Brief report

Uniting biobank resources reveals novel genetic pathways modulating susceptibility for atopic dermatitis

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Background: Atopic dermatitis (AD) is a common chronic inflammatory skin disease with high heritability. Previous genome-wide association studies have identified several loci predisposing to AD. These findings explain approximately 30% of the variance in AD susceptibility, suggesting that further work is required to fully understand the genetic underpinnings.

Objective: We sought to gain additional understanding of the genetic contribution to AD risk by using biobank resources.

Methods: We completed a genome-wide meta-analysis of AD in 796,661 individuals (N_{cases} = 22,474) from the FinnGen study, the Estonian Biobank, and the UK Biobank. We further performed downstream *in silico* analyses to characterize the risk variants at the novel loci.

Results: We report 30 loci associating with AD ($P < 5 \times 10^{-8}$), 5 of which are novel. In 2 of the novel loci, we identified missense mutations with deleterious predictions in desmocollin 1 and serpin family B member 7, genes encoding proteins crucial to epidermal strength and integrity.

Conclusions: These findings elucidate novel genetic pathways involved in AD pathophysiology. The likely involvement of desmocollin 1 and serpin family B member 7 in AD pathogenesis may offer opportunities for the development of novel treatment strategies for AD in the future. (J Allergy Clin Immunol 2021;■■■:■■■-■■■.)

Key words: *Atopic dermatitis, genome-wide association,* DSC1, SERPINB7, *FinnGen*

INTRODUCTION

Approximately 15% to 20% of children and 5% to 10% of adults are affected by atopic dermatitis (AD).[1] Typical AD hallmarks—dry skin, intense itching, and recurrent eczematous lesions—are thought to be triggered by environmental factors in genetically susceptible individuals.[1] The heritability of AD has been estimated to be up to 80% to 90% in twin studies,[2] indicating that genetic factors account for most of the variability in AD susceptibility. The key genetic risk factors include mutations in filaggrin, giving rise to epidermal barrier deficiency, or in immune-regulating genes, such as IL-6 receptor, which contribute to immune dysregulation.[3] To complement the understanding of the genetic pathways, we completed a genome-wide meta-analysis of association results obtained in FinnGen (8,383 cases, 236,161 controls), Estonian Biobank (11,187 cases, 125,537 controls), and UK Biobank (2,904 cases, 412,489 controls), adding up to 22,474 AD cases and 774,187 controls in the study.

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Abbreviations used
AD: Atopic dermatitis
DSC1: Desmocollin 1
SERPINB7: Serpin family B member 7
SNP: Single nucleotide polymorphism

RESULTS AND DISCUSSION

We identified 30 loci (5 novel) located more than 1 Mb apart containing at least 1 variant associated with AD at *P* less than 5×10^{-8} (Table I and Fig 1, *A*). An association peak spanning 1p21.1-1p21.3 and exceeding the 1-Mb locus definition is likely due to the same causal variants; these associations attenuated after conditioning the analyses for coding variants in filaggrin (Fig 2, *A*). The genome-wide significant variants were mostly annotated as intronic (Fig 1, *B*), and the genes assigned to these variants showed enrichment in multiple immune-regulating processes (Fig 1, *C*). The effect estimates of the lead variants were matching across the study populations (Fig 1, *D*). To test the validity of using *International Classification of Diseases, Tenth Revision* code L20 as case definition, we compared in FinnGen the effect estimates of the lead variants at the 30 loci obtained with the original case definition against 2 more rigorous definitions (see this article's Online Repository at www.jacionline.org). The effect estimates were highly comparable (Fig 1, *E*), indicating that the *International Classification of Diseases, Tenth Revision* code L20-derived case definition was adequately accurate for the purpose of genome-wide association study.

The associations at 3q24, 8q24.13, 12q15, 18q12.1, and 18q22.1 have not been reported previously. In these loci, we annotated all genes to identify the biologically most relevant candidate gene(s) potentially driving the AD associations and further applied the Data-driven Expression Prioritized Integration for Complex Trait framework[8] to provide statistical evidence for

