Multi-ethnic genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis

Citation

Published Version
doi:10.1038/ng.3424

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:27320465

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Multi-ethnic genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis

A full list of authors and affiliations appears at the end of the article.

Abstract

Genetic association studies have identified 21 loci associated with atopic dermatitis risk predominantly in populations of European ancestry. To identify further susceptibility loci for this common complex skin disease, we performed a meta-analysis of >15 million genetic variants in 21,399 cases and 95,464 controls from populations of European, African, Japanese and Latino ancestry, followed by replication in 32,059 cases and 228,628 controls from 18 studies. We identified 10 novel risk loci, bringing the total number of known atopic dermatitis risk loci to 31 (with novel secondary signals at 4 of these). Notably, the new loci include candidate genes with roles in regulation of innate host defenses and T-cell function, underscoring the important contribution of (auto-)immune mechanisms to atopic dermatitis pathogenesis.

Atopic dermatitis (eczema) is a common inflammatory skin disease affecting 15–30% of children and 5-10% of adults. Its pathogenesis involves skin barrier abnormalities and a T-cell-driven cutaneous inflammation. Atopic dermatitis has significant genetic contributions, with heritability estimates of up to 90% in Europeans. The strongest known risk factors are null mutations of the filaggrin (FLG) gene, resulting in epidermal barrier deficiency. Genome-wide association (GWA) studies have identified 20 additional loci (10 in Europeans, 8 in Japanese, 2 in Chinese populations), mostly implicated in immune dysregulation. Genetic modeling suggests further loci may be identified with well-powered GWAS. We therefore carried out a multi-ethnic meta-analysis of 26 studies comprising 21,399 cases and 95,464 controls imputed to the 1000 Genomes Project Phase 1...
reference panel (Supplementary Note 1 & Supplementary Table 1). 15,539,996 variants with ≥1% MAF were analyzed.

A fixed effects meta-analysis of the 22 European studies identified 21 genome-wide significant (\(p<5\times10^{-8}\)) loci (Table 1, Fig 1, Supplementary Figs 1-4), and a multi-ethnic meta-analysis identified an additional 6 loci with log10 Bayes Factor>6.1, 4 of which (10q21.2, 6p21.33, 11p13, 2p13.3) also showed nominal association in the European analysis (Table 1). These 27 loci included all 11 loci previously associated with atopic dermatitis in Europeans and 5 loci originally reported in Japanese. Three Japanese loci (6p21.33, 10q21.2, 2q12.1) were also strongly associated in the European analysis, whereas two (3q13.2, 11p15.4) may represent Japanese-specific signals (Supplementary Figs 1&2), with the European confidence interval ruling out all but very small effects (OR<1.03, Table 1). Furthermore, a locus originally reported in a Chinese GWAS (20q13.33) showed association in Europeans. We identified 11 novel loci for atopic dermatitis. Four (11q24.3, 10p15.1, 8q21.13, 2p25.1) were previously associated with self-reported allergy\(^{14}\), and another (8q21.13) with asthma\(^{15}\). Two novel variants (5p13.2 and 2p25.1) showed statistically significant evidence of heterogeneity between European and non-European studies (Cochran’s \(Q\) \(p<0.01\), Supplementary Table 2). Both showed little evidence for association in non-Europeans (particularly Japanese, Supplementary Fig.2). The CIs also overlapped for all variants when comparing pediatric (defined as onset by age 6) with any-age onset studies (Supplementary Fig.3). Within Europeans there was some evidence of heterogeneity in effect sizes between studies amongst known variants (e.g. 11q13.5 \(I^2=62.9\%, \ p<0.0001\); 11p13 \(I^2=55.6\%, \ p=0.0011\)) but little evidence amongst novel variants (\(I^2\) range=0-40%, all \(p>0.02\), Supplementary Fig.2). Nevertheless, studies with phenotype definition based on a dermatological exam tended to report larger effect sizes than studies using self-report (Supplementary Fig.4), which is to be expected, assuming a moderate degree of phenotypic misclassification in the latter. The inclusion of studies utilizing self-report is therefore likely to bias estimates of the effect size towards the null, and this should be borne in mind when interpreting the odds ratios from our study. Given the primary aim of GWA studies is the detection of novel loci, the increase in sample size achieved by including these studies is so large that any potential detrimental effect on statistical power is more than outweighed and the expected direction of bias means there is unlikely to be an issue of spurious findings (corroborated by Supplementary Fig.4).”

Seven of the 21 established asthma loci\(^{15-20}\), 7 of the 10 allergic sensitization loci\(^{21}\), and 6 of 14 self-reported allergy loci\(^{14}\) showed association with atopic dermatitis (\(p<0.05\)), all with consistent directions of effect, supporting common atopic mechanisms in atopic dermatitis and allergy (Supplementary Table 3). However, several studies used here contribute to multiple GWASs, which may bias this overlap. Nevertheless, a substantial proportion of the loci associated with other atopic conditions appear not to be strongly associated with atopic dermatitis.

Twenty-one of the 27 atopic dermatitis-associated loci have previously been implicated in other immune-mediated traits (Supplementary Table 4), most notably inflammatory bowel disease (IBD) and psoriasis. We therefore compared significant results from GWAS of IBD\(^{22}\), psoriasis\(^{23}\), ankylosing spondylitis\(^{24}\), multiple sclerosis\(^{25}\), rheumatoid arthritis\(^{26}\) and

\[\text{Nat Genet. Author manuscript; available in PMC 2016 June 01.}\]
type 1 diabetes\textsuperscript{27} with results from our present study of atopic dermatitis. Of 163 established IBD risk variants, 39 reached $p<0.05$ for atopic dermatitis (Supplementary Table 5, 8.1 expected, $p=2.4\times10^{-16}$), 35 with the same direction of effect (sign test $p<0.0001$), consistent with the observational association between the two diseases\textsuperscript{26-30}. Of the 36 known psoriasis variants, 15 reached $p<0.05$ for atopic dermatitis (Supplementary Table 6, 1.8 expected, $p=6\times10^{-11}$), 10 with the same direction of effect (sign test $p=0.30$). However, these conditions rarely clinically co-occur\textsuperscript{31} and the most strongly associated genetic variants show opposite directions of effect\textsuperscript{32}. Therefore our results, suggesting a more complex genetic relationship, might warrant further investigation. SNPs robustly associated with other auto-immune diseases were also more likely to be nominally associated with atopic dermatitis than expected by chance, but there was little evidence of any consistency in direction of effect (Supplementary Tables 7–10). These findings did not appear to be affected by contamination by common controls across studies. Analyses performed excluding common cohorts, yielded similar results (data not shown).

Conditional analysis showed evidence for secondary independent signals at 4 known atopic dermatitis loci (2q12.1, 4q27, 11p13, 5q31.1, Supplementary Table 11), one of which (5q31.1) has been previously reported\textsuperscript{9}. In the epidermal differentiation complex (1q21.2–3, where FLG is located) the signals near MRP52J (rs7512552) and IL6R (rs12730935 or the known functional mutation rs2228145) were independent from FLG, whereas the top signal near LCE3E (rs61813875) appears to be partially tagging the R501X FLG mutation ($r^2=0.49$) and showed no significant residual association ($P>0.05$) after conditioning on the 4 most prevalent FLG mutations (Supplementary Tables 12&13).

