Multi-ethnic genome-wide association study of 21,000 cases and 95,000 controls identifies new loci for atopic dermatitis
6 Population Health Research Institute, St George's, University of London, London, UK.

7 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

8 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

9 23andMe, Inc., Mountain View, CA, USA.

10 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

11 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

12 23andMe, Inc., Mountain View, CA, USA.

13 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

14 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

15 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

16 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

17 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

18 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

19 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

20 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

21 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

22 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

23 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

24 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

25 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

26 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

27 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

28 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

29 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester

30 Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.
27 Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.

28 Research Unit, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain.

29 University of Groningen, University Medical Center Groningen, Department of Pulmonology, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands.

30 University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands.

31 Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark.

32 Dept Biological Psychology, Netherlands Twin Register, VU University, Amsterdam, the Netherlands.

33 KCL Department of Twin Research and Genetic Epidemiology, King’s College London, London, UK.

34 School of Women's and Infants' Health, The University of Western Australia (UWA), Perth, Australia.

35 Medical Research Council (MRC) Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK.

36 Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA.

37 Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland.

38 University of Basel, Basel, Switzerland.

39 Centre for Genomic Regulation (CRG), Barcelona, Spain.

40 Pompeu Fabra University (UPF), Barcelona, Spain.

41 Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.

42 Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK.

43 Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, Sahlgrenska University Hospital, Gothenburg, Sweden.

44 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

45 Department of Human Genetics, University of Chicago, Chicago, IL, USA.

46 Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.
47 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.

48 Laboratory for Respiratory and Allergic Diseases, Center for Integrative Medical Sciences, Institute of Physical and Chemical Research (RIKEN), Yokohama, Japan.

49 Laboratory for Genotyping Development, Center for Integrative Medical Sciences, Institute of Physical and Chemical Research (RIKEN), Yokohama, Japan.

50 University of Queensland Diamantina Institute, Translational Research Institute, University of Queensland, Brisbane, Australia.

51 Klinik für Kinder- und Jugendmedizin, Technical University Dresden, Dresden, Germany.

52 Clinic and Polyclinic of Dermatology, University Medicine Greifswald, Greifswald, Germany.

53 Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany.

54 Institute for Community Medicine, Study of Health in Pomerania/KEF, University Medicine Greifswald, Greifswald, Germany.

55 Institute of Human Genetics, University of Bonn, Bonn, Germany.

56 Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany.

57 Division of Medical Genetics, University Hospital Basel, Basel, Switzerland.

58 Department of Biomedicine, University of Basel, Basel, Switzerland.

59 Institute of Neuroscience and Medicine (INM-1), Structural and Functional Organisation of the Brain, Genomic Imaging, Research Centre Jülich, Jülich, Germany.

60 Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany.

61 Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany.

62 Deutsches Forschungszentrum für Herz-Kreislauferkrankungen (DZHK) (German Research Centre for Cardiovascular Research), Munich Heart Alliance, Munich, Germany.

63 Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany.

64 Institute of Epidemiology, Christian-Albrechts University Kiel, Kiel, Germany.

65 Department of Dermatology and Allergy, University of Bonn Medical Center, Bonn, Germany.

66 Unit of Living Environment and Health, National Institute for Health and Welfare, Kuopio, Finland.

67 Department of Public Health, University of Helsinki, Helsinki, Finland.
68 Center for Life-course and Systems Epidemiology, Faculty of Medicine, University of Oulu, Finland.
69 Biocenter Oulu, University of Oulu, Finland.
70 Research Centre for Prevention and Health, Capital Region of Denmark, Copenhagen, Denmark.
71 The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
72 Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands.
73 Department of Dermatology, Erasmus MC, Rotterdam, the Netherlands.
74 Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia.
75 Lung Institute of Western Australia, QE II Medical Centre Nedlands, Western Australia, Australia.
76 School of Medicine and Pharmacology, University of Western Australia, Perth, Australia.
77 Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia.
78 Murdoch Children's Research Institute, Melbourne, Australia.
79 A full list of consortium members is provided in Supplementary Note 1, page 4.
80 National Children's Research Centre, Crumlin, Dublin, Ireland.
81 Our Lady's Children's Hospital, Crumlin, Dublin, Ireland.
82 Clinical Medicine, Trinity College Dublin, Dublin, Ireland.
83 Centre for Dermatology and Genetic Medicine, University of Dundee, Dundee, UK.
84 Department of Biology and Medical Genetics, University Hospital Motol and 2nd Faculty of Medicine of Charles University, Prague, Czech Republic.
85 Department of Clinical Allergology, Pomeranian, Pomeranian Medical University, Szczecin, Poland.
86 Ludwig-Maximilians-University of Munich, Dr. von Hauner Children's Hospital, Division of Metabolic Diseases and Nutritional Medicine, Munich, Germany.
87 Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, USA.
88 School of Nursing, University of Michigan, Ann Arbor, MI, USA.
89 Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK.
90 Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway.