TABLE I. Loci associated with AD in 796,661 Europeans

Locus	Nearest gene	Candidate gene(s)	Chr:Pos	Rsid	EA	OA	OR	95% CI	*P*	EAF	HetPVal	FIN enr.	Ref.
1q21.1*	*LINC02799*	*FLG**	1:143595936	rs188069315	a	g	2.36	1.77-3.15	4.76×10^{-09}	0.0015	.641	NA	*FLG**
1q21.2*	*LINC00624*	*FLG**	1:147506275	rs1035121917	a	c	1.94	1.53-2.45	4.24×10^{-08}	0.0017	.392	14.03	*FLG**
1q21.3*	*SEMA6C*	*FLG**	1:151143311	rs187325802	t	g	1.51	1.33-1.71	2.02×10^{-10}	0.0048	.205	19.47	3-5
1q21.3*	*FLG-AS1*	*FLG**	1:152312600	rs558269137	cactg	c	0.50	0.45-0.55	2.56×10^{-44}	0.9927	1.81×10^{-05}	0.60	3-6
1q21.3*	*PGLYRP4*	*FLG**	1:153330248	rs538763482	a	g	0.56	0.48-0.65	1.34×10^{-13}	0.9970	.198	9.74	3,6
1q21.3	*IL-6R*	*IL-6R*	1:154452980	rs12126142	a	g	1.06	1.04-1.09	6.21×10^{-09}	0.3617	.0037	0.77	3-5
1q24.3	*AL031599.1*	*TNFSF4*	1:172859340	rs17371133	a	c	0.94	0.92-0.96	2.07×10^{-10}	0.5170	.796	0.85	4,5
2q12.1	*IL1RL1*	*IL18RAP*	2:102350323	rs1861246	t	c	1.12	1.09-1.15	1.52×10^{-20}	0.2170	.032	1.05	3,4-6
3q24	***DIPK2A***	***DIPK2A***	**3:144401986**	**rs150979174**	**a**	**g**	**0.60**	**0.50-0.72**	$\mathbf{3.60 \times 10^{-08}}$	**0.9966**	**.802**	**1.18**	***Novel***
4q27	*KIAA1109*	*IL2, IL21*	4:122111486	rs7666843	t	c	0.89	0.86-0.92	6.16×10^{-11}	0.0942	1.000	0.99	4-6
5q31.1	*IL13*	*IL13*	5:132660977	rs847	t	c	1.10	1.07-1.12	3.75×10^{-17}	0.2607	.010	0.76	3,4
6p21.33	*HLA-B*	*HLA-B*	6:31336145	rs28752924	t	c	1.10	1.07-1.14	4.95×10^{-11}	0.6336	.948	NA	5,7
6p21.32	*HLA-DQA1*	*HLA-DQA1*	6:32626262	rs28383323	a	g	0.89	0.86-0.92	1.10×10^{-13}	0.2381	.860	NA	3,5
8q21.12	*ZBTB10*	*ZBTB10*	8:80363600	rs11786685	a	g	1.07	1.05-1.10	1.99×10^{-11}	0.3393	.165	1.07	3-5
8q24.13	***TRIB1***	***TRIB1***	**8:125597624**	**rs6996614**	**a**	**c**	**1.08**	**1.05-1.11**	$\mathbf{1.55 \times 10^{-08}}$	**0.4491**	**.048**	**1.06**	***Novel***
11p12	*PRR5L*	*PRR5L*	11:36412992	rs11033603	a	g	1.18	1.13-1.23	1.33×10^{-12}	0.0420	.0079	1.96	4-6
11q13.1	*OVOL1*	*OVOL1*	11:65784486	rs479844	a	g	0.93	0.91-0.95	2.41×10^{-12}	0.4280	.031	1.07	3-5
11q13.5	*EMSY*	*EMSY, LRRC32*	11:76588800	rs34455012	cccagtat	c	0.87	0.85-0.89	1.56×10^{-22}	0.6075	.171	0.86	3,4-6
11q24.3	*ETS1*	*ETS1*	11:128293267	rs533495047	a	ag	1.09	1.06-1.13	4.48×10^{-08}	0.8091	.362	1.09	3-5
12q13.2	*TESPA1*	*TESPA1*	12:54963054	rs183884396	a	g	1.86	1.54-2.26	2.28×10^{-10}	0.0023	.720	10.53	4,5
12q13.2	*PA2G4*	*STAT6*	12:56114625	rs4759228	c	g	1.07	1.04-1.09	4.61×10^{-08}	0.2738	.045	0.86	4,5
12q15	***IL22***	***IL22, IFNG***	**12:68258319**	**rs3947727**	**t**	**c**	**1.07**	**1.05-1.10**	$\mathbf{1.09 \times 10^{-11}}$	**0.5994**	**.0015**	**0.92**	***Novel***
14q13.2	*PRORP*	*PPP2R3C*	14:35185261	rs12586305	t	g	0.91	0.89-0.94	7.92×10^{-11}	0.8410	.257	0.92	3-5
16p13.13	*CLEC16A*	*CLEC16A*	16:11100223	rs3862469	t	c	0.93	0.91-0.95	3.59×10^{-12}	0.3130	.479	0.87	3,4-6
17q21.33	*ZNF652*	*ZNF652*	17:49345148	rs35073649	t	c	1.08	1.06-1.10	2.04×10^{-14}	0.3931	3.21×10^{-04}	1.16	4-6
18q12.1	***AC117569.1***	***DSC1***	**18:29549105**	**rs1361355315**	**t**	**c**	**1.54**	**1.32-1.79**	$\mathbf{3.53 \times 10^{-08}}$	**0.0036**	**.170**	**102.82**	***Novel***
18q22.1	***HMSD***	***SERPINB7***	**18:63945923**	**rs188720898**	**a**	**t**	**0.61**	**0.52-0.72**	$\mathbf{1.49 \times 10^{-09}}$	**0.9974**	**.017**	**NA**	***Novel***
19p13.2	*LINC01862*	*ACTL9*	19:8681318	rs35358447	a	ag	1.10	1.07-1.13	1.68×10^{-12}	0.1683	.022	1.56	3
20q13.33	*RTEL1*	*RTEL1*	20:63669458	rs3848669	t	g	1.11	1.08-1.13	2.84×10^{-15}	0.7791	2.14×10^{-04}	1.04	3,4-6
22q12.3	*CSF2RB*	*CSF2RB*	22:36922967	rs2075943	a	g	1.07	1.04-1.09	2.09×10^{-09}	0.5760	.295	1.11	5

Chr, Chromosome; *DIPK2A*, divergent protein kinase domain 2A; *EA*, effect allele; *EAF*, effect allele frequency; *FIN enr*, Finnish enrichment (calculated as FIN AF / NFEE AF in the Genome Aggregation Database [gnomAD], where FIN AF is the Finnish allele frequency and NFEE AF is the non-Finnish-non-Estonian European allele frequency); *FLG*, filaggrin; *HetPVal*, *P* value for heterogeneity; *IL-6R*, IL-6 receptor; *NA*, not available; *OA*, other allele; *OR*, odds ratio; *Pos*, position (build 38); *Ref.*, previous studies reporting AD risk associations within ±1 Mb from the lead variant; *TRIB1*, tribbles pseudokinase 1.

The tabulated variants represent distinct loci more than 1 Mb apart containing at least 1 variant identified to be associated with AD at $P < 5 \times 10^{-8}$ in a meta-analysis of 22,474 AD cases and 774,187 controls from FinnGen, Estonian Biobank, and the UK Biobank.

"Nearest gene" indicates the gene closest to the association lead variant. For the novel loci, "Candidate gene(s)" indicates the gene(s) that has its biological function most likely related to the pathogenesis of AD (for details, see this article's Methods section in the Online Repository) and, for the replicated loci, the same column indicates candidate gene(s) as assigned in previous studies. Novel loci are highlighted with bold font.

*The locus near *FLG* spans to a genomic region larger than ±1 Mb.

