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

FinnGen

2022-03

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

Eeva Sliz, PhD,[a,b] Laura Huilaja, MD, PhD,[c,d] Anu Pasanen, PhD,[c,d,e,f] Triin Laisk, PhD,[g] Ene Reimann, PhD,[g] Reedik Mägi, PhD,[g] FinnGen,* and Estonian Biobank Research Team,‡ Katariina Hannula-Jouppi, MD, PhD,[h,i,j,k] Sirkku Peltonen, MD, PhD,[l,m,n,o] Teea Salmi, MD, PhD,[p,q] Leena Koulu, MD, PhD,[l,m] Kaisa Tasanen, MD, PhD,[c,d§] and Johannes Kettunen, PhD[a,b§]   *Oulu, Helsinki, Turku, and Tampere, Finland; Tartu, Estonia; and Gothenburg, Sweden*

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 2022;149:1105-12.)

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

---

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

---

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.

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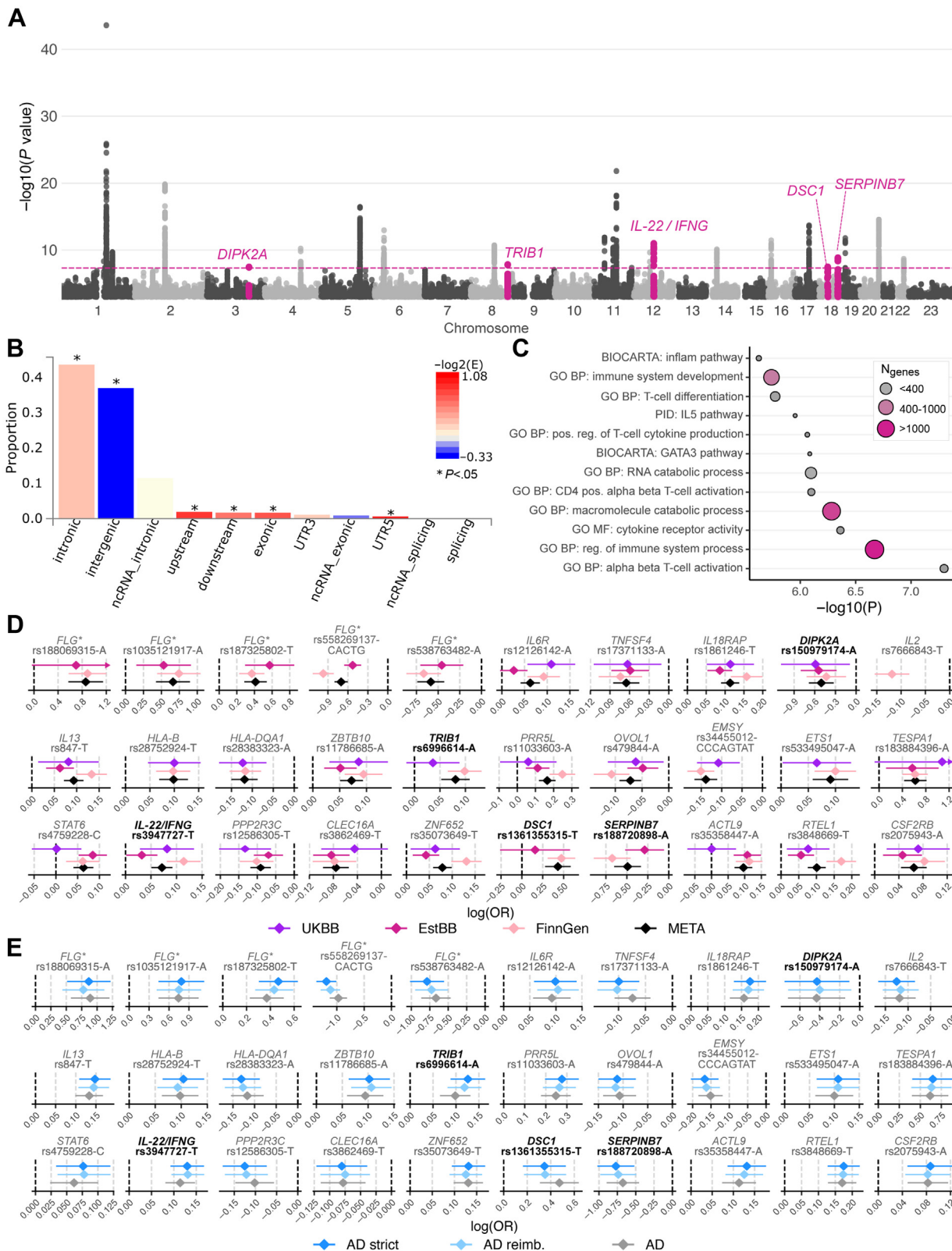
TABLE I. Loci associated with AD in 796,661 Europeans

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	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 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 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]