To identify additional variants of biological relevance not reaching genome-wide significance, we applied gene-set enrichment analysis using Meta-Analysis Gene-set Enrichment of variant Associations (MAGENTA)\textsuperscript{33} (Supplementary Table 14). A significant enrichment of 22 partially overlapping gene-sets (FDR$\leq0.01$) related to innate immune signaling and T-cell polarization was observed (Supplementary Fig.5).

For replication, we selected the lead SNPs from the 11 novel loci, 9 candidate SNPs from the MAGENTA analysis (with $p<10^{-5}$ mapping to gene-sets with FDR$<0.05$), and 3 SNPs representing potentially novel secondary signals. These were investigated in 18 studies (32,059 cases and 228,628 controls, Supplementary Table 1). Amongst the European studies, 11 of the 20 novel loci reached a Bonferroni-corrected threshold ($\alpha=0.0025$) with 1-sided tests in a fixed effects analysis (Table 2). However, one of these showed evidence of heterogeneity ($10p15.1$, $p=0.041$) and was not significant in a random effects analysis ($p=0.019$, Supplementary Table 15). Two of the gene-set selected SNPs reached genome-wide significance in the combined analysis (2q37.1, 12q15). A random effects analysis of all replication cohorts (European and other ethnicities) show broadly consistent results (though only 6 reach genome-wide significance), with no clear population-specific effects (Supplementary Table 16 & Fig.6).

All 3 secondary signals showed significant association in the replication-phase conditional analysis (Supplementary Table 11).
As a preliminary step towards understanding the functional underpinnings of the atopic dermatitis genetic associations, we established a ‘credible set’ of SNPs (all with strong association) for each locus as described in the online methods. We reviewed these SNPs’ functional annotations in ENCODE Consortium and Roadmap Epigenomics Consortium data, evaluated expression quantitative trait locus (eQTL) effects in MuTHER, reviewed evidence of differential expression, and surveyed relevant mouse mutants (see Supplementary Note 2 and Tables 17–21). Regions of DNase hypersensitivity from the ENCODE and Roadmap data were strongly enriched for atopic dermatitis association compared to the rest of the genome (Supplementary Fig. 7 & Table 22), particularly in immune cells (Th0, Th1, Th17 p<0.0001), this enrichment was observed well below the genome-wide significance threshold, indicating the presence of additional undetected risk variants. We observed multiple cis-eQTLs (Bonferroni-corrected p<7×10^{-4}) in lymphoblastoid cell lines (LCLs) or skin (Supplementary Tables 17&19). The most significant were two variants from the credible set at 2p13.3, which were strong eQTLs for CD207/langerin in skin (rs4852714 p=1.23×10^{-10}, rs6723629 p=1.67×10^{-10}, LD with lead SNP r^2=0.56, D'=0.96, and r^2=0.53, D'=0.93, respectively, 99% posterior probability that atopic dermatitis and eQTL signals colocalize). rs4852714 is also in an open-chromatin region with histone marks indicative of promoter/enhancer activity in LCLs (Supplementary Tables 18, 19 & Fig. 8).

CD207 encodes an intracellular pattern recognition receptor expressed in subpopulations of dendritic cells, in particular epidermal Langerhans cells (LCs) which play a vital role in the induction of tolerance and direction of adaptive immune responses. CD207 binds to carbohydrates present e.g. on microorganisms and exerts anti-viral/antifungal defense mechanisms. Of note, atopic dermatitis is characterized by an increased susceptibility towards skin infection with pathogens such as Staphylococcus aureus, herpes simplex virus, and Malassezia species, and differences in langerin function might contribute to this dysregulated cutaneous immunity.

There is longstanding evidence that skin barrier defects and inappropriate immune responses to environmental antigens contributes to atopic dermatitis. However, evidence for autoimmune mechanisms, in particular in the context of progression to the chronic phase, has only recently emerged. Interestingly, the majority of our novel susceptibility loci harbor candidate genes with functional annotations related to autoimmunity. At 14q13.2, the lead SNP (rs2038255) is intronic to PPP2R3C (a protein phosphatase component regulating B-cell maturation and survival), the dysregulation of which has been associated with murine autoimmunity and the signal colocalizes with a strong KIAA0391 eQTL signal (Supplementary Table 19). The lead 5p13.2 variant (rs10214237) is located 4kb downstream of the gene encoding the alpha-chain of the IL7 receptor (IL7R), which is a key mediator in T-cell-driven autoimmunity and inflammation. Of interest, the credible set contains an IL7R missense variant (rs6897932, p=1.6×10^{-7}, r^2=0.94 with lead SNP), which displays the same effect direction with multiple sclerosis. The risk allele leads to an enhanced bioavailability of IL7, which in mice causes severe dermatitis with intense pruritus and high IgE levels, i.e. atopic dermatitis-like features. Likewise, as part of the autosomal-dominant hyper-IgE syndrome, rare dominant negative mutations in the gene encoding STAT3 (in which our lead 17q21.2 variant is intronic) cause severe dermatitis and high serum IgE levels, as well as recurrent S. aureus skin infections, which may be driven by...
impaired Th17 cell differentiation and effector function\textsuperscript{48,49}. STAT3 might thus represent an example for risk gene/pathway shared between a complex trait and a related Mendelian condition\textsuperscript{50,51}, harboring highly penetrant severe effect rare mutations and common milder effect variants. At 8q21.13, the closest candidate gene is ZBTB10 encoding a zinc finger protein, which is a putative repressor of the Sp1, Sp3 and Sp4 transcription factors\textsuperscript{52}. Variants in moderate LD ($r^2>0.7$) with the lead variant for atopic dermatitis were previously associated with self-reported allergy\textsuperscript{14} and a combined asthma and hay fever phenotype\textsuperscript{53}. However, although not excluding ZBTB10 as the causal gene, the credible SNP set comprises a 47kb interval on the other side of a recombination peak (60cM/Mb). The variant most likely to be regulatory amongst this set, deletion rs5892724 ($r^2=0.82$ with lead SNP), is located in open chromatin in several cell types including CD4+ helper T-cells, and affects a STAT3 binding site\textsuperscript{49,54}. At 11q24.3 the most plausible candidate gene is ETS1, which encodes a transcription factor with a range of immune functions including Th17 and B-cell differentiation and function; ETS1-deficient mice display autoimmune features\textsuperscript{55}. ETS1 appears to be additionally involved in keratinocyte differentiation and formation of the cornified envelope\textsuperscript{56}. Additional variants identified through the gene-set approach implicate genes with cytokine signaling functions (INPP5D, TRAF3, SOCS3 and a cytokine cluster on 12q15).

In conclusion, we have identified 10 new loci robustly associated with atopic dermatitis in Europeans (6 of which also reach genome-wide significance in random effects analysis across studies of all ethnicities), bringing the total number of susceptibility loci to 31 (24 in Europeans), with evidence of secondary signals at 4 of these. Altogether, in the subset of European studies with clinically defined cases, previously established and newly identified variants explain approximately 12.3% and 2.6% of the variance in liability, respectively (Supplementary Table 23). All novel susceptibility loci are related to (auto-)immune regulation, in particular innate signaling and T-cell activation and specification, and there appears to be a substantial genetic overlap with other inflammatory and autoimmune diseases. Whilst not detracting from the importance of maintaining the skin barrier in the prevention and treatment of atopic dermatitis, our findings lend support to new therapeutic approaches targeted at immune modulation\textsuperscript{57}.