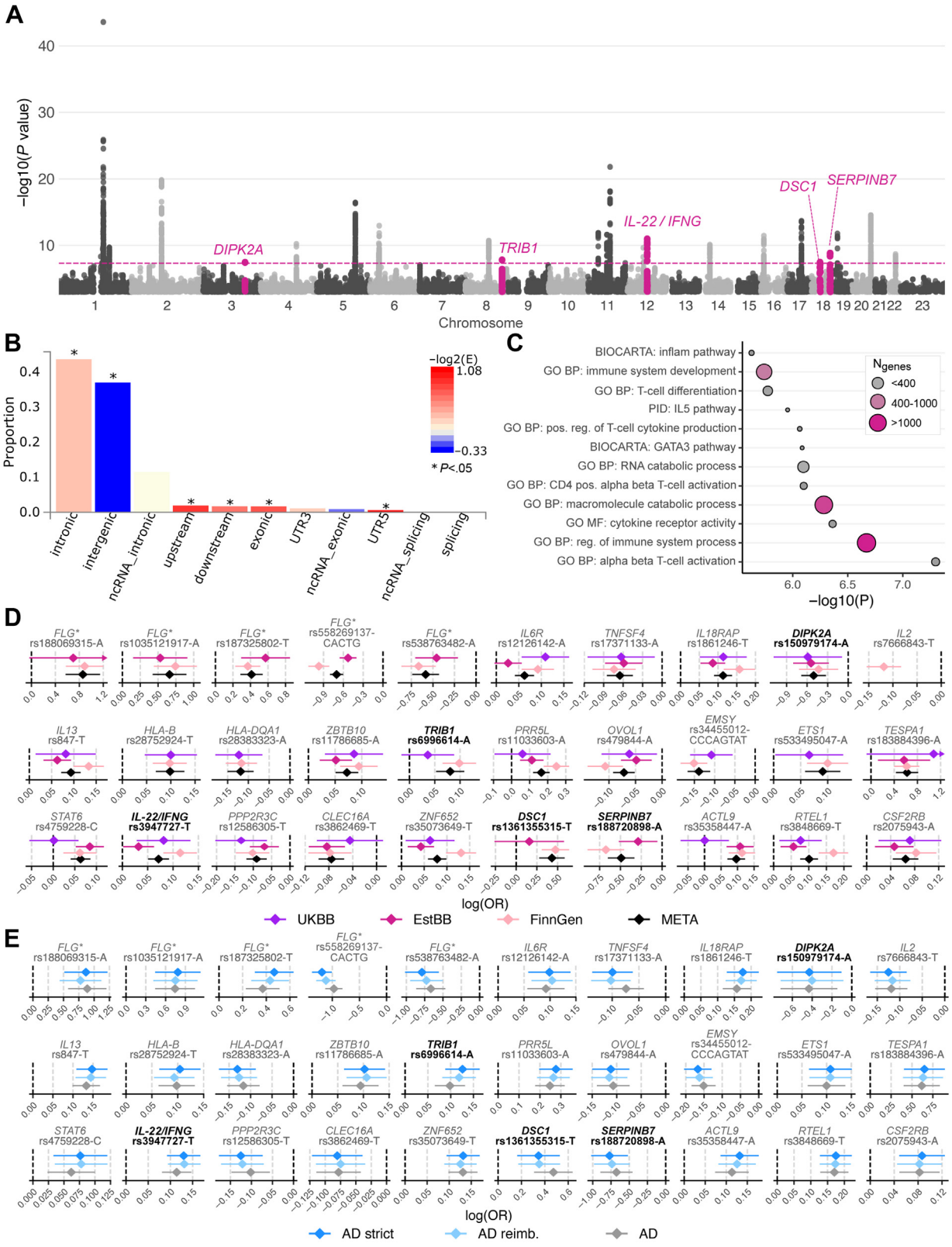

FIG 1. Genome-wide associations of AD. **A,** A Manhattan plot of AD in 796,661 Europeans. The pink dashed line corresponds to $P = 5 \times 10^{-8}$. The novel loci are highlighted with pink font. **B,** Functional annotation of the significant variants and variants in LD with significant variants (see this article's Online Repository at www.jacionline.org). Bars are colored by -$\log_2$(enrichment) relative to all variants in the reference panel. **C,** Significant ($P < 6.36 \times 10^{-6}$) gene sets obtained using MAGMA (see this article's Online Repository at www.jacionline.org). **D,** Population-specific effect sizes and corresponding 95% CIs of the lead variants in

the most likely causal gene (see this article's Online Repository at www.jacionline.org). The signals in chromosomes 3 and 8 fall within regions with relatively few genes with poorly understood functions. At 3q24, the gene closest to the AD association is divergent protein kinase domain 2A (Fig 3, *A*) encoding a paracrine protein stimulating cell-cycle progression and proliferation of cardiomyocytes.[9] Differential DNA methylation of divergent protein kinase domain 2A has been associated with melanoma subtypes,[10] suggesting a role for divergent protein kinase domain 2A in skin cancer. At 8q24.13, the association is near tribbles pseudokinase 1 (Fig 3, *B*), which interacts with E3 ubiquitin-protein ligase COP1 in protein degradation and myeloid cell differentiation.[11] In this locus, the Data-driven Expression Prioritized Integration for Complex Trait framework[8] analysis suggests tribbles pseudokinase 1 as a causal gene ($P = 7.67 \times 10^{-5}$), but an apparent biological link with AD pathophysiology remains unclear. In the other novel loci, the potential candidate genes have functions related to immune regulation or epidermal barrier function, as described below.

The novel association at 12q15 is near IL-22 (*IL22*) and IFN-γ (*IFNG*; Fig 3, *C*). IL-22 is a T-cell–derived cytokine acting mostly on cells of skin, kidney, digestive tract, and respiratory system.[12] Upregulated expression of genes encoding the subunits of IL-22 receptor suggests an elevated IL-22 sensitivity of keratinocytes under inflammatory conditions.[12] IFN-γ is a cytokine belonging to the type II interferon class, and it acts in cellular responses to viral and microbial infections.[13] Possible involvement of both IL-22 and IFN-γ in the pathogenesis of inflammatory skin diseases has been suggested,[14,15] but there is no genome-wide association study record of AD association until now. According to the Data-driven Expression Prioritized Integration for Complex Trait framework,[8] *IL22* is the causal gene in this locus ($P = 2.37 \times 10^{-4}$). RegulomeDB[16] annotation provided evidence for a possible regulatory mechanism for the detected association that may involve altered binding of early growth response 2 (Table II), a transcription factor that has been previously implicated in AD susceptibility in the Chinese Han population.[17] Of note, there was a suggestive association at 6q23.3 near genes IL-22 receptor subunit alpha-1 and IFN-γ receptor 1 ($P = 2.77 \times 10^{-7}$), providing additional evidence that IL-22 and/or IFN-γ may be involved in modulating AD risk.

