

European and multi-ancestry genome-wide association meta-analysis of atopic dermatitis highlights importance of systemic immune regulation

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A list of authors and their affiliations appears at the end of the paper

Atopic dermatitis (AD) is a common inflammatory skin condition and prior genome-wide association studies (GWAS) have identified 71 associated loci. In the current study we conducted the largest AD GWAS to date (discovery $N = 1,086,394$, replication $N = 3,604,027$), combining previously reported cohorts with additional available data. We identified 81 loci (29 novel) in the European-only analysis (which all replicated in a separate European analysis) and 10 additional loci in the multi-ancestry analysis (3 novel). Eight variants from the multi-ancestry analysis replicated in at least one of the populations tested (European, Latino or African), while two may be specific to individuals of Japanese ancestry. AD loci showed enrichment for DNase I hypersensitivity and eQTL associations in blood. At each locus we prioritised candidate genes by integrating multi-omic data. The implicated genes are predominantly in immune pathways of relevance to atopic inflammation and some offer drug repurposing opportunities.

Atopic dermatitis (AD, or eczema) is a common allergic disease, characterised by (often relapsing) skin inflammation affecting up to 20% of children and 10% of adults¹. Several genome-wide association studies (GWAS) have been performed in recent years, identifying genetic risk loci for AD.

Our most recent GWAS meta-analysis within the EAGLE (EARly Genetics and Lifecourse Epidemiology) consortium, published in 2015 uncovered 31 AD risk loci². Since then, additional GWAS have been published which have confirmed known risk loci^{3,4} and discovered novel loci⁵. Five novel loci were identified in a European meta-analysis⁶, and variants in 3 genes were implicated in a rare variant study in addition to 5 novel loci⁷. Four novel loci were reported in a Japanese population (and another 4 identified in a trans-ethnic meta-analysis in the same study)⁸, giving a total of 71 previously reported AD loci^{2–14} (defined as 1 Mb regions) of which 57 have been reported in European ancestry individuals, 18 have been reported in individuals of non-European ancestry and 29 in individuals across multiple ancestry groups (Supplementary Data 1).

The availability of several new large population-based studies has provided an opportunity to perform an updated GWAS of AD, aiming to incorporate data from all cohorts that have contributed to previously published AD GWAS, as well as data from additional cohorts, to present the most comprehensive GWAS of AD to date, including comparison of effects between European, East Asian, Latino and African ancestral groups. In this work we identify novel loci and use multi-omic data to further characterise these associations, prioritising candidate causal genes at individual loci and investigating the genetic architecture of AD in relation to tissues of importance and shared genetic risk with other traits.

Results

European GWAS

The discovery European meta-analysis ($N = 864,982$; 60,653 AD cases and 804,329 controls from 40 cohorts, summarised in Supplementary Data 2) identified 81 genome-wide significant independent associated loci (Fig. 1a and Supplementary Fig. 1). 52 were at

 e-mail: l.paternoster@bristol.ac.uk

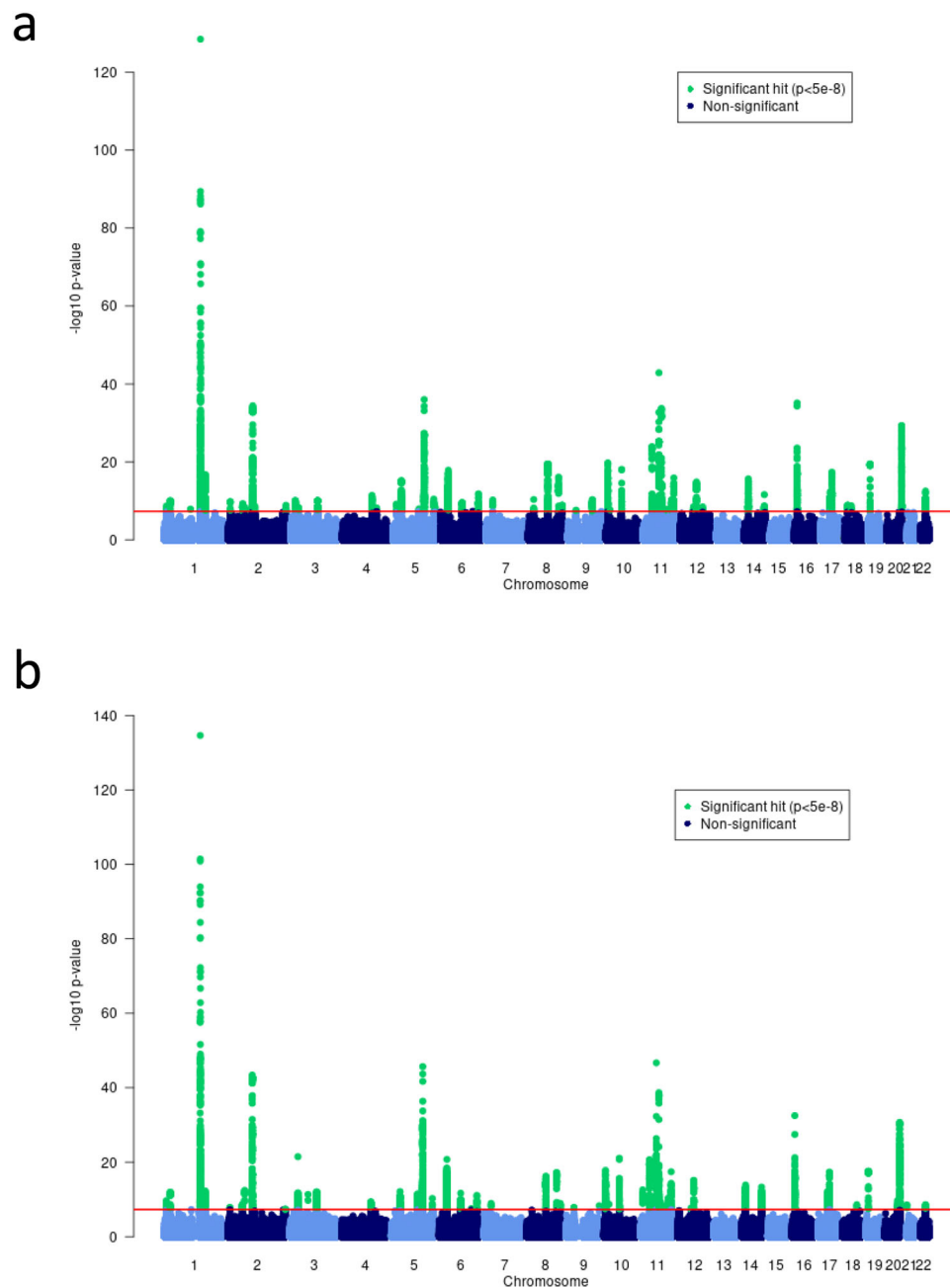


Fig. 1 | Manhattan plots of atopic dermatitis GWAS. (a) the European-only fixed effects meta-analysis ($n = 864,982$ individuals) and (b) the multi-ancestry MR-MEGA meta-analysis ($n = 1,086,394$ individuals). $-\log_{10}(P\text{-values})$ are displayed for all

variants in the meta-analysis. Variants that meet the genome-wide significance threshold (5×10^{-8} , red line) are shown in green.

previously reported loci (Table 1) and 29 (Table 2) were novel (according to criteria detailed in the methods). All 81 were associated in the European 23andMe replication analysis (Bonferroni corrected $P < 0.05/81 = 6 \times 10^{-4}$, $N = 2,904,664$, Table 1). There was little evidence of genomic inflation in the individual studies ($\lambda < 1.05$) and overall (1.06). Conditional analysis determined 44 additional secondary independent associations ($P < 1 \times 10^{-5}$) across 21 loci (Supplementary Data 3).

The SNP-based heritability (h^2_{SNP}) for AD was estimated to be 5.6% in the European discovery meta-analysis (LDSC intercept=1.042 (SE = 0.011)). This is low in comparison to heritability estimates for twin studies (~80%)^{15,16}, but comparable with previous h^2_{SNP} estimates for AD in Europeans (5.4%)⁶.

Multi-ancestry GWAS

In a multi-ancestry analysis including individuals of European, Japanese, Latino and African ancestry (Supplementary Data 2, $N = 1,086,394$; 65,107 AD cases and 1,021,287 controls), a total of 89 loci were identified as associated with AD (Fig. 1b and Supplementary Fig. 1). 75 of these were not independent of lead variants identified in the European-only analysis ($r^2 > 0.01$ in the relevant ancestry) and a further 9 showed some evidence for association (Bonferroni corrected $P < 0.05/89 = 5.6 \times 10^{-4}$) in the European analysis, but 5 were not associated ($P > 0.1$) in Europeans (Table 3, Supplementary Data 4).

Of the 14 loci that reached genome-wide significance in the multi-ancestry discovery analysis only (Table 3), 8 replicated in at least one of

Table 1 | Genome-wide significant loci in European-only analysis that have been previously reported

Variant	European discovery			Multi-ancestry discovery			23andMe European replication (N = 2,904,664)			Gene	Pathway/Function
	Chr:position	Alleles (EAF)	OR (CI)	P	N (studies)	P	N (studies)	OR (CI)	P		
rs7542147	1:25294618	C/T (0.49)	1.04 (1.03-1.06)	8.52E-11	860840 (38)	2.4E-09	870216 (42)	1.05 (1.04-1.05)	4.6E-56	RUNX3	Versatile transcription factor, incl. T cell differentiation
rs12123821	1:152179152	T/C (0.05)	1.40 (1.35-1.45)	4.05E-90	850727 (29)	2.3E-98	857207 (31)	1.27 (1.25-1.29)	1.4E-228	FLG	Skin barrier protein
rs61816766*	1:152319572	C/T (0.03)	1.66 (1.58-1.74)	6.44E-89	627936 (20)	1.1E-102	634416 (22)	1.41 (1.39-1.43)	1.4E-228	FLG	Skin barrier protein
rs72702900	1:152771963	A/T (0.04)	1.28 (1.24-1.33)	2.98E-46	851612 (29)	3.0E-49	853748 (30)	1.23 (1.22-1.25)	4.2E-163	FLG	Skin barrier protein
rs61815704	1:152893891	G/C (0.02)	1.78 (1.67-1.89)	3.21E-71	530473 (19)	9.2E-72	536953 (21)	1.36 (1.34-1.39)	5.5E-212	S100A9*	TLR4 signalling
rs12133641	1:154428283	G/A (0.39)	1.07 (1.05-1.08)	1.72E-21	857974 (37)	1.8E-22	1079390 (42)	1.04 (1.04-1.05)	3.0E-45	IL6R	Cytokine signalling in immune system
rs859723	1:172744543	A/G (0.36)	0.94 (0.93-0.96)	3.74E-14	522713 (37)	2.4E-14	744125 (42)	0.96 (0.96-0.97)	2.2E-39	TNFSF4*	Cytokine signalling in immune system
rs1181788	1:173150727	G/C (0.24)	1.07 (1.05-1.08)	1.85E-17	859747 (38)	3.1E-16	1081160 (43)	1.04 (1.04-1.05)	1.6E-39	TNFSF4	Cytokine signalling in immune system
rs891058	2:8442547	A/G (0.29)	0.96 (0.94-0.97)	1.76E-10	862482 (38)	2.2E-11	1083890 (43)	0.97 (0.97-0.98)	3.0E-18	ID2	Transcriptional regulator of many cellular processes
rs12111458	2:7110105	G/A (0.12)	0.94 (0.92-0.96)	5.50E-09	858567 (37)	1.4E-11	1079980 (42)	0.96 (0.95-0.97)	1.3E-21	CD207	Dendritic cell function
rs2272128	2:103039929	A/G (0.77)	0.91 (0.90-0.92)	8.14E-35	862259 (39)	3.8E-48	1083670 (44)	0.93 (0.93-0.94)	2.2E-100	IL18RAP	Cytokine signalling in immune system
rs4131280	3:18414570	A/G (0.57)	0.96 (0.95-0.98)	1.2E-08	864982 (40)	5.8E-08	1086390 (45)	0.97 (0.97-0.98)	2.2E-19	SATB1	Regulates chromatin structure and gene expression
rs13097010	3:18673161	G/A (0.34)	1.05 (1.03-1.06)	9.0E-11	864982 (40)	1.5E-08	1086390 (45)	1.02 (1.01-1.02)	1.4E-07	SATB1	Regulates chromatin structure and gene expression
rs35570272	3:33047662	T/G (0.40)	1.04 (1.03-1.05)	5.7E-09	864982 (40)	2.3E-20	1086390 (45)	1.03 (1.03-1.04)	1.6E-26*	GLB1	Sphingolipid metabolism
rs6808249	3:112648985	T/C (0.54)	0.96 (0.95-0.97)	9.05E-11	859747 (38)	3.8E-12	1081160 (43)	0.97 (0.96-0.97)	4.7E-29	CD200R1	Adaptive immune system
rs45599938	4:123386720	A/G (0.35)	1.05 (1.03-1.06)	4.61E-12	859747 (38)	3.7E-10	1081160 (43)	1.05 (1.05-1.06)	1.3E-62	KIAA1109	Endosomal transport
rs10214273	5:35883986	G/T (0.27)	0.94 (0.93-0.96)	5.97E-16	863209 (39)	1.8E-14	1084620 (44)	0.93 (0.93-0.94)	2.9E-99	IL7R	Cytokine signalling in immune system
rs17132590	5:110331899	C/T (0.10)	1.07 (1.05-1.10)	1.16E-08	525225 (38)	1.7E-08	746637 (43)	1.03 (1.02-1.04)	1.0E-07	CAMK4	Immune response, inflammation & memory consolidation
rs4706020	5:130674076	A/G (0.34)	0.95 (0.93-0.96)	1.12E-11	518425 (35)	2.7E-11	527801 (39)	0.98 (0.98-0.99)	6.4E-09	CDC42SE2	F-actin accumulation at immunological synapse of T cells
rs4705908	5:131347520	A/G (0.37)	0.95 (0.93-0.96)	6.80E-13	520344 (36)	1.6E-11	529720 (40)	0.98 (0.97-0.98)	8.0E-15	SLC22A5	Organic cation transport
rs20541	5:131995964	G/A (0.78)	0.91 (0.89-0.92)	1.00E-36	859747 (38)	8.4E-51	1076820 (42)	0.92 (0.91-0.92)	1.2E-129	SLC22A5	Organic cation transport
rs114503346	5:172192350	T/C (0.04)	0.89 (0.86-0.92)	3.62E-11	855569 (33)	1.3E-10	862049 (35)	0.94 (0.93-0.95)	3.2E-17	ERGIC1	Transport between endoplasmic reticulum and golgi
rs41293876	6:31466536	C/G (0.14)	0.90 (0.88-0.93)	7.02E-16	645820 (36)	6.5E-18	865966 (40)	0.95 (0.95-0.96)	4.3E-32	TNF	Cytokine signalling in immune system
rs12153855	6:32074804	C/T (0.10)	0.92 (0.90-0.94)	1.96E-11	812536 (37)	2.8E-10	821912 (41)	0.96 (0.95-0.97)	2.3E-18	ATF6B	Endoplasmic reticulum stress response
rs28383330	6:32600340	G/A (0.13)	0.88 (0.85-0.90)	1.42E-18	625716 (28)	1.8E-17	632956 (31)	0.94 (0.93-0.95)	2.4E-51	AGER	Immunoglobulin surface receptor
rs9275218	6:32658933	G/C (0.34)	1.06 (1.04-1.08)	5.36E-10	505320 (34)	1.0E-09	512560 (37)	1.01 (1.01-1.02)	1.0E-04	HLA-DRA	Immune response antigen presentation
rs629326	6:159496713	T/G (0.61)	0.95 (0.94-0.97)	1.7E-12	859747 (38)	4.5E-12	1081160 (43)	0.95 (0.95-0.96)	5.4E-61*	TAGAP*	T cell activation
rs952558	8:81288734	T/A (0.62)	0.94 (0.93-0.95)	3.60E-20	862259 (39)	1.3E-19	1083670 (44)	0.97 (0.96-0.97)	2.2E-31	ZBTB10	Transcriptional regulation
rs6996614	8:126609868	A/C (0.53)	1.07 (1.05-1.08)	8.48E-17	693031 (37)	1.0E-17	914443 (42)	1.03 (1.02-1.03)	1.5E-19	TRIB1	Protein kinase regulation
rs12251307	10:6123495	T/C (0.12)	1.10 (1.08-1.12)	1.98E-20	864982 (40)	8.4E-19	1086390 (45)	1.10 (1.09-1.11)	4.7E-107	IL2RA	Cytokine signalling in immune system
rs10796303	10:6627700	C/T (0.66)	0.96 (0.94-0.97)	8.69E-10	856884 (38)	8.5E-10	1078300 (43)	0.97 (0.96-0.97)	5.6E-25	PRKCC	T cell activation
rs10822037	10:64376558	C/T (0.61)	1.06 (1.05-1.08)	8.53E-19	864982 (40)	1.3E-24	1086390 (45)	1.05 (1.04-1.05)	4.0E-55	ADO	Taurine biosynthesis
rs10836538	11:36365253	T/G (0.34)	0.96 (0.94-0.97)	9.18E-11	863063 (39)	1.1E-13	1084480 (44)	0.95 (0.95-0.96)	6.2E-55	PRR5L	Protein phosphorylation
rs28520436	11:36428447	T/C (0.03)	1.20 (1.16-1.24)	1.22E-24	855865 (29)	4.1E-25	1074380 (32)	1.18 (1.16-1.20)	5.3E-81	PRR5L	Protein phosphorylation
rs10791824	11:65559266	G/A (0.58)	1.10 (1.08-1.11)	1.34E-43	864982 (40)	1.2E-51	1086390 (45)	1.07 (1.06-1.07)	1.2E-105	MAP3K11	Cytokine signalling in immune system
rs7936323	11:76293758	A/G (0.46)	1.08 (1.07-1.10)	2.07E-34	864982 (40)	1.8E-39	1086390 (45)	1.07 (1.07-1.08)	1.9E-133	LRRC32	TGF beta regulation incl. on T cells