**ONLINE METHODS**

**GWAS meta-analysis**

We carried out genome-wide association (GWA) analysis for atopic dermatitis case/control status in 26 individual studies (Supplementary Table 1), comprising a total of 21,399 cases and 95,464 controls. The majority of these studies included individuals of only European ancestry (22 studies, 18,900 cases, 84,166 controls). We also included one study of Japanese individuals (RIKEN, 1,472 cases, 7,966 controls), one study of African American individuals (SAPPHIRE, 422 cases and 844 controls), one study of Latin American individuals (GALA II, 300 cases, 1,592 controls) and one study with individuals of mixed non-European ancestry (Generation R, 305 cases, 896 controls).

Each cohort separately imputed their genetic data to 1000 Genomes Project Phase 1 (the majority to the March 2012 release, Supplementary Table 1) and carried out GWA analysis.
across all imputed variants. Before meta-analysis we restricted each study to only those variants with minor allele frequency (MAF)>1% and moderate imputation quality score (Rsq>0.3 for variants imputed in MACH and proper info>0.4 for IMPUTE). For some cohorts additional quality control filters were applied (full methods for each study are available in Supplementary Note 1).

Meta-analysis was conducted for Europeans only in GWAMA (using fixed effects) and for all ethnicities combined in MANTRA\(^60\). Rather than imposing a fixed or random effects model, MANTRA accounts for the heterogeneity of effects between ethnicities by allowing the studies to cluster according to allele frequency profile (and hence population genetic similarity). To prevent very small European studies (with less precise estimates of the allele frequencies) from having undue weight in our analysis we fixed the Europeans to cluster together by using the European fixed effects results in the MANTRA analysis. Variants with \(p<5\times10^{-8}\) in the European analysis were considered to be associated, as were any additional variants with \((\log_{10} \text{Bayes Factor (BF)})>6.1\) (equivalent to \(p<5\times10^{-8}\)) in the MANTRA analysis. Each locus is represented in the results table by the variant with the strongest evidence for association. Heterogeneity was assessed using the \(I^2\) statistic and Cochrane’s Q test. Meta-analysis results were also stratified according to ethnicity, method of case diagnosis and age of onset to explore sources of heterogeneity.

For the Epidermal-differentiation complex region (where the FLG gene is located and which has previously shown complex association results), we repeated the association tests (across the region between 150.2–154.5Mb on chromosome 1) conditioning on the four most common FLG variants (R501X, 2282del4, R2447X, S3247X) in the individual studies where these were available (10 studies, 20,384 individuals, Supplementary Table 12). These were meta-analyzed to identify whether there were any remaining independent association signals in this region.

**Identification of independent secondary signals at associated loci**

To identify secondary independent signals at each of the other associated loci, we carried out conditional analysis of the European meta-analysis results using GCTA\(^62\), with the ALSPAC 1000 Genomes imputation (restricted to variants with MAF>1% and imputation quality proper info score>0.8) serving as the reference. The regions tested were +/-250kb surrounding the top hit at each locus. Locus specific significance thresholds were estimated by first calculating the effective number of tests in each 500kb region using Nyholt’s procedure\(^63\) and the 1000 Genomes reference data (European). For each locus we estimated the new threshold for locus-wide error rate of 5% by dividing alpha (0.05) by the corresponding number of effective tests in that region (\(\alpha\)-values are shown in Supplementary Table 11). For 4q27 we defined the region as +/-500kb as a known hit was just less than 500kb from the top SNP in our analysis. We conditioned each region on the top hit from our meta-analysis. Any variant that surpassed the locus-specific threshold was considered an independent secondary signal.
MAGENTA gene-set enrichment analysis

We tested our meta-analysis results for enriched gene-sets using MAGENTA. This method assigns SNPs to genes based on genomic distance (SNPs are assigned if within 110kb upstream or 40kb downstream of each gene), and generates gene-based summary p-values. Subsequently, genes are assigned to gene-sets (using curated repositories including GO-data, Biocarta, PANTHER, KEGG, etc.) and each gene-set is assigned a p-value by comparing gene summary p-values to a null model where SNPs are drawn randomly 10,000 times (normalizing for the number of SNPs genotyped in each gene) and controlling for false discovery rate (FDR) at $\alpha=0.05$. 10,000 gene-sets were tested. As MAGENTA requires a p-value as input and to take account of the differing effects between populations, we re-analyzed our meta-analysis of all studies using a random effects model, to serve as input to the MAGENTA analysis. All genes in the HLA region (chr6:29710331–33150000) were removed from the analysis. In order to identify additional variants of interest to take forward to replication we examined any pathway with FDR<0.05. From these gene-sets we took forward to replication any additional loci with a genetic variant $p<10^{-5}$.

Cross-phenotype comparisons

The NHGRI GWAS catalog was mined for traits with reported associations at each of our genome-wide significant loci. To further investigate the genetic overlap between atopic dermatitis and auto-immune diseases, we took the genome-wide significant loci from recent GWAS of IBD and psoriasis, ankylosing spondylitis, multiple sclerosis, rheumatoid arthritis and type 1 diabetes and extracted the atopic dermatitis results for these variants from our European discovery GWAS, noting whether the variant was associated ($p<0.05$) with atopic dermatitis (testing enrichment of overlap using the 2-sided binomial exact test) and carried the same or opposite direction of effect between the two traits (tested using the sign test).

Replication

The top SNP from the 11 novel associated regions (log10BF>6.1 or $p<5\times10^{-8}$) were taken forward to replication, along with 9 suggestively associated SNPs ($p<10^{-5}$) that were in genes highlighted in the MAGENTA analysis as good candidates. In addition, we included any variants with evidence for being secondary independent signals at associated loci. Replication consisted of 18 studies (32,059 cases and 228,628 controls) with genome-wide imputed data available or custom genotyping (Supplementary Table 1). Studies of European ethnicity were combined in fixed effects meta-analyses in GWAMA. We also carried out random effects meta-analysis for the European studies to assess association for variants which showed evidence of heterogeneity ($p<0.05$). Significant association in the replication phase was determined by 1-sided p-values meeting a Bonferroni-corrected threshold ($\alpha=0.05/20=0.0025$). Random effects meta-analyses of replication studies of all ethnicities were also carried out and forest plots examined for evidence of population-specific effects. For the replication of the three secondary signals, the secondary SNPs were tested for association after conditioning on the top SNP in each of the European cohorts. These results were then combined in fixed effects meta-analyses.
Credible sets

In order to assemble a sensible list of variants at each locus for functional look-ups, we constructed credible sets\(^3\)\(^4\) that represent those SNPs most likely to be causal based on statistical evidence from the MANTRA analysis (or from the European analysis for the three variants that appeared to be European-specific). The European-only GWAS was repeated in MANTRA to generate BF\(s\) required for the credible set analysis. Bayes factors were used to calculate posterior probabilities for all SNPs in each region (+/−1Mb), the minimum set of SNPs that had a cumulative posterior probability of at least 95% made up each credible set. These sets can be interpreted similar to confidence intervals, in that assuming the association signal at a locus can be attributed to a single causal variant (and that the true causal variant is included in the analysis and has been well-imputed), the 95% credible set contains that causal variant with 95% probability. Given that a 1000 Genomes imputation analysis may not include the true causal variant or that the associations may be driven by more than one causal variant, we do not expect these credible sets to necessarily contain the causal variants at the suggested 95% probability. Nevertheless, they demonstrate in addition to the ‘top SNP’, which neighbouring variants also show strong association with atopic dermatitis and we find them useful in assessing the size of the regions of interest and for defining a set of variants to follow-up. As the posterior probabilities for the MAGENTA identified credible sets are extremely large (due to the weaker signals at these loci), we instead carried out functional look-ups for all variants with \(r^2\)\(\geq\)0.8 of the top hit for these loci.