At 18q12.1, the discovery of a novel association close to the desmocollin family of genes was likely facilitated by the more than 100-fold enrichment of the association lead variant in the Finnish population (Table I). Desmocollins, along with desmogleins, are proteins found primarily in epithelial cells where they are required for cell adhesion and formation of desmosomes, structures essential in resisting shearing forces in cells subject to mechanical stress.[13] A potentially interesting variant to drive the AD association in this locus is a rare missense variant (rs200047736; minor allele frequency = 0.4%) in desmocollin 1 (*DSC1*) that lies roughly 1.5 Mb away from the association lead variant (rs1361355315): we found no significant associations in this locus after conditioning the association test for the missense variant (Fig 2, *B*). This p.Pro575Arg substitution is predicted to be deleterious or disease causing according to 5 different algorithms (Table II). The variant introduces an amino acid residue that is larger in size and less hydrophobic than the wild-type residue, likely disrupting proper folding and hydrophobic interactions in the protein.[18] The variant also introduces a positive charge, which can cause repulsion of ligands or other residues with a positive charge.[18] These *in silico* estimates provide evidence that the missense variant in *DSC1* likely drives the AD risk association in this locus. Supportive to our findings, mice with disrupted *Dsc1* function develop an AD-like phenotype.[19]

The association signal at 18q22.1 locates near a cluster of serpin protease inhibitors (Fig 3, *E*). The nearest gene is serpin family B member 8, which functions in enhancing the mechanical stability of cell-cell adhesions in the skin.[13] Loss-of-function mutations in serpin family B member 8 have been reported in association with autosomal-recessive exfoliative ichthyosis,[20] a disorder characterized by palmoplantar peeling of the skin. In the same locus, a gene encoding serpin family B member 7 (*SERPINB7*) harbors a rare missense variant (rs201208667; minor allele frequency = 0.3%) that is in high linkage disequilibrium ($r^2 = 0.99$ in FinnGen) with the association lead variant (rs188720898). Conditioning the association for the missense variant abolished significant associations in this locus (Fig 2, *C*). *In silico* estimates supported the perception that this p.Cys379Tyr substitution may drive the AD risk association in this locus: the variant was predicted to be deleterious or damaging according to 2 estimates (Table II), and, in addition, tyrosine is larger in size and less hydrophobic than cysteine, which may disrupt protein folding and hydrophobic interactions.[18] Mutations in *SERPINB7* have been described in patients with Nagashima-type palmoplantar keratosis,[21] and the missense variant rs201208667 has been described as a plausible Finnish Nagashima-type palmoplantar keratosis founder mutation.[22] In FinnGen, the same variant showed a suggestive association ($P = 6.7 \times 10^{-7}$) with childhood allergy (<16 years), which is in line with known genetic comorbidity of AD and allergic disease.[23]

We found positive genetic correlations between AD and asthma and allergic diseases.[23,24] In line with this, we observed negative genetic correlations between AD and multiple lung function–related traits—these correlations, however, reached only nominal significance. In the present study, the lead variants near filaggrin, *IL-13*, *HLA-DQA1*, *TESPA1*, and *ZNF652* were also associated with asthma and/or allergic asthma in FinnGen,

the 30 reported loci. **E,** Association results of the lead variants in the 30 reported loci in FinnGen using 3 different AD case definitions (see this article's Online Repository at www.jacionline.org). "AD" cases had an entry of *ICD-10* code L20 or *ICD-8* code 691, and individuals with no record of these were considered as controls; participants with *ICD-9* code 6918X were excluded from the analyses. "AD reimb" cases had an entry of KELA reimbursement codes 134 (erythrodermia exfoliativa universalis), 395 (dupilumab), or 317 (topical calcineurin inhibitors). "AD strict" cases had an entry of *ICD-10* code L20.0, *ICD-9* code 6918B, or *ICD-8* code 69100. In Fig 1, *D* and *E*, novel variants are highlighted with bold black font. *BP*, Biological process; *DIPK2A*, divergent protein kinase domain 2A; *EstBB*, Estonian Biobank; *ICD-8*, *International Classification of Diseases, Eighth Revision*; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision; LD*, linkage disequilibrium; *MF*, molecular function; *PID*, primary immunodeficiency; *UKBB*, UK Biobank.

