nature genetics

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

To gain further insight into the genetic architecture of psoriasis, we conducted a meta-analysis of 3 genome-wide association studies (GWAS) and 2 independent data sets genotyped on the Immunochip, including 10,588 cases and 22,806 controls. We identified 15 new susceptibility loci, increasing to 36 the number associated with psoriasis in European individuals. We also identified, using conditional analyses, five independent signals within previously known loci. The newly identified loci shared with other autoimmune diseases include candidate genes with roles in regulating T-cell function (such as *RUNX3*, *TAGAP* and *STAT3*). Notably, they included candidate genes whose products are involved in innate host defense, including interferon-mediated antiviral responses (*DDX58*), macrophage activation (*ZC3H12C*) and nuclear factor (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.

Psoriasis is a chronic, potentially disfiguring immune-mediated inflammatory disease of the skin with a prevalence of 0.2–2%, depending on the population of origin. Approximately one-quarter of individuals with psoriatics develop painful and debilitating arthritis, and there is increasing awareness of comorbidities, including metabolic syndromes and cardiovascular disease[1,2]. Current evidence suggests that a dysregulated cutaneous immune response, characterized by tumor necrosis factor (TNF)-α dependence and exaggerated helper T cell 1 (T_H1) and 17 (T_H17) 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 individuals of European ancestry[3–6,10]. Several of these loci overlap with those identified as being associated with other autoimmune diseases (for example, Crohn's disease, ankylosing spondylitis and celiac disease), particularly those near genes involved in T_H17 differentiation and interleukin (IL)-17 responsiveness (for example, *IL23R*, *IL12B*, *IL23A* and *TRAF3IP2*)[11]. To accelerate the understanding of the genetic architecture of psoriasis, we helped design a custom SNP array—the Immunochip— with the aim of fine mapping previously identified genome-wide significant susceptibility loci (associated at $P < 5 \times 10^{-8}$) and exploring replication of thousands of SNPs representing additional promising signals[12,13]. In this study, we used Immunochip data to identify new susceptibility loci for psoriasis and to consider their association to other autoimmune disorders.

We combined three existing GWAS data sets (referred to as Kiel[3], the Collaborative Association Study of Psoriasis (CASP)[4] and the Wellcome Trust Case Control Consortium 2 (WTCCC2)[5]) with two independent case-control data sets of individuals of European descent 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) (data sets are described in **Supplementary Tables 1** and **2**). After quality control, the combined data set consisted of 10,588 individuals with psoriasis and 22,806 healthy controls. For each GWAS, we increased the SNP density through imputation, using European haplotype sequences generated by the 1000 Genomes Project (20100804 release) as templates. Overall, our analysis included 111,236 SNPs that were genotyped in both Immunochip data sets that also had good imputation quality in at least 2 of the 3 GWAS (Online Methods).

From meta-analysis of all five data sets, we confirmed associations at genome-wide significance for SNPs at 19 of the 21 known loci involved in psoriasis (**Table 1**, **Supplementary Fig. 1** and **Supplementary Table 3**). We found nominal evidence of association for the remaining two loci in the combined analysis (*ZMIZ1* and *PRDX5*, each with $P < 3 \times 10^{-6}$), as well as nominal evidence of association 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 associated at $P < 5 \times 10^{-8}$ (**Table 1**, **Supplementary Fig. 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 (**Supplementary Table 4**, disease overlap), although we also submitted three of these (rs11121129, rs10865331 and rs9504361) on the basis of a preliminary meta-analysis of our GWAS data sets. Notably, of the remaining six signals, four were submitted for psoriasis (rs11795343, rs4561177, rs11652075 and rs545979). The strongest new association was observed for rs892085 at 19p13.2 near the *ILF3* and *CARM1* genes (combined *P* value (P_{combined}) = 3.0×10^{-17}; odds ratio (OR) = 1.17). Despite its proximity (< 500 kb away) to *TYK2*, conditional analysis showed that this SNP represents 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*. The functional characteristics of notable genes from the newly identified loci are summarized in **Box 1**, and regional association plots are shown in **Supplementary Figure 2**.