Functional look-ups

For variants identified as part of a credible set, we carried out look-ups in the following functional data resources; (i) regulomeDB and Haploreg were mined for evidence of coding or regulatory function (these resources collate annotations [e.g., coding variation, regulatory chromatin marks, DNase I hypersensitivity, protein binding and motif alteration] from the ENCODE Consortium, the NIH Roadmap Epigenomics Mapping Consortium, and the literature over a wide range of tissues); (ii) cis-eQTL for skin or LCLs were identified from the MuTHER consortium\(^3\)\(^5\) (with variants considered eQTLs if association with any transcript within 1Mb was \(p<7\times10^{-4}\), corresponding to a bonferroni correction for 36 loci and 2 tissues); (iii) differential expression reported for implicated genes between uninvolved skin from cases and skin from controls\(^6\)\(^5\) and between lesional and non-lesional skin in atopic dermatitis patients in a study deposited in the Gene Expression Omnibus (Accession=GDS4444)\(^6\)\(^6\); and (iv) mouse mutants of implicated genes were examined in the MGI database.

Colocalization of atopic dermatitis GWAS signals and eQTLs in the MuTHER data was investigated using the R package coloc\(^6\)\(^7\). All SNPs within 100kb of the lead atopic dermatitis SNP were included in the analysis and we report the posterior probabilities that the two signals colocalize in Supplementary Table 19.

To identify and visualize cell types implicated in atopic dermatitis pathogenesis, the tendency of disease associated loci to fall in cell-type specific regulatory DNase Hypersensitive Sites (DHS) (a proxy for accessible and/or regulatory DNA) was calculated for the full range of p-values, essentially as done by Maurano et al.\(^6\)\(^8\). This enrichment was
computed for 168 cell types and cell lines in the ENCODE Roadmap repository\textsuperscript{36}. Duplicates and directly redundant cell types were removed before analysis. One-sided p-values for enrichment were calculated from an empirical null distribution of loci overlap for DHS-regions, generated by 10,000 random permutations of overlapping an identical number of random loci as found at p\textless{}1\times{}10^{-10} with all DHS-regions for all cell- and tissue types.

**Variance in liability explained**

We estimated the proportion of variance in atopic dermatitis liability explained by the established and novel variants in a subset of studies that had clinically diagnosed cases (GENEVA/KORAF4/POPGEN, NCRC-ADC, GENUFADex-SHIP1, GENUFAD-SHIP2, GENEVA(replication), CECCS) using the method of So et al. (2011)\textsuperscript{69}.

**Data access**

Genome-wide results are available on request to the corresponding author, on condition of signing any Data Transfer Agreements required according the IRB-approved protocols of contributing studies.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Authors**

Lavinia Paternoster\textsuperscript{1,2}, Marie Standl\textsuperscript{3}, Johannes Waage\textsuperscript{4}, Hansjörg Baurecht\textsuperscript{5}, Melanie Hotze\textsuperscript{6}, David P Strachan\textsuperscript{6}, John A Curtin\textsuperscript{7}, Klaus Bønnelykke\textsuperscript{4}, Chao Tian\textsuperscript{8}, Atsushi Takahashi\textsuperscript{9}, Jorge Esparza-Gordillo\textsuperscript{10,11}, Alexessander Couto Alves\textsuperscript{12}, Jacob P Thyssen\textsuperscript{13}, Herman T den Dekker\textsuperscript{14,15,16}, Manuel A Ferreira\textsuperscript{17}, Elisabeth Altmaier\textsuperscript{18,19,20}, Patrick MA Sleiman\textsuperscript{21,22}, Feng Li Xiao\textsuperscript{23}, Juan R Gonzalez\textsuperscript{24}, Ingo Marenholz\textsuperscript{10,11}, Birgit Kalb\textsuperscript{10,25}, Maria Pino Yanes\textsuperscript{26,27,28}, Chengjian Xu\textsuperscript{29,30}, Lisbeth Carstensen\textsuperscript{31}, Maria G Groen-Blokhuis\textsuperscript{32}, Cristina Venturini\textsuperscript{33}, Craig E Pennell\textsuperscript{34}, Sheila J Barton\textsuperscript{35}, Albert M Levin\textsuperscript{36}, Ivan Curjuric\textsuperscript{37,38}, Mariona Bustamante\textsuperscript{24,39,40,41}, Eskil Kreiner-Møller\textsuperscript{4}, Gabrielle A Lockett\textsuperscript{42}, Jonas Bacelis\textsuperscript{43}, Suninda Bunyavanich\textsuperscript{44}, Rachel A Myers\textsuperscript{45}, Anja Matanovic\textsuperscript{10,11}, Ashish Kumar\textsuperscript{37,38,46,47}, Joyce Y Tung\textsuperscript{8}, Tomomitsu Hirota\textsuperscript{48}, Michiaki Kubo\textsuperscript{49}, Wendy L Mc Ardle\textsuperscript{2}, A J Henderson\textsuperscript{2}, John P Kemp\textsuperscript{1,2,50}, Jie Zheng\textsuperscript{1,2}, George Davey Smith\textsuperscript{1,2}, Franz Rüscheidorff\textsuperscript{10}, Anja Bauerfeind\textsuperscript{10}, Min Ae Lee-Kirsch\textsuperscript{51}, Andreas Arnold\textsuperscript{52}, Georg Homuth\textsuperscript{53}, Carsten O Schmidt\textsuperscript{54}, Elisabeth Mangold\textsuperscript{55}, Sven Cichon\textsuperscript{55,56,57,58,59}, Thomas Keil\textsuperscript{60,61}, Elke Rodríguez\textsuperscript{5}, Annette Peters\textsuperscript{19,62}, André Franke\textsuperscript{63}, Wolfgang Lieb\textsuperscript{64}, Natalja Novak\textsuperscript{65}, Regina Förster-Holst\textsuperscript{6}, Momoko Horikoshi\textsuperscript{47}, Juha Pekkalanen\textsuperscript{66,67}, Sylvain Sebe\textsuperscript{68,69}, Lise L Husemoen\textsuperscript{70}, Niels Grarup\textsuperscript{71}, Johan C de Jongste\textsuperscript{14}, Fernando Rivadeneira\textsuperscript{15,16,72}, Albert Hofman\textsuperscript{15}, Vincent WV Jaddoe\textsuperscript{14,15,16}, Suzanne GMA Pasmans\textsuperscript{73}, Niels J Elbert\textsuperscript{16,73}, André G Uitterlinden\textsuperscript{15,72}, Guy B Marks\textsuperscript{74}, Philip J Thompson\textsuperscript{75,76}, Melanie C Matheson\textsuperscript{77}, Colin F Robertson\textsuperscript{78}, Australian Asthma Genetics Consortium (AAGC)\textsuperscript{79}, Janina S Ried\textsuperscript{20}, Jin Li\textsuperscript{21}, Xian Bo Zuo\textsuperscript{23}, Xiao Dong Zheng\textsuperscript{23}, Xian Yong Yin\textsuperscript{23}, Liang Dan