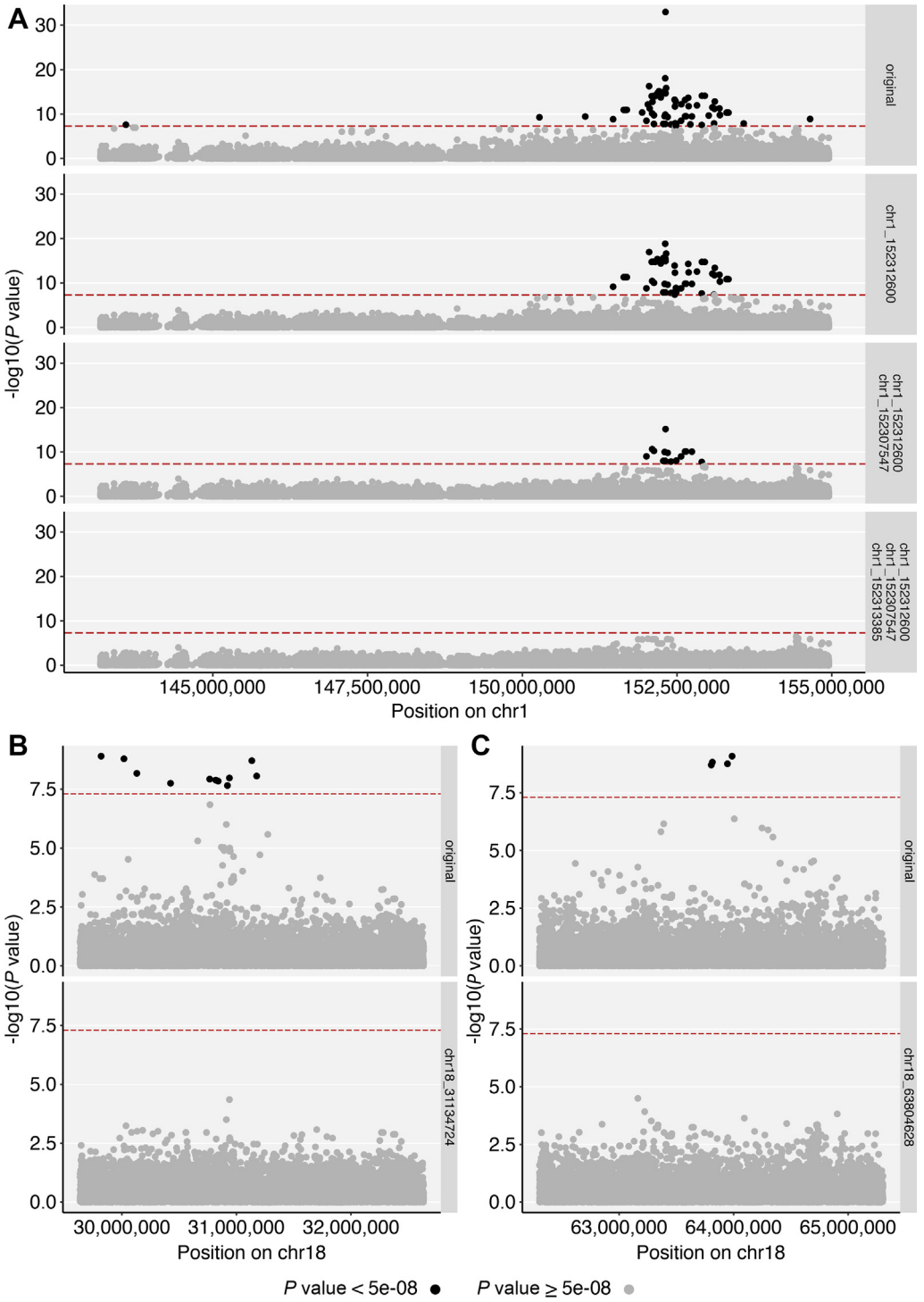

FIG 2. Conditional analyses on AD association near **(A)** *FLG*, **(B)** *DSC1*, and **(C)** *SERPINB7*. The association tests were performed using the Scalable and Accurate Implementation of Generalized software as described in this article's Online Repository at www.jacionline.org. **A,** The conditional association test was completed within chr1:143095936-154952980 to cover all the genome-wide significant AD associations at 1q21.1-1q21.3. The plot shows the association test results as obtained in the original analysis in FinnGen (*top row*), and the results further adjusted for rs558269137 (*second row from top*; chr1:152312600 CACTG>C; frameshift indel p.Ser761CysfsTer36; INFO = 0.91), rs138726443 (*third row from top*; chr1:152307547 G>A; stop gained p.Arg2447Ter; INFO = 0.99), and rs61816761 (*bottom row*; chr1:152313385 G>A; stop gained p.Arg501Ter; INFO = 0.96). **B,** The plot shows the association test results as obtained in the original analysis in FinnGen (*top row*), and the results further adjusted for *DSC1* variant rs200047736 (*bottom row*; chr18:31134724 G>C; missense p.Pro575Arg; INFO = 0.99). **C,** The plot shows the association test results as obtained in the original analysis in FinnGen (*top row*), and the results further adjusted for *SERPINB7* variant rs201208667 (*bottom row*; chr18:63804628 G>A; missense p.Cys379Tyr; INFO = 0.99). *FLG*, Filaggrin.

