

UCSF

UC San Francisco Previously Published Works

Title

Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity

Permalink

<https://escholarship.org/uc/item/9n84k1s0>

Journal

Nature Genetics, 44(12)

ISSN

1061-4036

Authors

Tsoi, Lam C
Spain, Sarah L
Knight, Jo
[et al.](#)

Publication Date

2012-12-01

DOI

10.1038/ng.2467

Peer reviewed



Published in final edited form as:

Nat Genet. 2012 December ; 44(12): 1341–1348. doi:10.1038/ng.2467.

Identification of fifteen new psoriasis susceptibility loci highlights the role of innate immunity

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

Summary

To gain further insight into the genetic architecture of psoriasis, we conducted a meta-analysis of three genome-wide association studies (GWAS) and two independent datasets genotyped on the Immunochip, involving 10,588 cases and 22,806 controls in total. We identified 15 new disease susceptibility regions, increasing the number of psoriasis-associated loci to 36 for Caucasians. Conditional analyses identified five independent signals within previously known loci. The newly identified shared disease regions encompassed a number of genes whose products regulate T-cell function (e.g. *RUNX3*, *TAGAP* and *STAT3*). The new psoriasis-specific regions were notable for candidate genes whose products are involved in innate host defense, encoding proteins with roles in interferon-mediated antiviral responses (*DDX58*), macrophage activation (*ZC3H12C*), and NF- κ B signaling (*CARD14* and *CARM1*). These results portend a better understanding of shared and distinctive genetic determinants of immune-mediated inflammatory disorders and emphasize the importance of the skin in innate and acquired host defense.

Users may view, print, copy, download and text and data- mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: http://www.nature.com/authors/editorial_policies/license.html#terms

[†]Corresponding authors: Richard C. Trembath, Division of Genetics and Molecular Medicine, King's College London School of Medicine, Guy's Hospital, London SE1 9RT, UK; Queen Mary University of London, Barts and the London School of Medicine and Dentistry, London E1 2AD, UK, vp-health@qmul.ac.uk. Goncalo R. Abecasis, Department of Biostatistics, School of Public Health M4614 SPH I, University of Michigan, Box 2029, Ann Arbor, MI 48109-2029, USA, phone (734) 763-4901, goncalo@umich.edu. James T. Elder, 7412 Medical Sciences Building 1, University of Michigan Medical School, 1301 E. Catherine, Ann Arbor, Michigan 48109-5675, USA, phone (734) 647-8070, jelder@umich.edu.

*These authors contributed equally to this work

⁴⁹A list of members and affiliations appears in the Supplementary Note

AUTHOR CONTRIBUTIONS

J.T.E., R.C.T. and G.R.A. designed and directed the study. R.P.N., M.W., J.D., J.V., J.T.E., F.C., J.N.B., M.A., C.S., A.D.B., C.G., A.R., J.Ke., X.E., W.W., J.Wo., R.T.A., M.S., G.N., L.S., R.M., M.C., J.S., A.F., S.W., S.K., K.K., T.E., A.M., A.B., G.K., D.G., P.R., U.M., F.N., A.H., J.W., S.S., C.W., C.L., S.E., R.A., V.C., and C.F.R., and H.B. contributed to sample collection and phenotyping. J.K. coordinated the GAP consortium's samples and datasets. J.T.E. coordinated the PAGE samples and datasets. P.De., A.S., G.B., R.D.P., D.V., and C.C.A.S. contributed to the design of the Immunochip. J.K., P.E.S., G.R.A., and H.M.K. advised on the statistical analysis. C.L., S.E., R.A., H.B., E.E., P.H., and R.P.N. performed genotyping. E.E., S.L.S., L.C.T., and H.M.K. performed the genotype calling. S.L.S., L.C.T., Y.L., and D.J. performed genotype imputation and statistical analysis. F.C., J.N.B., J.E.G., T.T., J.T.E., and A.F. prepared Box 1. L.C.T., S.L.S., F.C. and J.T.E. drafted the manuscript, and prepared the figures and tables. E.E., J.E.G., J.K., P.E.S., R.P.N., R.C.T., T.T., G.R.A., J.N.K., and A.F. edited and revised the manuscript. All authors approved the final draft.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Note: Supplementary information is available on the Nature Genetics website.

URLS

WTCCC common controls: <http://www.wtccc.org.uk> 1000 Genomes Project data are available at: <ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20100804/> National Human Genome Research Institute (NHGRI) GWAS catalog: <http://www.genome.gov/gwastudies> eQTL database: <http://www.sph.umich.edu/csg/junding/eQTL/TableDownload/>

METHODS

Methods and any associated references are available in the online version of the paper at <http://www.nature.com/naturegenetics/>.

Psoriasis is a chronic, potentially disfiguring, immune-mediated inflammatory disease of the skin with a prevalence of 0.2 to 2%, depending on the population of origin. About one-quarter of psoriatics develop a painful and debilitating arthritis, and there is increasing awareness of co-morbidities, including metabolic syndrome and cardiovascular disease^{1,2}. Current evidence suggests that a dysregulated cutaneous immune response characterized by tumor necrosis factor- α (TNF) dependence and exaggerated Th1 and Th17 activation occurs in genetically susceptible individuals^{1,2}. Recent large-scale association studies have identified 26 loci that are associated with psoriasis^{3–10}, 21 of which show association in Caucasians^{3–6,10}. Several of these signals overlap with other autoimmune diseases (e.g. Crohn's disease, ankylosing spondylitis, and celiac disease), particularly those near genes involved in Th17 differentiation and IL-17 responsiveness (e.g. *IL23R*, *IL12B*, *IL23A*, *TRAF3IP2*)¹¹. To accelerate our understanding of the genetic architecture of this disease, we helped design a custom single-nucleotide polymorphism (SNP) array (the "ImmunoChip"). The aims of the ImmunoChip are to fine-map genome-wide significant (i.e. $P < 5 \times 10^{-8}$) susceptibility loci and to explore replication of thousands of SNPs representing additional promising signals^{12,13}. In this study, we use ImmunoChip data to identify new genetic determinants of psoriasis, and to relate them to other autoimmune disorders.

We combined three existing GWAS datasets (hereafter referred to as Kiel³, CASP⁴ and WTCCC2⁵) with two independent European-descent case-control datasets genotyped on the ImmunoChip: the Psoriasis Association Genetics Extension (PAGE: 3,580 cases and 5,902 controls) and the Genetic Analysis of Psoriasis Consortium (GAPC: 2,997 cases and 9,183 controls) (datasets are described in Supplementary Tables 1 and 2). After quality control, the combined dataset consisted of 10,588 patients with psoriasis and 22,806 healthy controls. For each GWAS, we increased the SNP density through imputation by using European haplotype sequences generated by the 1000 Genomes Project as templates (20100804 release). Overall, our analysis includes 111,236 SNPs that were genotyped in both ImmunoChip datasets and also had good imputation quality in at least two of the three GWAS (see **Online Methods**).

Meta-analysis of all five datasets yielded genome-wide significance for 19 of the 21 known psoriasis loci (Supplementary Fig 1, Table 1, Supplementary Table 3). We found nominal evidence for the remaining two loci in the combined analysis (*ZMIZ1* and *PRDX5*, each with $P < 3 \times 10^{-6}$) as well as nominal evidence for all loci in separate analyses including only GWAS (all with $P < 5 \times 10^{-3}$) or ImmunoChip data (all with $P < 4 \times 10^{-4}$). In addition, we identified 15 new risk loci at $P < 5 \times 10^{-8}$ (Supplementary Fig 1, Table 1, and Supplementary Table 3). Nine of the new signals were submitted, during design of the ImmunoChip, as genome-wide significant ImmunoChip loci by at least one other disease consortium (see "Disease Overlap" column in Supplementary Table 4), though we also submitted three of these (rs11121129, rs10865331, and rs9504361) based on a preliminary meta-analysis of our GWAS datasets. Notably, of the remaining six signals, four were submitted as genome-wide significant loci for psoriasis (SNPs rs11795343, rs4561177, rs11652075, and rs545979). The strongest new association was observed for rs892085 at 19p13.2, near the *ILF3* and *CARM1* genes (combined Pvalue (P_{comb}) = 3.0×10^{-17} ; OR = 1.17). Despite its proximity (< 500kb) to *TYK2*, conditional analysis demonstrated that this is an independent signal

(Supplementary Table 5). Other associated loci included 1p36.11 near *RUNX3*; 6p25.3 near *EXOC2* and *IRF4*; 9p21.1 near *DDX58*; 11q22.3 near *ZC3H12C*, 11q24.3 in the *ETS1* gene and 17q21.2 near *STAT3*, *STAT5A* and *STAT5B*. Box 1 summarizes the functional characteristics of notable genes from the newly identified loci, and the regional association plots are shown in Supplementary Fig 2.

Box 1

The function of notable genes in the regions of newly identified associations

***RERE*, *SLC45A1*, *ERRF1*, *TNFRSF9* (1p36.23)**

This signal falls between the *RERE*, *SLC45A1*, *ERRF1*, and *TNFRSF9* genes. *RERE* encodes an arginine-glutamic acid dipeptide repeat-containing protein that controls retinoic acid signalling³⁸. *ERRF1* encodes a feedback inhibitor of the EGF receptor³⁹. *SLC45A1* encodes a solute carrier protein that mediates the uptake of glucose⁴⁰. The *TNFRSF9* gene encodes a co-stimulatory molecule that has a role in generation of memory CD8⁺ T-cells.