\textit{Nat Genet.} Author manuscript; available in PMC 2016 June 01.
Sun\textsuperscript{23}, Maeve A McAleer\textsuperscript{80,81}, Grainne M O'Regan\textsuperscript{81}, Caoimhe MR Fahy\textsuperscript{82}, Linda E Campbell\textsuperscript{83}, Milan Macek\textsuperscript{84}, Michael Kurek\textsuperscript{85}, Donglei Hu\textsuperscript{26}, Celeste Eng\textsuperscript{26}, Dirkje S Postma\textsuperscript{29}, Bjarke Feenstra\textsuperscript{31}, Frank Geller\textsuperscript{31}, Tim Spector\textsuperscript{33}, Carla MT Tiesler\textsuperscript{3,86}, Elisabeth Thiering\textsuperscript{3,86}, Badri Pahukasahasram\textsuperscript{87}, James J Yang\textsuperscript{88}, Medea Imboden\textsuperscript{37,38}, Scott Huntsman\textsuperscript{26}, Natàlia Vilor-Tejedor\textsuperscript{24,40,41}, Cilla Söderhäll\textsuperscript{93,94}, Erik Melén\textsuperscript{46,95}, Carole Ober\textsuperscript{45}, Benjamin A Raby\textsuperscript{81}, Angela Simpson\textsuperscript{7}, Bo Jacobsson\textsuperscript{43,90}, John W Holloway\textsuperscript{42,96}, WH Irwin McLean\textsuperscript{83}, Alan D Irvine\textsuperscript{80,81,82}, Hakon Hakonarson\textsuperscript{21,22}, Christian Gieger\textsuperscript{18,19,20}, Nicholas G Martin\textsuperscript{17}, Liesbeth Duijts\textsuperscript{18,19,20}, Allan Lineeberg\textsuperscript{70,101,107}, Markus M Noethen\textsuperscript{55,56}, Susanne Lau\textsuperscript{25}, Norbert Hübner\textsuperscript{10}, Mayumi Tamari\textsuperscript{48}, Joachim Heinrich\textsuperscript{3}, David M Evans\textsuperscript{1,2,50,113}, and Stephan Weidinger\textsuperscript{5,113} for the EArly Genetics & Lifecourse Epidemiology (EAGLE) eczema consortium\textsuperscript{114}

Affiliations

\textsuperscript{1}Medical Research Council (MRC) Integrative Epidemiology Unit, University of Bristol, Bristol, UK. \textsuperscript{2}School of Social and Community Medicine, University of Bristol, Bristol, UK. \textsuperscript{3}Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. \textsuperscript{4}Copenhagen Prospective Studies on Asthma in Childhood (COPSAC), Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark. \textsuperscript{5}Department of Dermatology, Allergology and Venerology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany. \textsuperscript{6}Population Health Research Institute, St George’s, University of London, London, UK. \textsuperscript{7}Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom. \textsuperscript{8}National Allergy Research Centre, Department of Dermatology and Allergology, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark. \textsuperscript{9}Department of Pediatrics, Erasmus MC, Rotterdam, the Netherlands. \textsuperscript{10}The Generation R Study Group, Erasmus MC, Rotterdam, the Netherlands. \textsuperscript{11}QIMR Berghofer Medical Research Institute, Brisbane, Australia. \textsuperscript{12}Research Unit of

\textit{Nat Genet.} Author manuscript; available in PMC 2016 June 01.
Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. 19Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. 20Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. 21The Center for Applied Genomics, The Children's Hospital of Philadelphia, PA, USA. 22Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. 23Institute of Dermatology, Anhui Medical University, Hefei, Anhui, China. 24Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain. 25Pediatric Pneumology and Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany. 26Department of Medicine, University of California, San Francisco, CA, USA. 27Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. 28Research Unit, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain. 29University of Groningen, University Medical Center Groningen, Department of Pulmonology, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands. 30University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands. 31Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark. 32Dept Biological Psychology, Netherlands Twin Register, VU University, Amsterdam, the Netherlands. 33KCL Department of Twin Research and Genetic Epidemiology, King’s College London, London, UK. 34School of Women's and Infants' Health, The University of Western Australia (UWA), Perth, Australia. 35Medical Research Council (MRC) Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK. 36Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA. 37Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland. 38University of Basel, Basel, Switzerland. 39Centre for Genomic Regulation (CRG), Barcelona, Spain. 40Pompeu Fabra University (UPF), Barcelona, Spain. 41Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain. 42Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK. 43Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, Sahlgrenska University Hospital, Gothenburg, Sweden. 44Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. 45Department of Human Genetics, University of Chicago, Chicago, IL, USA. 46Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. 47Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. 48Laboratory for Respiratory and Allergic Diseases, Center for Integrative Medical Sciences, Institute of Physical and Chemical Research (RIKEN), Yokohama, Japan. 49Laboratory for Genotyping Development, Center for Integrative Medical Sciences, Institute of Physical and Chemical Research (RIKEN), Yokohama, Japan. 50University of Queensland
Diamantina Institute, Translational Research Institute, University of Queensland, Brisbane, Australia. 51Klinik für Kinder- und Jugendmedizin, Technical University Dresden, Dresden, Germany. 52Clinic and Polyclinic of Dermatology, University Medicine Greifswald, Greifswald, Germany. 53Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany. 54Institute for Community Medicine, Study of Health in Pomerania/KEF, University Medicine Greifswald, Greifswald, Germany. 55Institute of Human Genetics, University of Bonn, Bonn, Germany. 56Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. 57Division of Medical Genetics, University Hospital Basel, Basel, Switzerland. 58Department of Biomedicine, University of Basel, Basel, Switzerland. 59Institute of Neuroscience and Medicine (INM-1), Structural and Functional Organisation of the Brain, Genomic Imaging, Research Centre Jülich, Jülich, Germany. 60Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany. 61Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany. 62Deutsches Forschungszentrum für Herz-Kreislauferkrankungen (DZHK) (German Research Centre for Cardiovascular Research), Munich Heart Alliance, Munich, Germany. 63Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany. 64Institute of Epidemiology, Christian-Albrechts University Kiel, Kiel, Germany. 65Department of Dermatology and Allergy, University of Bonn Medical Center, Bonn, Germany. 66Unit of Living Environment and Health, National Institute for Health and Welfare, Kuopio, Finland. 67Department of Public Health, University of Helsinki, Helsinki, Finland. 68Center for Life-course and Systems Epidemiology, Faculty of Medicine, University of Oulu, Finland. 69Biocenter Oulu, University of Oulu, Finland. 70Research Centre for Prevention and Health, Capital Region of Denmark, Copenhagen, Denmark. 71The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. 72Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands. 73Department of Dermatology, Erasmus MC, Rotterdam, the Netherlands. 74Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia. 75Lung Institute of Western Australia, QE II Medical Centre Nedlands , Western Australia, Australia. 76School of Medicine and Pharmacology, University of Western Australia, Perth, Australia. 77Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia. 78Murdoch Children's Research Institute, Melbourne, Australia. 79A full list of consortium members is provided in Supplementary Note 1, page 4. 80National Children's Research Centre, Crumlin, Dublin, Ireland. 81Our Lady's Children's Hospital, Crumlin, Dublin, Ireland. 82Clinical Medicine, Trinity College Dublin, Dublin, Ireland. 83Centre for Dermatology and Genetic Medicine, University of Dundee, Dundee, UK. 84Department of Biology and Medical Genetics, University Hospital Motol and 2nd Faculty of Medicine of Charles University, Prague, Czech Republic. 85Department of Clinical Allergology, Pomeranian, Pomeranian Medical University, Szczecin, Poland. 86Ludwig-Maximilians-University
of Munich, Dr. von Hauner Children's Hospital, Division of Metabolic Diseases and Nutritional Medicine, Munich, Germany. 87Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, USA. 88School of Nursing, University of Michigan, Ann Arbor, MI, USA. 89Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK. 90Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway. 91Channing Division of Network Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA. 92Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC, USA. 93Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. 94Center for Innovative Medicine (CIMED), Karolinska Institutet, Stockholm, Sweden. 95Sachs' Children's Hospital, Stockholm, Sweden. 96Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK. 97Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain. 98Department of Internal Medicine, Henry Ford Health System, Detroit, MI, USA. 99National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton National Health Service (NHS) Foundation Trust, Southampton, UK. 100Institute for Health and Care Research (EMGO), VU University, Amsterdam, the Netherlands. 101Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. 102Department of Medicine, Stanford School of Medicine, Stanford, California, USA. 103University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatric Pulmonology and Pediatric Allergology, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands. 104Respiratory Epidemiology, Occupational Medicine and Public Health; National Heart and Lung Institute; Imperial College; London, UK. 105Medical Research Council-Public Health England Centre for Environment and Health, School of Public Health, Imperial College London, London, UK. 106Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA, USA. 107Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark. 108Department of Epidemiology and Biostatistics, Medical Research Council (MRC) Health Protection Agency (HPE) Centre for Environment and Health, School of Public Health, Imperial College London, London, UK. 109Center for Life Course Epidemiology, Faculty of Medicine, University of Oulu, Oulu, Finland. 110Unit of Primary Care, Uulu University Hospital, Oulu, Finland. 111Department of Dermatology, Ninewells Hospital and Medical School, Dundee, UK. 113These authors jointly directed this work. 114All authors.