---

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.
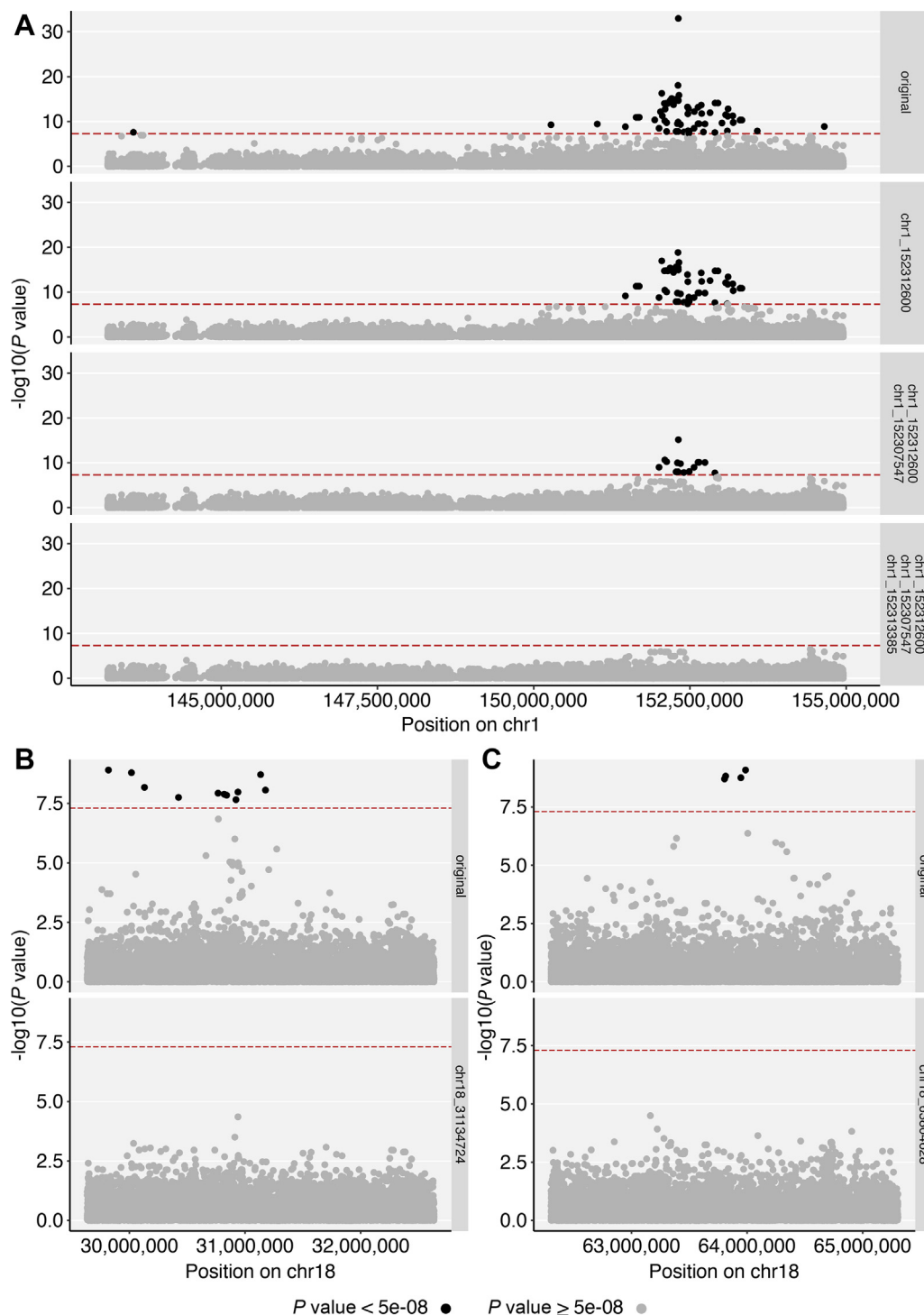
FIG 2. Conditional analyses on AD association near **(A)** *FLG*, **(B)** *DSC1*, and **(C)** *SERPINB7*. The association tests were performed using the Scalable and Accurate Implementation of Generalized software as described in this article's Online Repository at www.jacionline.org. **A,** The conditional 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.
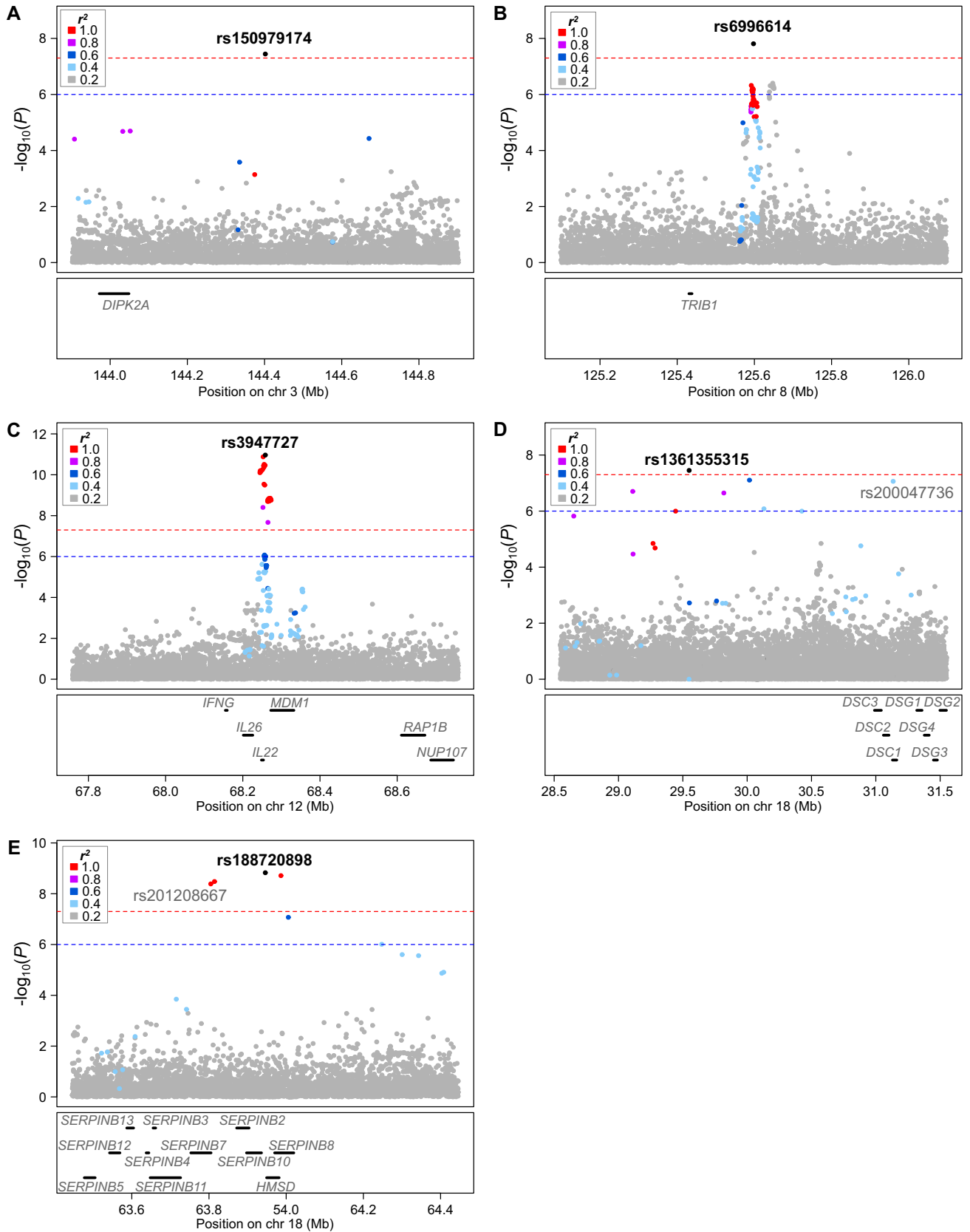
FIG 3. Regional association plots of the novel AD risk loci. The regional association plots are shown for the novel AD associations at (**A**) 3q24, (**B**) 8q24.13, (**C**) 12q15, (**D**) 18q12.1, and (**E**) 18q22.1. The red dashed line corresponds to the threshold of genome-wide significance ($P = 5 \times 10^{-8}$), 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.