***RUNX3* (1p36.11)**

RUNX3 is a member of the Runt domain-containing family of transcription factors and has an essential role in T-cell biology, particularly in the generation of CD8⁺ cells. *RUNX3* also has a role in promoting Th1 differentiation through binding with T-bet⁴¹.

***B3GNT2* (2p15)**

B3GNT2 is a member of the beta-1,3-N-acetylglucosaminyl transferase family. It catalyzes the initiation and elongation of poly-N-acetyllactosamine chains⁴². Deficiency has shown to result in hyperactivation of lymphocytes⁴³.

***EXOC2*, *IRF4* (6p25.3)**

EXOC2 encodes a component of the multi-protein complex which mediates the docking of exocytic vesicles to the plasma membrane⁴⁴. *IRF4* encodes a transcription factor that regulates *IL17A* promoter activity and controls ROR γ t-dependent Th17 colitis *in vivo*^{45,46}. *IRF4* also plays a role in stabilization of the Th17 phenotype through IL-21⁴⁷ and may regulate CD4/CD8 differentiation through regulation of *RUNX3* expression⁴⁸.

***TAGAP* (6q25.3)**

This gene is a Rho-GTPase activating protein that is involved in T-cell activation⁴⁹.

***ELMO1* (7p14.2-7p14.1)**

ELMO1 is a member of the engulfment and cell motility protein family, which binds to *DOCK2*, and is essential for *TLR7*- and *TLR9*-mediated IFN- α induction by plasmacytoid dendritic cells⁵⁰ and plasmacytoid dendritic cell migration.⁵¹ *DOCK2* also has a role in antigen-uptake and presentation, and lymphocyte trafficking⁵¹.

***DDX58* (9p21.1)**

DDX58 encodes the RIG-I innate antiviral receptor, which recognizes cytosolic double-stranded RNA.⁵² It is induced by IFN- γ ⁵³ and regulates type I and type II IFN production⁵⁴.

***KLF4* (9p31.2)**

KLF4 is a Kruppel-like transcription factor, which is required for the establishment of skin barrier function⁵⁵ and regulates key signaling pathways related to macrophage activation⁵⁶. *KLF4* also binds to the promoter of *IL17A* and positively regulates its expression.

***ZC3H12C* (11q22.3)**

Zinc-finger protein regulating macrophage activation⁵⁷.

***ETSI* (11q24.3)**

Transcription factor activated downstream of the Ras-MAPK pathway, involved in homeostasis of squamous epithelia⁵⁸. Involved in CD8 lineage differentiation and acts in part by promoting RUNX3 expression⁵⁹. Negative regulator of Th17 differentiation⁶⁰

***SOCS1* (16p13.13)**

SOCS1 is a member of the suppressor of cytokine signalling family of proteins and inhibits signalling events downstream of IFN- γ ⁶¹. It regulates Th17 differentiation by maintaining *STAT3* transcriptional activity⁶² and interacts with TYK2 in cytokine signalling⁶³.

***STAT3* , *STAT5A/5B* (17q21.2)**

STAT3 and *STAT5A/5B* are members of the STAT family of transcription activators. *STAT3* participates in signalling downstream of multiple cytokines implicated in psoriasis such as *IL-6*, *IL-10*, *IL-20*, *IL-22* and *IL-23* and may have a role in mediating the innate immune response in psoriatic epidermis⁶⁴. *STAT3* is required for the differentiation of Th17 cells⁶⁵. *STAT5A/5B* participate in signalling downstream of the *IL-2* family of cytokines, including *IL-2*, *IL-7*, *IL-15* and *IL-21*. Both proteins contribute to the development of Treg cells and inhibit the differentiation of Th17 cells⁶⁶.

***CARD14* (17q25.3)**

Member of a family of Caspase Recruitment Domain containing scaffold proteins, known as CARD- and membrane-associated guanylate kinase-like domain-containing protein (CARMA). *CARD14/CARMA2* is primarily expressed in epithelial tissues and mediates recruitment and activation of the NF- κ B pathway⁶⁷.

***MBD2,POLI* ,*STARD6* (18q21.2)**

MBD2 is a transcriptional repressor that binds to methylated DNA and has a role in the generation of memory CD8+ T-cells⁶⁸. *POLI* is an error-prone DNA polymerase, which contributes to the hyper-mutation of immunoglobulin genes⁶⁹. Sterol transport is mediated by vesicles or by soluble protein carriers, such as steroidogenic acute regulatory protein (STAR; MIM 600617). STAR is homologous to a family of proteins containing a

200- to 210-amino acid STAR-related lipid transfer (START) domain, including STARD6.

ILF3, CARM1 (19p13.2)

ILF3 encodes a double-stranded RNA (dsRNA) binding protein that complexes with other proteins, dsRNAs, small noncoding RNAs, and mRNAs to regulate gene expression and stabilize mRNAs. It is a subunit of the nuclear factor of activated T-cells (NFAT); a transcription factor required for T-cell expression of *IL-2*. *CARM1* is a transcriptional coactivator of NF- κ B and functions as a promoter-specific regulatory of NF- κ B recruitment to chromatin.

To identify independent secondary signals, we performed conditional analysis using as covariates the strongest signals from the 34 loci achieving genome-wide significance in this study. We identified secondary signals in five loci: 2q24.2, 5q15, 5q33.3, 6p21.33, and 19q13.2 (Supplementary Figs. 3 and 4, Supplementary Tables 6 and 7). The strongest signal from the conditional analysis maps to the MHC region near the *MICA* gene (rs13437088: $P=3.1 \times 10^{-40}$; OR = 1.32), in agreement with a previous conditional analysis¹⁴. The 5q15 conditional signal is in the *ERAP2* gene (rs2910686: $P = 2.0 \times 10^{-8}$), which did not show any evidence of association in the unconditional analysis ($P = 0.46$). Further investigation revealed that the risk-increasing alleles at *ERAP1* and the risk-decreasing alleles at *ERAP2* preferentially appear on the same haplotype, and the signal near *ERAP2* is thus masked by *ERAP1* prior to conditional analysis (Supplementary Note). The strongest conditional signal in the 19q13.2 region was rs12720356 in the *TYK2* gene (OR=1.25, $MAF_{controls}=0.09$, $P = 3.2 \times 10^{-10}$). The association of this SNP with psoriasis has been previously reported⁵ and is independent of the strongest *TYK2* signal identified by our meta-analysis (rs34536443, OR=1.88, $MAF_{cases}=0.03$, $P = 1.5 \times 10^{-39}$). As rs34536443 was a low-frequency imputed SNP and manifested the highest effect size outside of the MHC, we directly genotyped this SNP in 3,390 independent Michigan samples (1,844 cases and 1,546 controls), robustly replicating the association (OR = 2.80, $MAF_{cases} = 0.02$, $P = 7.8 \times 10^{-14}$) and experimentally confirming the validity of our imputation procedures.

We next tested for statistical interaction among the top SNPs in the 34 significant loci (Supplementary Note; Supplementary Table 8). We identified two significant pairwise interactions after correction for multiple testing ($P < 5 \times 10^{-5}$): *HLA-C* (rs4406273)-*LCE* (rs6677595) and *HLA-C* (rs4406273)-*ERAP1* (rs27432). These interactions confirm results of previous studies^{5,15,16}.

In order to identify potential causal alleles in coding sequence, we looked for missense variants in tight LD ($r^2 > 0.9$ in 1000 Genomes Project European samples) with the lead SNPs from each of the 34 identified loci (Table 1 and Supplementary Table 6). We found 10 potentially causal SNPs (Table 2), nine of which were included in our meta-analysis. For the known loci near *TRAF3IP2* and *TYK2*, damaging non-synonymous substitutions were themselves the index SNPs in our initial and conditional analyses. Among the newly identified loci, the index SNP from *CARD14*, a gene that harbors Mendelian variants predisposing to psoriasis¹⁷, was also a common and damaging variant as has been described elsewhere¹⁸. For the remaining loci, we could account for essentially all index SNP signals

by conditioning on nearby missense SNPs, consistent with the possibility that they are causal. Notable non-synonymous variants include the protective c.R381Q polymorphism in *IL23R*¹⁹; a SNP in the *PRSS53* gene²⁰, which is also the most highly over-expressed gene in psoriatic skin in this locus⁶; and a variant in *YDJC* that also increases risk for celiac disease²¹, rheumatoid arthritis²² and Crohn's disease²³.

Utilizing the results of a large-scale study of gene expression in psoriatic vs. normal skin²⁴, we found 14 up-regulated genes (*IL12RB2*, *LCE3D*, *REL*, *PUS10*, *CDSN*, *PRSS53*, *PRSS8*, *NOS2*, *DDX58*, *ZC3H12C*, *SOCS1*, *STAT3*, *CARD14*, *IFIH1*) and 4 down-regulated genes (*MICA*, *RNF114*, *PTRF*, *POLI*) in the 34 associated regions (FDR<0.05 and fold-change>1.5 or <0.67; Supplementary Table 9). The number of differentially expressed genes in psoriasis susceptibility loci was not greater than expected by chance (P=0.39). None of the 34 top SNPs met the Bonferroni corrected ($P < 1 \times 10^{-7}$) threshold as expression quantitative trait loci (eQTL) in skin tissue, as assessed by microarray analysis of mRNA levels²⁵. However, rs2910686, one of the five SNPs identified by conditional analysis, was a cis-eQTL for *ERAP2* in both normal and psoriatic skin (see Supplementary Note for details). Genetic control of *ERAP2* expression has been noted previously^{26,27} and has been suggested as a determinant of balancing selection at this locus²⁸.