Table 1 (continued)

Variant	Chr:position	Alleles (EAF)	European discovery			Multi-ancestry discovery			23andMe European replication (N = 2,904,664)			Gene	Pathway/Function
			OR (CI)	P	N (studies)	P	N (studies)	OR (CI)	P	N (studies)			
rs11236813	11:76343427	C/G (0.10)	0.93 (0.91–0.95)	1.94E-12	864646 (39)	4.8E-12	1086060 (44)	0.95 (0.94–0.96)	2.6E-26	LRR32	TGF beta regulation incl. on T cells		
rs10790275	11:118745884	C/G (0.80)	1.06 (1.04–1.07)	5.46E-11	859747 (38)	4.8E-09	1081160 (43)	1.02 (1.02–1.03)	1.0E-10	DDX6 ^b	mRNA degradation		
rs7127307	11:128187383	C/T (0.49)	0.95 (0.93–0.96)	1.29E-16	859747 (38)	1.0E-17	1081160 (43)	0.96 (0.95–0.96)	6.1E-52	FLI1	NF-kappaB signalling		
rs705699	12:56384804	A/G (0.40)	1.04 (1.03–1.05)	3.31E-09	864982 (40)	6.7E-08	1086390 (45)	1.03 (1.03–1.04)	8.7E-27	RPS26	Peptide chain elongation		
rs2227491	12:68646521	C/T (0.61)	1.05 (1.04–1.07)	1.46E-15	864982 (40)	1.9E-15	1086390 (45)	1.05 (1.05–1.06)	1.2E-71	IL22	Cytokine signalling in immune system		
rs2415269	14:35638937	A/G (0.26)	0.94 (0.93–0.96)	2.26E-16	862613 (39)	9.3E-15	1084020 (44)	0.96 (0.96–0.97)	3.8E-32	SRP54	Peptide chain elongation		
rs4906263	14:103249127	C/G (0.65)	1.06 (1.04–1.07)	2.65E-12	693031 (37)	1.5E-10	702407 (41)	1.04 (1.03–1.04)	2.9E-36	TRAF3	Cytokine signalling in immune system		
rs2041733	16:11229589	C/T (0.54)	0.92 (0.91–0.93)	7.85E-36	864982 (40)	5.8E-40	1086390 (45)	0.94 (0.94–0.95)	4.2E-95	RMI2	DNA repair		
rs1358175	17:38757789	T/C (0.63)	1.05 (1.03–1.06)	1.99E-11	864982 (40)	1.4E-14	1086390 (45)	1.03 (1.03–1.04)	1.2E-26	CCR7	B and T lymphocyte activation		
rs17881320	17:40485239	T/G (0.08)	1.09 (1.07–1.12)	5.34E-13	862032 (38)	2.0E-11	870142 (41)	1.07 (1.06–1.08)	9.8E-39	STAT3 ^b	Cytokine signalling in immune system		
rs4247364	17:43336687	C/G (0.70)	0.96 (0.95–0.98)	4.54E-08	862470 (39)	1.3E-07	1083880 (44)	0.97 (0.97–0.98)	1.7E-17	DCAKD ^b	Coenzyme A biosynthetic process		
rs56308324	17:45819206	T/A (0.13)	1.06 (1.04–1.08)	4.89E-10	860694 (38)	1.1E-08	1082110 (43)	1.03 (1.02–1.04)	2.6E-11	TBX21 ^b	Th1 differentiation		
rs28406364	17:47454507	T/C (0.38)	1.06 (1.05–1.07)	5.01E-18	864982 (40)	2.3E-18	1086390 (45)	1.04 (1.03–1.04)	1.5E-34	GNG72	G protein signalling		
rs2967677	19:8789721	T/C (0.15)	1.08 (1.07–1.10)	3.35E-20	861624 (38)	5.8E-23	1083040 (43)	1.06 (1.05–1.07)	7.5E-49	CERS4	Sphingolipid metabolism		
rs6062486	20:62302539	A/G (0.69)	1.09 (1.07–1.10)	5.03E-30	782263 (37)	4.4E-32	1003680 (42)	1.07 (1.07–1.08)	4.5E-109	RTEL1	DNA repair		
rs4821569	22:37316873	G/A (0.53)	1.05 (1.04–1.06)	3.14E-13	863063 (39)	1.6E-11	1084480 (44)	1.04 (1.04–1.05)	5.4E-50	CSF2RB	Cytokine signalling in immune system		

The lead SNP at each independent locus is displayed, along with the results from the European-only discovery, multi-ancestry discovery and European replication. The top ranked gene from our gene prioritisation is listed, along with a description of the pathway/function of the gene. The evidence implicating each gene is presented in Supplementary Data 11.

Alleles are listed as effect allele/other allele, the effect allele frequency (EAF) in Europeans (average EAF, weighted by the sample size of each cohort).

Association statistics. Odds ratios (with 95% confidence intervals) and (unadjusted, two-sided) P-values are displayed for the fixed effects European-only meta-analysis and the replication analysis. P-values (unadjusted, two-sided) only are available from the MR-MEGA meta-regression multi-ancestry analysis.

Genome build = GRCh37/hg19.

^aImputation batch effect observed in 23andMe data.

^bOne of two or three tied genes at these loci are shown.

Table 2 | Novel genome-wide significant loci in European-only analysis

Variant	European Discovery			Multi-ancestry discovery			23andMe European replication (N = 2,904,664)			Gene	Pathway
	Chr-position	Alleles (EAF)	OR (CI)	P	N (studies)	P	N (studies)	OR (CI)	P		
rs301804 ^b	1:8476441	G/C (0.30)	1.05 (1.03-1.07)	2.3E-09	698266 (39)	8.5E-09	707642 (43)	1.03 (1.02-1.03)	5.5E-16	REX1	Apoptosis
rs61776548	1:12091024	A/G (0.47)	1.04 (1.02-1.05)	4.2E-08	787144 (39)	1.4E-07	1008560 (44)	1.02 (1.01-1.02)	5.6E-09	TNFRSF1B	Cytokine signalling in immune response
rs12565349	1:110371629	G/C (0.15)	1.05 (1.03-1.07)	1.3E-08	862259 (39)	1.9E-07	1083670 (44)	1.03 (1.02-1.04)	5.8E-15	CSF1	Cytokine signalling in immune response
rs187080438	1:150374354	T/C (0.03)	1.17 (1.11-1.23)	3.7E-10	758729 (20)	2.2E-12	765209 (22)	1.14 (1.12-1.16)	2.0E-41	CTSS	Antigen presentation in immune response
rs146527530 ^b	1:151059196	G/T (0.02)	1.27 (1.20-1.35)	5.5E-15	744128 (13)	7.4E-19	744128 (13)	1.25 (1.22-1.28)	1.5E-88	CTSS	Antigen presentation in immune response
rs115161931 ^b	1:151063299	T/C (0.04)	1.18 (1.13-1.23)	1.0E-13	472565 (26)	3.2E-12	479045 (28)	1.09 (1.08-1.11)	2.0E-32	CTSS	Antigen presentation in immune response
rs17625130 ^b	1:151625094	A/G (0.04)	1.23 (1.18-1.28)	2.4E-27	770827 (25)	7.2E-30	772963 (26)	1.17 (1.16-1.19)	1.7E-89	RORC ^c	Cytokine signalling in immune response
rs149199808 ^b	1:151626396	T/C (0.03)	1.32 (1.26-1.38)	4.4E-30	756174 (19)	8.7E-34	762654 (21)	1.24 (1.22-1.26)	3.1E-134	RORC	Cytokine signalling in immune response
rs821429 ^b	1:153275443	A/G (0.96)	0.86 (0.84-0.89)	5.9E-18	852224 (30)	8.2E-16	858704 (32)	0.91 (0.89-0.92)	2.7E-38	STO0A7	Differentiation regulation incl. in the innate immune system
rs12138773	1:153843489	A/C (0.03)	1.11 (1.07-1.16)	2.3E-08	851937 (28)	1.3E-09	858417 (30)	1.07 (1.05-1.09)	3.5E-16	STO0A12 ^c	Regulation of inflammatory processes and immune response
rs67766926 ^b	2:61163581	G/C (0.23)	1.05 (1.03-1.06)	5.7E-10	863063 (39)	2.9E-11	1084480 (44)	1.05 (1.04-1.05)	1.2E-41	AHSA2P	Protein folding
rs112385344	2:112275538	T/C (0.12)	1.06 (1.04-1.08)	2.8E-09	852837 (34)	3.9E-08	862213 (38)	1.04 (1.03-1.05)	1.5E-18	MERTK ^c	Inhibits TLR-mediated innate immune response
rs62193132	2:242788256	T/C (0.46)	1.04 (1.03-1.06)	1.5E-09	832761 (26)	7.1E-08	1052040 (30)	1.03 (1.02-1.03)	1.5E-19	NEU4	Sphingolipid metabolism
rs10833 ^b	4:142654547	C/T (0.65)	1.04 (1.03-1.06)	7.3E-09	859747 (38)	6.0E-08	1081160 (43)	1.02 (1.02-1.03)	3.4E-15	IL15	Cytokine signalling in immune response
rs148161264 ^b	5:14604521	G/C (0.04)	1.10 (1.07-1.14)	7.4E-10	850619 (29)	2.0E-08	857099 (31)	1.05 (1.03-1.06)	1.6E-08	OTULINL	Endoplasmic reticulum component
rs7701967	5:130059750	A/G (0.31)	0.95 (0.94-0.97)	3.4E-09	520344 (36)	3.6E-09	529720 (40)	0.99 (0.98-0.99)	1.1E-06	LYRM7	Mitochondrial respiratory chain complex assembly
rs4532376 ^b	5:176774403	A/G (0.30)	1.04 (1.03-1.06)	3.5E-09	859747 (38)	2.3E-09	1081160 (43)	1.03 (1.02-1.03)	1.4E-18	RGS14	G-alpha signalling
rs72925996 ^b	6:90930513	C/T (0.33)	0.96 (0.94-0.97)	3.2E-10	862259 (39)	5.4E-09	1083670 (44)	0.96 (0.95-0.96)	2.2E-44	BACH2	NF-kappaB proinflammatory signalling
rs989437	7:28830498	G/A (0.61)	0.96 (0.95-0.97)	6.1E-11	864982 (40)	1.0E-09	1086390 (45)	0.97 (0.96-0.97)	6.9E-31	CREB5 ^e	AMPK & A TK signalling
rs34215892	8:21767240	A/G (0.03)	0.87 (0.83-0.90)	4.7E-11	436369 (24)	2.0E-09	442849 (26)	0.89 (0.88-0.91)	1.0E-36	DOK2	Immune response IL-23 signalling
rs118162691	8:21767809	A/C (0.05)	0.92 (0.89-0.94)	7.8E-09	856229 (30)	1.8E-07	862709 (32)	0.90 (0.88-0.91)	1.1E-44	DOK2	Immune response IL-23 signalling
rs7843258	8:141601542	C/T (0.82)	1.05 (1.04-1.07)	1.5E-09	859747 (38)	3.6E-10	1081160 (43)	1.04 (1.03-1.05)	7.0E-25	AGO2	siRNA-mediated gene silencing
rs7857407	9:33430707	A/T (0.40)	1.04 (1.02-1.05)	2.5E-08	864982 (40)	9.0E-09	1086390 (45)	1.03 (1.02-1.03)	5.1E-18	AQP3	Aquaporin-mediated transport
rs10988863	9:102331281	C/A (0.21)	0.95 (0.93-0.96)	5.1E-11	862259 (39)	3.0E-09	1083670 (44)	0.97 (0.97-0.98)	1.3E-13	NR4A3	Transcriptional activator
rs17368814	11:102748695	G/A (0.13)	0.95 (0.93-0.97)	1.4E-08	858117 (37)	6.8E-07	1078260 (41)	0.95 (0.95-0.96)	1.2E-27	MMP12	Extracellular matrix organisation
rs1126206	11:116843425	G/C (0.07)	1.10 (1.07-1.14)	5.5E-10	557183 (35)	2.9E-10	778595 (40)	1.04 (1.03-1.05)	8.5E-15	SIK3	LKB1 signalling
rs5005507 ^b	12:94611908	C/G (0.74)	1.05 (1.03-1.06)	3.6E-09	859747 (38)	9.6E-08	1081160 (43)	1.03 (1.02-1.04)	2.7E-18	PLXNC1	Semaphorin interactions incl. in immune response
rs7147439	14:105523663	A/G (0.73)	0.96 (0.95-0.97)	4.7E-08	781909 (37)	6.6E-07	1003320 (42)	0.97 (0.96-0.97)	4.8E-24	GPR132	GPCR signalling
rs2542147	18:12775851	T/G (0.84)	0.95 (0.93-0.96)	1.5E-09	862470 (39)	7.5E-08	1083880 (44)	0.96 (0.95-0.97)	2.6E-26	PTPN2	Cytokine signalling in immune response