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, 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.

biopankkitoiminta), and Terveystalo Biobank (www.terveystalo.com/fi/
Yritystietoa/Terveystalo-Biopankki/Biopankki/). All Finnish biobanks
are members of BBMRI.fi infrastructure (www.bbmri.fi) and FinBB
(https://finbb.fi/).

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.**

REFERENCES

1. Weidinger S, Novak N. Atopic dermatitis. Lancet 2016;387:1109-22.
2. Bataille V, Lens M, Spector TD. The use of the twin model to investigate the genetics and epigenetics of skin diseases with genomic, transcriptomic and methylation data. J Eur Acad Dermatology Venereol 2012;26:1067-73.
3. 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.
4. Kichaev G, Bhatia G, Loh PR, Gazal S, Burch K, Freund MK, et al. Leveraging polygenic functional enrichment to improve GWAS power. Am J Hum Genet 2019;104:65-75.
5. Johansson Å, Rask-Andersen M, Karlsson T, Ek WE. Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema. Hum Mol Genet 2019;28:4022-41.
6. Ellinghaus D, Baurecht H, Esparza-gordillo J, Rodríguez E, Marenholz I, Hübner N, et al. High density genotyping study identifies four new susceptibility loci for atopic dermatitis. Nat Genet 2013;45:808-12.
7. Marenholz I, Esparza-Gordillo J, Rüschendorf F, Bauerfeind A, Strachan DP, Spycher BD, et al. Meta-analysis identifies seven susceptibility loci involved in the atopic march. Nat Commun 2015;6:8804.
8. Pers TH, Karjalainen JM, Chan Y, Westra HJ, Wood AR, Yang J, et al. Biological interpretation of genome-wide association studies using predicted gene functions. Nat Commun 2015;6:5890.
9. Beigi F, Schmeckpeper J, Pow-Anpongkul P, Payne JA, Zhang L, Zhang Z, et al. C3orf58, a novel paracrine protein, stimulates cardiomyocyte cell-cycle progression through the PI3K-AKT-CDK7 pathway. Circ Res 2013;113:372-80.
10. Pradhan D, Jour G, Milton D, Vasudevaraja V, Tetzlaff MT, Nagarajan P, et al. Aberrant DNA methylation predicts melanoma-specific survival in patients with acral melanoma. Cancers (Basel) 2019;11:1-18.
11. Bateman A. UniProt: a worldwide hub of protein knowledge. Nucleic Acids Res 2019;47:D506-15.
12. Wolk K, Witte E, Witte K, Warszawska K, Sabat R. Biology of interleukin-22. Semin Immunopathol 2010;32:17-31.
13. Clark K, Karsch-Mizrachi I, Lipman DJ, Ostell J, Sayers EW. GenBank. Nucleic Acids Res 2016;44:D67-72.
14. Fukaya T, Fukui T, Uto T, Takagi H, Nasu J, Miyanaga N, et al. Pivotal role of IL-22 binding protein in the epithelial autoregulation of interleukin-22 signaling in the control of skin inflammation. Front Immunol 2018;9:1-13.
15. Feingold KR. The adverse effect of IFN gamma on stratum corneum structure and function in psoriasis and atopic dermatitis. J Invest Dermatol 2014;134:597-600.
16. 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.
17. Cai XY, Cheng L, Yu CX, Wu YY, Fang L, Zheng XD, et al. GWAS follow-up study discovers a novel genetic signal on 10q21.2 for atopic dermatitis in Chinese Han population. Front Genet 2019;10:1-8.
18. Venselaar H, te Beek TAH, Kuipers RKP, Hekkelman ML, Vriend G. Protein structure analysis of mutations causing inheritable diseases. An e-Science approach with life scientist friendly interfaces. BMC Bioinformatics 2010;11:548.
19. Chidgey M, Brakebusch C, Gustafsson E, Cruchley A, Hail C, Kirk S, et al. Mice lacking desmocollin 1 show epidermal fragility accompanied by barrier defects and abnormal differentiation. J Cell Biol 2001;155:821-32.
20. Pigors M, Sarig O, Heinz L, Plagnol V, Fischer J, Mohamad J, et al. Loss-of-function mutations in SERPINB8 linked to exfoliative ichthyosis with impaired mechanical stability of intercellular adhesions. Am J Hum Genet 2016;99:430-6.
21. Kubo A, Shiohama A, Sasaki T, Nakabayashi K, Kawasaki H, Atsugi T, et al. Mutations in SERPINB7, encoding a member of the serine protease inhibitor superfamily, cause Nagashima-type palmoplantar keratosis. Am J Hum Genet 2013;93:945-56.
22. Hannula-Jouppi K, Harjama L, Einarsdottir E, Elomaa O, Kettunen K, Saarela J, et al. Nagashima-type palmoplantar keratosis in Finland caused by a SERPINB7 founder mutation. J Am Acad Dermatol 2020;83:643-5.
23. 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.
24. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics 2017;33:272-9.
25. Yang J, Zeng J, Goddard ME, Wray NR, Visscher PM. Concepts, estimation and interpretation of SNP-based heritability. Nat Genet 2017;49:1304-10.