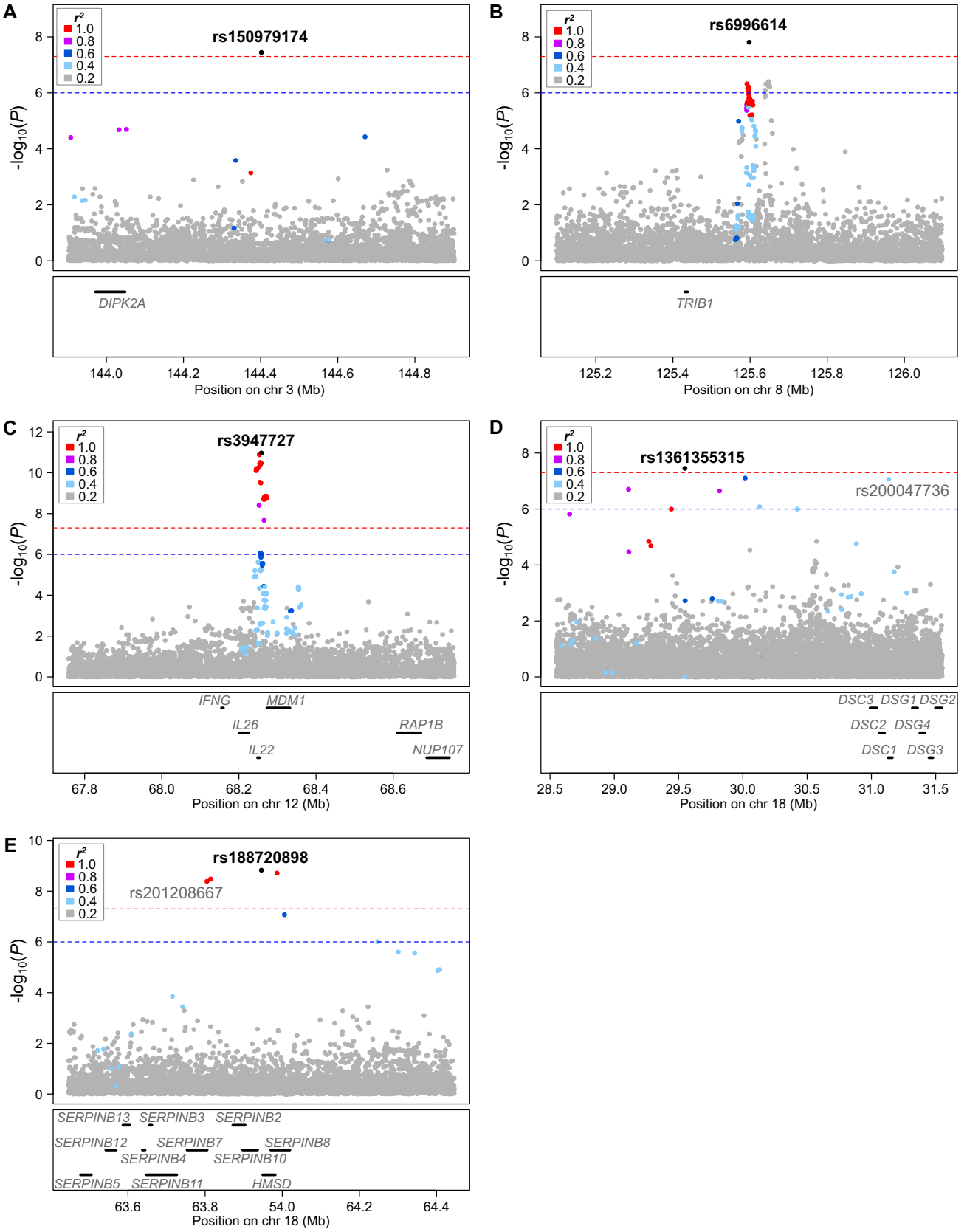

FIG 3. Regional association plots of the novel AD risk loci. The regional association plots are shown for the novel AD associations at (**A**) 3q24, (**B**) 8q24.13, (**C**) 12q15, (**D**) 18q12.1, and (**E**) 18q22.1. The red dashed line corresponds to the threshold of genome-wide significance ($P = 5 \times 10^{-8}$), and the blue dashed line corresponds to $P = 1 \times 10^{-6}$. Black points represent the association lead variants. In Fig 3, *D* and *E*, the missense variants in *DSC1* and *SERPINB7* are indicated (rs200047736 and rs201208667, respectively). Linkage disequilibrium (LD) values are based on FinnGen data.

TABLE II. Estimated consequences of the novel AD risk variants near *IL22/IFNG*, *DSC1*, and *SERPINB7*

Consequences of a regulatory variant near IL-22 and IFNG

Variant	Method	Peak location	Biosample	Targets	Organ	Data set	File	Value	Strand
rs1026788	ChIP-seq	chr12:68651061..68651521	HEK293	ZFHX2	Kidney	ENCSR632SIM	ENCFF170OWD	80.58446	—
rs1026788	ChIP-seq	chr12:68651062..68651492	HEK293	EGR2	Kidney	ENCSR919CZU	ENCFF632ZBP	35.61558	—

Consequences of missense variants in *DSC1* and *SERPINB7*

Variant	Gene	Transcript (strand)	AA	SIFT	PolyPhen	CADD	REVEL	MetaLR	Mutation assessor
rs200047736	ENSG00000134765 HGNC: *DSC1*	ENST00000257197.7 (−) biotype: protein_coding	P/R	Deleterious (0)	Probably damaging (0.998)	Likely benign[5]	Likely disease causing (0.846)	Damaging (0.848)	High (0.974)
rs200047736	ENSG00000134765 HGNC: *DSC1*	ENST00000257198.6 (−) biotype: protein_coding	P/R	Deleterious (0)	Probably damaging (0.998)	Likely benign[5]	Likely disease causing (0.846)	Damaging (0.848)	High (0.974)
rs201208667	ENSG00000166396 HGNC: *SERPINB7*	ENST00000336429.6 (+) biotype: protein_coding	C/Y	Deleterious (0.01)	Probably damaging (0.972)	Likely benign[7]	Likely benign (0.206)	Tolerated (0.068)	Medium (0.554)
rs201208667	ENSG00000166396 HGNC: *SERPINB7*	ENST00000398019.7 (+) biotype: protein_coding	C/Y	Deleterious (0.01)	Probably damaging (0.972)	Likely benign[7]	Likely benign (0.206)	Tolerated (0.068)	Medium (0.554)
rs201208667	ENSG00000166396 HGNC: *SERPINB7*	ENST00000540675.5 (+) biotype: protein_coding	C/Y	Deleterious (0)	Probably damaging (0.931)	Likely benign[7]	Likely benign (0.206)	Tolerated (0.068)	Medium (0.554)
rs201208667	ENSG00000166396 HGNC: *SERPINB7*	ENST00000546027.5 (+) biotype: protein_coding	C/Y	Deleterious (0.01)	Probably damaging (0.972)	Likely benign[7]	Likely benign (0.206)	Tolerated (0.068)	Medium (0.554)

EGR2, Early growth response 2.

Among the variants showing genome-wide significant ($P < 5 \times 10^{-8}$) association with AD at 12q15, the variant rs1026788 showed the highest probability (0.935) of being a regulatory variant[16]; ChIP-seq data for this variant were extracted from RegulomeDB on November 16, 2020. The predicted consequences of the missense variants were extracted from https://www.ensembl.org on November 4, 2020.

providing supportive evidence of the shared genetic pathways in AD and asthma.

Linkage disequilibrium score regression–derived single nucleotide polymorphism (SNP)-based heritability (h^2_{SNP}) estimate for AD was 14.3% in the FinnGen sample but only 5.4% in the meta-analyzed sample. In the present study and previous reports,[3,24] h^2_{SNP} estimates for AD are low compared with heritability estimates obtained in twin studies (exceeding 80%).[2] Others have suggested that reanalysis of a cleaner AD phenotype could potentially improve the estimate.[24] Our data did not support this hypothesis, because the h^2_{SNP} estimates were similar for the 3 different AD case definitions in FinnGen (h^2_{SNP} estimates were 14.3%, 13.2%, and 13.1% for AD, AD strict, and AD reimb, respectively). The low estimates likely arise from the fact that, by definition, h^2_{SNP} estimates are smaller than total heritability, because genotyping methods commonly used in genome-wide association studies tag the causal variants imperfectly.[25] This further suggests that there will be other, rare, genetic variants contributing to AD susceptibility that are yet to be discovered.

Our study has limitations. Differing analytical procedures and varying AD prevalence (due to differences in case recruitment and the efficacy to identify AD cases based on registry data) may have added to the heterogeneity observed in the effect estimates between cohorts. The novel associations near tribbles pseudokinase 1 and *DSC1* are strongly based on findings in FinnGen, and, thus, replication in other populations would be of high value. We were not able to derive statistical evidence for the causal genes in all the loci because relevant information is not available in public data for the rare AD lead variants. Also, the results of *in silico* analyses should be interpreted with caution due to discrepancies in the predictions and the fact that chip-seq data were based on kidney and not skin cells.

To conclude, the missense variants in *DSC1* and *SERPINB7* likely disrupt the proper folding of proteins contributing to the mechanical stability and barrier development in the epidermis. The present findings may offer opportunities for the development of novel treatment strategies for AD in the future.

For detailed methods, please see the Methods section in this article's Online Repository at www.jacionline.org.