This study increases the number of psoriasis-associated regions in European ancestry samples to 36, with conditional analysis increasing the number of independent signals to 41. The 39 independent signals with $P < 5 \times 10^{-8}$ in the current study collectively account for 14.3% of the total variance in psoriasis risk, or approximately 22% of its estimated heritability²⁹ (see Supplementary Table 10 for details), indicating that further genetic studies, including fine mapping studies and searches for uncommon susceptibility variants are in order.

Sharing of susceptibility loci between autoimmune diseases has been demonstrated previously¹¹ and we find similar patterns in this study. Notably, ten of the psoriasis susceptibility loci reported here overlap with Crohn's disease and ten others with celiac disease, two diseases that are enriched in individuals with psoriasis^{30,31} (Supplementary Table 4; illustrated in Supplementary Fig. 5). We caution that the statistical significance of these overlaps is hard to assess, given the ongoing process of gene discovery for many autoimmune disorders and biases in the list of SNPs evaluated for association in this experiment.

As the primary interface with the external environment, the skin provides a critical first line of host defense to microbial pathogens. Consistent with this function, it possesses a diverse and well-conserved set of innate immune mechanisms^{32,33}, which emerged long before the development of adaptive immunity³⁴. In this context, we found it interesting that five of the six newly identified loci that are thus far uniquely associated with psoriasis are involved in innate immune responses (*DDX58*, *KLF4*, *ZC3H12C*, *CARD14* and *CARM1*, Supplementary Table 4 and Box 1). Among all confirmed psoriasis susceptibility loci, 11 out of 14 psoriasis specific loci (the five listed above along with *IL28RA*, *LCE3D*, *NOS2*, *FBXL19*, *NFKBIA* and *RNF114*) encode plausible regulators of innate host defense^{1,2,35}. Conversely, only 6 out of 20 loci shared with other autoimmune diseases contain genes (*REL*, *IFIH1*, *TNIP1*,

TNFAIP3, *IRF4* and *ELMO1*) that contribute to innate immunity. These provisional comparisons further illustrate the insights that can be gained by developing and comparing complete and well-annotated sets of risk loci for autoimmune disorders.

The known and newly identified psoriasis susceptibility loci implicated by this study encode several proteins engaged in the TNF, IL-23, and IL17 signaling pathways targeted by highly effective biologic therapies³⁶. Interestingly, our strongest non-MHC signal directly implicates *TYK2*, a druggable target that contributes to several autoimmune diseases. Agents targeting the closely related JAK kinases are showing encouraging results in clinical trials³⁷. Our findings will help prioritize and interpret the results of sequencing and gene expression studies. Further genomic studies will allow us to identify the underlying causal variants within psoriasis susceptibility loci and lead to increased understanding of pathogenetic mechanisms and new therapeutic targets.

Online Methods

Sample Collections

The samples used in the 3 GWAS data sets (Kiel, CASP and WTCCC2) were previously described^{3–5}. Samples of the Psoriasis/Arthritis Genetics Extension (**PAGE**) and the Genetic Analysis of Psoriasis Consortium (**GAPC**) datasets (Supplementary Table 1 and 2) were collected from subjects of European Caucasian descent at the participating institutions after obtaining informed consent in adherence with the Declaration of Helsinki Principles. DNA was isolated from blood or EBV-immortalized lymphoblastoid cell lines using standard methods.

The collections used in the **GAPC** and **PAGE** ImmunoChip studies are described in Supplementary Table 2.

The samples from **GAPC** substantially overlapped with those described as replication datasets in Strange et al. 2010⁵. All cases had been diagnosed as having psoriasis vulgaris. The GAPC cases and the Irish and Spanish controls were genotyped at the Wellcome Trust Sanger Institute (WTSI) and all samples were provided by the relevant groups given in Supplementary Table 2 and listed in the GAP consortium members list (Supplementary Note 2). The UK controls were the WTCCC common controls that did not overlap with samples included in the original GWA studies (the dataset consisted of 6,740 1958 British Birth cohort and 2,900 UK Blood Service samples genotyped at the WTSI and the University of Virginia). The German controls were obtained from the PopGen biobank and genotyped at the Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel. The Finland control data were from the DILGOM (Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome) collection⁷⁰. The Irish controls were provided by the Irish Blood Transfusion Service / TCD Biobank and the Irish cases collected with the aid of the Dublin Centre for Clinical Research. We did not include specific controls from Austria or Sweden, but PCA analysis suggested that the cases from these cohorts were well matched to the controls from the Netherlands and Germany.

For the **PAGE** ImmunoChip study, samples also substantially overlapped with previously published replication datasets. The German cases (described as a replication dataset in Ellinghaus et al. 2010³), all samples from the United States and Canada, as well as 439 Estonian cases from the University of Tartu were genotyped at the Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel. The respective samples were provided by the groups given in Supplementary Table 2 and listed in the PAGE members list (Supplementary Note). The German controls were obtained from a population-based sample from the general population living in the region of Augsburg, Southern Germany (Collaborative Health Research in the Region of Augsburg; KORA S4/F4⁷¹), which was genotyped at the Helmholtz Center in Munich, and from the population-based epidemiological Heinz-Nixdorf Recall study (HNR), which was genotyped at the Life and Brain Center at the University Clinic in Bonn. The remaining Estonian samples were obtained from and genotyped at the Estonian Genome Center University of Tartu (EGCUT).

Genotyping panel and SNPs

The ImmunoChip is a custom Illumina Infinium high-density array consisting of 196,524 variants (after Illumina quality control) compiled largely from variants identified in previous GWAS of 12 different immune-mediated inflammatory diseases, including psoriasis¹³. The main aims of the ImmunoChip were deeper replication and fine-mapping of genome-wide significant loci, as well as increasing power to promote promising but less significant SNPs to genome-wide significance. For fine mapping, SNPs within 0.2 cM on either side of the GWAS top SNPs for 186 loci were selected from 1000 Genomes Project⁷² low coverage pilot CEU sequencing data as well as additional variants identified by resequencing from groups involved in the chip design. For promotion of promising signals and those not quite reaching genome-wide significance, each disease-focused group was allowed to submit approximately 3,000 additional SNPs. We submitted 17 of the 19 confirmed genome-wide significant psoriasis regions (Table 1) for fine mapping based on a preliminary meta-analysis of our data, while one of the confirmed signals (*IL28RA*) and nine of the new psoriasis signals (indicated in the “disease overlap” column of Supplementary Table 5) were submitted for fine mapping by other disease groups (though we also submitted three of them as part of our additional SNP allocation SNPs: rs11121129, rs10865331, and rs9504361). Six additional signals were detected based on individual groups additional SNP allocation; four of these (rs11795343, rs4561177, rs11652075, and rs545979) were submitted by our group. All ImmunoChip samples were genotyped as described in Illumina’s protocols.

Genotype calling

For the PAGE dataset genotype calling was performed using Illumina’s GenomeStudio Data Analysis software and the custom-generated cluster file of Trynka *et al.* (based on an initial clustering of 2000 UK samples with the GenTrain2.0 algorithm and subsequent manual readjustment and quality control)¹³. The genotype calling for the GAPC dataset was performed using GenoSNP⁷³ from allele intensities, except for the German, Italian, Dutch and Finnish controls, which were called using the same method described for the PAGE dataset.

Imputation

To increase the number of overlapping SNPs between datasets, we performed imputation on the 3 GWAS datasets using minimac⁷⁴ (Kiel and CASP) and IMPUTE2^{75,76} (WTCCC2) based on CEU reference haplotypes from the 1000 Genomes Project⁷²; December 2010 version of the 10/08/04 sequence and alignment release containing 629 individuals of European descent). SNPs with low imputation quality ($r^2 < 0.3$ for minimac, info score < 0.5 for IMPUTE2) were removed. For all 3 datasets, cases and controls were imputed together.

Sample and genotype quality control

For the ImmunoChip datasets, we first excluded SNPs with a call rate below 95% or with a Hardy-Weinberg p-value $< 1 \times 10^{-6}$. Samples with less than 98% SNP call rates were then excluded. Because the ImmunoChip includes a large proportion of fine-mapping SNPs that are associated with autoimmune disease, we used a set of independent SNPs which have p-values > 0.5 from the meta-analysis of the 3 GWAS datasets as a quality control tool for each individual ImmunoChip dataset. Using the HapMap 3 samples as reference⁷⁷, we performed principal component (PC) analysis to identify and remove samples with non-European ancestry. We also removed samples with extreme inbreeding coefficients or heterozygosity values computed by PLINK⁷⁸.

To assess possible stratification in the datasets, principal components analysis was also performed in each of the ImmunoChip datasets separately (excluding HapMap). There was no evidence of stratification between the cases and controls of each sample group. However, as expected, the top principal components (PCs) do separate the samples well by country of origin. The use of the top 10 eigenvectors as covariates in the analysis did not completely correct for this stratification and so a linear mixed model method (Efficient Mixed-Model Association eXpedited (EMMAX)) was used for the association analysis instead. These methods have been shown to outperform PCs at correcting for this type of population stratification and cryptic relatedness⁷⁹, which is becoming more common as sample sizes get larger and studies comprise of more collaborative efforts.

