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

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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-κB 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.

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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.

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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. $P<5\times10^{-8}$) 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 Kiel[3], CASP[4] and WTCCC2[5]) 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 $P < 3\times10^{-6}$) as well as nominal evidence for all loci in separate analyses including only GWAS (all with $P < 5\times10^{-3}$) or Immunochip data (all with $P < 4\times10^{-4}$). In addition, we identified 15 new risk loci at $P < 5\times10^{-8}$ (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, ERRFI1, TNFRSF9* (1p36.23)**

This signal falls between the *RERE*, *SLC45A1*, *ERRFI1*, and *TNFRSF9* genes. *RERE* encodes an arginine-glutamic acid dipeptide repeat-containing protein that controls retinoic acid signalling[38]. *ERRFI1* encodes a feedback inhibitor of the EGF receptor[39]. *SLC45A1* encodes a solute carrier protein that mediates the uptake of glucose[40]. 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-bet[41].

***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 chains[42]. Deficiency has shown to results in hyperactivation of lymphocytes[43].

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

EXOC2 encodes a component of the multi-protein complex which mediates the docking of exocytic vesicles to the plasma membrane[44]. *IRF4* encodes a transcription factor that regulates *IL17A* promoter activity and controls RORyt-dependent Th17 colitis *in vivo*[45,46]. *IRF4* also plays a role in stabilization of the Th17 phenotype through IL-21[47] and may regulate CD4/CD8 differentiation through regulation of *RUNX3* expression[48].

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

This gene is a Rho-GTPase activating protein that is involved in T-cell activation[49].

***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 cells[50] and plasmacytoid dendritic cell migration.[51] DOCK2 also has a role in antigen-uptake and presentation, and lymphocyte trafficking[51].

***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 production[54].

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

KLF4 is a Kruppel-like transcription factor, which is required for the establishment of skin barrier function[55] and regulates key signaling pathways related to macrophage activation[56]. *KLF4* also binds to the promoter of *IL17A* and positively regulates its expression.

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

Zinc-finger protein regulating macrophage activation[57].

***ETS1* (11q24.3)**

Transcription factor activated downstream of the Ras-MAPK pathway, involved in homeostasis of squamous epithelia[58]. Involved in CD8 lineage differentiation and acts in part by promoting RUNX3 expression[59]. Negative regulator of Th17 differentiation[60]

***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 activity[62] and interacts with TYK2 in cytokine signalling[63].

***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 epidermis[64]. *STAT3* is required for the differentiation of Th17 cells[65]. *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 cells[66].

***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-κB pathway[67].

***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-cells[68]. *POLI* is an error-prone DNA polymerase, which contributes to the hyper-mutation of immunoglobulin genes[69]. 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-κB and functions as a promoter-specific regulatory of NF-κB 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 analysis[14]. 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 reported[5] 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 psoriasis[17], was also a common and damaging variant as has been described elsewhere[18]. 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* gene[20], which is also the most highly over-expressed gene in psoriatic skin in this locus[6]; and a variant in *YDJC* that also increases risk for celiac disease[21], rheumatoid arthritis[22] and Crohn's disease[23].

Utilizing the results of a large-scale study of gene expression in psoriatic vs. normal skin[24], 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 ($P < 1\times10^{-7}$) threshold as expression quantitative trait loci (eQTL) in skin tissue, as assessed by microarray analysis of mRNA levels[25]. 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 locus[28].

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 $P < 5\times10^{-8}$ in the current study collectively account for 14.3% of the total variance in psoriasis risk, or approximately 22% of its estimated heritability[29] (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 previously[11] 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 immunity[34]. 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 therapies[36]. 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 trials[37]. 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. 2010[5]. 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) collection[70]. 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. 2010[3]), 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/F4[71]), 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 psoriasis[13]. 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 Project[72] 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 GenoSNP[73] 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 minimac[74] (Kiel and CASP) and IMPUTE2[75,76] (WTCCC2) based on CEU reference haplotypes from the 1000 Genomes Project[72]; December 2010 version of the 10/08/04 sequence and alignment release containing 629 individuals of European descent). SNPs with low imputation quality ($r^2 \leq 0.3$ 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 reference[77], 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 PLINK[78].

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 relatedness[79], 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 PLINK[78], with the criterion 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 covariates[3–5].

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 diseases[12], using all independent SNPs from the chip would not give an accurate estimate of the genomic control[80] (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

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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	*IL28RA*	*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	*IL23R*	*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	*LCE3B, LCE3D*	*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	*FLJ16341, REL*	*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	*KCNH7, IFIH1*	*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	*ERAP1*	*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	*IL13, IL4*	*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	*TNIP1*	*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	*IL12B*	*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	*HLA-B, HLA-C*	*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	*TRAF3IP2*	*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	*TNFAIP3*	*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	*ZMIZ1*	*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	*RPS6KA4, PRDX5*	*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	*STAT2, IL23A*	*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	*NFKBIA*	*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	*PRSS53, FBXL19*	*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	*NOS2*	*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	*TYK2*	*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	*RNF114*	*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	*UBE2L3*	*16*
Newly Identified Loci											
rs11121129	1	8,268,095	7.3×10^{-5}	4.6×10^{-5}	1.7×10^{-8}	A/G	0.308	0.287	1.13	*SLC45A1, TNFRSF9*	*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	*POL1, 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*

[a]The overall OR was calculated using the effective sample size-weighted approach.

Table 2

SNPs that are missense mutations from the 1000 Genome Project and that are in LD (r^2>=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.

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)
rs9988642	0.93	454bp downstream *IL23R*	rs11209026	0.94	*IL23R*	R381Q (P)	0.91	1.1×10^{-26}	1.5×10^{-26}	0.13
rs27432	0.29	Intron *ERAP1*	rs27044	0.29	*ERAP1*	Q730E	1	1.9×10^{-20}	2.3×10^{-20}	0.14
rs1295685	0.77	3′ UTR *IL13*	rs20541	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*	rs2066807	0.93	*STAT2*	M594I	0.9	5.4×10^{-17}	5.1×10^{-16}	0.036
rs12445568	0.36	Intron *STX1B*	rs7199949	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*	rs2298428	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.