.07	[1.05-1.1]		
132	Atopic dermatitis	LAYN - SIK2	rs659529	intergenic_variant	5.00E-10	1.07	[1.05-1.1]		
133	Atopic dermatitis	CSF2RB	rs2075943	intron_variant	2.00E-09	1.07	[1.04-1.09]		
134	Atopic dermatitis	LINC02676 - LINC00709	rs1444789	intergenic_variant	3.00E-08	1.07	[1.05-1.1]		
135	Atopic dermatitis	PA2G4 - RPL41	rs4759228	intergenic_variant	5.00E-08	1.07	[1.04-1.09]		
136	Atopic dermatitis	LINC02098 - ETS1	rs7127307	intergenic_variant	2.00E-18	1.0638298			
137	Atopic dermatitis	RPL13AP18 - RNU6-1213P	rs6473227	intergenic_variant	2.00E-16	1.0638298			
138	Atopic dermatitis	IL7R - CAPSL	rs10214237	intergenic_variant	3.00E-14	1.0638298			
139	Atopic dermatitis	CD207 - LINC01143	rs112111458	intergenic_variant	9.00E-09	1.0638298			
140	Atopic dermatitis	NFILZ	rs2967677	3_prime_UTR_variant	8.00E-49	1.06	[1.05-1.07]		
141	Atopic dermatitis	HLA-DQB1 - MTCO3P1	rs9275218	intergenic_variant	5.00E-10	1.06	[1.04-1.08]		
142	Atopic dermatitis	OVOL1	rs10791824	intron_variant	9.00E-10	1.06	[1.04-1.09]		
143	Atopic dermatitis	TNFRSF11A	rs8086340	intron_variant	2.00E-09	1.06	[1.04-1.08]		
144	Atopic dermatitis	ZBTB38	rs6785012	intron_variant	3.00E-09	1.06	[1.04-1.08]		
145	Atopic dermatitis	IL2RA	rs12244238	intron_variant	5.00E-09	1.06	[1.04-1.08]		
146	Atopic dermatitis	IL6R	rs12126142	intron_variant	6.00E-09	1.06	[1.04-1.09]		
147	Atopic dermatitis	PRR5L	rs61878692	intron_variant	2.00E-08	1.06	[1.04-1.09]		
148	Atopic dermatitis	IL6R	rs4845373	intron_variant	5.00E-08	1.06	[1.04-1.08]		
149	Atopic dermatitis	IL22	rs2227491	intron_variant	1.00E-71	1.05	[1.05-1.06]		
150	Atopic dermatitis	IL2 - IL21	rs45599938	intergenic_variant	1.00E-62	1.05	[1.05-1.06]		
151	Atopic dermatitis	RUNX3 - MIR4425	rs7542147	intergenic_variant	5.00E-56	1.05	[1.04-1.05]		
152	Atopic dermatitis	LINC02929	rs10822037	intron_variant	4.00E-55	1.05	[1.04-1.05]		
153	Atopic dermatitis	REL - NONOP2	rs67766926	intergenic_variant	1.00E-41	1.05	[1.04-1.05]		
154	Atopic dermatitis	IL15RA - IL2RA	rs6602364	intergenic_variant	1.00E-10	1.05	[1.03-1.06]		
155	Atopic dermatitis	OTULINL	rs148161264	intron_variant	2.00E-08	1.05	[1.03-1.06]		
156	Atopic dermatitis	PUS10	rs4643526	intron_variant	6.00E-08	1.05	[1.03-1.07]		
157	Atopic dermatitis	CIART - MRPS21	rs7512552	regulatory_region_variant	5.00E-09	1.0416667			
158	Atopic dermatitis	LINC00299	rs10199605	intergenic_variant	4.00E-08	1.0416667			
159	Atopic dermatitis	CSF2RB	rs4821569	intron_variant	5.00E-50	1.04	[1.04-1.05]		
160	Atopic dermatitis	IL6R	rs12133641	intron_variant	3.00E-45	1.04	[1.04-1.05]		
161	Atopic dermatitis	TNFSF4	rs11811788	intron_variant	2.00E-39	1.04	[1.04-1.05]		
162	Atopic dermatitis	TRAF3	rs4906263	intron_variant	3.00E-36	1.04	[1.03-1.04]		
163	Atopic dermatitis	ZNF652-AS1	rs28406364	intergenic_variant	2.00E-34	1.04	[1.03-1.04]		
164	Atopic dermatitis	AGO2	rs7843258	intron_variant	7.00E-25	1.04	[1.03-1.05]		

	A	B	C	D	E	F	G	H	I
165	Atopic dermatitis	SOCAR, MIR4435-2HG	rs112385344	intergenic_variant	2.00E-18	1.04	[1.03-1.05]		
166	Atopic dermatitis	SIK3	rs11216206	intron_variant	9.00E-15	1.04	[1.03-1.05]		
167	Atopic dermatitis (moderate to severe)	RBMS3	rs6778759	intron_variant	2.00E-10	1.039	[0.719-1.359] unit increase		
168	Atopic dermatitis	RAB5B	rs705699	intron_variant	9.00E-27	1.03	[1.03-1.04]		
169	Atopic dermatitis	CCR7 - SMARCE1	rs1358175	intergenic_variant	1.00E-26	1.03	[1.03-1.04]		
170	Atopic dermatitis	GLB1	rs35570272	intron_variant	2.00E-26	1.03	[1.03-1.04]		
171	Atopic dermatitis	NEU4 - PDCD1	rs62193132	intergenic_variant	2.00E-19	1.03	[1.02-1.03]		
172	Atopic dermatitis	TRIB1AL - LINC02964	rs6996614	intergenic_variant	2.00E-19	1.03	[1.02-1.03]		
173	Atopic dermatitis	LMAN2	rs4532376	intron_variant	1.00E-18	1.03	[1.02-1.03]		
174	Atopic dermatitis	PLXNC1	rs5005507	intron_variant	3.00E-18	1.03	[1.02-1.04]		
175	Atopic dermatitis	AQP7 - AQP3	rs7857407	intergenic_variant	5.00E-18	1.03	[1.02-1.03]		
176	Atopic dermatitis	RERE	rs301804	intron_variant	6.00E-16	1.03	[1.02-1.03]		
177	Atopic dermatitis	LINC01768	rs12565349	intergenic_variant	6.00E-15	1.03	[1.02-1.04]		
178	Atopic dermatitis	TBX21	rs56308324	intron_variant	3.00E-11	1.03	[1.02-1.04]		
179	Atopic dermatitis	FLG, CCDST	rs558269137	frameshift_variant	1.00E-18	1.0276	[0.8-1.26] unit increase		
180	Atopic dermatitis	IL15	rs10833	3_prime_UTR_variant	3.00E-15	1.02	[1.02-1.03]		
181	Atopic dermatitis	Y_RNA - CXCR5	rs10790275	intergenic_variant	1.00E-10	1.02	[1.02-1.03]		
182	Atopic dermatitis	MIIP	rs61776548	intron_variant	6.00E-09	1.02	[1.01-1.02]		
183	Atopic dermatitis	FLG, CCDST	rs61816761	stop_gained	2.00E-13	1.01	[0.74-1.28] increase		