The lead SNP at each independent locus is displayed, along with the results from the European-only discovery, multi-ancestry discovery and European replication. The top-ranked gene from our gene prioritisation is listed, along with a description of the pathway/function of the gene. The evidence implicating each gene is presented in Supplementary Data 11.

Alleles are listed as Effect allele/other allele, the effect allele frequency (EAF) in Europeans (average EAF, weighted by the sample size of each cohort). Genome build = GRCh37/hg19.

^ars4643526 at the same locus was previously identified in the discovery analysis of Paternoster et al. ². However, this association did not replicate in that study.

^bWhilst not identified in any GWAS AD papers, these loci have previously shown evidence for association with AD in supplementary material of methodological papers ^{67,83}.

^cOne of two or three tied genes at these loci are shown.

Table 3 | Additional loci associated with the multi-ancestry analysis

Variant	Chr:position	Alleles (EAF)	Multi-ancestry discovery	European discovery	RIKEN - Bio-bank Japan	23andMe Latino	23andMe African	23andMe European	Known	Novel
			N = 992,907 P	N = 864,982 P	N = 118,287 P	N = 525,348 P	N = 174,015 P	N = 2,904,664 P	Associations	Associations
rs114059822*	1:19804918	T/G (0.03)	8.59E-09	0.25	-	0.07	0.03	0.87	NA	NA
rs9247	2:234113301	T/C (0.21)	1.92E-09	7.32E-08	7.71E-05	1.49E-13	7.23E-03	2.93E-51		all ^b
rs9864845	3:112383847	A/G (0.37)	2.17E-12	0.22	3.92E-13	0.75	0.23	0.12	Japanese (Tanaka et al. ⁹)	
rs34599047	6:106629690	C/T (0.18)	3.32E-08	1.29E-07	0.03	7.18E-04	0.02	3.23E-22		all ^b
rs7773987	6:135707486	T/C (0.60)	1.22E-08	9.57E-08	0.15	0.18	1.95E-03	5.93E-13		European, African
rs118029610*	9:1894613	T/C (0.03)	1.89E-08	2.97E-04	-	0.5	0.31	0.78	NA	NA
rs117137535	9:140500443	A/G (0.03)	1.99E-08	5.50E-08	-	3.99E-07	0.33	9.25E-19	European (Grosche et al. ⁷)	Latino
rs4312054	11:7977161	G/T (0.43)	3.21E-12	0.86	3.46E-15	0.4	0.33	0.52	Japanese (Tanaka et al. ⁹)	
rs150113720*	11:83439186	G/C (0.02)	5.52E-10	0.40	-	0.1	0.22	0.14	NA	NA
rs115148078*	11:101361300	T/C (0.02)	5.91E-09	0.37	-	3.69E-03	0.91	0.89	NA	NA
rs4262739	11:128421175	A/G (0.50)	2.20E-08	6.03E-07	2.28E-03	1.89E-06	0.09	1.45E-36	European & Japanese (Tanaka et al. ⁹)	Latino
rs1059513	12:57489709	C/T (0.08)	5.15E-09	1.57E-07	0.33	3.06E-04	0.17	6.95E-16	European (Tanaka et al. ⁹)	Latino
rs4574025	18:60009814	T/C (0.55)	7.00E-10	1.48E-06	2.67E-05	2.59E-04	1.24E-05	2.96E-05	European & Japanese (Tanaka et al. ⁹)	Latino, African
rs6023002	20:52797237	C/G (0.52)	4.05E-10	2.26E-06	2.82E-07	5.96E-03	0.07	3.22E-28	European & Japanese (Tanaka et al. ⁹)	Latino

For loci that were associated in the multi-ancestry discovery analysis, but not the European discovery analysis, we show the (unadjusted two-sided) P-values for association across 4 diverse ancestral groups, European, Japanese, Latino and African. Full association statistics (including OR and 95% CI) for each variant can be viewed in Supplementary Data 4 (and results across all cohorts individually are depicted in Supplementary Fig. 2).

Alleles are reported as effect allele/other allele.

Genome build = GRCh37/hg19.

NA indicates finding not replicated and likely to be false-positive in discovery.

Bold is used in the novel column to denote the 3 associations that are entirely novel (i.e. locus has not been associated in any ancestry previously).

- Variant was not available in dataset.

*Genome-wide significant loci without replication that are assumed to be false positives in the discovery data.

^bWhilst not identified in any GWAS AD papers, these loci have previously shown evidence for association with AD in the supplementary material of methodological papers^{9,10} or GWAS of combined allergic disease phenotype⁵.

the replication samples (of European, Latino and/or African ancestry; Bonferroni corrected $P < 0.05/14 = 3.6 \times 10^{-3}$). Two index SNPs which did not replicate in any of the samples (rs9864845 (near *CCDC80*), rs4312054 (near *NLRP10*)) appear to have been driven by association in the Japanese RIKEN study only (Supplementary Data 4, Supplementary Figs. 2, 3). Whilst the allele frequencies of these index SNPs are similar between Europeans and Japanese (37% vs 42% for rs9864845, 41% vs 46% for rs4312054, Supplementary Data 5), in a multi-ancestry fixed effect meta-analysis at both these loci there were neighbouring (previously reported)⁸ SNPs with stronger evidence of association (rs72943976, $P = 2 \times 10^{-9}$ and rs59039403 $P = 2 \times 10^{-35}$, Supplementary Fig. 3), that did show large allele frequencies for Japanese (~34% and 13%, respectively) but <1% in Europeans. A further 4 loci did not replicate, and on closer examination (Supplementary Fig. 2, and MAF in cases <1%), their association in the discovery analysis appeared to be driven by a false positive outlying result in a single European cohort.

Seven of the loci in Table 3 have been previously reported as associated with AD. Two (rs117137535 (near *ARRDC1*)⁷ and rs1059513 (near *STAT6*)⁸) were previously only associated with Europeans (and these were variants that were just below the genome-wide significance threshold in our European only analysis). Three (rs4262739 (near *ETS1*), rs4574025 (within *TNFRSF11A*) and rs6023002 (near *CYP24A1*)) were previously associated in Japanese and Europeans⁸, while 2 were previously associated only in Japanese^{8,10}, using the same Japanese data (RIKEN) that we include here. Therefore, in our multi-ancestry analysis (and replication) we identify 3 loci that have not previously been reported in a GWAS of AD of any ancestry (rs9247 (near *INPP5D*), rs34599047 (near *ATG5*) and rs7773987 (near *AH11*)), all of which are associated in two or more populations in our data (Table 3).

In addition, for 5 loci which had previously been associated with individuals of European and/or Japanese ancestry, we now show evidence that these are also associated with individuals of Latino ancestry and one is also associated in individuals of African ancestry (Table 3).

Comparison of associations between ancestries

Effect sizes of the index SNPs were remarkably similar between individuals of European and Latino ancestry (Supplementary Fig. 4A). There were only two variants with any evidence for a difference (where Latino $P > 5 \times 10^{-4}$ and the 95% confidence intervals didn't overlap), but the plot shows that these were only marginally different and likely to be due to chance. Effect size comparison of the index SNPs between individuals of European and African ancestry showed greater differences (Supplementary Fig. 4B). 17 SNPs showed some evidence for being European-specific in that comparison. The confidence intervals in the Japanese data were much wider but there was weak evidence for one SNP being European-specific and stronger evidence for two SNPs being Japanese-specific (Supplementary Fig. 4C). These were rs4312054 (JAP CI: 0.75-0.84, EUR CI: 0.99-1.01) and rs9864845 (JAP CI: 1.16-1.30, EUR CI: 0.99-1.06), mentioned earlier as the SNPs that appeared to be driven only by Japanese individuals in the multi-ancestry meta-analysis (Supplementary Data 4).

Established associations

A review of previous work in this field (Supplementary Data 1) shows that a total of 202 unique variants (across a much smaller number of loci) have been reported to be associated with AD. We found evidence for all but 7 variants of these being nominally associated in the current GWAS (81% in the European and 96% in the multi-ancestry analysis). Variants we did not find to be associated were either rare variants (MAF < 0.01), or insertion/deletion mutations, which were not included in our analysis.

Genetic correlation between AD and other traits

LD score regression analyses showed high genetic correlation, as expected, between AD and related allergic traits, e.g. asthma ($rg = 0.53$, $P = 2 \times 10^{-32}$), hay fever ($rg = 0.51$, $P = 7 \times 10^{-17}$) and eosinophil count ($rg = 0.27$, $P = 1 \times 10^{-7}$) (Supplementary Fig. 5 and Supplementary Data 6). In addition, depression and anxiety showed notable

genetic correlation with AD ($r_g = 0.17$, $P = 2 \times 10^{-7}$), a relationship which has been reported previously, but causality has not been established¹⁷. Furthermore, gastritis also showed substantial genetic correlation ($r_g = 0.31$, $P = 1 \times 10^{-5}$), which may be due to the AD genetic signal including variants with pervasive inflammatory function or the observed correlation could indicate a shared risk locus for inflammation or microbiome alteration in the upper gastrointestinal tract, or it may reflect the use of systemic corticosteroid treatment for atopic disease which in some cases causes gastritis as a side effect.

Tissue, cell and gene-set enrichment

The tissue enrichment analyses using distinct molecular evidence (representing open chromatin and gene expression) both found blood to be the tissue showing strongest enrichment of GWAS loci (Fig. 2). The Garfield test for enrichment of genome-wide loci (with $P < 1 \times 10^{-8}$) in DNase I hypersensitive sites (DHS broad peaks) found evidence of enrichment ($P < 0.00012$) in 41 blood tissue analyses, a greater signal than another tissue or cell type (Fig. 2a and Supplementary Data 7). The strongest enrichment ($OR > 5.5$ and $P < 1 \times 10^{-10}$) was seen for T-cell, B-cell and natural killer lymphocytes (CD3+, CD4+, CD56+ and CD19+). As expected for AD, Th2 showed stronger enrichment ($OR = 4.3$, $P = 1 \times 10^{-8}$) than Th1 ($OR = 2.3$, $P = 2 \times 10^{-4}$). The strongest enrichment in tissue samples representing skin was seen for foreskin keratinocytes ($OR = 2.0$, $P = 0.008$), but this did not meet a Bonferroni-corrected P -value threshold ($0.05/425 = 1 \times 10^{-4}$).

The most enriched tissue type in MAGMA gene expression enrichment analysis was whole blood ($P = 2 \times 10^{-14}$). Others that met our Bonferroni-corrected P -value ($P < 0.0009$) were spleen, EBV-transformed lymphocytes, sun-exposed and unexposed skin, small intestine and lung (Fig. 2b and Supplementary Data 8).

DEPICT cell-type enrichment analysis identified a similar set of enriched cell-types: blood, leucocytes, lymphocytes and natural killer cells, but with the addition that the strongest enrichment was seen for synovial fluid ($P = 2 \times 10^{-7}$), which may be due to its immune cell component.

The DEPICT pathway analysis found 420 GO terms with enrichment ($FDR < 5\%$) amongst the genes from our GWAS loci (Supplementary Data 9). The pathway with the strongest evidence of enrichment was 'hemopoietic or lymphoid organ development' ($P = 1 \times 10^{-16}$). All terms with $FDR < 5\%$ are represented in Supplementary Fig. 6, where the terms are grouped according to similarity and the parent terms labelled illustrating the strong theme of immune system development and signalling.

Gene prioritisation and biological interpretation in silico

The top genes prioritised using our composite score from publicly available data for each of the established European AD loci are shown in Table 1 and Fig. 3a (and the evidence that makes up the prioritisation scores is shown in Supplementary Fig. 7). The top three prioritised genes at each independent locus are shown in Supplementary Data 10 and a summary of all evidence for all genes reviewed in silico is presented in Supplementary Data 11.