91 Channing Division of Network Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA.

92 Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC, USA.

93 Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden.

94 Center for Innovative Medicine (CIMED), Karolinska Institutet, Stockholm, Sweden.

95 Sachs' Children's Hospital, Stockholm, Sweden.

96 Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK.

97 Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain.

98 Department of Internal Medicine, Henry Ford Health System, Detroit, MI, USA.

99 National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton National Health Service (NHS) Foundation Trust, Southampton, UK.

100 Institute for Health and Care Research (EMGO), VU University, Amsterdam, the Netherlands.

101 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

102 Department of Medicine, Stanford School of Medicine, Stanford, California, USA.

103 University 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.

104 Respiratory Epidemiology, Occupational Medicine and Public Health; National Heart and Lung Institute; Imperial College; London, UK.

105 Medical Research Council-Public Health England Centre for Environment and Health, School of Public Health, Imperial College London, London, UK.

106 Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA, USA.

107 Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark.

108 Department 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.
109 Center for Life Course Epidemiology, Faculty of Medicine, University of Oulu, Oulu, Finland.

110 Unit of Primary Care, Oulu University Hospital, Oulu, Finland.

111 Department of Dermatology, Ninewells Hospital and Medical School, Dundee, UK.

112 These authors contributed equally to this work.

113 These authors jointly directed this work.

114 All authors.

Corresponding author: Lavinia Paternoster l.paternoster@bristol.ac.uk
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\(^1\). 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%\(^2\) in Europeans. The strongest known risk factors are null mutations of the filaggrin (FLG) gene, resulting in epidermal barrier deficiency\(^3,5\). 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\(^6,12\). Genetic modeling suggests further loci may be identified with well-powered GWAS\(^13\). 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<5x10\(^{-8}\)) 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 type 1 diabetes$^{27}$ 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=2.4x10^{-16}), 35 with the same direction of effect (sign test p<0.0001), consistent with the observational association between the two diseases$^{28-30}$. Of the 36 known psoriasis variants, 15 reached p<0.05 for atopic dermatitis (Supplementary Table 6, 1.8 expected, p=6x10^{-11}), 10 with the same direction of effect (sign test p=0.30). However, these conditions rarely clinically co-occur$^{31}$ and the most strongly associated genetic variants show opposite directions of effect$^{32}$. Therefore our results, suggesting a more complex genetic relationship, might warrant further investigation. SNPs robustly associated with other autoimmune
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. In the epidermal differentiation complex (1q21.2–3, where FLG is located) the signals near MRPS21 (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) (Supplementary Table 14). A significant enrichment of 22 partially overlapping gene-sets (FDR<0.01) 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\textsuperscript{34}. We reviewed these SNPs' functional annotations in ENCODE Consortium and Roadmap Epigenomics Consortium data, evaluated expression quantitative trait locus (eQTL) effects in MuTHER\textsuperscript{35}, 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\textsuperscript{36,37} 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<7x10\textsuperscript{-8}) 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=1.23x10\textsuperscript{-10}, rs6723629 p=1.67x10\textsuperscript{-10}, LD with lead SNP), which displays the presence of additional undetected risk variants. 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. STAT3 might thus represent an example for risk gene/pathway shared between a complex trait and a related Mendelian condition, 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. Variants in moderate LD (r²>0.7) with the lead variant for atopic dermatitis were previously associated with self-reported allergy and a combined asthma and hay fever phenotype. 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 (r²=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. 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. ETS1 appears to be additionally involved in keratinocyte differentiation and formation of the cornified envelope. 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.

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 (FT130101709) and a Medical Research Council program grant (MC_UU_12013/4). Individual study acknowledgement and funding statements can be found in the Supplementary material.

Author Contributions


AAGC provided results for the discovery analysis.

References

**Figure Legend**

**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.