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 (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, age², Age² × 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.

CONTRIBUTORS OF FINNGEN
Steering Committee

Aarno Palotie   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mark Daly   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Pharmaceutical companies

Bridget Riley-Gills   Abbvie, Chicago, Ill

Howard Jacob   Abbvie, Chicago, Ill

Dirk Paul   Astra Zeneca, Cambridge, United Kingdom

Heiko Runz   Biogen, Cambridge, Mass

Sally John   Biogen, Cambridge, Mass

Robert Plenge   Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Mark McCarthy   Genentech, San Francisco, Calif

Julie Hunkapiller   Genentech, San Francisco, Calif

Meg Ehm   GlaxoSmithKline, Brentford, United Kingdom

Caroline Fox   Merck, Kenilworth, NJ

Anders Mälarstig   Pfizer, New York, NY

Katherine Klinger   Sanofi, Paris, France

Katherine Call   Sanofi, Paris, France

Tim Behrens   Maze Therapeutics, San Francisco, Calif

Robert Yang   Janssen Biotech, Beerse, Belgium

Richard Siegel   Novartis, Basel, Switzerland

University of Helsinki and Biobanks

Tomi Mäkelä   HiLIFE, University of Helsinki, Helsinki, Finland

Jaakko Kaprio   Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland

Petri Virolainen   Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland

Antti Hakanen   Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland

Terhi Kilpi   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Markus Perola   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Jukka Partanen   Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland

Anne Pitkäranta   Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Juhani Junttila Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland

Raisa Serpi Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland

Tarja Laitinen Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland

Johanna Mäkelä Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland

Veli-Matti Kosma Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland

Urho Kujala Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland

Other experts/nonvoting members

Outi Tuovila Business Finland, Helsinki, Finland
Raimo Pakkanen Business Finland, Helsinki, Finland

Scientific Committee

Pharmaceutical companies. Jeffrey Waring Abbvie, Chicago, Ill

Ali Abbasi Abbvie, Chicago, Ill

Mengzhen Liu Abbvie, Chicago, Ill

Ioanna Tachmazidou Astra Zeneca, Cambridge, United Kingdom

Chia-Yen Chen Biogen, Cambridge, Mass

Heiko Runz Biogen, Cambridge, Mass

Shameek Biswas Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Julie Hunkapiller Genentech, San Francisco, Calif

Meg Ehm GlaxoSmithKline, Brentford, United Kingdom

Neha Raghavan Merck, Kenilworth, NJ

Aparna Chhibber Merck, Kenilworth, NJ

Anders Mälarstig Pfizer, New York, NY

Xinli Hu Pfizer, New York, NY

Katherine Call Sanofi, Paris, France

Katherine Klinger Sanofi, Paris, France

Matthias Gossel Sanofi, Paris, France

Robert Graham Maze Therapeutics, San Francisco, Calif

Tim Behrens Maze Therapeutics, San Francisco, Calif

Beryl Cummings Maze Therapeutics, San Francisco, Calif

Wilco Fleuren Janssen Biotech, Beerse, Belgium

Dawn Waterworth Janssen Biotech, Beerse, Belgium

Nicole Renaud Novartis, Basel, Switzerland

Aviv Madar Novartis, Basel, Switzerland

Maen Obeidat Novartis, Basel, Switzerland

University of Helsinki and Biobanks. Samuli Ripatti Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland

Johanna Schleutker Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland

Markus Perola THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Mikko Arvas Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland

Olli Carpén Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Reetta Hinttala Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland

Johannes Kettunen Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland

Johanna Mäkelä Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland

Arto Mannermaa Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland

Jari Laukkanen Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland

Urho Kujala Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland

Clinical groups

Neurology Group. Reetta Kälviäinen Northern Savo Hospital District, Kuopio, Finland

Valtteri Julkunen Northern Savo Hospital District, Kuopio, Finland

Hilkka Soininen Northern Savo Hospital District, Kuopio, Finland

Anne Remes Northern Ostrobothnia Hospital District, Oulu, Finland

Mikko Hiltunen Northern Savo Hospital District, Kuopio, Finland

Jukka Peltola Pirkanmaa Hospital District, Tampere, Finland

Pentti Tienari Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Juha Rinne Hospital District of Southwest Finland, Turku, Finland

Roosa Kallionpää Hospital District of Southwest Finland, Turku, Finland

Ali Abbasi Abbvie, Chicago, Ill

Adam Ziemann Abbvie, Chicago, Ill

Jeffrey Waring Abbvie, Chicago, Ill

Sahar Esmaeeli Abbvie, Chicago, Ill

Nizar Smaoui Abbvie, Chicago, Ill

Anne Lehtonen Abbvie, Chicago, Ill

Susan Eaton Biogen, Cambridge, Mass

Heiko Runz Biogen, Cambridge, Mass

Sanni Lahdenperä Biogen, Cambridge, Mass

Janet van Adelsberg Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Shameek Biswas Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Julie Hunkapiller Genentech, San Francisco, Calif