To identify duplicate pairs or highly related individuals among datasets, we used a panel of 873 independent SNPs that were genotyped in both the GWAS and ImmunoChip samples, and performed pairwise comparisons using the 'genome' function in PLINK⁷⁸, with the criterion $\text{Pi-HAT} > 0.5$. We identified 1,142 (885 from GAPC and 257 from PAGE) related sample pairs (mostly duplicates) and removed one sample from each pair. We also removed 4,828 controls from the UK common ImmunoChip controls owing to duplication in the WTCCC2 GWAS sample. For GWAS samples that were duplicated in the ImmunoChip datasets (the majority of duplicates), we removed the samples from the ImmunoChip datasets to keep the previously published datasets intact.

The GWAS datasets underwent quality control as previously described and were analysed for association using the top PCs from the previous analyses, as covariates³⁻⁵.

We visually checked the signal intensity cluster plots for all SNPs meeting genome-wide significance to confirm high quality genotype calling.

Genomic Control

Genomic control inflation factors for the five datasets were 1.09 (**Kiel**), 1.06 (**CASP**), 1.04 (**WTCCC2**), 0.99 (**PAGE**), and 0.96 (**GAPC**), indicating that population structure and cryptic relatedness were adequately controlled for in these datasets. Because the ImmunoChip was designed for deep replication and fine mapping of loci associated with autoimmune diseases¹², using all independent SNPs from the chip would not give an accurate estimate of the genomic control⁸⁰ (λ_{GC}) value. Therefore, we selected common (MAF > 0.05) SNPs from the ImmunoChip that had p-values > 0.5 based on a meta-analysis combining the CASP, Kiel, and the WTCCC2 GWAS, and then performed LD-pruning to identify an independent SNP set to compute λ_{GC} for the association results from the ImmunoChip datasets. Due to the SNP selection bias, the genomic control of the final meta-analysis was computed using a set of independent SNPs associated with “reading and writing ability” (personal communication, J.C. Barrett). We further removed SNPs that were within ± 500 kb of previously detected psoriasis loci (± 3 Mb was used for the MHC region), and the remaining 1,426 SNPs yielded a λ_{GC} value of 1.11 for the meta-analysis overall. By using the λ_{1000} ⁸¹, the genomic control inflation factor for an equivalent study of 1000 cases and 1000 controls, the rescaled λ equals 1.01.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Lam C Tsoi^{1,*}, Sarah L Spain^{2,*}, Jo Knight^{3,4,*}, Eva Ellinghaus^{5,*}, Philip E Stuart⁶, Francesca Capon², Jun Ding¹, Yanming Li¹, Trilokraj Tejasvi⁶, Johann E. Gudjonsson⁶, Hyun M Kang¹, Michael H Allen², Ross McManus^{7,8}, Giuseppe Novelli^{9,10}, Lena Samuelsson¹¹, Joost Schalkwijk¹², Mona Ståhle¹³, A. David Burden¹⁴, Catherine H Smith¹⁵, Michael J Cork¹⁶, Xavier Estivill¹⁷, Anne M Bowcock¹⁸, Gerald G. Krueger¹⁹, Wolfgang Weger²⁰, Jane Worthington²¹, Rachid Tazi-Ahnini¹⁶, Frank O Nestle², Adrian Hayday²², Per Hoffmann^{23,24}, Juliane Winkelmann^{25,26,27}, Cisca Wijmenga²⁸, Cordelia Langford²⁹, Sarah Edkins²⁹, Robert Andrews²⁹, Hannah Blackburn²⁹, Amy Strange³⁰, Gavin Band³⁰, Richard D Pearson³⁰, Damjan Vukcevic³⁰, Chris CA Spencer³⁰, Panos Deloukas²⁹, Ulrich Mrowietz³¹, Stefan Schreiber^{5,32,33}, Stephan Weidinger³¹, Sulev Koks³⁴, Külli Kingo³⁵, Tonu Esko³⁶, Andres Metspalu³⁶, Henry W Lim³⁷, John J Voorhees⁶, Michael Weichenthal³¹, H. Erich Wichmann^{38,39,40}, Vinod Chandran⁴¹, Cheryl F Rosen⁴², Proton Rahman⁴³, Dafna D Gladman⁴¹, Christopher EM Griffiths⁴⁴, Andre Reis⁴⁵, Juha Kere^{46,47,48}, Collaborative Association Study of Psoriasis⁴⁹, Genetic Analysis of Psoriasis Consortium⁴⁹, Psoriasis Association Genetics Extension⁴⁹, Wellcome Trust Case Control Consortium 2⁴⁹, Rajan P Nair⁶, Andre Franke⁵, Jonathan NWN Barker^{2,15}, Goncalo R Abecasis^{1,‡}, James T Elder^{6,50,‡}, and Richard C Trembath^{2,51,‡}

Affiliations

¹Department of Biostatistics, Center for Statistical Genetics, University of Michigan Ann Arbor, MI 48109, USA ²Division of Genetics and Molecular Medicine, King's College London, London, UK ³Neuroscience Research, Centre for Addiction and Mental Health, Toronto, ON, Canada M5T 1R8 ⁴National Institute for Health Research (NIHR), Biomedical Research Centre, Guy's and St. Thomas' NHS Foundation Trust ⁵Institute of Clinical Molecular Biology, Christian-Albrechts-University, 24105 Kiel, Germany ⁶Department of Dermatology, University of Michigan, Ann Arbor, MI 48109, USA ⁷Department of Clinical Medicine Trinity College Dublin, Ireland ⁸Institute of Molecular Medicine, Trinity College Dublin, Ireland ⁹National Agency for Evaluation of Universities and Research Institutes (ANVUR) ¹⁰Research Center San Pietro Hospital, Rome, Italy ¹¹Department of Medical and Clinical Genetics, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden ¹²Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands ¹³Dermatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden ¹⁴Department of Dermatology, Western Infirmary, Glasgow, UK ¹⁵St John's Institute of Dermatology, King's College London, London, UK ¹⁶Academic Unit of Dermatology Research, Department of Infection and Immunity, The University of Sheffield, Sheffield, UK ¹⁷Genes and Disease Programme, Centre for Genomic Regulation (CRG) and UPF, Hospital del Mar Research Institute (CRG) and Public Health and Epidemiology Network Biomedical Research Centre (CIBERESP), Barcelona, Spain ¹⁸Division of Human Genetics, Department of Genetics, Washington University School of Medicine, St. Louis, MO ¹⁹Department of Dermatology, University of Utah, Salt Lake City, UT ²⁰Department of Dermatology, Medical University of Graz, Graz, Austria ²¹Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK ²²Division of Immunology, Infection and Inflammatory Disease; King's College London, London, UK ²³Institute of Human Genetics, University of Bonn, 54127 Bonn, Germany ²⁴Department of Genomics, Life & Brain Center, University of Bonn, 54127 Bonn, Germany ²⁵Department of Neurology, Technische Universität München, Munich, Germany ²⁶Institute of Human Genetics, Technische Universität München, Munich, Germany ²⁷Institute of Human Genetics, Helmholtz Zentrum Munich, German Research Center for Environmental Health, Munich, Germany ²⁸Genetics Department, University Medical Center and University of Groningen, Groningen, The Netherlands ²⁹Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK ³⁰Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK ³¹Department of Dermatology, University Hospital, Schleswig-Holstein, Christian-Albrechts-University, 24105 Kiel, Germany ³²Institute of Clinical Molecular Biology, Christian-Albrechts-University, 24105 Kiel, Germany ³³PopGen biobank, University Hospital S.-H., Kiel, Germany ³⁴Department of Physiology, Centre of Translational Medicine and Centre for Translational Genomics, University of Tartu, 50409 Tartu, Estonia ³⁵Department of Dermatology and Venerology, University of Tartu, 50409 Tartu, Estonia ³⁶Estonian Genome

Center, University of Tartu, 51010 Tartu, Estonia ³⁷Department of Dermatology, Henry Ford Hospital, Detroit, MI, 48202, USA ³⁸Institute of Epidemiology I, Helmholtz Centre Munich, German Research Center for Environmental Health, 85764 Neuherberg, Germany ³⁹Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University, 81377 Munich, Germany ⁴⁰Klinikum Grosshadern, 81377 Munich, Germany ⁴¹Department of Medicine, Division of Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, Ontario M5T 2S8, Canada ⁴²Department of Medicine, Division of Dermatology, University of Toronto, Toronto Western Hospital, Toronto, Ontario M5T 2S8 ⁴³Department of Medicine, Memorial University, St. John's, Newfoundland A1C 5B8, Canada ⁴⁴Dermatological Sciences, Salford Royal NHS Foundation Trust, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK ⁴⁵Institute of Human Genetics, University of Erlangen-Nuremberg, Erlangen, Germany ⁴⁶Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden ⁴⁷Folkhälsan Institute of Genetics, Helsinki, Finland ⁴⁸Department of Medical Genetics, University of Helsinki, Finland ⁵⁰Ann Arbor Veterans Affairs Hospital, Ann Arbor, MI, 48105, USA ⁵¹Queen Mary University of London, Barts and the London School of Medicine and Dentistry, London, UK

Acknowledgments

Major support for this study was provided by the National Institutes of Health, the Wellcome Trust, and the German Research Foundation. We acknowledge use of the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council (G0000934) and the Wellcome Trust (068545/Z/02), and of the UK National Blood Service controls funded by the Wellcome Trust. We acknowledge the Collaborative Association Study of Psoriasis (CASP) for the contribution of GWAS data, as well as the provision of control DNA samples by the Cooperative Research in the Region of Augsburg (KORA) and Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) study (HNR), and genotyping data generated by the Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) consortium. We thank the Barbara and Neal Henschel Charitable Foundation for their support of the National Psoriasis Victor Henschel BioBank. We thank Jeffrey C Barrett for contribution to the design of the ImmunoChip and helpful analytical discussion, as well as Emma Gray, Suzannah Bumpstead, Douglas Simpkin and staff of the Wellcome Trust Sanger Institute Sample Management and Genotyping teams for their genotyping and analytical contributions. We acknowledge the Genetic repository in Ireland for Psoriasis and Psoriatic Arthritis (GRIPPSA), the Irish blood transfusion service / TCD Biobank and the Dublin Centre for Clinical Research (funded by HRB and the Wellcome Trust). Detailed consortium contributorship lists and relevant funding support are detailed in the Supplementary Note.