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Key messages

- **Study of large-scale biobank data facilitated the discovery of novel risk loci for AD.**
- **Missense mutations with deleterious predictions in *DSC1* and *SERPINB7* likely disrupt proper folding of proteins crucial to the mechanical stability and barrier function of the epidermis.**
- **The newly discovered loci may provide opportunities for developing novel therapies for AD.**

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METHODS

Study populations

The FinnGen research project (www.finngen.fi) was launched in 2017 with an aim to improve human health through genetic research. The project combines genome information with digital health care data from national registries: the genotype data are linked to national hospital discharge, death, cancer, and medication reimbursement registries using the national personal identification numbers. The FinnGen study will combine approximately 200,000 existing samples from Finnish biobanks with approximately 300,000 samples from ongoing collections. Once final, the data resource will cover roughly 10% of the Finnish population. The present study comprised data of 244,544 Finnish adults (8,383 AD cases; 236,161 controls) from FinnGen Preparatory Phase Data Freeze 6.

Patients and control subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, older research cohorts, collected before the start of FinnGen (in August 2017), were collected on the basis of study-specific consents and later transferred to the Finnish biobanks after approval by Fimea, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the FinnGen study (protocol no. HUS/990/2017).

The FinnGen study is approved by the Finnish Institute for Health and Welfare (permit nos. THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019, THL/1524/5.05.00/2020, and THL/2364/14.02/2020), digital and population data service agency (permit nos. VRK43431/2017-3, VRK/6909/2018-3, and VRK/4415/2019-3), the Social Insurance Institution (permit nos. KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 138/522/2019, KELA 2/522/2020, and KELA 16/522/2020), and Statistics Finland (permit nos. TK-53-1041-17 and TK-53-90-20).

The Biobank Access Decisions for FinnGen samples and data used in FinnGen Data Freeze 6 include THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, Auria Biobank AB17-5154, Biobank Borealis of Northern Finland_2017_1013, Biobank of Eastern Finland 1186/2018, Finnish Clinical Biobank Tampere MH0004, Central Finland Biobank 1-2017, and Terveystalo Biobank STB 2018001.

The Estonian Biobank cohort is a volunteer-based sample of the Estonian resident adult population (age ≥ 18 years). Estonians represent 83%, Russians 14%, and other nationalities 3% of all participants. The current number of participants is close to 200,000 and represents more than 15% of the Estonian adult population. General practitioners and medical personnel in the special recruitment offices have recruited participants throughout the country. At baseline, the general practitioners performed a standardized health examination of the participants, who also donated blood samples for DNA, white blood cells, and plasma tests and filled out a 16-module questionnaire on health-related topics such as lifestyle, diet, and clinical diagnoses described in World Health Organization *International Classification of Diseases, Tenth Revision* (*ICD-10*). A significant part of the cohort has whole-genome sequencing (3,000), whole-exome sequencing (2,500), genome-wide SNP array data (200,000), and/or NMR metabolome data (11,000) available. The data are continuously updated through periodical linking to national electronic databases and registries. A part of the cohort has been recontacted for follow-up purposes and resampling, and targeted invitations are possible for specific purposes, for example, people with a specific diagnosis. For the current AD genome-wide association study (GWAS), data from 136,724 participants (11,187 AD cases; 125,537 controls) were analyzed.

The UK Biobank recruited hundreds of thousands of individuals aged between 40 and 69 years across the United Kingdom during the period 2006 to 2010. These individuals' genotype data have been paired to electronic health records and survey measures. In this study, AD GWAS results, as reported in the Pan-UKB project[E1] (pan.ukbb.broadinstitute.org), comprising data from 2,904 AD cases and 412,489 controls with European ancestry, were included in the meta-analysis.

Phenotype descriptions

In FinnGen, cases were required to have an entry of *ICD-10* code L20, *International Classification of Diseases, Ninth Revision* (*ICD-9*) code 6918, or *International Classification of Diseases, Eighth Revision* (*ICD-8*) code 691 in the Hospital Discharge Registry, cause of death registry, or Finnish Social Insurance Institution (KELA) registry. Patients with *ICD-9* code 6918X were excluded. Individuals with no record of *ICD-10* code L20, *ICD-9* code 6918, or *ICD-8* code 691 were considered as controls. In the Estonian Biobank and the UK Biobank, participants with *ICD-10* code L20 were considered as AD cases and participants with no record of *ICD-10* code L20 were deemed as controls.

Because the AD case definition based on *ICD-10* code L20, *ICD-9* code 6918, or *ICD-8* code 691 has slight heterogeneity (eg, *ICD-8* code 691 covers also 6910A [nappy rash], 6918A [eczema infantum], and 691C [constitution atopica]), we performed sensitivity analyses in FinnGen using 2 stricter phenotype definitions: here, cases were required to have an entry of (1) *ICD-10* code L20.0, *ICD-9* code 6918B, or *ICD-8* code 69100 ("AD strict"), or (2) KELA reimbursement codes 134 (erythrodermia exfoliativa universalis), 395 (dupilumab), or 317 (topical calcineurin inhibitors) ("AD reimb"). According to the "AD strict" definition, the numbers of cases were 6,412 and controls 253,666, whereas the numbers of cases and controls according to the "AD reimb" definition were 6,739 and 236,030, respectively.

Genotyping, imputation, and quality control

In FinnGen, genotyping of the samples was performed using Illumina and Affymetrix arrays (Illumina Inc, San Diego, and Thermo Fisher Scientific, Santa Clara, Calif). Sample quality control (QC) was performed to exclude individuals with high genotype missingness (>5%), ambiguous sex, excess heterozygosity (±4 SD), and non-Finnish ancestry. Regarding variant QC, all variants with low Hardy-Weinberg equilibrium P value ($<1 \times 10^{-6}$), high missingness (>2%), and minor allele count less than 3 were excluded. Chip-genotyped samples were prephased with Eagle 2.3.5, with the number of conditioning haplotypes set to 20,000. Genotype imputation was carried out by using the Finnish population-specific SISu v3 reference panel with Beagle 4.1 (version 08Jun17.d8b) as described in the following protocol: dx.doi.org/10.17504/protocols.io.nmndc5e. In postimputation QC, variants with imputation INFO less than 0.6 were excluded.