Natalie Bowers Genentech, San Francisco, Calif

Edmond Teng Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Onuralp Soylemez Merck, Kenilworth, NJ

Kari Linden Pfizer, New York, NY

Fanli Xu GlaxoSmithKline, Brentford, United Kingdom

David Pulford GlaxoSmithKline, Brentford, United Kingdom

Kirsi Auro GlaxoSmithKline, Brentford, United Kingdom

Laura Addis GlaxoSmithKline, Brentford, United Kingdom

John Eicher GlaxoSmithKline, Brentford, United Kingdom

Minna Raivio Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Sarah Pendergrass Genentech, San Francisco, Calif

Beryl Cummings Maze Therapeutics, San Francisco, Calif

Juulia Partanen Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Gastroenterology Group. Martti Färkkilä Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Jukka Koskela Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Sampsa Pikkarainen Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Airi Jussila Pirkanmaa Hospital District, Tampere, Finland

Katri Kaukinen Pirkanmaa Hospital District, Tampere, Finland

Timo Blomster Northern Ostrobothnia Hospital District, Oulu, Finland

Mikko Kiviniemi Northern Savo Hospital District, Kuopio, Finland

Markku Voutilainen Hospital District of Southwest Finland, Turku, Finland

Ali Abbasi Abbvie, Chicago, Ill

Graham Heap Abbvie, Chicago, Ill

Jeffrey Waring Abbvie, Chicago, Ill

Nizar Smaoui Abbvie, Chicago, Ill

Fedik Rahimov Abbvie, Chicago, Ill

Anne Lehtonen Abbvie, Chicago, Ill

Keith Usiskin Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Tim Lu Genentech, San Francisco, Calif

Natalie Bowers Genentech, San Francisco, Calif

Danny Oh Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Kirsi Kalpala Pfizer, New York, NY

Melissa Miller Pfizer, New York, NY

Xinli Hu Pfizer, New York, NY

Linda McCarthy GlaxoSmithKline, Brentford, United Kingdom

Onuralp Soylemez Merck, Kenilworth, NJ

Mark Daly Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Rheumatology Group. Kari Eklund Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Antti Palomäki Hospital District of Southwest Finland, Turku, Finland

Pia Isomäki Pirkanmaa Hospital District, Tampere, Finland

Laura Pirilä Hospital District of Southwest Finland, Turku, Finland

Oili Kaipiainen-Seppänen Northern Savo Hospital District, Kuopio, Finland

Johanna Huhtakangas Northern Ostrobothnia Hospital District, Oulu, Finland

Ali Abbasi Abbvie, Chicago, Ill

Jeffrey Waring Abbvie, Chicago, Ill

Fedik Rahimov Abbvie, Chicago, Ill

Apinya Lertratanakul Abbvie, Chicago, Ill

Nizar Smaoui Abbvie, Chicago, Ill

Anne Lehtonen Abbvie, Chicago, Ill

David Close Astra Zeneca, Cambridge, United Kingdom

Marla Hochfeld Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Natalie Bowers Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Onuralp Soylemez Merck, Kenilworth, NJ

Kirsi Kalpala Pfizer, New York, NY

Nan Bing Pfizer, New York, NY

Xinli Hu Pfizer, New York, NY

Jorge Esparza Gordillo GlaxoSmithKline, Brentford, United Kingdom

Kirsi Auro GlaxoSmithKline, Brentford, United Kingdom

Dawn Waterworth Janssen Biotech, Beerse, Belgium

Nina Mars Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland

Pulmonology Group. Tarja Laitinen Pirkanmaa Hospital District, Tampere, Finland

Margit Pelkonen Northern Savo Hospital District, Kuopio, Finland

Paula Kauppi Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Hannu Kankaanranta Pirkanmaa Hospital District, Tampere, Finland

Terttu Harju Northern Ostrobothnia Hospital District, Oulu, Finland

Riitta Lahesmaa Hospital District of Southwest Finland, Turku, Finland

Nizar Smaoui Abbvie, Chicago, Ill

Alex Mackay Astra Zeneca, Cambridge, United Kingdom

Glenda Lassi Astra Zeneca, Cambridge, United Kingdom

Susan Eaton Biogen, Cambridge, Mass

Steven Greenberg Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Hubert Chen Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Natalie Bowers Genentech, San Francisco, Calif

Joanna Betts GlaxoSmithKline, Brentford, United Kingdom

Soumitra Ghosh GlaxoSmithKline, Brentford, United Kingdom

Kirsi Auro GlaxoSmithKline, Brentford, United Kingdom

Rajashree Mishra GlaxoSmithKline, Brentford, United Kingdom

Sina Rüeger Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Cardiometabolic Diseases Group. Teemu Niiranen The National Institute of Health and Welfare, Helsinki, Finland

Felix Vaura The National Institute of Health and Welfare, Helsinki, Finland

Veikko Salomaa The National Institute of Health and Welfare, Helsinki, Finland

Markus Juonala Hospital District of Southwest Finland, Turku, Finland

Kaj Metsärinne Hospital District of Southwest Finland, Turku, Finland

Mika Kähönen Pirkanmaa Hospital District, Tampere, Finland

Juhani Junttila Northern Ostrobothnia Hospital District, Oulu, Finland

Markku Laakso Northern Savo Hospital District, Kuopio, Finland

Jussi Pihlajamäki Northern Savo Hospital District, Kuopio, Finland

Daniel Gordin Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Juha Sinisalo Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Marja-Riitta Taskinen Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Tiinamaija Tuomi Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Jari Laukkanen Central Finland Health Care District, Jyväskylä, Finland