References

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009; 361:496–509. [PubMed: 19641206]
2. Elder JT, et al. Molecular dissection of psoriasis: integrating genetics and biology. *J Invest Dermatol*. 2010; 130:1213–26. [PubMed: 19812592]
3. Ellinghaus E, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. *Nat Genet*. 2010; 42:991–5. [PubMed: 20953188]
4. Nair RP, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet*. 2009; 41:199–204. [PubMed: 19169254]
5. Strange A, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet*. 2010; 42:985–90. [PubMed: 20953190]
6. Stuart PE, et al. Genome-wide association analysis identifies three psoriasis susceptibility loci. *Nat Genet*. 2010; 42:1000–4. [PubMed: 20953189]

7. Sun LD, et al. Association analyses identify six new psoriasis susceptibility loci in the Chinese population. *Nat Genet.* 2010; 42:1005–9. [PubMed: 20953187]
8. Zhang XJ, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. *Nat Genet.* 2009; 41:205–10. [PubMed: 19169255]
9. de Cid R, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat Genet.* 2009; 41:211–5. [PubMed: 19169253]
10. Ellinghaus D, et al. Combined Analysis of Genome-wide Association Studies for Crohn Disease and Psoriasis Identifies Seven Shared Susceptibility Loci. *Am J Hum Genet.* 2012; 90:636–47. [PubMed: 22482804]
11. Cotsapas C, et al. Pervasive sharing of genetic effects in autoimmune disease. *PLoS Genet.* 2011; 7:e1002254. [PubMed: 21852963]
12. Cortes A, Brown MA. Promise and pitfalls of the Immunochip. *Arthritis Res Ther.* 2011; 13:101. [PubMed: 21345260]
13. Trynka G, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nat Genet.* 2011; 43:1193–201. [PubMed: 22057235]
14. Feng BJ, et al. Multiple Loci within the major histocompatibility complex confer risk of psoriasis. *PLoS Genet.* 2009; 5:e1000606. [PubMed: 19680446]
15. Zheng HF, et al. Variants in MHC, LCE and IL12B have epistatic effects on psoriasis risk in Chinese population. *J Dermatol Sci.* 2011; 61:124–8. [PubMed: 21208785]
16. Riveira-Munoz E, et al. Meta-analysis confirms the LCE3C_LCE3B deletion as a risk factor for psoriasis in several ethnic groups and finds interaction with HLA-Cw6. *J Invest Dermatol.* 2011; 131:1105–9. [PubMed: 21107349]
17. Jordan CT, et al. PSORS2 is due to mutations in CARD14. *Am J Hum Genet.* 2012; 90:784–95. [PubMed: 22521418]
18. Jordan CT, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet.* 2012; 90:796–808. [PubMed: 22521419]
19. Di Meglio P, et al. The IL23R R381Q gene variant protects against immune-mediated diseases by impairing IL-23-induced Th17 effector response in humans. *PLoS One.* 2011; 6:e17160. [PubMed: 21364948]
20. Cal S, et al. Identification and characterization of human polyserase-3, a novel protein with tandem serine-protease domains in the same polypeptide chain. *BMC Biochem.* 2006; 7:9. [PubMed: 16566820]
21. Dubois PC, et al. Multiple common variants for celiac disease influencing immune gene expression. *Nat Genet.* 2010; 42:295–302. [PubMed: 20190752]
22. Zhernakova A, et al. Meta-analysis of genome-wide association studies in celiac disease and rheumatoid arthritis identifies fourteen non-HLA shared loci. *PLoS Genet.* 2011; 7:e1002004. [PubMed: 21383967]
23. Franke A, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet.* 2010; 42:1118–25. [PubMed: 21102463]
24. Gudjonsson JE, et al. Assessment of the psoriatic transcriptome in a large sample: additional regulated genes and comparisons with in vitro models. *J Invest Dermatol.* 2010; 130:1829–40. [PubMed: 20220767]
25. Ding J, et al. Gene expression in skin and lymphoblastoid cells: Refined statistical method reveals extensive overlap in cis-eQTL signals. *Am J Hum Genet.* 2010; 87:779–89. [PubMed: 21129726]
26. Mason CC, et al. Bimodal distribution of RNA expression levels in human skeletal muscle tissue. *BMC Genomics.* 2011; 12:98. [PubMed: 21299892]
27. Song MY, Kim HE, Kim S, Choi IH, Lee JK. SNP-based large-scale identification of allele-specific gene expression in human B cells. *Gene.* 2011; 493:211–8. [PubMed: 22178530]
28. Andres AM, et al. Balancing selection maintains a form of ERAP2 that undergoes nonsense-mediated decay and affects antigen presentation. *PLoS Genet.* 2010; 6:e1001157. [PubMed: 20976248]

29. Grjibovski AM, Olsen AO, Magnus P, Harris JR. Psoriasis in Norwegian twins: contribution of genetic and environmental effects. *J Eur Acad Dermatol Venereol.* 2007; 21:1337–43. [PubMed: 17958839]
30. Najarian DJ, Gottlieb AB. Connections between psoriasis and Crohn's disease. *J Am Acad Dermatol.* 2003; 48:805–21. quiz 822–4. [PubMed: 12789169]
31. Ludvigsson JF, Lindelof B, Zingone F, Ciacci C. Psoriasis in a nationwide cohort study of patients with celiac disease. *J Invest Dermatol.* 2011; 131:2010–6. [PubMed: 21654830]
32. Modlin RL. Innate immunity: ignored for decades, but not forgotten. *J Invest Dermatol.* 2012; 132:882–6. [PubMed: 22158552]
33. Nakatsuji T, Gallo RL. Antimicrobial peptides: old molecules with new ideas. *J Invest Dermatol.* 2011; 132:887–95. [PubMed: 22158560]
34. Wolffe U, Martin S, Emde M, Schempp C. Dermatology in the Darwin anniversary. Part 2: Evolution of the skin-associated immune system. *J DtschDermatol Ges.* 2009; 7:862–9.
35. Capon F, Burden AD, Trembath RC, Barker JN. Psoriasis and other complex trait dermatoses: from Loci to functional pathways. *J Invest Dermatol.* 2012; 132:915–22. [PubMed: 22158561]
36. Gudjonsson, JE.; Elder, JT. Psoriasis. In: Goldsmith, L., et al., editors. *Dermatology in General Medicine.* Vol. 1. McGraw-Hill; New York: 2012. p. 197-231.
37. Garber K. Psoriasis: from bed to bench and back. *Nat Biotechnol.* 2011; 29:563–6. [PubMed: 21747375]
38. Vilhais-Neto GC, et al. Rere controls retinoic acid signalling and somite bilateral symmetry. *Nature.* 2010; 463:953–7. [PubMed: 20164929]
39. Ferby I, et al. Mig6 is a negative regulator of EGF receptor-mediated skin morphogenesis and tumor formation. *Nat Med.* 2006; 12:568–73. [PubMed: 16648858]
40. Amler LC, et al. Identification and characterization of novel genes located at the t(1;15)(p36.2;q24) translocation breakpoint in the neuroblastoma cell line NGP. *Genomics.* 2000; 64:195–202. [PubMed: 10729226]
41. Djuretic IM, et al. Transcription factors T-bet and Runx3 cooperate to activate Ifng and silence Il4 in T helper type 1 cells. *Nat Immunol.* 2007; 8:145–53. [PubMed: 17195845]
42. Shiraishi N, et al. Identification and characterization of three novel beta 1,3-N-acetylglucosaminyltransferases structurally related to the beta 1,3-galactosyltransferase family. *J Biol Chem.* 2001; 276:3498–507. [PubMed: 11042166]
43. Togayachi A, et al. Beta3GnT2 (B3GNT2), a major polylectosamine synthase: analysis of B3GNT2-deficient mice. *Methods Enzymol.* 2010; 479:185–204. [PubMed: 20816167]
44. Grindstaff KK, et al. Sec6/8 complex is recruited to cell-cell contacts and specifies transport vesicle delivery to the basal-lateral membrane in epithelial cells. *Cell.* 1998; 93:731–40. [PubMed: 9630218]
45. Biswas PS, et al. Phosphorylation of IRF4 by ROCK2 regulates IL-17 and IL-21 production and the development of autoimmunity in mice. *J Clin Invest.* 2010; 120:3280–95. [PubMed: 20697158]
46. Mudter J, et al. IRF4 regulates IL-17A promoter activity and controls RORgammat-dependent Th17 colitis in vivo. *Inflamm Bowel Dis.* 2011; 17:1343–58. [PubMed: 21305677]
47. Huber M, et al. IRF4 is essential for IL-21-mediated induction, amplification, and stabilization of the Th17 phenotype. *Proc Natl Acad Sci U S A.* 2008; 105:20846–51. [PubMed: 19088203]
48. Bowcock AM, et al. Insights into psoriasis and other inflammatory diseases from large-scale gene expression studies. *Hum Mol Genet.* 2001; 10:1793–805. [PubMed: 11532989]
49. Chang IF, Hsiao HY. Induction of RhoGAP and pathological changes characteristic of Alzheimer's disease by UAHFEMF discharge in rat brain. *Curr Alzheimer Res.* 2005; 2:559–69. [PubMed: 16375659]
50. Gotoh K, et al. Selective control of type I IFN induction by the Rac activator DOCK2 during TLR-mediated plasmacytoid dendritic cell activation. *J Exp Med.* 2010; 207:721–30. [PubMed: 20231379]