Acknowledgements

This publication is the work of the authors and Lavinia Paternoster will serve as guarantor for the contents of this paper. This research was specifically funded by an MRC Population Health Scientist Fellowship awarded to Dr L. Paternoster (MR/J012165/1). D.M.E. is supported by an Australian Research Council Future Fellowship (FT130101079) and a Medical Research Council program grant (MC_UU_12013/4). Individual study acknowledgement and funding statements can be found in the Supplementary material.

Nat Genet. Author manuscript; available in PMC 2016 June 01.
Author Contributions


AAGC provided results for the discovery analysis.

References


Methods-only references


Figure 1. Atopic dermatitis GWAS meta-analysis results
(A) Manhattan plot of European fixed effects meta-analysis. (B) Manhattan plot of the multi-ethnic MANTRA meta-analysis of all studies. Arrows mark variants not associated in the European-only analysis. (C) QQ plot of the European analysis - lambda=1.054.
Table 1

Discovery Results. The index variant for loci with $p<5\times 10^{-8}$ in the European analysis or $\log10BF>6.1$ in the multi-ethnic MANTRA analysis. Previous atopy trait associations with these loci are listed.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Locus</th>
<th>Nearest Gene$^d$</th>
<th>EA/OA</th>
<th>N (studies)</th>
<th>EAF</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>N (studies)</th>
<th>log10 BF</th>
<th>trait</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KNOWN LOCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs61813875</td>
<td>1q21.3</td>
<td>CRCT1/LCE3E (FLG)$^f$</td>
<td>G/C</td>
<td>93,326 (18)</td>
<td>0.02</td>
<td>1.61 (1.48–1.75)</td>
<td>$5.6\times 10^{-29}$</td>
<td>96,419 (20)</td>
<td>25.53</td>
<td>AD</td>
<td>3,4,5</td>
</tr>
<tr>
<td>rs10791824</td>
<td>1q13.1</td>
<td>OVOL1</td>
<td>G/A</td>
<td>102,761 (21)</td>
<td>0.57</td>
<td>1.12 (1.09–1.15)</td>
<td>$2.1\times 10^{-19}$</td>
<td>116,556 (25)</td>
<td>21.56</td>
<td>AD</td>
<td>9</td>
</tr>
<tr>
<td>rs12188917</td>
<td>5q31.1</td>
<td>RAD50/IL13</td>
<td>C/T</td>
<td>102,761 (21)</td>
<td>0.21</td>
<td>1.14 (1.10–1.17)</td>
<td>$4.0\times 10^{-17}$</td>
<td>116,554 (25)</td>
<td>17.24</td>
<td>AD, A, J, E</td>
<td>9, 18, 58</td>
</tr>
<tr>
<td>rs6419573</td>
<td>2q12.1</td>
<td>IL18R1/IL18RAP</td>
<td>T/C</td>
<td>102,760 (21)</td>
<td>0.26</td>
<td>1.11 (1.08–1.14)</td>
<td>$1.5\times 10^{-13}$</td>
<td>116,557 (25)</td>
<td>18.10</td>
<td>AD, A, S, SRA</td>
<td>8, 14, 18, 21</td>
</tr>
<tr>
<td>rs2212434</td>
<td>11q3.5</td>
<td>C1orf30/LRRC32</td>
<td>T/C</td>
<td>102,761 (21)</td>
<td>0.45</td>
<td>1.09 (1.07–1.12)</td>
<td>$4.6\times 10^{-13}$</td>
<td>116,557 (25)</td>
<td>13.02</td>
<td>AD, A, S, R, A</td>
<td>11, 14, 15, 21, 59</td>
</tr>
<tr>
<td>rs4809219</td>
<td>20q13.33</td>
<td>RTE1L–TNFRSF6B</td>
<td>C/A</td>
<td>102,760 (21)</td>
<td>0.27</td>
<td>0.90 (0.87–0.93)</td>
<td>$7.0\times 10^{-12}$</td>
<td>116,555 (25)</td>
<td>11.98</td>
<td>AD</td>
<td>7, 10</td>
</tr>
<tr>
<td>rs2918307</td>
<td>19p13.2</td>
<td>ADAMTS10/ACTL9</td>
<td>G/A</td>
<td>100,707 (20)</td>
<td>0.16</td>
<td>1.12 (1.08–1.16)</td>
<td>$4.6\times 10^{-12}$</td>
<td>114,504 (24)</td>
<td>12.98</td>
<td>AD</td>
<td>9</td>
</tr>
<tr>
<td>rs2041733</td>
<td>16p13.13</td>
<td>CLEC16A</td>
<td>C/T</td>
<td>103,066 (22)</td>
<td>0.55</td>
<td>0.92 (0.90–0.94)</td>
<td>$2.5\times 10^{-11}$</td>
<td>116,862 (26)</td>
<td>10.11</td>
<td>AD, A, HF</td>
<td>7, 53</td>
</tr>
<tr>
<td>rs12739095</td>
<td>1q21.3</td>
<td>IL6R</td>
<td>A/G</td>
<td>102,760 (21)</td>
<td>0.39</td>
<td>1.08 (1.05–1.11)</td>
<td>$6.1\times 10^{-11}$</td>
<td>116,556 (25)</td>
<td>7.15</td>
<td>AD, A</td>
<td>12, 15</td>
</tr>
<tr>
<td>4:132434559</td>
<td>4q27</td>
<td>KIAA109 (IL2)$^f$</td>
<td>R/I</td>
<td>102,760 (21)</td>
<td>0.37</td>
<td>1.08 (1.05–1.10)</td>
<td>$4.2\times 10^{-11}$</td>
<td>107,119 (24)</td>
<td>7.32</td>
<td>AD, A, S, A</td>
<td>7, 14, 21</td>
</tr>
<tr>
<td>rs4713555</td>
<td>6p21.32</td>
<td>HLA-DRB1/HLA-DQA1</td>
<td>T/G</td>
<td>91,217 (15)</td>
<td>0.27</td>
<td>0.91 (0.89–0.94)</td>
<td>$5.4\times 10^{-9}$</td>
<td>105,014 (19)</td>
<td>10.76</td>
<td>AD, A, S, R, A</td>
<td>6, 8, 14, 18, 21</td>
</tr>
<tr>
<td>rs2944452</td>
<td>10q21.2</td>
<td>ZNF365</td>
<td>C/G</td>
<td>102,762 (21)</td>
<td>0.41</td>
<td>0.94 (0.92–0.96)</td>
<td>$1.2\times 10^{-6}$</td>
<td>116,559 (25)</td>
<td>7.56</td>
<td>AD</td>
<td>8, 10</td>
</tr>
<tr>
<td>rs145809981</td>
<td>6p21.33</td>
<td>MICB</td>
<td>T/C</td>
<td>97,697 (19)</td>
<td>0.14</td>
<td>0.91 (0.88–0.95)</td>
<td>$1.5\times 10^{-6}$</td>
<td>110,228 (22)</td>
<td>7.33</td>
<td>AD, A, S, A</td>
<td>8, 14, 21</td>
</tr>
<tr>
<td>rs3120545</td>
<td>11p15.4</td>
<td>OR10A3/NLRP10</td>
<td>G/T</td>
<td>102,760 (21)</td>
<td>0.41</td>
<td>1.00 (0.97–1.02)</td>
<td>$7.4\times 10^{-6}$</td>
<td>116,556 (25)</td>
<td>7.00</td>
<td>AD</td>
<td>8</td>
</tr>
<tr>
<td>rs1249910</td>
<td>3q13.2</td>
<td>CCDC80/CD200R1L</td>
<td>A/G</td>
<td>99,164 (20)</td>
<td>0.34</td>
<td>0.98 (0.96–1.01)</td>
<td>$1.0\times 10^{-6}$</td>
<td>112,960 (24)</td>
<td>6.86</td>
<td>AD</td>
<td>8</td>
</tr>
<tr>
<td>rs2592555</td>
<td>11p13</td>
<td>PRSS5</td>
<td>T/C</td>
<td>102,760 (21)</td>
<td>0.27</td>
<td>0.93 (0.90–0.96)</td>
<td>$8.7\times 10^{-7}$</td>
<td>116,551 (25)</td>
<td>6.78</td>
<td>AD</td>
<td>7</td>
</tr>
</tbody>
</table>