In most cases the top prioritised gene had been implicated (in previous GWAS) or is only superseded marginally by an alternative candidate. One interesting exception is on chromosome 11, where *MAP3K11* (with a role in cytokine signalling – regulating the JNK signalling pathway) is markedly prioritised over the previously implicated *OVOL1*¹⁸ (involved in hair formation and spermatogenesis), although the prioritisation of *MAP3K11* is predominantly driven by TWAS evidence in multiple cell types rather than colocalisation or other evidence.

There are three instances where multiple associations in the region implicate additional novel genes. Two are genes involved in TLR4 signalling: *SIOO49* (prioritised in addition to the established *FLG*

and *IL6R* on chromosome 1) and *AGER* (prioritised in addition to *HLA-DRA* on chromosome 6). The third has a likely role in T-cell activation: *CDC42SE2* (prioritised in addition to *SLC22A5* on chromosome 5).

The top prioritised gene at each of the novel European loci are shown in Table 2 and Fig. 3b. Many are in pathways already identified by previous findings (e.g. cytokine signalling—specially IL-23, antigen presentation and NF-kappaB proinflammatory response). At one locus, the index SNP, rs34215892 is a missense (Pro274Leu) mutation within the *DOK2* gene, although this mutation is categorised as tolerated or benign by SIFT and PolyPhen. The genes with the highest prioritisation score amongst the novel loci were *GPRI32* (total evidence Score=24), *NEU4* (score=22), *TNFRSF1B* (score = 19) and *RGS14* (score=19) and each show biological plausibility as candidates for AD pathogenesis.

GPRI32 is a proton-sensing transmembrane receptor, involved in modulating several downstream biological processes, including immune regulation and inflammatory response, as reported previously in an investigation of this protein's role in inflammatory bowel disease¹⁹. The index SNP at this locus, rs7147439 (which was associated with Europeans, Latinos, Africans, but not Japanese), is an intronic variant within the *GPRI32* gene. The AD GWAS association at this locus colocalises with the eQTL association for *GPRI32* in several immune cell types (macrophages²⁰, neutrophils²¹, several T-cell datasets²²) as well as in colon, lung and small intestine in GTEx²³. *GPRI32* has also been shown to be upregulated in lesional and nonlesional skin in AD patients, compared to skin from control individuals^{24,25}. OpenTargets and POSTGAP both prioritise *GPRI32* for this locus.

The SNP rs62193132 (which showed consistent effects in European, Latino and Japanese individuals, but little evidence for association in African individuals, Supplementary Fig. 2), is in an intergenic region between *NEU4* (-26 kb) and *PDCDI* (-4 kb away) on chromosome 2. *NEU4* was the highest scoring in our gene prioritisation pipeline (score=22). However, *PDCDI* also scores highly (score = 18, Supplementary Data 10). *NEU4* is an enzyme that removes sialic acid residues from glycoproteins and glycolipids, whereas *PDCDI* is involved in the regulation of T cell function. The AD GWAS association at this locus colocalises with the eQTL for *NEU4* in several monocyte and macrophage datasets^{22,26–28} as well as in the ileum, colon and skin^{23,29}. The eQTL for *PDCDI* also colocalises in monocytes and macrophages^{27,28} as well as T-cells²², skin and whole blood²³. In addition to the eQTL evidence, *PDCDI* is upregulated in lesional and nonlesional skin in AD patients compared to skin from control individuals^{24,25}. OpenTargets and PoPs prioritise *NEU4*, whilst POSTGAP prioritises *PDCDI* at this locus.

TNFRSF1B is part of the TNF receptor, with an established role in cytokine signalling. rs61776548 (which showed consistent associations across all major ancestries tested) is 136 kb upstream of *TNFRSF1B*, actually within an intron of *MIIP*. *MIIP* encodes Migration and Invasion-Inhibitory Protein, which may function as a tumour suppressor. However, *TNFRSF1B* is a stronger candidate gene since the AD GWAS association at this locus colocalises with the eQTL for *TNFRSF1B* T cells^{22,30}, macrophages²⁰, fibroblasts³¹ and platelets²⁹. Furthermore, *TNFRSF1B* gene expression and the corresponding protein are upregulated in lesional and nonlesional skin compared to controls^{24,25,32} and the PoPs method prioritised this gene at this locus.

RGS14 is a multifunctional cytoplasmic-nuclear shuttling protein which regulates G-protein signalling, but whose role in the immune system is yet to be established. rs4532376 is 10.5 kb upstream of *RGS14* and within an intron of *LMAN2*. The AD GWAS association at this locus colocalises with the eQTL for *RGS14* in macrophages²⁰, CD8 T-cells²², blood³³ and colon²³. *RGS14* has also been shown to be upregulated in lesional skin of AD cases compared to skin from control individuals²⁵ and DEPICT prioritises this gene. However, at this locus *LMAN2* is also a reasonably promising candidate (score=15) based on colocalisation and differential expression evidence (Supplementary Data 11). OpenTargets and POSTGAP prioritise this alternative gene at this locus and

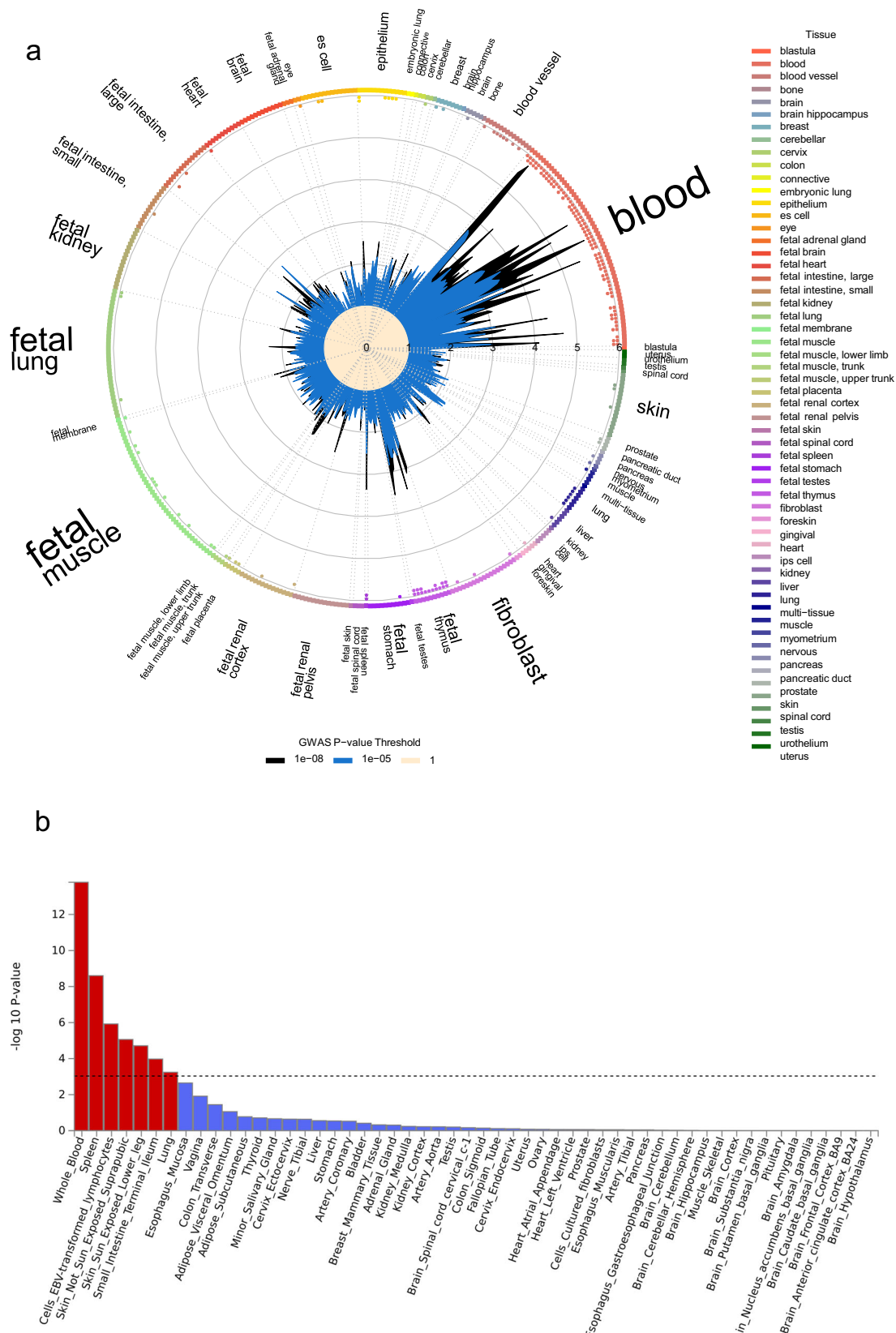


Fig. 2 | Cell type tissue enrichment analysis. a GARFIELD enrichment analysis of open chromatin data. Plot shows enrichment for AD associated variants in DNase I Hypersensitive sites (broad peaks) from ENCODE and Roadmap Epigenomics datasets across cell types. Cell types are sorted and labelled by tissue type. ORs for enrichment are shown for variants at GWAS thresholds of $P < 1 \times 10^{-8}$ (black) and $P < 1 \times 10^{-5}$ (blue) after multiple-testing correction for the number of effective annotations. Outer dots represent enrichment thresholds of $P < 1 \times 10^{-5}$ (one dot)

and $P < 1 \times 10^{-6}$ (two dots). Font size of tissue labels corresponds to the number of cell types from that tissue tested. **b** MAGMA enrichment analysis of gene expression data. Plot shows P -value for MAGMA enrichment for AD associated variants with gene expression from 54 GTEx ver.8 tissue types. The enrichment $-\log_{10}(P\text{-value})$ for each tissue type is plotted on the y-axis. The Bonferroni corrected threshold $P = 0.0009$ is shown as a dotted line and the 7 tissue types that meet this threshold are highlighted as red bars.

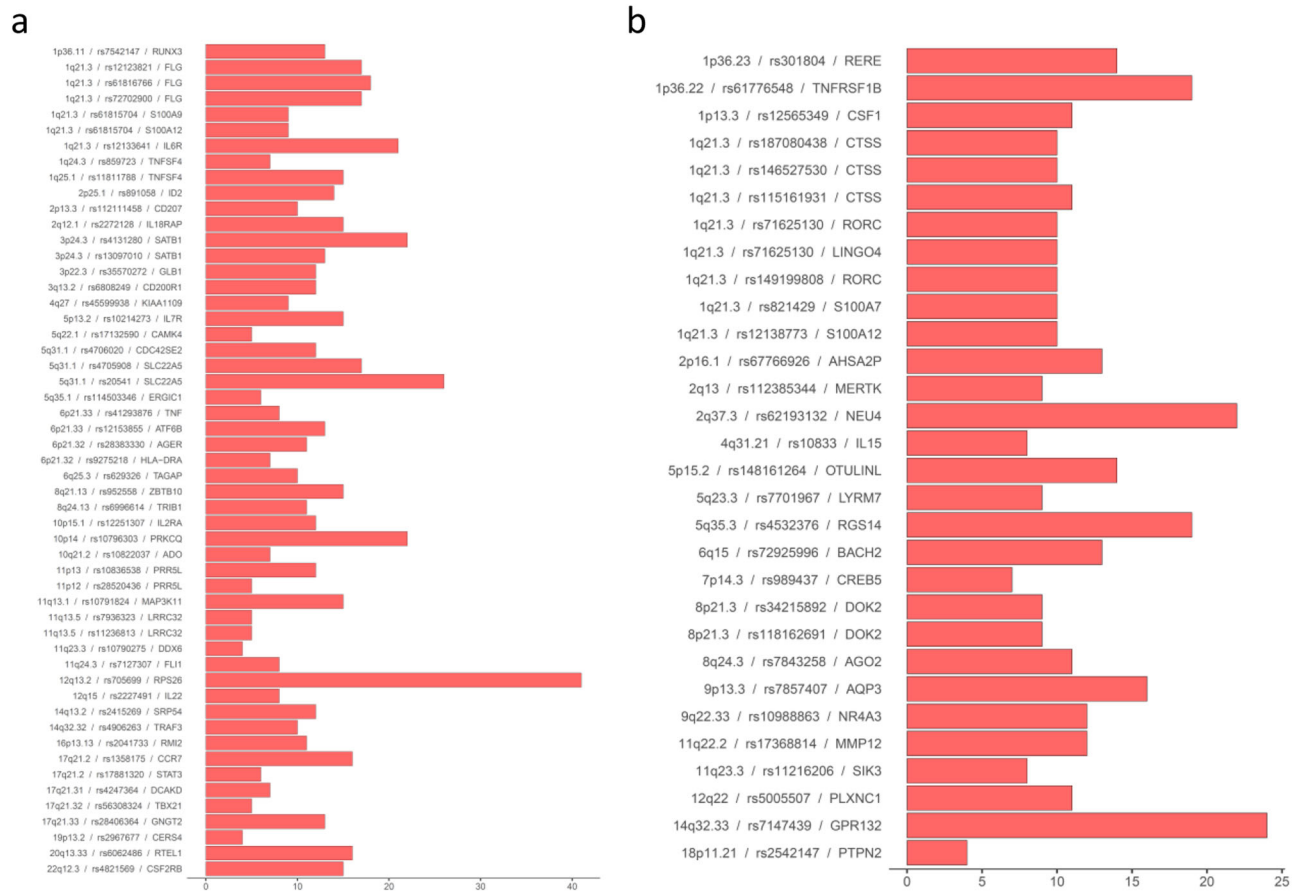


Fig. 3 | Prioritised genes at GWAS loci. Prioritised genes at known (a) and novel (b) loci. For each independent GWAS locus the top prioritised gene (or genes if they were tied) from our bioinformatic analysis is presented along with a bar representing the total evidence score for that gene. A more detailed breakdown of the

constituent parts of this evidence score is presented in Supplementary Fig. 5 and the total evidence scores for the top 3 genes at each locus are presented in Supplementary Data 10. NB. There are some cases of two independent GWAS signals implicating the same gene.

it is possible that genetic variants at this locus influence AD risk through both genetic mechanisms.