51. Ippagunta SK, et al. The inflammasome adaptor ASC regulates the function of adaptive immune cells by controlling Dock2-mediated Rac activation and actin polymerization. *Nat Immunol.* 2011; 12:1010–6. [PubMed: 21892172]
52. Loo YM, Gale M Jr. Immune signaling by RIG-I-like receptors. *Immunity.* 2011; 34:680–92. [PubMed: 21616437]
53. Cui XF, Imaizumi T, Yoshida H, Borden EC, Satoh K. Retinoic acid-inducible gene-I is induced by interferon-gamma and regulates the expression of interferon-gamma stimulated gene 15 in MCF-7 cells. *Biochem Cell Biol.* 2004; 82:401–5. [PubMed: 15181474]
54. Negishi H, et al. A critical link between Toll-like receptor 3 and type II interferon signaling pathways in antiviral innate immunity. *Proc Natl Acad Sci U S A.* 2008; 105:20446–51. [PubMed: 19074283]
55. Patel S, Xi ZF, Seo EY, McGaughey D, Segre JA. Klf4 and corticosteroids activate an overlapping set of transcriptional targets to accelerate in utero epidermal barrier acquisition. *Proc Natl Acad Sci U S A.* 2006; 103:18668–73. [PubMed: 17130451]
56. Feinberg MW, et al. Kruppel-like factor 4 is a mediator of proinflammatory signaling in macrophages. *J Biol Chem.* 2005; 280:38247–58. [PubMed: 16169848]
57. Liang J, et al. A novel CCCH-zinc finger protein family regulates proinflammatory activation of macrophages. *J Biol Chem.* 2008; 283:6337–46. [PubMed: 18178554]
58. Nagarajan P, et al. Ets1 blocks terminal differentiation of keratinocytes and induces expression of matrix metalloproteases and innate immune mediators. *J Cell Sci.* 2010; 123:3566–75. [PubMed: 20930145]
59. Zamisch M, et al. The transcription factor Ets1 is important for CD4 repression and Runx3 up-regulation during CD8 T cell differentiation in the thymus. *J Exp Med.* 2009; 206:2685–99. [PubMed: 19917777]
60. Moisan J, Grenningloh R, Bettelli E, Oukka M, Ho IC. Ets-1 is a negative regulator of Th17 differentiation. *J Exp Med.* 2007; 204:2825–35. [PubMed: 17967903]
61. Sakamoto H, et al. A Janus kinase inhibitor, JAB, is an interferon-gamma-inducible gene and confers resistance to interferons. *Blood.* 1998; 92:1668–76. [PubMed: 9716595]
62. Tanaka K, et al. Loss of suppressor of cytokine signaling 1 in helper T cells leads to defective Th17 differentiation by enhancing antagonistic effects of IFN-gamma on STAT3 and Smads. *J Immunol.* 2008; 180:3746–56. [PubMed: 18322180]
63. Piganis RA, et al. Suppressor of cytokine signaling (SOCS) 1 inhibits type I interferon (IFN) signaling via the interferon alpha receptor (IFNAR1)-associated tyrosine kinase Tyk2. *J Biol Chem.* 2011; 286:33811–8. [PubMed: 21757742]
64. Sano S, et al. Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. *Nat Med.* 2005; 11:43–9. [PubMed: 15592573]
65. Harris TJ, et al. Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. *J Immunol.* 2007; 179:4313–7. [PubMed: 17878325]
66. Wei L, Laurence A, O’Shea JJ. New insights into the roles of Stat5a/b and Stat3 in T cell development and differentiation. *Semin Cell Dev Biol.* 2008; 19:394–400. [PubMed: 18708155]
67. Blonska M, Lin X. NF-kappaB signaling pathways regulated by CARMA family of scaffold proteins. *Cell Res.* 2011; 21:55–70. [PubMed: 21187856]
68. Kersh EN. Impaired memory CD8 T cell development in the absence of methyl-CpG-binding domain protein 2. *J Immunol.* 2006; 177:3821–6. [PubMed: 16951344]
69. Faili A, et al. Induction of somatic hypermutation in immunoglobulin genes is dependent on DNA polymerase iota. *Nature.* 2002; 419:944–7. [PubMed: 12410315]
70. Inouye M, et al. An immune response network associated with blood lipid levels. *PLoS Genet.* 2010; 6
71. Wichmann HE, Gieger C, Illig T. KORA-gen—resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen.* 2005; 67 (Suppl 1):S26–30. [PubMed: 16032514]
72. 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature.* 2010; 467:1061–73. [PubMed: 20981092]

73. Giannoulatou E, Yau C, Colella S, Ragoussis J, Holmes CC. GenoSNP: a variational Bayes within-sample SNP genotyping algorithm that does not require a reference population. *Bioinformatics*. 2008; 24:2209–14. [PubMed: 18653518]
74. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis G. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nature Genetics*. 2012; 44:955–959. [PubMed: 22820512]
75. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet*. 2007; 39:906–13. [PubMed: 17572673]
76. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet*. 2009; 5:e1000529. [PubMed: 19543373]
77. Altshuler DM, et al. Integrating common and rare genetic variation in diverse human populations. *Nature*. 2010; 467:52–8. [PubMed: 20811451]
78. Purcell S, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007; 81:559–75. [PubMed: 17701901]
79. Kang HM, et al. Variance component model to account for sample structure in genome-wide association studies. *Nat Genet*. 2010; 42:348–54. [PubMed: 20208533]
80. Devlin B, Roeder K. Genomic control for association studies. *Biometrics*. 1999; 55:997–1004. [PubMed: 11315092]
81. Freedman ML, et al. Assessing the impact of population stratification on genetic association studies. *Nat Genet*. 2004; 36:388–93. [PubMed: 15052270]

Consortia

Wellcome Trust Case Control Consortium 2

Peter Donnelly^{30,52}, Leena Peltonen²⁹, Jenefer M Blackwell^{53,54}, Elvira Bramon^{55,56}, Matthew A Brown⁵⁷, Juan P Casas⁵⁸, Aiden Corvin⁵⁹, Nicholas Craddock⁶⁰, Audrey Duncanson⁶¹, Janusz Jankowski⁶², Hugh S Markus⁶³, Christopher G Mathew², Mark I McCarthy⁶⁴, Colin NA Palmer⁶⁵, Robert Plomin⁶⁶, Anna Rautanen³⁰, Stephen J Sawcer⁶⁷, Nilesh Samani⁶⁸, Ananth C Viswanathan^{69,70}, Nicholas W Wood⁷¹, Céline Bellenguez³⁰,

⁵²Dept Statistics, University of Oxford, Oxford OX1 3TG, UK;

⁵³Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, 100 Roberts Road, Suciaco, Western Australia 6008;

⁵⁴Genetics and Infection Laboratory, Cambridge Institute of Medical Research, Addenbrooke's Hospital, Cambridge CB2 0XY, UK;

⁵⁵Division of Psychological Medicine and Psychiatry, Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King's College London

⁵⁶The South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AF, UK;

⁵⁷Diamantina Institute of Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Brisbane, Queensland, Australia;

⁵⁸Dept Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK;

⁵⁹Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin 2, Eire;

⁶⁰Dept Psychological Medicine, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN, UK;

⁶¹Molecular and Physiological Sciences, The Wellcome Trust, London NW1 2BE;

⁶²Centre for Gastroenterology, Bart's and the London School of Medicine and Dentistry, London E1 2AT, UK;

⁶³Clinical Neurosciences, St George's University of London, London SW17 0RE;

⁶⁴Oxford Centre for Diabetes, Endocrinology and Metabolism (ICDEM), Churchill Hospital, Oxford OX3 7LJ, UK;

⁶⁵Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK;

⁶⁶Social, Genetic and Developmental Psychiatry Centre, King's College London Institute of Psychiatry, Denmark Hill, London SE5 8AF, UK;

⁶⁷University of Cambridge Dept Clinical Neurosciences, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK;

⁶⁸Dept Cardiovascular Science, University of Leicester, Glenfield Hospital, Leicester LE3 9QP;

⁶⁹Glaucoma Research Unit, Moorfields Eye Hospital NHS Foundation Trust, London EC1V 2PD, UK;

⁷⁰Dept Genetics, University College London Institute of Ophthalmology, London EC1V 9EL, UK;

⁷¹Dept Molecular Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK;

Colin Freeman³⁰, Garrett Hellenthal³⁰, Eleni Giannoulidou³⁰, Matti Pirinen³⁰, Zhan Su³⁰, Sarah E Hunt²⁹, Rhian Gwilliam²⁹, Suzannah J Bumpstead²⁹, Serge Dronov²⁹, Matthew Gillman²⁹, Emma Gray²⁹, Naomi Hammond²⁹, Alagurevathi Jayakumar²⁹, Owen T McCann²⁹, Jennifer Liddle²⁹, Marc L Perez²⁹, Simon C Potter²⁹, Radhi Ravindrarajah²⁹, Michelle Ricketts²⁹, Matthew Waller²⁹, Paul Weston²⁹, Sara Widaa²⁹, Pamela Whittaker²⁹.