**NOVEL LOCI**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Locus</th>
<th>Nearest Gene</th>
<th>EA/OA</th>
<th>N (studies)</th>
<th>EAF</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>N (studies)</th>
<th>log10 BF</th>
<th>trait</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2038255</td>
<td>1q13.2</td>
<td>PPP2R3C</td>
<td>T/C</td>
<td>102,760 (21)</td>
<td>0.18</td>
<td>1.11 (1.07–1.14)</td>
<td>$1.8\times 10^{-10}$</td>
<td>116,557 (25)</td>
<td>8.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7127309</td>
<td>1q24.3</td>
<td>−ETS1</td>
<td>C/T</td>
<td>103,066 (22)</td>
<td>0.47</td>
<td>0.93 (0.90–0.95)</td>
<td>$3.9\times 10^{-10}$</td>
<td>116,855 (26)</td>
<td>9.08</td>
<td>SRA</td>
<td>14</td>
</tr>
<tr>
<td>rs7515252</td>
<td>1q21.2</td>
<td>C1orf51/MRPS21</td>
<td>T/C</td>
<td>102,762 (21)</td>
<td>0.49</td>
<td>0.93 (0.91–0.95)</td>
<td>$9.1\times 10^{-10}$</td>
<td>116,544 (25)</td>
<td>6.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs6473227</td>
<td>8q21.13</td>
<td>MIR5708/ZBTB10</td>
<td>A/C</td>
<td>102,761 (21)</td>
<td>0.61</td>
<td>0.93 (0.91–0.95)</td>
<td>$1.4\times 10^{-9}$</td>
<td>116,557 (25)</td>
<td>7.54</td>
<td>(AD), SRA, A+HF</td>
<td>9, 14, 53</td>
</tr>
<tr>
<td>rs6602364</td>
<td>10p15.1</td>
<td>IL15RA/IL2RA</td>
<td>G/C</td>
<td>103,065 (22)</td>
<td>0.45</td>
<td>1.08 (1.05–1.10)</td>
<td>$1.5\times 10^{-9}$</td>
<td>116,855 (26)</td>
<td>7.86</td>
<td>SRA</td>
<td>14</td>
</tr>
<tr>
<td>Variant</td>
<td>Locus</td>
<td>Nearest Gene&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>EA/OA</td>
<td>N (studies)</td>
<td>EAF</td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>N (studies)</td>
<td>log10 BF</td>
<td>trait</td>
<td>references</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>---------------------------</td>
<td>-------</td>
<td>-------------</td>
<td>------</td>
<td>-------------------</td>
<td>----------</td>
<td>-------------</td>
<td>----------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>rs10214237</td>
<td>5p13.2</td>
<td>IL7R/CAFLSL</td>
<td>C/T</td>
<td>102,761 (21)</td>
<td>0.27</td>
<td>0.93 (0.90-0.95)</td>
<td>2.9×10&lt;sup&gt;-8&lt;/sup&gt;</td>
<td>116,554 (25)</td>
<td>4.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10199605</td>
<td>2p25.1</td>
<td>LINC003099/−</td>
<td>A/G</td>
<td>102,760 (21)</td>
<td>0.30</td>
<td>0.93 (0.90-0.95)</td>
<td>3.4×10&lt;sup&gt;-8&lt;/sup&gt;</td>
<td>116,557 (25)</td>
<td>4.67</td>
<td>(SRA)</td>
<td>14</td>
</tr>
<tr>
<td>rs4643526</td>
<td>2p16.1</td>
<td>PUS10</td>
<td>A/G</td>
<td>103,066 (22)</td>
<td>0.19</td>
<td>1.09 (1.06-1.12)</td>
<td>3.5×10&lt;sup&gt;-8&lt;/sup&gt;</td>
<td>107,425 (25)</td>
<td>6.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs12951971</td>
<td>17q21.2</td>
<td>STAT3</td>
<td>G/T</td>
<td>102,761 (21)</td>
<td>0.09</td>
<td>1.13 (1.08-1.17)</td>
<td>4.1×10&lt;sup&gt;-8&lt;/sup&gt;</td>
<td>107,120 (24)</td>
<td>5.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7625909</td>
<td>3p21.1</td>
<td>SFMBT1/RFT1</td>
<td>T/C</td>
<td>102,761 (21)</td>
<td>0.32</td>
<td>1.07 (1.05-1.10)</td>
<td>4.9×10&lt;sup&gt;-8&lt;/sup&gt;</td>
<td>116,558 (25)</td>
<td>5.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs112111458</td>
<td>2p13.3</td>
<td>CD207/VAX2</td>
<td>G/A</td>
<td>102,760 (21)</td>
<td>0.13</td>
<td>0.91 (0.87-0.94)</td>
<td>1.4×10&lt;sup&gt;-7&lt;/sup&gt;</td>
<td>116,553 (25)</td>
<td>6.57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* in LD with known functional mutation rs2228145 (r<sup>2</sup>=0.86)  
† nearby SNP (rs6827756, bp position: 123184411) in LD (r<sup>2</sup>=0.97 in 1000genomes) showed similar association, log10BF=7.21, European fixed effects p-value 3×10<sup>-9</sup>  
‡ Nearest genes are the two flanking genes if intergenic (with the closer gene in **bold**, - indicates no gene within 250kb), single genes denote the variant is intronic.  