We did not include the 3 novel variants from the multi-ancestry analysis in the comprehensive gene prioritisation pipeline because the available resources used predominantly represent European samples only. We did however investigate these variants using Open Targets Genetics, to identify any evidence implicating specific genes at these loci. rs9247 is a missense variant in *INPP5D*, encoding SHIP1, a protein that functions as a negative regulator of myeloid cell proliferation and survival. The *INPP5D* gene has been implicated in hay fever and/or eczema⁵ and other epithelial barrier disorders including inflammatory bowel disease. rs7773987 is intronic for *AHLI* (Abelson helper integration site 1) which is involved with brain development but expressed in a range of tissues throughout the body; single cell analysis in skin shows expression in multiple cell types including specialised immune cells and keratinocytes, but the highest abundance is in endothelial cells (data available from v21.1 proteinatlas.org). The closest genes to rs34599047 are *ATG5* (involved in autophagic vesicle formation) and *PRDMI* (which encodes a master regulator of B cells).

Network analysis

STRING network analysis of the 70 human proteins encoded by genes listed in Tables 1 and 2 showed a protein-protein interaction (PPI) enrichment p -value $< 1 \times 10^{-16}$. The five most highly significant (FDR $P = 1 \times 10^{-9}$) Gene Ontology (GO) terms for biological process relate to immune system activation and regulation (Supplementary Data 12). The network described by the highly enriched term 'Regulation of immune system process' (GO:0002682) is shown in Fig. 4.

Extending the network to include the less well characterised genes/proteins from the multi-ancestry analysis further strengthened this predicted network: The PPI enrichment was again $P < 1 \times 10^{-16}$ and 'Regulation of immune system process' was the most enriched term (FDR $P = 5 \times 10^{-13}$).

Discussion

We present the results of a comprehensive genome-wide association meta-analysis of AD in which we have identified a total of 91 associated loci. This includes 81 loci identified amongst individuals of European ancestry replicated in a further sample of 2.9 million European individuals (as well as many showing replication in data for other ancestries). Of the additional 10 loci identified in a multi-ancestry analysis, 8 replicated in at least one of the populations tested (European, Latino and African ancestry) and a further 2 may be specific to individuals of East Asian ancestry (but require replication).

The majority of the loci associated with AD are shared between the ancestry groups represented in our data, though there were some notable exceptions. We report two previously identified loci with associations that appear to be specific to the Japanese cohort (although driven by just one cohort and still require independent replication). Whilst these have been previously reported⁸, this used the same data as examined here. However, rs59039403 within *NLRP10* is a likely deleterious missense mutation at reasonable frequency in Japanese (13%) that is present at a far lower frequency (<1%) in Europeans. Equally, previous further investigation of the association near *CCDC80* found a putative functional variant (rs12637953) that affects the expression of an enhancer (associated with *CCDC80* promoter) in

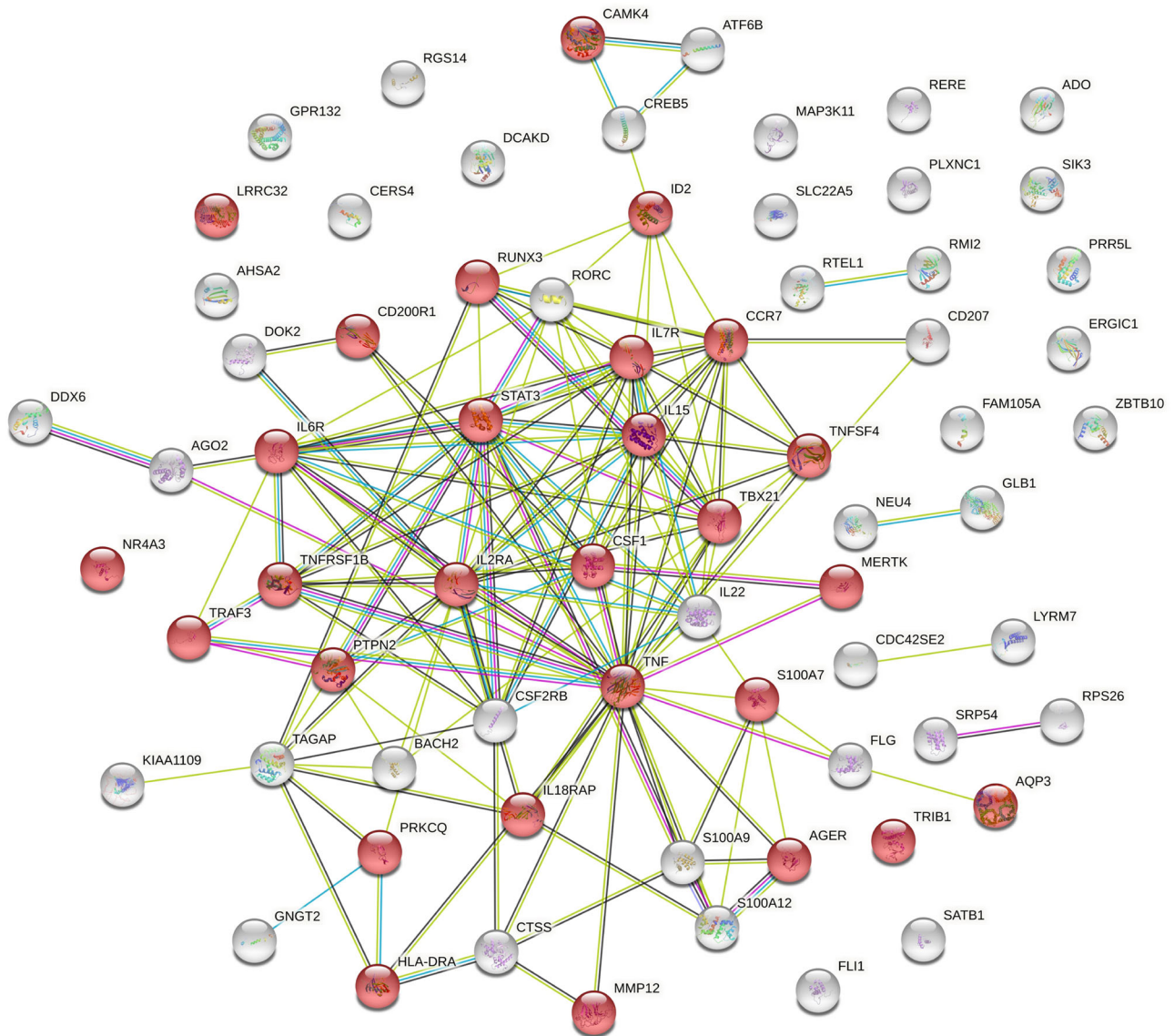


Fig. 4 | Predicted interaction network of proteins encoded by the top prioritised genes from known and novel European GWAS loci. Protein-protein interaction analysis carried out in STRING v11.5; nodes coloured red represent the GO

term 'Regulation of immune system process' (GO:0002682) for which 28/1514 proteins are included (FDR $P = 1 \times 10^{-9}$). Full results for all identified pathways are available in Supplementary Data 12.

epidermis and Langerhans cells⁸, increasing the evidence that these Japanese-specific loci are real. Furthermore, we have identified several loci with association in Europeans (many of which also showed association in individuals of Japanese or Latino ancestry) but which showed no evidence of association in individuals of African ancestry. It is tempting to speculate, using our knowledge of the differing AD phenotypes between European, Asian and African people^{34,35} that the differing genetic associations at some loci may contribute to these clinical observations. rs7773987 within an intron of *AH11* may, for example, indicate a mechanism contributing to neuronal sensitisation leading to the marked lichenification and nodular prurigo-type lesions³⁶ that characterise AD in some people of African and European ethnicities³⁷. Large-scale population cohorts (as used here) have been useful for identifying associated variants. However, we do note that the variants identified should be further examined with respect to specific aspects of AD (age of onset, severity and longitudinal classes³⁸) in future analysis.

The dominance of blood as the tissue showing most enrichment of our GWAS signals in regions of DNase hypersensitivity and of eQTLs suggests the importance of systemic inflammation in AD and this is in

keeping with knowledge of the multisystem comorbidities associated with AD³⁹. The dominance of blood also supports the utility of this easily accessible tissue when characterising genetic risk mechanisms, and for the measurement of biomarkers for many of the implicated loci. However, skin tissue also showed enrichment and there are likely to be some genes for which the effect is only seen in skin. For example, we know that two genes previously implicated in AD, *FLG* and *CD207*^{2,18} are predominantly expressed in the skin and in our gene prioritisation investigations there was no evidence from blood linking *FLG* to the rs61816766 association and only one analysis of monocytes separated from peripheral blood mononuclear cell (PBMC) samples²⁸ which implicated *CD207* for the rs112111458 association, amongst an abundance of evidence from skin for both genes playing a role in AD (Supplementary Data 11). So, whilst the enrichment analysis suggests blood as a useful tissue for genome scale studies of AD and a reasonable tissue to include for further investigation at specific loci, it does not preclude skin as the more relevant tissue for a subset of important genes.

At many of the loci identified in this GWAS, our gene prioritisation analysis, as well as the DEPICT pathway analysis, implicated genes from

pathways that are already known to have a role in AD pathology. The overwhelming majority of these are in pathways related to immune system function; STRING network analysis highlighted the importance of immune system regulation, in keeping with an increasing awareness of the importance of balance in opposing immune mechanisms that can cause paradoxical atopic or psoriatic skin inflammation⁴⁰. Whilst our *in silico analyses* cannot definitively identify specific causal genes (rather, we present a prioritised list of all genes at each locus along with the corresponding evidence for individual evaluation), it is of note that for many of the previously known loci (Table 1) our approach identifies genes which have been validated in experimental settings, e.g. *FLG*⁴¹, *TNF*⁴² and *IL22*⁴³. The individual components of the gene prioritisation analysis have their limitations, particularly the high probability that findings, whilst demonstrating correlation, do not necessarily provide evidence for a causal relationship. This has been particularly highlighted with respect to colocalisation of GWAS and eQTL associations, where high co-regulation can implicate many potentially causal genes⁴⁴. Another limitation is that only cell types (and conditions) that have been studied and made available are included in the *in silico* analysis, and gaps in the data may prove crucial. However, we believe this broad-reaching review of complementary datasets and methods is a useful initial approach to summarise the available evidence, prioritise genes for follow-up and provide information to inform functional experiments. The best evidence is likely to be produced from triangulation of multiple experiments and/or datasets and we have presented our workflow and findings in a way to allow readers to make their own assessments. Another important limitation of our gene prioritisation, is that we only undertook the comprehensive approach for loci associated in European individuals, given that the majority of datasets used come from (and may only be relevant for) European individuals. Expansion of resources that allow for similarly comprehensive follow-up of GWAS loci in individuals of non-European ancestry are urgently needed⁴⁵. However, we do report some evidence that implicates certain genes at loci from our multi-ancestry analysis, whilst noting that these require further investigation in appropriate samples from representative populations.

Amongst the genes prioritised at the novel loci identified in this study, four are targets of existing drugs (and have the required direction of action consistent with the AD risk allele's direction of effect on the gene expression) as reported by Open Targets⁴⁶: *CSFI* is targeted by a macrophage colony-stimulating factor 1 inhibiting antibody (in phase II trials as cancer therapy but also for the treatment of rheumatoid arthritis and cutaneous lupus); *CTSS* is targeted by a small molecule cathepsin S inhibitor (in phase I-II trials for coeliac disease and Sjogren syndrome); *IL15*, targeted by an anti-IL-15 antibody (in phase II trials for autoimmune conditions including vitiligo and psoriasis); and *MMP12*, targeted by small molecule matrix metalloprotease inhibitors (in phase III studies for breast and lung cancer, plus phase II for cystic fibrosis and COPD)⁴⁷. These may offer valuable drug repurposing opportunities.

We have presented the largest GWAS of AD to date, identifying 91 robustly associated loci, 22 with some evidence of population-specific effects. This represents a significant increase in knowledge of AD genetics compared to previous efforts, taking the number of GWAS hits identified in a single study from 31 to 91 and making available the well-powered summary statistics to enable many future important studies (e.g. Mendelian Randomization to investigate causal relationships). To aid translation we have undertaken comprehensive post-GWAS analyses to prioritise potentially causal genes at each locus, implicating many immune system genes and pathways and identifying potential novel drug targets.

Methods

Appropriate ethical approval was obtained for all cohorts by their ethics committees as detailed in the Supplementary Methods.

Phenotype definition

Cases were defined as those who have “ever had atopic dermatitis”, according to the best definition for the cohort, where doctor-diagnosed cases were preferred. Controls were defined as those who had never had AD. Further details on the phenotype definitions for the included studies can be found in Supplementary Methods and Supplementary Data 2.

GWAS analysis and quality control of summary data

We performed genome-wide association analysis (GWAS) for AD case-control status across 40 cohorts including 60,653 AD cases and 804,329 controls of European ancestry. We also included cohorts with individuals of mixed ancestry (Generation R), as well as Japanese (Biobank Japan), African American (SAGE II and SAPPHERE) and Latino (GALA II) studies, giving a total of 65,107 AD cases and 1,021,287 controls.

Genetic data was imputed separately for each cohort with the majority of European cohorts using the haplotype reference consortium (HRC version r1.1) reference panel⁴⁸ (imputed with either the Michigan or Sanger server). 8 European and 2 non-European cohorts instead used the 1000 Genomes Project Phase 1 reference panel for imputation. GWAS was performed separately for each cohort while adjusting for sex and ancestry principal components derived from a genotype matrix (as appropriate in each cohort). Genetic variants were restricted to a MAF > 1% and an imputation quality score > 0.5 unless otherwise specified in the Supplementary Methods. In order to robustly incorporate cohorts with small sample sizes, we applied additional filtering based on the expected minor allele count (EMAC) as previously demonstrated⁴⁹. EMAC combines information on sample size, MAF and imputation quality ($2 \times N \times \text{MAF} \times \text{imputation quality score}$) and a threshold of >50 EMAC was used to include variants for all cohorts. QQ-plots and Manhattan plots for each cohort were generated and visually inspected as part of the quality control process.