Genetic Analysis of Psoriasis Consortium (GAPC)

Alexandros Onoufriadis², Michael E Weale², Angelika Hofer²⁰, Wolfgang Salmhofer²⁰, Peter Wolf²⁰, Kati Kainu⁷², Ulpu Saarialho-Kere⁷², Sari Suomela⁷², Petra Badorf⁴⁵, Ulrike Hüffmeier⁴⁵, Werner Kurrat⁷³, Wolfgang Küster⁷⁴, Jesus Lascorz⁷⁵, Rotraut Mössner⁷⁶, Funda Schürmeier-Horst⁷⁷, Markward Ständer⁷⁸, Heiko Traupe⁷⁷, Judith G M Bergboer¹², Martin den Heijer^{79,80}, Peter C. van de Kerkhof¹², Patrick L J M Zeeuwen¹², Louise Barnes^{7,8}, Linda E Campbell⁸¹, Catriona Cusack⁸², Ciara Coleman^{7,8}, Judith Conroy^{7,8}, Sean Ennis^{7,8}, Oliver Fitzgerald⁸³, Phil Gallagher⁸³, Alan D Irvine⁸⁴, Brian Kirby⁸³, Trevor Markham⁸², WH Irwin McLean⁸¹, Joe McPartlin^{7,8}, Sarah F Rogers⁸³, Anthony W Ryan^{7,8}, Agnieszka Zawirska⁸³, Emiliano Giardina⁹, Tiziana Lepre⁹, Carlo Perricone⁹, Gemma Martín-Ezquerro⁸⁵, Ramon M Pujol⁸⁵, Eva Riveira-Munoz¹⁷, Annica Inerot⁸⁶, Åsa T Naluai¹¹, Lotus Mallbris¹³, Katarina Wolk¹³, Joyce Leman¹⁴, Anne Barton²¹, Richard B Warren⁴⁴, Helen S Young⁴⁴, Isis Ricano-Ponce²⁸, Gosia Trynka²⁸

Collaborative Association Study of Psoriasis (CASP)

Kristina Callis Duffin¹⁹, Cindy Helms¹⁸, David Goldgar¹⁹, Yun Li¹, Justin Paschall⁸⁷, M. J. Malloy⁸⁸, C. R. Pullinger⁸⁸, J. P. Kane⁸⁸, J. Gardner¹⁸, A. Perlmutter⁸⁹, A. Miner⁸⁹, Bing Jian Feng¹⁹, Ravi Hiremagalore⁶, Robert W. Ike⁹⁰, Enno Christophers³¹, Tilo Henseler³¹, Andreas Ruether⁵, Steven J. Schrodi⁹¹, Sampath Prahald⁹², Stephen L Guthery⁹², Judith

⁷²Department of Dermatology and Venerology, University of Helsinki, Helsinki, Finland;

⁷³Asklepios Nordseeklinik, Westerland/Sylt, Germany;

⁷⁴TOMESA Clinics, Bad Salschlirf, Germany;

⁷⁵Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany;

⁷⁶Department of Dermatology, University of Göttingen, Göttingen, Germany;

⁷⁷Department of Dermatology, University of Münster, Münster, Germany;

⁷⁸Psoriasis Rehabilitation Hospital, Bad Bentheim, Germany;

⁷⁹Department of Endocrinology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;

⁸⁰Department of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;

⁸¹University of Dundee, Dundee, UK;

⁸²University College Hospital Galway, Galway, Ireland;

⁸³St Vincent's University Hospital, Dublin, Ireland;

⁸⁴Department of Clinical Medicine, Trinity College Dublin, Our Lady's Children's Hospital Crumlin, Dublin, Ireland;

⁸⁵Dermatology Service, Hospital del Mar-IMAS, Barcelona, Spain;

⁸⁶Department of Dermatology and Venereology, Sahlgrenska University Hospital, Gothenburg, Sweden;

⁸⁷National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA;

⁸⁸Cardiovascular Research Institute and Center for Human Genetics, University of California-San Francisco, CA;

⁸⁹Department of Psychiatry, Washington University School of Medicine, St. Louis, MO;

⁹⁰Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI;

⁹¹Celera, 1401 Harbor Bay Parkway, Alameda, CA;

⁹²Departments of Pediatrics, Rheumatology and Gastroenterology, University of Utah, Salt Lake City, UT;

Fischer⁹³, Wilson Liao⁹⁴, Pui Kwok⁹⁴, Alan Menter⁹⁵, G. Mark Lathrop⁹³, C. Wise⁹⁶, Ann B. Begovich⁹¹

Psoriasis Association Genetics Extension (PAGE)

Fawnda J Pellett⁴¹, Andrew Henschel⁹⁷, Marin Aurand⁹⁷, Bruce Bebo⁹⁷

Cooperative Research in the Region of Augsburg (KORA)

Christian Gieger⁹⁸, Thomas Illig⁹⁹

Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) study (HNR)

Susanne Moebus¹⁰⁰, Karl-Heinz Jöckel¹⁰⁰, Raimund Erbel¹⁰¹

⁹³Centre National de Génotypage, Institut Génomique, Commissariat à l'Énergie Atomique, Evry, France;

⁹⁴Department of Dermatology, University of California, San Francisco;

⁹⁵Department of Dermatology, Baylor University Medical Center, Dallas, TX;

⁹⁶Seay Center for Musculoskeletal Research, Texas Scottish Rite Hospital for Children, Dallas, TX;

⁹⁷National Psoriasis Foundation, Portland, OR 97223 USA;

⁹⁸Institute of Genetic Epidemiology, Helmholtz Centre Munich, German Research Center for Environmental Health, 85764 Neuherberg, Germany;

⁹⁹Research Unit Molecular Epidemiology, Helmholtz Centre Munich, German Research Center for Environmental Health, 85764 Neuherberg, Germany;

¹⁰⁰Institute for Medical Informatics, Biometry and Epidemiology (IMIBE), University of Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany;

¹⁰¹Clinic of Cardiology, West German Heart Centre, University Hospital of Essen, University Duisburg-Essen, Essen, Germany.

Table 1

Meta-analysis results for psoriasis loci. For known loci, the most significant SNP within 500kb (3Mb for MHC region) of the previously published SNP is shown. rs34536443 was the most strongly associated SNP in the *TYK2* region, but found to be independent of the previously published SNP (rs12720356). 'GWAS P value': P value from the meta-analysis of the 3 GWAS datasets. 'Immunochip P value': the result of the meta-analysis of the two Immunochip datasets. 'Combined P-value': the P-value from the meta-analysis including all 5 datasets, RAF: Risk allele frequency, 'Notable genes': genes most likely to have an effect on the development of psoriasis.