Genotyping of the samples from the Estonian Biobank was conducted in the Core Genotyping Lab of the Institute of Genomics, University of Tartu, using the following Illumina (Illumina Inc, San Diego, Calif) arrays: GSAMD-24v1, GSAMD-24v2, ESTchip-1_GSAv2-MD, and ESTchip-2_GSAv3-MD. As above, in sample QC, individuals with high missingness (>5%) or ambiguous sex were excluded. In variant QC, variants with call rate less than 95% were excluded as well as the variants with low Hardy-Weinberg equilibrium P value ($<1 \times 10^{-4}$). Samples were prephased with Eagle v2.3, with the number of conditioning haplotypes set to 20,000, and genotype imputation was carried out with Beagle v.28Sep18.793 using an Estonian-specific reference panel.[E2] Before imputation, variants with minor allele frequency less than 1% and indels were removed.

In the UK Biobank, imputed variants from the UK Biobank version 3 were analyzed and variants with INFO scores more than 0.8 were retained.[E1]

GWAS and meta-analysis

In all the study populations, GWAS was completed using the Scalable and Accurate Implementation of Generalized software.[E3] In FinnGen and the Estonian Biobank, the association models were adjusted for age, sex, and the first 10 genetic principal components (and additionally for genotyping batch in FinnGen); here, only those variants with minimum allele count of 5 were included in the analysis. In the UK Biobank, the models were adjusted for age, sex, Age × Sex, age^2, Age^2 × Sex, and the first 10 genetic principal components, and variants with an allele count of at least 20 were retained.[E1]

METAL software[E4] was used to perform fixed-effect inverse variance–weighted meta-analysis of the summary statistics obtained from FinnGen, the Estonian Biobank, and the UK Biobank. Statistical significance

was considered at the standard genome-wide significance level ($P < 5 \times 10^{-8}$). Genomic inflation factor of the meta-analyzed results was estimated using an automated LD score (LDSC) regression pipeline.[E5]

Conditional analyses

Conditional analyses in FinnGen data were conducted to evaluate (1) whether 1p21.1-1p21.3 harbors multiple association signals independent of the coding variants in *FLG*, and (2) whether the missense variants in *DSC1* and *SERPINB7* explain the AD associations at 18q12.1 and 18q22.1, respectively.

The association tests were repeated within a large region at chromosome 1 (chr1:143095936-154952980) to cover all the genome-wide significant associations at 1q21.1-1q21.3. Here, the association models were further adjusted for rs558269137, the AD association lead variant (a frameshift indel in *FLG*), and subsequently for rs138726443 and rs61816761 (stop gain variants in *FLG*) until there were no genome-wide significant associations in this locus.

The conditional tests near *DCS1* and *SERPINB7* were conducted within a 2-Mb window around the missense variants. The association models were further adjusted for rs200047736 in *DSC1* locus and for rs201208667 in *SERPINB7* locus.

Characterization of association signals

All genes within ±1-Mb window from the association lead variant were annotated to identify the potential candidate gene(s) in each locus: databases provided by GenBank[E6] and UniProt[E7] were explored to determine the functions of the genes, and genes having their biological function most likely related to the pathogenesis of AD were prioritized. To complement the information available in these databases, a broad literature search was performed to inspect previous work published regarding the genes of interest. To provide statistical evidence for the most likely causal gene in each locus, we applied the Data-driven Expression Prioritized Integration for Complex Trait framework[E8] as implemented in the Complex-Traits Genetics Virtual Lab[E9] on the meta-analyzed summary statistics. The Data-driven Expression Prioritized Integration for Complex Trait framework uses coregulation of gene expression in conjunction with previously annotated gene sets to predict gene function on the basis of a "guilt-by-association" procedure[E8]; it can be used to prioritize the most likely causal genes, investigate enriched pathways, and identify cell or tissue types where genes from the associated loci are highly expressed.

In addition, we used FUMA, a web-based platform combining information from multiple resources to facilitate functional annotation of GWAS results,[E10] to perform functional gene mapping and gene-based association and enrichment tests. FUMA identifies variants showing genome-wide significant association ($P < 5 \times 10^{-8}$) with the study trait and, among the significant variants, identifies variants in low linkage disequilibrium ($r^2 < 0.6$) as "independent significant variants," and further identifies variants in linkage disequilibrium ($r^2 > 0.6$) with the independent significant variants; ANNOVAR[E11] annotations are performed for all these variants to obtain information on the functional consequences of the key variants. FUMA uses MAGMA[E12] to perform gene-based association testing and gene-set enrichment analyses: gene-based *P* value is computed for protein-coding genes by mapping variants to genes, and subsequent enrichment analyses are performed for the significant genes using 4728 curated gene sets and 6166 Gene Ontology (GO) terms as reported in MsigDB.[E10]

We further used RegulomeDB[E13] to discover regulatory elements overlapping with the intergenic variants in the novel loci showing genome-wide significant association with AD risk.

Compared with intergenic variants, coding variants with functional consequences are more likely to have phenotypic effects,[E14] and, therefore, such variants were prioritized when determining the potential candidate genes and association-driving variants within each locus. The structural effects of the missense variants in the *DSC1* and *SERPINB7* loci were analyzed with HOPE.[E15] and *in silico* algorithms, including SIFT,[E16] PolyPhen,[E17] CADD,[E18] REVEL,[E19] MetaLR,[E20] and Mutation Assessor,[E21] were used to predict deleteriousness of the missense variants.

SNP-based heritability and LDSC regression

LDSC regression is a method that enables estimation of SNP-based heritability (h^2_{SNP}) of complex traits and the genetic correlation between different phenotypes using GWAS summary statistics.[E5] We used LDSC software[E22] to estimate h^2_{SNP} for AD. Here, h^2_{SNP} was estimated on liability scale using population prevalence (–pop-prev) 0.15 as done previously[E23] and sample prevalence (–samp-prev) 0.028 in the meta-analyzed sample and 0.034, 0.025, and 0.028 in FinnGen samples with standard, AD strict, and AD reimb case definitions, respectively.

We used LD Hub,[E5] a web interface for performing automated LDSC regression, to estimate genetic correlation of AD with other phenotypes. To avoid bias from variants with disproportionately large effect sizes, variants within the *FLG* locus (±1 Mb from the association lead variant) as well as within the major histocompatibility complex region were excluded from the analyses.[E5] We analyzed all traits available in the LD Hub database, and, thus, statistical significance was considered at $P < 6 \times 10^{-5}$ to correct for 830 traits analyzed.

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