Meta-analysis

For the discovery phase, meta-analysis of the European cohorts was performed with GWAMA⁴⁷ for 12,147,822 variants assuming fixed effects, while the multi-ancestry analysis of all cohorts was conducted in MR-MEGA⁵⁰ (which models the heterogeneity in allelic effects that is correlated with ancestry). The latter included only 8,684,278 variants as MR-MEGA excludes variants where the number of contributing cohorts is less than 6. $P < 5 \times 10^{-8}$ was used to define genome-wide significance. Clumping was performed (in PLINK 1.90⁵¹) to identify independent loci. We formed clumps of all SNPs which were ± 500 kb of each index SNP with a linkage disequilibrium $r^2 > 0.001$. Only the index SNP within each clump is reported. For multi-ancestry index variants within 500 kb of index SNPs identified in the European-only analysis, we considered these to be independent if the lead multi-ancestry SNP was not in LD ($r^2 < 0.01$) with the lead neighbouring European variant. Multi-ancestry fixed effect meta-analysis was also performed for comparison with the MR-MEGA results.

Known/Novel assignment

Novel associations are defined as a SNP that had not been reported in a previous GWAS (Supplementary Data 1), or was not correlated ($r^2 < 0.1$ in the relevant ancestry) with a known SNP from this list. In addition, following the assignment of genes to loci (see gene prioritisation) any locus annotated with a gene that has been previously reported were also moved to the ‘known’ list. Therefore, some loci which are reported in Open Targets^{52,53} (but not reported in a published AD GWAS study) have been classed as novel. These loci are marked as such in Table 2.

Conditional analysis

Conditional analysis was performed to identify any independent secondary associations in the European meta-analysis. Genome-wide

complex trait analysis-conditional and joint analysis (GCTA-COJO⁵⁴) was used to test for independent associations 250 kb either side of the index SNPs using UK Biobank HRC imputed data as the reference. COJO-slc was used to determine which SNPs in the region were conditionally independent (using default $P < 1 \times 10^{-5}$) and therefore represent independent secondary associations. COJO-cond was then used to condition on the top hit in each region to determine the conditional effect estimates.

Replication

The genome-wide index SNPs identified from the European and mixed-ancestry discovery meta-analyses were taken forward for replication in 23andMe, Inc. Individuals of European ($N = 2,904,664$), Latino ($N = 525,348$) and African ancestry ($N = 174,015$) were analysed separately. Full details are available in the Supplementary Methods.

LD score regression

Linkage disequilibrium score (LDSC) regression software (version 1.0.1)⁵⁵ was used to estimate the SNP-based heritability (h^2_{SNP}) for AD. This was performed with the summary statistics of the European discovery meta-analysis. The h^2_{SNP} was estimated on liability scale with a population prevalence of 0.15 and a sample prevalence of 0.070.

Genetic correlation with other traits was assessed using all the traits available on CTG-VL⁵⁶ (accessed on 5th November 2021). We considered phenotypes with p -values below the Bonferroni-corrected alpha threshold (i.e., $0.05/1376 = 4 \times 10^{-5}$) to be genetically correlated with AD (a conservative threshold given the likely correlation between many traits tested).

Bioinformatic analysis

For the following analyses we defined the regions within which the true causal SNP resides to be determined by boundaries containing furthest distanced SNPs with $r^2 \geq 0.2$ within $\pm 500\text{kb}$ of the index SNP¹⁸. We refer to such regions as locus intervals and we used them as input for the analyses described below.

Enrichment analysis

Enrichment of tissues and cell types and gene sets for AD GWAS loci was investigated using DEPICT⁵⁷ and GARFIELD (GWAS analysis of regulatory or functional information enrichment with LD correction)⁵⁸ ran with default settings, as well as MAGMA v.1.06⁵⁹ (using GTEX ver. 8²³ on the FUMA⁶⁰ platform). In addition, we used MendelVar⁶¹ run with default settings to check for enrichment of any ontology terms assigned to Mendelian disease genes within the locus interval regions.

By default, MAGMA only assigns variants within genes. DEPICT maps all genes within a given LD ($r^2 > 0.5$) boundary of the index variant. DEPICT gene set enrichment results for GO terms only were grouped (using the Biological Processes ontology) and displayed using the *rrvgo* package. The default scatter function was adapted to only plot parent terms⁶².

Prioritisation of candidate genes

To prioritise candidate genes at each of the loci identified in the European GWAS, we investigated all genes within $\pm 500\text{kb}$ of each index SNP (selected to capture an estimated 98% of causal genes)⁶³. The approach used has been previously described by Sobczyk et al.¹⁸. For each gene we collated evidence from a range of approaches (as described below) to link SNP to gene, resulting in 14 annotation categories (represented as columns in Supplementary Fig. 7). We summarised these annotations for each gene into a score in order to prioritise genes at each locus. We present the top prioritised gene in the main tables, but strength of evidence varies and so we encourage readers to use our full evaluation (of all the evidence presented in Supplementary Data II for all genes at each locus) for loci of interest.

We tested for colocalisation with molecular QTLs, where full summary statistics were available, using *coloc*⁶⁴ method (with betas as input). We used the eQTL Catalogue⁶⁵ and Open GWAS⁶⁶ to download a range of eQTL datasets from all skin, whole blood and immune cell types as well as additional tissue types which showed enrichment for our GWAS loci, such as spleen and oesophagus mucosa¹⁸. A complete list of eQTL datasets^{20–23,26–31,33,67–71} is displayed in Supplementary Data 13. pQTL summary statistics for plasma proteins⁷² were downloaded from Open GWAS. An annotation was included in our gene prioritisation pipeline if there was a posterior probability >95% that the associations from the AD GWAS and the relevant QTL analysis shared the same causal variant.

Additional colocalisation methods were also applied. TWAS (Transcriptome-Wide association Study)-based S-MultiXcan⁷³ and SMR (Summary-based Mendelian Randomization)⁷⁴ were run on datasets available via the CTG-VL platform (including GTEX tissue types and 2 whole blood pQTL^{72,75} datasets available for the SMR pipeline). For S-MultiXcan and SMR, we report only results with p -values below the alpha threshold established with Bonferroni correction, as well as no evidence of heterogeneity (HEIDI P -value > 0.05) in SMR analysis.

Genes were also annotated if they were included in any of the globally enriched ontology/pathway terms from the MendelVar analysis described above or if they were identified in direct look-ups of keywords: “skin”, “kera”, “derma” in their OMIM⁷⁶ descriptions, or Human Phenotype Ontology⁷⁷/Disease Ontology⁷⁸ terms.

We also used machine learning candidate gene prioritisation pipelines – DEPICT⁵⁷, PoPs⁷⁹, POSTGAP⁸⁰ and Open Targets Genetics⁵³ Variant 2 Gene mapping tool as well as gene-based MAGMA⁵⁹ test. We added annotations to genes reported in the top 3 (by each of the pipelines).

We mined the literature for a list of differential expression studies and found 9 RNA-Seq/microarray plus 4 proteomic analyses involving comparisons of AD lesional^{25,32,81–84} or AD nonlesional^{24,25,32,82,85–87} skin vs healthy controls. Studies with comparisons of AD lesional acute vs chronic⁸⁸, blood proteome in AD vs healthy control³² and *FLG* knock-down vs control in living skin-equivalent⁸⁹ were also included. We annotated each gene (including direction of effect, i.e. upregulated/downregulated) with FDR < 0.05 in any dataset.

Lastly, we annotated genes where the index SNP resided within the coding region according to VEP (Variant Effect Predictor)⁹⁰ analysis.

For each candidate gene, we established a pragmatic approach to combine all available evidence in order to prioritise which the most plausible candidate gene(s). This prioritisation was carried out as follows:

- The number of annotations (each representing one piece of evidence) were summed across all methods and datasets, to derive a ‘total evidence score’, i.e., if coloc evidence was observed for 5 datasets for a particular gene, this would add 5 to the score for that gene.
- Additionally, to assess if evidence was coming from multiple datasets using the same method, or evidence was coming from diverse approaches, we counted ‘evidence types’, summing up the methods (as opposed to datasets) with an annotation for each gene tested (up to a maximum of 14), i.e., in the same example of coloc evidence observed in 5 datasets, this would add 1 to this measure for this gene. Evidence types are represented by the columns in Supplementary Fig. 7.
- In order to prioritise genes with the most evidence, whilst ensuring there was some evidence of triangulation across methods, at each locus we prioritised the gene with the highest ‘total evidence score’ with a minimum ‘evidence type’ of 3. ‘Evidence type’ was also used to break ties.

Network analysis

Network analysis of the prioritised genes was carried out using standard settings (minimum interaction score 0.4) in STRING v11.5⁹¹.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Summary statistics of the GWAS meta-analyses generated in this study have been deposited in the GWAS Catalog under study accession IDs [GCST90244787](https://www.ebi.ac.uk/gwas/studies/GCST90244787) and [GCST90244788](https://www.ebi.ac.uk/gwas/studies/GCST90244788). The variant-level data for the 23andMe replication dataset are fully disclosed in the main tables and supplementary tables. Individual-level data are protected and are not available due to data privacy laws, and in accordance with the IRB-approved protocol under which the study was conducted.

Code availability

Code for the bioinformatic analysis is available here: https://github.com/marynias/eczema_gwas_fu/tree/bc4/new_gwas.

References

- Weidinger, S. et al. Atopic dermatitis. *The Lancet* **387**, 1109–1122 (2016).
- Paternoster, L. 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.* **47**, 1449–1456 (2015).
- Paternoster, L. et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. *Nat. Genet.* **44**, 187–192 (2012).
- Weidinger, S. et al. A genome-wide association study of atopic dermatitis identifies loci with overlapping effects on asthma and psoriasis. *Hum. Mol. Genet.* **22**, 4841–4856 (2013).
- Johansson, Å., Rask-Andersen, M., Karlsson, T. & Ek, W. E. Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema. *Assoc. Stud. Article* **28**, 4022–4041 (2019).
- Sliz, E. et al. Uniting biobank resources reveals novel genetic pathways modulating susceptibility for atopic dermatitis. *J. Allergy Clin. Immunol.* **149**, 1105–1112.e9 (2022).
- Grosche, S. et al. Rare variant analysis in eczema identifies exonic variants in DUSP1, NOTCH4 and SLC9A4. *Nat. Commun.* **12**, 1–11 (2021).
- Tanaka, N. et al. Eight novel susceptibility loci and putative causal variants in atopic dermatitis. *J. Allergy Clin. Immunol.* **148**, 1293–1306 (2021).
- Schaarschmidt, H. et al. A genome-wide association study reveals 2 new susceptibility loci for atopic dermatitis. *J. Allergy Clin. Immunol.* **136**, 802–806 (2015).
- Hirota, T. et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. *Nat. Genet.* **44**, 1222–1226 (2012).
- Kim, K. W. et al. Genome-wide association study of recalcitrant atopic dermatitis in Korean children. *J. Allergy Clin. Immunol.* **136**, 678–684.e4 (2015).
- Sun, L.-D. et al. Genome-wide association study identifies two new susceptibility loci for atopic dermatitis in the Chinese Han population. *Nat. Genet.* **43**, 690–694 (2011).
- Esparza-Gordillo, J. et al. A functional IL-6 receptor (IL6R) variant is a risk factor for persistent atopic dermatitis. *J. Allergy Clin. Immunol.* **132**, 371–377 (2013).
- Ellinghaus, D. et al. High-density genotyping study identifies four new susceptibility loci for atopic dermatitis. *Nat. Genet.* **45**, 808–812 (2013).
- Larsen, F. S., Holm, N. V. & Henningsen, K. Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. *J. Am. Acad. Dermatol.* **15**, 487–494 (1986).
- Schultz Larsen, F. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J. Am. Acad. Dermatol.* **28**, 719–723 (1993).
- Budu-Aggrey, A. et al. Investigating the causal relationship between allergic disease and mental health. *Clin. Exp. Allergy* **51**, 1449–1458 (2021).
- Sobczyk, M. K. et al. Triangulating molecular evidence to prioritize candidate causal genes at established atopic dermatitis loci. *J. Invest. Dermatol.* **141**, 2620–2629 (2021).
- Zeng, Z. et al. Roles of G protein-coupled receptors in inflammatory bowel disease. *World J. Gastroenterol.* **26**, 1242–1261 (2020).
- Alasoo, K. et al. Shared genetic effects on chromatin and gene expression indicate a role for enhancer priming in immune response. *Nat. Genet.* **50**, 424 (2018).
- Chen, L. et al. Genetic drivers of epigenetic and transcriptional variation in human immune cells. *Cell* **167**, 1398–1414.e24 (2016).
- Schmiedel, B. J. et al. Impact of genetic polymorphisms on human immune cell gene expression. *Cell* **175**, 1701–1715.e16 (2018).
- GTE Consortium. The GTE Consortium atlas of genetic regulatory effects across human tissues. *Science* **369**, 1318–1330 (2020).
- Winge, M. C. G. et al. Filaggrin genotype determines functional and molecular alterations in skin of patients with atopic dermatitis and ichthyosis vulgaris. *PLoS ONE* **6**, e28254 (2011).
- He, H. et al. Tape strips detect distinct immune and barrier profiles in atopic dermatitis and psoriasis. *J. Allergy Clin. Immunol.* **147**, 199–212 (2021).
- Fairfax, B. P. et al. Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. *Science* **343**, 1246949 (2014).
- Nédélec, Y. et al. Genetic ancestry and natural selection drive population differences in immune responses to pathogens. *Cell* **167**, 657–669.e21 (2016).
- Quach, H. et al. Genetic adaptation and neandertal admixture shaped the immune system of human populations. *Cell* **167**, 643–656.e17 (2016).
- Momozawa, Y. et al. IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. *Nat. Commun.* **9**, 2427 (2018).
- Kasela, S. et al. Pathogenic implications for autoimmune mechanisms derived by comparative eQTL analysis of CD4+ versus CD8+ T cells. *PLoS Genet.* **13**, e1006643 (2017).
- Gutierrez-Arcelus, M. et al. Passive and active DNA methylation and the interplay with genetic variation in gene regulation. *Elife* **2**, e00523 (2013).
- Pavel, A. B. et al. The proteomic skin profile of moderate-to-severe atopic dermatitis patients shows an inflammatory signature. *J. Am. Acad. Dermatol.* **82**, 690–699 (2020).
- Buil, A. et al. Gene-gene and gene-environment interactions detected by transcriptome sequence analysis in twins. *Nat. Genet.* **47**, 88–91 (2015).
- Nomura, T., Wu, J., Kabashima, K. & Guttman-Yassky, E. Endophenotypic variations of atopic dermatitis by age, race, and ethnicity. *J. Allergy Clin. Immunol. Pract.* **8**, 1840–1852 (2020).
- Yew, Y. W., Thyssen, J. P. & Silverberg, J. I. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. *J. Am. Acad. Dermatol.* **80**, 390–401 (2019).
- Ständer, H. F., Elmariah, S., Zeidler, C., Spellman, M. & Ständer, S. Diagnostic and treatment algorithm for chronic nodular prurigo. *J. Am. Acad. Dermatol.* **82**, 460–468 (2020).