SNP	Chr.	Position (bp)	GWAS P-value (meta)	Immunochip p-value (meta)	Combined P-value	Risk/Non-risk allele	RAF (Case)	RAF (Ctrls)	OR ^a (meta)	Notable genes	No. of genes +/- 500kb
Known Loci											
rs7552167	1	24,518,643	2.3×10 ⁻⁵	8.4×10 ⁻⁸	8.5×10 ⁻¹²	G/A	0.878	0.858	1.21	<i>IL28RA</i>	26
rs9988642	1	67,726,104	2.5×10 ⁻¹³	3.5×10 ⁻¹⁵	1.1×10 ⁻²⁶	T/C	0.952	0.929	1.52	<i>IL23R</i>	17
rs6677595	1	152,590,187	8.1×10 ⁻¹⁵	2.7×10 ⁻²⁰	2.1×10 ⁻³³	T/C	0.689	0.640	1.26	<i>LCE3B, LCE3D</i>	43
rs62149416	2	61,083,506	3.4×10 ⁻¹⁰	3.2×10 ⁻⁹	1.8×10 ⁻¹⁷	T/C	0.671	0.635	1.17	<i>FLJ16341, REL</i>	9
rs17716942	2	163,260,691	4.1×10 ⁻⁹	1.0×10 ⁻¹⁰	3.3×10 ⁻¹⁸	T/C	0.891	0.863	1.27	<i>KCNH7, IFIH1</i>	7
rs27432	5	96,119,273	4.4×10 ⁻⁸	7.5×10 ⁻¹⁴	1.9×10 ⁻²⁰	A/G	0.309	0.274	1.20	<i>ERAP1</i>	7
rs1295685	5	131,996,445	8.5×10 ⁻⁶	6.7×10 ⁻⁶	3.4×10 ⁻¹⁰	G/A	0.807	0.798	1.18	<i>IL13, IL4</i>	21
rs2233278	5	150,467,189	4.9×10 ⁻¹⁷	5.2×10 ⁻²⁷	2.2×10 ⁻⁴²	C/G	0.090	0.058	1.59	<i>TNIP1</i>	17
rs12188300	5	158,829,527	7.5×10 ⁻²³	3.3×10 ⁻³²	3.2×10 ⁻⁵³	T/A	0.132	0.095	1.58	<i>IL12B</i>	5
rs4406273	6	31,266,090	5.3×10 ⁻³⁰⁰	3.6×10 ⁻⁴²⁷	4.5×10 ⁻⁷²³	A/G	0.259	0.092	4.32	<i>HLA-B, HLA-C</i>	56
rs33980500	6	111,913,262	4.3×10 ⁻²⁰	7.6×10 ⁻²⁷	4.2×10 ⁻⁴⁵	T/C	0.108	0.074	1.52	<i>TRAF3IP2</i>	8
rs582757	6	138,197,824	2.0×10 ⁻¹⁴	3.7×10 ⁻¹³	2.2×10 ⁻²⁵	C/T	0.315	0.273	1.23	<i>TNFAIP3</i>	5
rs1250546	10	81,032,532	5.1×10 ⁻⁴	3.2×10 ⁻⁴	6.8×10 ⁻⁷	A/G	0.605	0.579	1.10	<i>ZMIZ1</i>	9
rs645078	11	64,135,298	4.7×10 ⁻³	1.5×10 ⁻⁴	2.2×10 ⁻⁶	A/C	0.626	0.609	1.09	<i>RPS6KA4, PRDX5</i>	36
rs2066819	12	56,750,204	7.5×10 ⁻¹²	8.9×10 ⁻⁸	5.4×10 ⁻¹⁷	C/T	0.948	0.934	1.39	<i>STAT2, IL23A</i>	40
rs8016947	14	35,832,666	1.4×10 ⁻⁹	1.6×10 ⁻⁹	2.5×10 ⁻¹⁷	G/T	0.600	0.564	1.16	<i>NFKBIA</i>	11
rs12445568	16	31,004,812	1.2×10 ⁻⁶	1.8×10 ⁻¹¹	1.2×10 ⁻¹⁶	C/T	0.403	0.368	1.16	<i>PRSS53, FBXL19</i>	46
rs28998802	17	26,124,908	3.6×10 ⁻⁶	1.7×10 ⁻¹¹	3.3×10 ⁻¹⁶	A/G	0.170	0.145	1.22	<i>NOS2</i>	9
rs34536443	19	10,463,118	5.1×10 ⁻¹⁰	2.6×10 ⁻²²	9.1×10 ⁻³¹	G/C	0.974	0.953	1.88	<i>TYK2</i>	42
rs1056198	20	48,556,229	6.2×10 ⁻⁹	1.6×10 ⁻⁷	1.5×10 ⁻¹⁴	C/T	0.600	0.573	1.16	<i>RNF114</i>	11
rs4821124	22	21,979,289	5.4×10 ⁻⁵	1.2×10 ⁻⁴	3.8×10 ⁻⁸	C/T	0.208	0.189	1.13	<i>UBE2L3</i>	16
Newly Identified Loci											
rs1112129	1	8,268,095	7.3×10 ⁻⁵	4.6×10 ⁻⁵	1.7×10 ⁻⁸	A/G	0.308	0.287	1.13	<i>SLC45A1, TNFRSF9</i>	15

SNP	Chr.	Position (bp)	GWAS P-value (meta)	ImmunoChip p-value (meta)	Combined P-value	Risk/Non-risk allele	RAF (Case)	RAF (Ctrls)	OR ^a (meta)	Notable genes	No. of genes +/- 500kb
rs7536201	1	25,293,084	7.8×10 ⁻⁵	6.4×10 ⁻⁹	2.3×10 ⁻¹²	C/T	0.528	0.494	1.13	RUNX3	18
rs10865331	2	62,551,472	4.5×10 ⁻⁴	2.6×10 ⁻⁷	4.7×10 ⁻¹⁰	A/G	0.404	0.374	1.12	B3GNT2	6
rs9504361	6	577,820	5.1×10 ⁻⁷	4.2×10 ⁻⁶	2.1×10 ⁻¹¹	A/G	0.574	0.546	1.12	EXOC2, IRF4	5
rs2451258	6	159,506,600	4.4×10 ⁻⁴	2.0×10 ⁻⁵	3.4×10 ⁻⁸	C/T	0.362	0.348	1.12	TAGAP	8
rs2700987	7	37,386,237	3.3×10 ⁻⁷	4.6×10 ⁻⁴	4.3×10 ⁻⁹	A/C	0.591	0.564	1.11	ELMO1	3
rs11795343	9	32,523,737	2.8×10 ⁻⁷	2.1×10 ⁻⁵	8.4×10 ⁻¹¹	T/C	0.628	0.597	1.11	DDX58	7
rs10979182	9	110,817,020	2.8×10 ⁻⁵	1.2×10 ⁻⁴	2.3×10 ⁻⁸	A/G	0.617	0.591	1.12	KLF4	0
rs4561177	11	109,962,432	1.1×10 ⁻⁴	1.4×10 ⁻⁹	7.7×10 ⁻¹³	A/G	0.617	0.581	1.14	ZC3H12C	4
rs3802826	11	128,406,438	1.1×10 ⁻³	2.0×10 ⁻⁷	9.5×10 ⁻¹⁰	A/G	0.505	0.484	1.12	ETS1	7
rs367569	16	11,365,500	2.6×10 ⁻⁴	4.6×10 ⁻⁵	4.9×10 ⁻⁸	C/T	0.729	0.709	1.13	PRM3, SOCS1	14
rs963986	17	40,561,579	9.9×10 ⁻⁵	1.2×10 ⁻⁵	5.3×10 ⁻⁹	C/G	0.169	0.154	1.15	PTRF, STAT3, STAT5A/B	42
rs11652075	17	78,178,893	1.3×10 ⁻³	7.0×10 ⁻⁶	3.4×10 ⁻⁸	C/T	0.530	0.502	1.11	CARD14	16
rs545979	18	51,819,750	1.4×10 ⁻⁶	2.4×10 ⁻⁵	3.5×10 ⁻¹⁰	T/C	0.317	0.291	1.12	POLL, STARD6, MBD2	6
rs892085	19	10,818,092	1.2×10 ⁻⁷	4.5×10 ⁻¹¹	3.0×10 ⁻¹⁷	A/G	0.593	0.558	1.17	ILF3, CARM1	37

^aThe overall OR was calculated using the effective sample size-weighted approach.

SNPs that are missense mutations from the 1000 Genome Project and that are in LD ($r^2 \geq 0.9$) with primary signals from the known and newly identified loci that achieve genomewide significance in the meta-analysis, or with secondary signals from the conditional analysis ("Index SNP"). The "Index SNP" columns show the information of SNPs with the most significant P-value in our analysis, and the "Potential causal SNP" columns show the information for the SNPs that have high LD with our strongest signal. The "Combined p-value" column shows the meta-analysis P-value for the index SNP, potential causal SNP, and the P-values for the index SNPs while conditioning on the potential causal SNPs, respectively. Note the potential causal SNP rs7199949 is not present in our meta-analysis study therefore its P-value is not shown.

Table 2

Index SNP				Potential Causal SNP				Combined P-value		
Marker ^a	RAF	Annotation	Marker ^c	RAF	Gene with variant	Amino acid substitution (Damaging effect ^d)	r ²	Index SNP	Potential causal SNP	Index SNP (conditioning on causal SNP)
rs988642	0.93	454bp downstream	IL23R	0.94	IL23R	R381Q (P)	0.91	1.1×10 ⁻²⁶	1.5×10 ⁻²⁶	0.13
rs27432	0.29	Intron	ERAP1	0.29	ERAP1	Q730E	1	1.9×10 ⁻²⁰	2.3×10 ⁻²⁰	0.14
rs1295685	0.77	3' UTR	IL13	0.77	IL13	R144Q	0.97	3.4×10 ⁻¹⁰	3.5×10 ⁻¹⁰	0.78
rs33980500	0.09	Missense	Self	0.09	TRAF3IP2	D19N (S/P)	1	4.2×10 ⁻⁴⁵	4.2×10 ⁻⁴⁵	NA
rs2066819	0.93	Intron	STAT2	0.93	STAT2	M594I	0.9	5.4×10 ⁻¹⁷	5.1×10 ⁻¹⁶	0.036
rs12445568	0.36	Intron	STX1B	0.37	PRSS53	P406A	0.9	1.2×10 ⁻¹⁶	NA	NA
rs11652075	0.51	Missense	Self	0.51	CARD14	R820W (S)	1	3.4×10 ⁻⁸	3.4×10 ⁻⁸	NA
rs34536443	0.97	Missense	Self	0.97	TYK2	P1104A (S/P)	1	1.5×10 ⁻³⁹	1.5×10 ⁻³⁹	NA
rs12720356 ^b	0.9	Missense	Self	0.9	TYK2	I684S (S/P)	1	3.2×10 ⁻¹⁰	3.2×10 ⁻¹⁰	NA
rs4821124	0.19	966bp downstream	UBE2L3	0.18	YDJC	A263T	0.96	3.8×10 ⁻⁸	6.2×10 ⁻⁸	0.48

^a SNPs with the most significant p-value in our analysis.

^b The meta-analysis p-value from the conditional analysis is shown.

^c SNPs that are missense mutations and have high LD with our strongest signal.

^d High confidence damaging effect predicted by SIFT (S) or Polyphen (P). RAF: Risk Allele Frequency. For the potential causal SNP rs7199949, the P value is 'NA' as the SNP was not included on the Immunochip.