Benjamin Challis Astra Zeneca, Cambridge, United Kingdom

Dirk Paul Astra Zeneca, Cambridge, United Kingdom

Julie Hunkapiller Genentech, San Francisco, Calif

Natalie Bowers Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Onuralp Soylemez Merck, Kenilworth, NJ

Jaakko Parkkinen Pfizer, New York, NY

Melissa Miller Pfizer, New York, NY

Russell Miller Pfizer, New York, NY

Audrey Chu GlaxoSmithKline, Brentford, United Kingdom

Kirsi Auro GlaxoSmithKline, Brentford, United Kingdom

Keith Usiskin Celgene, Summit, NJ, United States / Bristol Myers Squibb, New York, NY

Amanda Elliott Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Joel Rämö Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Samuli Ripatti Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mary Pat Reeve Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Sanni Ruotsalainen Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Oncology Group. Tuomo Meretoja Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Heikki Joensuu Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Olli Carpén Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Lauri Aaltonen Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Johanna Mattson Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Annika Auranen Pirkanmaa Hospital District, Tampere, Finland

Peeter Karihtala Northern Ostrobothnia Hospital District, Oulu, Finland

Saila Kauppila Northern Ostrobothnia Hospital District, Oulu, Finland

Päivi Auvinen Northern Savo Hospital District, Kuopio, Finland

Klaus Elenius Hospital District of Southwest Finland, Turku, Finland

Johanna Schleutker Hospital District of Southwest Finland, Turku, Finland

Relja Popovic Abbvie, Chicago, Ill

Jeffrey Waring Abbvie, Chicago, Ill

Bridget Riley-Gillis Abbvie, Chicago, Ill

Anne Lehtonen Abbvie, Chicago, Ill

Jennifer Schutzman Genentech, San Francisco, Calif

Julie Hunkapiller Genentech, San Francisco, Calif

Natalie Bowers Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Andrey Loboda Merck, Kenilworth, NJ

Aparna Chhibber Merck, Kenilworth, NJ

Heli Lehtonen Pfizer, New York, NY

Stefan McDonough Pfizer, New York, NY

Marika Crohns Sanofi, Paris, France

Sauli Vuoti Sanofi, Paris, France

Diptee Kulkarni GlaxoSmithKline, Brentford, United Kingdom

Kirsi Auro GlaxoSmithKline, Brentford, United Kingdom

Esa Pitkänen Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Nina Mars Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mark Daly Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Opthalmology Group. Kai Kaarniranta Northern Savo Hospital District, Kuopio, Finland

Joni A. Turunen Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Terhi Ollila Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Sanna Seitsonen Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Hannu Uusitalo Pirkanmaa Hospital District, Tampere, Finland

Vesa Aaltonen Hospital District of Southwest Finland, Turku, Finland

Hannele Uusitalo-Järvinen Pirkanmaa Hospital District, Tampere, Finland

Marja Luodonpää Northern Ostrobothnia Hospital District, Oulu, Finland

Nina Hautala Northern Ostrobothnia Hospital District, Oulu, Finland

Mengzhen Liu Abbvie, Chicago, Ill

Heiko Runz Biogen, Cambridge, Mass

Stephanie Loomis Biogen, Cambridge, Mass

Erich Strauss Genentech, San Francisco, Calif

Natalie Bowers Genentech, San Francisco, Calif

Hao Chen Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Anna Podgornaia Merck, Kenilworth, NJ

Juha Karjalainen Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Esa Pitkänen Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Dermatology Group. Kaisa Tasanen Northern Ostrobothnia Hospital District, Oulu, Finland

Laura Huilaja Northern Ostrobothnia Hospital District, Oulu, Finland

Katariina Hannula-Jouppi Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Teea Salmi Pirkanmaa Hospital District, Tampere, Finland

Sirkku Peltonen Hospital District of Southwest Finland, Turku, Finland

Leena Koulu Hospital District of Southwest Finland, Turku, Finland

Kirsi Kalpala Pfizer, New York, NY

Ying Wu Pfizer, New York, NY

David Choy Genentech, San Francisco, Calif

Sarah Pendergrass Genentech, San Francisco, Calif

Nizar Smaoui Abbvie, Chicago, Ill

Fedik Rahimov Abbvie, Chicago, Ill

Anne Lehtonen   Abbvie, Chicago, Ill

Dawn Waterworth   Janssen Biotech, Beerse, Belgium

Odontology Group. Pirkko Pussinen   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Aino Salminen   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Tuula Salo   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

David Rice   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Pekka Nieminen   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Ulla Palotie   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Juha Sinisalo   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Maria Siponen   Northern Savo Hospital District, Kuopio, Finland

Liisa Suominen   Northern Savo Hospital District, Kuopio, Finland

Päivi Mäntylä   Northern Savo Hospital District, Kuopio, Finland

Ulvi Gursoy   Hospital District of Southwest Finland, Turku, Finland

Vuokko Anttonen   Northern Ostrobothnia Hospital District, Oulu, Finland

Kirsi Sipilä   Northern Ostrobothnia Hospital District, Oulu, Finland

Sarah Pendergrass   Genentech, San Francisco, Calif

Women's Health and Reproduction Group. Hannele Laivuori   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Venla Kurra Pirkanmaa   Hospital District, Tampere, Finland

Oskari Heikinheimo   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Ilkka Kalliala   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Laura Kotaniemi-Talonen   Pirkanmaa Hospital District, Tampere, Finland

Kari Nieminen   Pirkanmaa Hospital District, Tampere, Finland

Päivi Polo   Hospital District of Southwest Finland, Turku, Finland

Kaarin Mäkikallio   Hospital District of Southwest Finland, Turku, Finland

Eeva Ekholm   Hospital District of Southwest Finland, Turku, Finland

Marja Vääräsmäki   Northern Ostrobothnia Hospital District, Oulu, Finland

Outi Uimari   Northern Ostrobothnia Hospital District, Oulu, Finland

Laure Morin-Papunen   Northern Ostrobothnia Hospital District, Oulu, Finland

Marjo Tuppurainen   Northern Savo Hospital District, Kuopio, Finland

Katja Kivinen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Elisabeth Widen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Taru Tukiainen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mary Pat Reeve   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mark Daly   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Liu Aoxing   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Eija Laakkonen   University of Jyväskylä, Jyväskylä, Finland