37. Sangha, A. M. Dermatological conditions in SKIN OF COLOR: managing atopic dermatitis. *J. Clin. Aesthet. Dermatol.* **14**, S20–S22 (2021).
38. Paternoster, L. et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J. Allergy Clin. Immunol.* **141**, 964–971 (2018).
39. Langan, S. M., Irvine, A. D. & Weidinger, S. Atopic dermatitis. *Lancet* **396**, 345–360 (2020).
40. Al-Janabi, A., Foulkes, A. C., Griffiths, C. E. M. & Warren, R. B. Paradoxical eczema in patients with psoriasis receiving biologics: a case series. *Clin. Exp. Dermatol.* **47**, 1174–1178 (2022).
41. McAleer, M. A. & Irvine, A. D. The multifunctional role of filaggrin in allergic skin disease. *J. Allergy Clin. Immunol.* **131**, 280–291 (2013).
42. Danso, M. O. et al. TNF- α and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. *J. Invest. Dermatol.* **134**, 1941–1950 (2014).
43. Gutowska-Owsiak, D., Schaupp, A. L., Salimi, M., Taylor, S. & Ogg, G. S. Interleukin-22 downregulates filaggrin expression and affects expression of profilaggrin processing enzymes. *Br. J. Dermatol.* **165**, 492–498 (2011).
44. Wainberg, M. et al. Opportunities and challenges for transcriptome-wide association studies. *Nat. Genet.* **51**, 592–599 (2019).
45. Hindorff, L. A. et al. Prioritizing diversity in human genomics research. *Nat. Rev. Genet.* **19**, 175–185 (2018).
46. Ochoa, D. et al. Open Targets Platform: supporting systematic drug–target identification and prioritisation. *Nucleic Acids Res.* **49**, D1302–D1310 (2021).
47. Mägi, R. & Morris, A. P. GWAMA: software for genome-wide association meta-analysis. *BMC Bioinform.* **11**, 288 (2010).
48. McCarthy, S. et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
49. Bustamante, M. et al. A genome-wide association meta-analysis of diarrhoeal disease in young children identifies FUT2 locus and provides plausible biological pathways. *Hum. Mol. Genet.* **25**, 4127–4142 (2016).
50. Mägi, R. et al. Trans-ethnic meta-regression of genome-wide association studies accounting for ancestry increases power for discovery and improves fine-mapping resolution. *Hum. Mol. Genet.* **26**, 3639–3650 (2017).
51. Purcell, S. et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
52. Ghousaini, M. et al. Open Targets Genetics: systematic identification of trait-associated genes using large-scale genetics and functional genomics. *Nucleic Acids Res.* **49**, D1311–D1320 (2021).
53. Mountjoy, E. et al. An open approach to systematically prioritize causal variants and genes at all published human GWAS trait-associated loci. *Nat. Genet.* **53**, 1527–1533 (2021).
54. Yang, J. et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* **44**, 369–375, (2012).
55. Zheng, J. 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* **33**, 272–279 (2017).
56. Cuéllar-Partida, G. et al. Complex-Traits Genetics Virtual Lab: A community-driven web platform for post-GWAS analyses. *bioRxiv* <https://doi.org/10.1101/518027> (2019)
57. Pers, T. H. et al. Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6**, 5890 (2015).
58. Iotchkova, V. et al. GARFIELD classifies disease-relevant genomic features through integration of functional annotations with association signals. *Nat. Genet.* **51**, 343–353 (2019).
59. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
60. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun* **8**, 1–11 (2017).
61. Sobczyk, M. K., Gaunt, T. R. & Paternoster, L. MendelVar: gene prioritization at GWAS loci using phenotypic enrichment of Mendelian disease genes. *Bioinformatics* **37**, 1–8 (2021).
62. Sayols, S. rrvgo: a Bioconductor package for interpreting lists of Gene Ontology terms. *MicroPubl. Biol.* <https://doi.org/10.17912/micropub.biology.000811> (2023)
63. Stacey, D. et al. ProGeM: a framework for the prioritization of candidate causal genes at molecular quantitative trait loci. *Nucleic Acids Res.* **47**, e3–e3 (2019).
64. Giambartolomei, C. et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet.* **10**, e1004383 (2014).
65. Kerimov, N. et al. A compendium of uniformly processed human gene expression and splicing quantitative trait loci. *Nat. Genet.* **53**, 1290–1299 (2021).
66. Elsworth, B. et al. The MRC IEU OpenGWAS data infrastructure. *bioRxiv* <https://doi.org/10.1101/2020.08.10.244293> (2020)
67. Vösa, U. et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat. Genet.* **53**, 1300–1310 (2021).
68. Fairfax, B. P. et al. Genetics of gene expression in primary immune cells identifies cell type-specific master regulators and roles of HLA alleles. *Nat. Genet.* **44**, 502–510 (2012).
69. Lappalainen, T. et al. Transcriptome and genome sequencing uncovers functional variation in humans. *Nature* **501**, 506–511 (2013).
70. Lepik, K. et al. C-reactive protein upregulates the whole blood expression of CD59 - an integrative analysis. *PLoS Comput. Biol.* **13**, e1005766 (2017).
71. Naranbhai, V. et al. Genomic modulators of gene expression in human neutrophils. *Nat. Commun.* **6**, 7545 (2015).
72. Sun, B. B. et al. Genomic atlas of the human plasma proteome. *Nature* **558**, 73–79 (2018).
73. Barbeira, A. N. et al. Integrating predicted transcriptome from multiple tissues improves association detection. *PLoS Genet.* **15**, e1007889 (2019).
74. Zhu, Z. et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–487 (2016).
75. Suhre, K. et al. Connecting genetic risk to disease end points through the human blood plasma proteome. *Nat. Commun.* **8**, 14357 (2017).
76. Amberger, J. S., Bocchini, C. A., Scott, A. F. & Hamosh, A. OMIM.org: leveraging knowledge across phenotype-gene relationships. *Nucleic Acids Res.* **47**, D1038–D1043 (2019).
77. Köhler, S. et al. Expansion of the Human Phenotype Ontology (HPO) knowledge base and resources. *Nucleic Acids Res.* **47**, D1018–D1027 (2019).
78. Schriml, L. M. et al. Human Disease Ontology 2018 update: classification, content and workflow expansion. *Nucleic Acids Res.* **47**, D955–D962 (2019).
79. Weeks, E. M. et al. Leveraging polygenic enrichments of gene features to predict genes underlying complex traits and diseases. *medRxiv* <https://doi.org/10.1101/2020.09.08.20190561> (2020)
80. Peat, G. et al. The open targets post-GWAS analysis pipeline. *Bioinformatics* **36**, 2936–2937 (2020).

81. Rojahn, T. B. et al. Single-cell transcriptomics combined with interstitial fluid proteomics defines cell type-specific immune regulation in atopic dermatitis. *J. Allergy Clin. Immunol.* **146**, 1056–1069 (2020).
82. Pavel, A. B. et al. Tape strips from early-onset pediatric atopic dermatitis highlight disease abnormalities in nonlesional skin. *Allergy* **76**, 314–325 (2021).
83. Dyjack, N. et al. Minimally invasive skin tape strip RNA sequencing identifies novel characteristics of the type 2-high atopic dermatitis disease endotype. *J. Allergy Clin. Immunol.* **141**, 1298–1309 (2018).
84. Molin, S. et al. The hand eczema proteome: imbalance of epidermal barrier proteins. *Br. J. Dermatol.* **172**, 994–1001 (2015).
85. Cole, C. et al. Filaggrin-stratified transcriptomic analysis of pediatric skin identifies mechanistic pathways in patients with atopic dermatitis. *J. Allergy Clin. Immunol.* **134**, 82–91 (2014).
86. Ewald, D. A. et al. Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways. *BMC Med. Genomics* **8**, 60 (2015).
87. Morelli, P. et al. Proteomic analysis from skin swabs reveals a new set of proteins identifying skin impairment in atopic dermatitis. *Exp. Dermatol.* **30**, 811–819 (2021).
88. Tsoi, L. C. et al. Progression of acute-to-chronic atopic dermatitis is associated with quantitative rather than qualitative changes in cytokine responses. *J. Allergy Clin. Immunol.* **145**, 1406–1415 (2020).
89. Elias, M. S. et al. Proteomic analysis of filaggrin deficiency identifies molecular signatures characteristic of atopic eczema. *J. Allergy Clin. Immunol.* **140**, 1299–1309 (2017).
90. McLaren, W. et al. The ensembl variant effect predictor. *Genome Biol.* **17**, 122 (2016).
91. Szklarczyk, D. et al. STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res.* **47**, D607–D613 (2019).
92. Kichaev, G. et al. Leveraging polygenic functional enrichment to improve GWAS power. *Am. J. Hum. Genet.* **104**, 65–75 (2019).
93. Neale, B. GWAS results round 2. <http://www.nealelab.is/uk-biobank/> (2018).

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Author contributions

Designed and co-ordinated the study: M.St., L.P. Performed the meta-analysis: A.B.-A., A. Ki. Performed the bioinformatic analysis: M.K.S. Performed the STRING analysis: S.J. Br. Performed statistical analysis within cohorts: A.B.-A., A. Ki, R. Mi, K.R., R. Mä, M.N., N.T., B.M.B., L.F.T., P.S.N., C.F., A.E.O., E.H.L., J.V.T.L., J.B.J., I.M., A.A.-S., A.J., H. Ba., E.R., A. Ku., C.M.G., C.H., C.Q., P.T., E.A., J.F., C.A.W., E.T., B.W., S.K., D.M.K., L.K., J.D., H.Z., C.A., V.U., R.K., A. Sz., A.C.S.N.J., A.G., M.I., M. M.-Nu., T.S.A., M.B., C.G., M.P.Y., D.P.S., N.G., Y.A.L., A.D.I., L.K.W., C.M., S.J. Br. Data acquisition/supported analysis/interpretation of data: A.B.-A., A. Ki, A.R., P.S.N., A.J., C.j.X., S.E.H., J.F., E.T., S.K., H.Z., S.H., T. Ho., E.J., H.C., N.R., P.N., O.A.A., S.J., C.A., T.G., V.U., P.K.E.M., E.G.B., J.P.T., T. Ha., L.L.K., T.M.D., A.Ar., G.H., S.L., M.M. Nö., N.H., M.I., T.S.Ah., J.S., B.C., A.M.M.S., A.E., S.Ar., T.E., L.A.M., A.M., C.T., K.A., M.L., K.H., B.J., D.P.S., Y.A.L., N.P.H., S.W., A.D.I., D.J., T.N., L.D., J.M.V., G.H.K., K.M.G., B.F., C.E.P., P.D.S., P.G.Ho., H. Bi., K.B., J.C., A. Si., T.S., S.J. Br., M.St., L.P. Wrote the paper: A.B.-A., A. Ki, M.K.S., S.J. Br., M.S., L.P. Approved final version of paper: A.B.-A., A. Ki, M.K.S., S.S.S., R. Mi, K.R., A.R., R. Mä, M.N., N.T., B.M.B., L.F.T., P.S.N., C.F., A.E.O., E.H.L., J.V.T.L., J.B.J., I.M., A.A.-S., A.J., K.A.F., H. Ba., E.R., A.C.A., A. Ku., P.M.S., X.C., C.M.G., C.H., C.j.X., C.Q., S.E.H., P.T., E.A., J.F., C.A.W., E.T., B.W., S.K., D.M.K., L.K., J.D., H.Z., S.H., T. Ho., E.J., H.C., N.R., P.N., O.A.A., S.J., C.A., T.G., V.U., R.K., P.K.E.M., A. Sz., E.G.B., J.P.T., T. Ha., L.L.K., T.M.D., A.C.S.N.J., A.G., A.Ar., G.H., S.L., M.M. Nö., N.H., M.I., A.V., M.F., V.B., P.Hy., N.B., D.I.B., J.J.H., M.M.-Nu., T.S.Ah., J.S., B.C., A.M.M.S., A.E., M.B., B.R., S.Ar., C.G., T.E., L.A.M., A.M., C.T., K.A., M.L., K.H., B.J., M.P.Y., D.P.S., N.G., A.L., Y.A.L., N.P.H., S.W., M.R.J., E.M., H.H., A.D.I., D.J., T.N., L.D., J.M.V., G.H.K., K.M.G., S.J. Ba., B.F., C.E.P., P.D.S., P.G.Ho., L.K.W., H. Bi., K.B., J.C., A. Si., C.M., T.S., S.Bu., S.T.W., J.W.H., J.L.M., S.J. Br., M.St., L.P.

Competing interests

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Correspondence and requests for materials should be addressed to Lavinia Paternoster.