§ at 1q21.2: variant is closest to LCE3A, but previously associated FLG is within 250kb, at 4q27: variant is within an intron of KIAA109, but previously associated IL2 is within 150kb, AD= atopic dermatitis, A=asthma, AS=allergic sensitization, SRA=self-reported allergy, AR=allergic rhinitis, A+HF=asthma and hayfever combined.  
P-values and −log 10 Bayes Factors (BF) in **bold** indicate genome-wide significant results  
EA/OA=effect allele/other allele, EAF=effect allele frequency, OR=odds ratio, CI=confidence interval, N=sample size, BF=Bayes factor
Table 2
Replication results for the novel genome-wide significant loci and loci identified in the MAGENTA gene-set enrichment analysis. Discovery, replication and combined results are shown.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Nearest Gene</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>Nearest Gene</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>Nearest Gene</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5123552</td>
<td>C1orf51/MRPS21</td>
<td>0.49</td>
<td>102762 (21)</td>
<td>0.93 (0.91–0.95)</td>
<td>9.1x10^{-10}</td>
<td>257019 (15)</td>
<td>0.98 (0.96–0.99)</td>
<td>0.0048</td>
<td></td>
</tr>
<tr>
<td>rs10199605</td>
<td>LINC0289</td>
<td>0.30</td>
<td>102760 (21)</td>
<td>0.93 (0.90–0.95)</td>
<td>3.4x10^{-8}</td>
<td>256958 (15)</td>
<td>0.97 (0.95–0.99)</td>
<td>0.0045</td>
<td></td>
</tr>
<tr>
<td>rs4643354</td>
<td>PUS10</td>
<td>0.19</td>
<td>103066 (22)</td>
<td>1.09 (1.06–1.12)</td>
<td>3.5x10^{-8}</td>
<td>257050 (14)</td>
<td>1.03 (1.01–1.05)</td>
<td>0.0058</td>
<td></td>
</tr>
<tr>
<td>rs112111458</td>
<td>CD207/VAX2</td>
<td>0.13</td>
<td>102760 (21)</td>
<td>0.91 (0.87–0.94)</td>
<td>1.4x10^{-7}</td>
<td>257019 (15)</td>
<td>0.95 (0.93–0.98)</td>
<td>7.9x10^{-4}</td>
<td></td>
</tr>
<tr>
<td>rs1923593</td>
<td>SFRBTR/RT1</td>
<td>0.32</td>
<td>102761 (21)</td>
<td>1.07 (1.04–1.10)</td>
<td>9.7x10^{-8}</td>
<td>257002 (15)</td>
<td>1.01 (1.00–1.03)</td>
<td>0.2600</td>
<td></td>
</tr>
<tr>
<td>rs10214237</td>
<td>IL7R/CAPSL</td>
<td>0.27</td>
<td>102761 (21)</td>
<td>0.93 (0.90–0.95)</td>
<td>2.9x10^{-8}</td>
<td>257010 (15)</td>
<td>0.94 (0.93–0.96)</td>
<td>6.7x10^{-8}</td>
<td></td>
</tr>
<tr>
<td>rs4673227</td>
<td>MR5708/ZBTB10</td>
<td>0.61</td>
<td>102761 (21)</td>
<td>0.93 (0.91–0.95)</td>
<td>1.4x10^{-9}</td>
<td>257006 (15)</td>
<td>0.95 (0.93–0.97)</td>
<td>4.5x10^{-9}</td>
<td></td>
</tr>
<tr>
<td>rs6602364</td>
<td>IL15RA/IL2RA</td>
<td>0.45</td>
<td>103065 (22)</td>
<td>1.08 (1.05–1.10)</td>
<td>1.5x10^{-9}</td>
<td>256993 (15)</td>
<td>1.03 (1.01–1.05)</td>
<td>3.9x10^{-4}</td>
<td></td>
</tr>
<tr>
<td>rs7127307</td>
<td>~ETS1</td>
<td>0.47</td>
<td>103066 (22)</td>
<td>0.93 (0.90–0.95)</td>
<td>3.9x10^{-9}</td>
<td>257034 (15)</td>
<td>0.94 (0.93–0.96)</td>
<td>2.5x10^{-10}</td>
<td></td>
</tr>
<tr>
<td>rs1435480</td>
<td>PPP2R3C</td>
<td>0.17</td>
<td>102761 (21)</td>
<td>1.10 (1.07–1.14)</td>
<td>6.8x10^{-10}</td>
<td>349940 (12)</td>
<td>1.07 (1.04–1.09)</td>
<td>9.9x10^{-8}</td>
<td></td>
</tr>
<tr>
<td>rs7883320</td>
<td>STAT3</td>
<td>0.08</td>
<td>96796 (19)</td>
<td>1.12 (1.07–1.17)</td>
<td>2.0x10^{-6}</td>
<td>349949 (12)</td>
<td>1.05 (1.02–1.09)</td>
<td>1.4x10^{-3}</td>
<td></td>
</tr>
</tbody>
</table>

* rs11923593 replaces rs7625909 (r^2=0.98), rs2143950 replaces rs2038255 (r^2=0.94), rs17881320 replaces rs12951971 (r^2=0.75) in the replication analysis

† rs1799986 is within LRP1, but was selected in the MAGENTA analysis due to its proximity to STAT6. rs2227483 is with IL22, but was selected due to its proximity to both IL22 and IFNG. rs11657987 is within PGS1, but was selected due to its proximity to SOCS3

** P-value for overall European fixed effects, het, random effects p-values
Replication p-values for a 1-sided test

Replication p-values in **bold** were considered significant (p<0.0025), overall p-values in **bold** are genome-wide significant, heterogeneity p-values<0.05 are in bold.

EA/OA= effect allele/other allele, EAF = effect allele frequency, OR=odds ratio, CI=confidence interval, N= sample size, het=heterogeneity.