Niko Välimäki   University of Helsinki, Helsinki, Finland

Lauri Aaltonen   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Johannes Kettunen   Northern Ostrobothnia Hospital District, Oulu, Finland

Mikko Arvas   Finnish Red Cross Blood Service, Helsinki, Finland

Jeffrey Waring   Abbvie, Chicago, Ill

Bridget Riley-Gillis   Abbvie, Chicago, Ill

Mengzhen Liu   Abbvie, Chicago, Ill

Janet Kumar   GlaxoSmithKline, Brentford, United Kingdom

Kirsi Auro   GlaxoSmithKline, Brentford, United Kingdom

Andrea Ganna   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Sarah Pendergrass   Genentech, San Francisco, Calif

FinnGen Analysis Working Group

Justin Wade Davis   Abbvie, Chicago, Ill

Bridget Riley-Gillis   Abbvie, Chicago, Ill

Danjuma Quarless   Abbvie, Chicago, Ill

Fedik Rahimov   Abbvie, Chicago, Ill

Sahar Esmaeeli   Abbvie, Chicago, Ill

Slavé Petrovski   Astra Zeneca, Cambridge, United Kingdom

Eleonor Wigmore   Astra Zeneca, Cambridge, United Kingdom

Adele Mitchell   Biogen, Cambridge, Mass

Benjamin Sun   Biogen, Cambridge, Mass

Ellen Tsai   Biogen, Cambridge, Mass

Denis Baird   Biogen, Cambridge, Mass

Paola Bronson   Biogen, Cambridge, Mass

Ruoyu Tian   Biogen, Cambridge, Mass

Stephanie Loomis   Biogen, Cambridge, Mass

Yunfeng Huang   Biogen, Cambridge, Mass

Joseph Maranville   Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Shameek Biswas   Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Elmutaz Mohammed   Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Samir Wadhawan   Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Erika Kvikstad   Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Minal Caliskan   Celgene, Summit, NJ / Bristol Myers Squibb, New York, NY

Diana Chang   Genentech, San Francisco, Calif

Julie Hunkapiller   Genentech, San Francisco, Calif

Tushar Bhangale   Genentech, San Francisco, Calif

Natalie Bowers   Genentech, San Francisco, Calif

Sarah Pendergrass   Genentech, San Francisco, Calif

Kirill Shkura   Merck, Kenilworth, NJ

Victor Neduva   Merck, Kenilworth, NJ

Xing Chen   Pfizer, New York, NY

Åsa Hedman   Pfizer, New York, NY

Karen S. King   GlaxoSmithKline, Brentford, United Kingdom

Padhraig Gormley   GlaxoSmithKline, Brentford, United Kingdom

Jimmy Liu   GlaxoSmithKline, Brentford, United Kingdom

Clarence Wang   Sanofi, Paris, France

Ethan Xu   Sanofi, Paris, France

Franck Auge   Sanofi, Paris, France

Clement Chatelain   Sanofi, Paris, France

Deepak Rajpal   Sanofi, Paris, France

Dongyu Liu   Sanofi, Paris, France

Katherine Call   Sanofi, Paris, France

Tai-He Xia   Sanofi, Paris, France

Beryl Cummings   Maze Therapeutics, San Francisco, Calif

Matt Brauer   Maze Therapeutics, San Francisco, Calif

Huilei Xu   Novartis, Basel, Switzerland

Amy Cole   Novartis, Basel, Switzerland

Jonathan Chung   Novartis, Basel, Switzerland

Jaison Jacob   Novartis, Basel, Switzerland

Katrina de Lange   Novartis, Basel, Switzerland

Jonas Zierer   Novartis, Basel, Switzerland

Mitja Kurki   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Samuli Ripatti   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mark Daly   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Juha Karjalainen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Aki Havulinna   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Juha Mehtonen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Priit Palta   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Shabbeer Hassan   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Pietro Della Briotta Parolo   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Wei Zhou   Broad Institute, Cambridge, Mass

Mutaamba Maasha   Broad Institute, Cambridge, Mass

Shabbeer Hassan   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Susanna Lemmelä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Manuel Rivas   University of Stanford, Stanford, Calif

Aarno Palotie   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Arto Lehisto   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Andrea Ganna   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Vincent Llorens   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Hannele Laivuori   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Sina Rüeger   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mari E. Niemi   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Taru Tukiainen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mary Pat Reeve   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Henrike Heyne   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Nina Mars   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Kimmo Palin   University of Helsinki, Helsinki, Finland

Javier Garcia-Tabuenca   University of Tampere, Tampere, Finland

Harri Siirtola   University of Tampere, Tampere, Finland

Tuomo Kiiskinen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Jiwoo Lee   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Kristin Tsuo   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Amanda Elliott   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Kati Kristiansson   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Mikko Arvas   Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland

Kati Hyvärinen   Finnish Red Cross Blood Service, Helsinki, Finland

Jarmo Ritari   Finnish Red Cross Blood Service, Helsinki, Finland

Miika Koskinen   Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Olli Carpén   Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Johannes Kettunen   Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland

Katri Pylkäs   University of Oulu, Oulu, Finland

Marita Kalaoja   University of Oulu, Oulu, Finland

Minna Karjalainen   University of Oulu, Oulu, Finland

Tuomo Mantere   Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland

Eeva Kangasniemi   Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland

Sami Heikkinen   University of Eastern Finland, Kuopio, Finland

Arto Mannermaa   Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland

Eija Laakkonen   University of Jyväskylä, Jyväskylä, Finland

Samuel Heron   University of Turku, Turku, Finland

Dhanaprakash Jambulingam   University of Turku, Turku, Finland

Venkat Subramaniam Rathinakannan   University of Turku, Turku, Finland

Nina Pitkänen   Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland

Biobank directors

Lila Kallio   Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland

Sirpa Soini   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Jukka Partanen   Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland

Eero Punkka   Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Raisa Serpi   Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland

Johanna Mäkelä   Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland

Veli-Matti Kosma   Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland

Teijo Kuopio   Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland

FinnGen teams

Administration. Anu Jalanko   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Huei-Yi Shen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Risto Kajanne   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Mervi Aavikko   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Analysis. Mitja Kurki   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Juha Karjalainen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland / Broad Institute, Cambridge, Mass

Pietro Della Briotta Parolo   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Sina Rüeger   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Arto Lehisto   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Juha Mehtonen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Wei Zhou   Broad Institute, Cambridge, Mass

Masahiro Kanai   Broad Institute, Cambridge, Mass

Mutaamba Maasha   Broad Institute, Cambridge, Mass

Clinical end point development. Hannele Laivuori   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Aki Havulinna   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Susanna Lemmelä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Tuomo Kiiskinen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

L. Elisa Lahtela   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Matti Peura   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Communication. Mari Kaunisto   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Data management and IT infrastructure. Elina Kilpeläinen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Timo P. Sipilä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Georg Brein   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Oluwaseun A. Dada   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Awaisa Ghazal   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Anastasia Shcherban   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Genotyping. Kati Donner   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Timo P. Sipilä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Sample collection coordination. Anu Loukola   Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Sample logistics. Päivi Laiho   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Tuuli Sistonen   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Essi Kaiharju   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Markku Laukkanen   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Elina Järvensivu   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Sini Lähteenmäki   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Lotta Männikkö   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Regis Wong   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Registry data operations. Hannele Mattsson   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Kati Kristiansson   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Susanna Lemmelä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Sami Koskelainen   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Tero Hiekkalinna   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Teemu Paajanen   THL Biobank / The National Institute of Health and Welfare, Helsinki, Finland

Sequencing informatics. Priit Palta   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Kalle Pärn   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Shuang Luo   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Vishal Sinha   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

Trajectory team. Tarja Laitinen Pirkanmaa Hospital District, Tampere, Finland

Harri Siirtola   University of Tampere, Tampere, Finland

Javier Gracia-Tabuenca   University of Tampere, Tampere, Finland

Data protection officer. Tero Jyrhämä Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland

FinBB—Finnish Biobank Cooperative. Marco Hautalahti

Laura Mustaniemi

Mirkka Koivusalo

Sarah Smith

Tom Southerington

ESTONIAN BIOBANK RESEARCH TEAM

Mari Nelis

Lili Milani

Tõnu Esko

Andres Metspalu

REFERENCES

E1. Pan-UKB Team. 2020. Available at: https://pan.ukbb.broadinstitute.org. Accessed April 6, 2020.

E2. Mitt M, Kals M, Pärn K, Gabriel SB, Lander ES, Palotie A, et al. Improved imputation accuracy of rare and low-frequency variants using population-specific high-coverage WGS-based imputation reference panel. Eur J Hum Genet 2017; 25:869-76.

E3. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat Genet 2018;50:1335-41.

E4. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190-1.

E5. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics 2017;33:272-9.

E6. Clark K, Karsch-Mizrachi I, Lipman DJ, Ostell J, Sayers EW. GenBank. Nucleic Acids Res 2016;44:D67-72.

E7. Bateman A. UniProt: a worldwide hub of protein knowledge. Nucleic Acids Res 2019;47:D506-15.

E8. Pers TH, Karjalainen JM, Chan Y, Westra HJ, Wood AR, Yang J, et al. Biological interpretation of genome-wide association studies using predicted gene functions. Nat Commun 2015;6:5890.

E9. Cuellar-Partida G, Lundberg M, Kho PF, D'Urso S, Gutierrez-Mondragon L, Hwang L-D. Complex-Traits Genetics Virtual Lab: a community-driven web platform for post-GWAS analyses. bioRxiv 2019;518027.

E10. Watanabe K, Taskesen E, Van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun 2017;8:1-11.

E11. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res 2010;38:1-7.

E12. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol 2015;11:1-19.

E13. 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.

E14. Majewski J, Schwartzentruber J, Lalonde E, Montpetit A, Jabado N. What can exome sequencing do for you? J Med Genet 2011;48:580-9.

E15. Venselaar H, te Beek TAH, Kuipers RKP, Hekkelman ML, Vriend G. Protein structure analysis of mutations causing inheritable diseases. An e-Science approach with life scientist friendly interfaces. BMC Bioinformatics 2010;11: 548.

E16. Sim NL, Kumar P, Hu J, Henikoff S, Schneider G, Ng PC. SIFT web server: predicting effects of amino acid substitutions on proteins. Nucleic Acids Res 2012;40:452-7.

E17. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. Nat Methods 2010;7:248-9.

E18. Kircher M, Witten DM, Jain P, O'roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet 2014;46:310-5.

E19. Ioannidis NM, Rothstein JH, Pejaver V, Middha S, McDonnell SK, Baheti S, et al. REVEL: an ensemble method for predicting the pathogenicity of rare missense variants. Am J Hum Genet 2016;99:877-85.

E20. Dong C, Wei P, Jian X, Gibbs R, Boerwinkle E, Wang K, et al. Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. Hum Mol Genet 2015;24:2125-37.

E21. Reva B, Antipin Y, Sander C. Predicting the functional impact of protein mutations: application to cancer genomics. Nucleic Acids Res 2011;39:37-43.

E22. Bulik-Sullivan B, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 2015;47:291-5.

E23. 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.