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Ashley Budu-Aggrey^{1,2,124}, **Anna Kilanowski**^{3,4,5,124}, **Maria K. Sobczyk**^{1,2}, **23andMe Research Team**, **Suyash S. Shringarpure**⁶, **Ruth Mitchell**^{1,2}, **Kadri Reis**⁷, **Anu Reigo**⁷, **Estonian Biobank Research Team**, **Reedik Mägi**⁷, **Mari Nelis**^{7,8}, **Nao Tanaka**^{9,10}, **Ben M. Brumpton**^{11,12,13}, **Laurent F. Thomas**^{11,14,15,16}, **Pol Sole-Navais**¹⁷, **Christopher Flatley**¹⁷, **Antonio Espuela-Ortiz**¹⁸, **Esther Herrera-Luis**¹⁸, **Jesus V. T. Lominchar**¹⁹, **Jette Bork-Jensen**¹⁹, **Ingo Marenholz**^{20,21}, **Aleix Arnau-Soler**^{20,21}, **Ayoung Jeong**^{22,23}, **Katherine A. Fawcett**²⁴, **Hansjorg Baurecht**²⁵, **Elke Rodriguez**²⁶, **Alexsander Couto Alves**²⁷, **Ashish Kumar**²⁸, **Patrick M. Sleiman**^{29,30,31}, **Xiao Chang**²⁹, **Carolina Medina-Gomez**^{32,33}, **Chen Hu**^{32,34}, **Cheng-jian Xu**^{35,36,37,38}, **Cancan Qi**^{35,36}, **Sarah El-Heis**³⁹, **Philip Titcombe**³⁹, **Elie Antoun**^{40,41}, **João Fadista**^{42,43,44,45}, **Carol A. Wang**^{46,47}, **Elisabeth Thiering**^{3,4}, **Baojun Wu**⁴⁸, **Sara Kress**⁴⁹, **Dilini M. Kothalawala**^{50,51}, **Latha Kadalayil**⁵⁰, **Jiasong Duan**⁵², **Hongmei Zhang**⁵², **Sabelo Hadebe**⁵³, **Thomas Hoffmann**^{54,55}, **Eric Jorgenson**⁵⁶, **Hélène Choquet**⁵⁷, **Neil Risch**^{54,55}, **Pål Njølstad**^{58,59}, **Ole A. Andreassen**^{60,61}, **Stefan Johansson**^{58,62}, **Catarina Almqvist**^{63,64}, **Tong Gong**⁶³, **Vilhelmina Ullemar**⁶³, **Robert Karlsson**⁶³, **Patrik K. E. Magnusson**⁶³, **Agnieszka Sz wajda**⁶³, **Esteban G. Burchard**^{65,66}, **Jacob P. Thyssen**⁶⁷, **Torben Hansen**¹⁹, **Line L. Kårhus**⁶⁸, **Thomas M. Dantoft**⁶⁸, **Alexander C.S.N. Jeanrenaud**^{20,21}, **Ahla Ghauri**^{20,21}, **Andreas Arnold**⁶⁹, **Georg Homuth**⁷⁰, **Susanne Lau**⁷¹, **Markus M. Nöthen**⁷², **Norbert Hübner**^{20,73}, **Medea Imboden**^{22,23}, **Alessia Visconti**⁷⁴, **Mario Falchi**⁷⁴, **Veronique Bataille**^{74,75}, **Pirro Hysi**⁷⁴, **Natalia Ballardini**²⁸, **Dorret I. Boomsma**^{76,77}, **Jouke J. Hottenga**⁷⁶, **Martina Müller-Nurasyid**^{78,79,80}, **Tarunveer S. Ahluwalia**^{81,82,83}, **Jakob Stokholm**^{81,84}, **Bo Chawes**⁸¹, **Ann-Marie M. Schoos**^{81,84}, **Ana Esplugues**^{85,86}, **Mariona Bustamante**^{87,88,89}, **Benjamin Raby**⁹⁰, **Syed Arshad**^{91,92}, **Chris German**⁶, **Tõnu Esko**⁷, **Lili A. Milani**⁷, **Andres Metspalu**⁷, **Chikashi Terao**^{9,93,94}, **Katrina Abuabara**⁹⁵, **Mari Løset**^{11,96}, **Kristian Hveem**^{11,97}, **Bo Jacobsson**^{17,98}, **Maria Pino-Yanes**^{18,99,100}, **David P. Strachan**¹⁰¹, **Niels Grarup**¹⁹, **Allan Linneberg**^{68,102}, **Young-Ae Lee**^{20,21}, **Nicole Probst-Hensch**^{22,23}, **Stephan Weidinger**¹⁰³, **Marjo-Riitta Jarvelin**^{104,105,106}, **Erik Melén**²⁸, **Hakon Hakonarson**^{29,107,108}, **Alan D. Irvine**¹⁰⁹, **Deborah Jarvis**^{110,111}, **Tamar Nijsten**³⁴, **Liesbeth Duijts**^{112,113}, **Judith M. Vonk**^{36,114}, **Gerard H. Koppelman**^{35,36}, **Keith M. Godfrey**¹¹⁵, **Sheila J. Barton**³⁹, **Bjarke Feenstra**⁴³, **Craig E. Pennell**^{46,47}, **Peter D. Sly**^{116,117}, **Patrick G. Holt**¹¹⁸, **L. Keoki Williams**⁴⁸, **Hans Bisgaard**^{81,126}, **Klaus Bønnelykke**⁸¹, **John Curtin**¹¹⁹, **Angela Simpson**¹¹⁹, **Clare Murray**¹¹⁹, **Tamara Schikowski**¹²⁰, **Supinda Bunyavanich**¹²¹, **Scott T. Weiss**⁹⁰, **John W. Holloway**^{50,91}, **Josine L. Min**^{1,2}, **Sara J. Brown**¹²², **Marie Standl**^{3,123} & **Lavinia Paternoster**^{1,2,125} ✉

¹Medical Research Council Integrative Epidemiology Unit, Bristol Medical School, University of Bristol, Bristol, England. ²Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, England. ³Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. ⁴Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, Germany. ⁵Pettenkofer School of Public Health, Ludwig-Maximilians University Munich, Munich, Germany. ⁶23andMe, Inc., Sunnyvale, CA, USA. ⁷Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia. ⁸Core Facility of Genomics, University of Tartu, Tartu, Estonia. ⁹Laboratory for Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. ¹⁰Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan. ¹¹K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim 7030, Norway. ¹²HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger 7600, Norway. ¹³Clinic of Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim 7030, Norway. ¹⁴Department of Clinical and Molecular Medicine, NTNU Norwegian University of Science and Technology, Trondheim, Norway. ¹⁵BioCore - Bioinformatics Core Facility, NTNU, Norwegian University of Science and Technology, Trondheim, Norway. ¹⁶Clinic of Laboratory Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. ¹⁷Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ¹⁸Genomics and Health Group, Department of Biochemistry, Microbiology, Cell Biology and Genetics, Universidad de La Laguna, La Laguna, Tenerife, Spain. ¹⁹Novo Nordisk Foundation Center for Basic Metabolic

Research, Faculty of Health and Medical Sciences, University of Copenhagen, København, Denmark. ²⁰Max-Delbrück-Center for Molecular Medicine, Berlin, Germany. ²¹Clinic for Pediatric Allergy, Experimental and Clinical Research Center, Charité-Universitätsmedizin Berlin, Berlin, Germany. ²²Swiss Tropical and Public Health Institute, CH-4123 Basel, Switzerland. ²³University of Basel, CH-4001 Basel, Switzerland. ²⁴Department of Health Sciences, University of Leicester, Leicester LE1 7RH, UK. ²⁵Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany. ²⁶Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Kiel, Germany. ²⁷School of Biosciences and Medicine, University of Surrey, Guildford, UK. ²⁸Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Solna, Sweden. ²⁹Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA. ³⁰Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA. ³¹Rhythm Pharmaceuticals, 222 Berkley Street, Boston 02116, USA. ³²The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ³³Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ³⁴Department of Dermatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ³⁵University of Groningen, University Medical Center Groningen, Department of Pediatric Pulmonology and Pediatric Allergy, Beatrix Children's Hospital, Groningen, The Netherlands. ³⁶University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, The Netherlands. ³⁷Centre for Individualized Infection Medicine, CiIM, a joint venture between Hannover Medical School and the Helmholtz Centre for Infection Research, Hannover, Germany. ³⁸TWINCORE, Centre for Experimental and Clinical Infection Research, a joint venture between the Hannover Medical School and the Helmholtz Centre for Infection Research, Hannover, Germany. ³⁹MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK. ⁴⁰Faculty of Medicine, University of Southampton, Southampton, UK. ⁴¹Institute of Developmental Sciences, University of Southampton, Southampton, UK. ⁴²Department of Bioinformatics & Data Mining, Måløv, Denmark. ⁴³Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark. ⁴⁴Department of Clinical Sciences, Lund University Diabetes Centre, Malmö, Sweden. ⁴⁵Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. ⁴⁶School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia. ⁴⁷Hunter Medical Research Institute, Newcastle, NSW, Australia. ⁴⁸Center for Individualized and Genomic Medicine Research (CIGMA), Department of Medicine, Henry Ford Health, Detroit, MI 48104, USA. ⁴⁹Environmental Epidemiology of Lung, Brain and Skin Aging, IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany. ⁵⁰Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK. ⁵¹NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK. ⁵²Division of Epidemiology, Biostatistics, and Environmental Health, School of Public Health, University of Memphis, Memphis, TN, USA. ⁵³Division of Immunology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa. ⁵⁴Institute for Human Genetics, UCSF, San Francisco, CA 94143, USA. ⁵⁵Department of Epidemiology and Biostatistics, UCSF, San Francisco, CA 94158, USA. ⁵⁶Regeneron Genetics Center, Tarrytown, NY, USA. ⁵⁷Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA. ⁵⁸Center for Diabetes Research, Department of Clinical Science, University of Bergen, NO-5020 Bergen, Norway. ⁵⁹Children and Youth Clinic, Haukeland University Hospital, NO-5021 Bergen, Norway. ⁶⁰NORMENT Centre, Institute of Clinical Medicine, University of Oslo, 0450 Oslo, Norway. ⁶¹Division of Mental Health and Addiction, Oslo University Hospital, 0450 Oslo, Norway. ⁶²Department of Medical Genetics, Haukeland University Hospital, NO-5021 Bergen, Norway. ⁶³Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ⁶⁴Pediatric Lung and Allergy Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden. ⁶⁵Department of Medicine, University of California San Francisco, San Francisco, CA, USA. ⁶⁶Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA. ⁶⁷Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark. ⁶⁸Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark. ⁶⁹Clinic and Polyclinic of Dermatology, University Medicine Greifswald, Greifswald, Germany. ⁷⁰Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany. ⁷¹Department of Pediatric Respiratory Medicine, Immunology, and Critical Care Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany. ⁷²Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany. ⁷³Charite-Universitätsmedizin Berlin, Berlin, Germany. ⁷⁴Department of Twin Research & Genetics Epidemiology, Kings College London, London, UK. ⁷⁵Dermatology Department, West Herts NHS Trust, Watford, UK. ⁷⁶Dept Biological Psychology, Netherlands Twin Register, VU University, Amsterdam, the Netherlands. ⁷⁷Institute for Health and Care Research (EMGO), VU University, Amsterdam, the Netherlands. ⁷⁸Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. ⁷⁹IBE, Faculty of Medicine, LMU Munich, Munich, Germany. ⁸⁰Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center, Johannes Gutenberg University, Mainz, Germany. ⁸¹COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark. ⁸²Steno Diabetes Center Copenhagen, Herlev, Denmark. ⁸³Department of Biology, University of Copenhagen, Copenhagen, Denmark. ⁸⁴Department of Pediatrics, Slagelse Hospital, Slagelse, Denmark. ⁸⁵Nursing School, University of Valencia, FISABIO-University Jaume I-University of Valencia, Valencia, Spain. ⁸⁶Joint Research Unit of Epidemiology and Environmental Health, CIBERESP, Valencia, Spain. ⁸⁷ISGlobal, Institute for Global Health, Barcelona, Spain. ⁸⁸Universitat Pompeu Fabra (UPF), Barcelona, Spain. ⁸⁹CIBER Epidemiología y Salud Pública, Madrid, Spain. ⁹⁰Channing Division of Network Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA. ⁹¹Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK. ⁹²David Hide Asthma and Allergy Research Centre, Isle of Wight, UK. ⁹³Clinical Research Center, Shizuoka General Hospital, Shizuoka, Japan. ⁹⁴Department of Applied Genetics, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan. ⁹⁵Department of Dermatology, University of California San Francisco, San Francisco, CA, USA. ⁹⁶Department of Dermatology, Clinic of Orthopaedy, Rheumatology and Dermatology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. ⁹⁷HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway. ⁹⁸Department of Genetics and Bioinformatics, Norwegian Institute of Public Health, Oslo, Norway. ⁹⁹CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. ¹⁰⁰Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, San Cristóbal de La Laguna, Santa Cruz de Tenerife, Spain. ¹⁰¹Population Health Research Institute, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK. ¹⁰²Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ¹⁰³Department of Dermatology, Allergology and Venereology, University Hospital Schleswig-Holstein, Kiel, Germany. ¹⁰⁴Department of Epidemiology and Biostatistics, MRC-PHE Centre for Environment & Health, School of Public Health, Imperial College London, London, UK. ¹⁰⁵Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland. ¹⁰⁶Biocenter Oulu, University of Oulu, Oulu, Finland. ¹⁰⁷Department of Pediatrics, Divisions of Human Genetics and Pulmonary Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA. ¹⁰⁸Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland. ¹⁰⁹Department of Clinical Medicine, Trinity College, Dublin, Ireland. ¹¹⁰Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College London, London, United Kingdom. ¹¹¹Medical Research Council and Public Health England Centre for Environment and Health, London, United Kingdom. ¹¹²Department of Pediatrics, division of Respiratory Medicine and Allergology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ¹¹³Department of Pediatrics, division of Neonatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ¹¹⁴University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, The Netherlands. ¹¹⁵MRC Lifecourse Epidemiology Centre and




NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK. ¹¹⁶Children's Health and Environment Program, Child Health Research Centre, The University of Queensland, South Brisbane 4101 Queensland, Australia. ¹¹⁷Australian Infectious Diseases Research Centre, The University of Queensland, St Lucia 4072 QLD, Australia. ¹¹⁸Telethon Kids Institute, University of Western Australia, Perth, WA, Australia. ¹¹⁹Division of Immunology, Immunity to Infection and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester Academic Health Science Centre, and Manchester University NHS Foundation Trust, Manchester, England. ¹²⁰Environmental Epidemiology of Lung, Brain and Skin Aging, Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany. ¹²¹Division of Allergy and Immunology, Department of Pediatrics, and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹²²Centre for Genomics and Experimental Medicine, Institute for Genetics and Cancer, University of Edinburgh, Crewe Road, Edinburgh UK EH4 2XU, Scotland. ¹²³German Center for Lung Research (DZL), Munich, Germany. ¹²⁴These authors contributed equally: Ashley Budu-Aggrey, Anna Kilanowski. ¹²⁵These authors jointly supervised this work: Marie Standl, Lavinia Paternoster. ¹²⁶Deceased: Hans Bisgaard.

✉ e-mail: l.paternoster@bristol.ac.uk

23andMe Research Team

Suyash S. Shringarpure ⁶ & Chris German⁶

Estonian Biobank Research Team

Reedik Mägi ⁷, Mari Nelis^{7,8}, Tõnu Esko⁷, Lili A. Milani ⁷ & Andres Metspalu ⁷