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Received 7 May; accepted 17 October; published online 11 November 2012; doi:10.1038/ng.2467

Table 1 Meta-analysis results for loci associated with psoriasis in a weighted analysis

SNP	Chr.	Position (bp)	GWAS *P* value (meta)	Immunochip *P* value (meta)	Combined *P* value	Risk/ non-risk allele	RAF (case)	RAF (control)	OR[a] (meta)	Notable genes	Number of genes ± 500 kb
Known susceptibility loci											
rs7552167	1	24518643	2.3×10^{-5}	8.4×10^{-8}	8.5×10^{-12}	G/A	0.878	0.858	1.21	*IL28RA*	26
rs9988642	1	67726104	2.5×10^{-13}	3.5×10^{-15}	1.1×10^{-26}	T/C	0.952	0.929	1.52	*IL23R*	17
rs6677595	1	152590187	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	61083506	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	163260691	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	96119273	4.4×10^{-8}	7.5×10^{-14}	1.9×10^{-20}	A/G	0.309	0.274	1.20	*ERAP1*	7
rs1295685	5	131996445	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	150467189	4.9×10^{-17}	5.2×10^{-27}	2.2×10^{-42}	C/G	0.090	0.058	1.59	*TNIP1*	17
rs12188300	5	158829527	7.5×10^{-23}	3.3×10^{-32}	3.2×10^{-53}	T/A	0.132	0.095	1.58	*IL12B*	5
rs4406273	6	31266090	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	111913262	4.3×10^{-20}	7.6×10^{-27}	4.2×10^{-45}	T/C	0.108	0.074	1.52	*TRAF3IP2*	8
rs582757	6	138197824	2.0×10^{-14}	3.7×10^{-13}	2.2×10^{-25}	C/T	0.315	0.273	1.23	*TNFAIP3*	5
rs1250546	10	81032532	5.1×10^{-4}	3.2×10^{-4}	6.8×10^{-7}	A/G	0.605	0.579	1.10	*ZMIZ1*	9
rs645078	11	64135298	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	56750204	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	35832666	1.4×10^{-9}	1.6×10^{-9}	2.5×10^{-17}	G/T	0.600	0.564	1.16	*NFKBIA*	11
rs12445568	16	31004812	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	26124908	3.6×10^{-6}	1.7×10^{-11}	3.3×10^{-16}	A/G	0.170	0.145	1.22	*NOS2*	9
rs34536443	19	10463118	5.1×10^{-10}	2.6×10^{-22}	9.1×10^{-31}	G/C	0.974	0.953	1.88	*TYK2*	42
rs1056198	20	48556229	6.2×10^{-9}	1.6×10^{-7}	1.5×10^{-14}	C/T	0.600	0.573	1.16	*RNF114*	11
rs4821124	22	21979289	5.4×10^{-5}	1.2×10^{-4}	3.8×10^{-8}	C/T	0.208	0.189	1.13	*UBE2L3*	16
Newly identified susceptibility loci											
rs11121129	1	8268095	7.3×10^{-5}	4.6×10^{-5}	1.7×10^{-8}	A/G	0.308	0.287	1.13	*SLC45A1*, *TNFRSF9*	15
rs7536201	1	25293084	7.8×10^{-5}	6.4×10^{-9}	2.3×10^{-12}	C/T	0.528	0.494	1.13	*RUNX3*	18
rs10865331	2	62551472	4.5×10^{-4}	2.6×10^{-7}	4.7×10^{-10}	A/G	0.404	0.374	1.12	*B3GNT2*	6
rs9504361	6	577820	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	159506600	4.4×10^{-4}	2.0×10^{-5}	3.4×10^{-8}	C/T	0.362	0.348	1.12	*TAGAP*	8
rs2700987	7	37386237	3.3×10^{-7}	4.6×10^{-4}	4.3×10^{-9}	A/C	0.591	0.564	1.11	*ELMO1*	3
rs11795343	9	32523737	2.8×10^{-7}	2.1×10^{-5}	8.4×10^{-11}	T/C	0.628	0.597	1.11	*DDX58*	7
rs10979182	9	110817020	2.8×10^{-5}	1.2×10^{-4}	2.3×10^{-8}	A/G	0.617	0.591	1.12	*KLF4*	0
rs4561177	11	109962432	1.1×10^{-4}	1.4×10^{-9}	7.7×10^{-13}	A/G	0.617	0.581	1.14	*ZC3H12C*	4
rs3802826	11	128406438	1.1×10^{-3}	2.0×10^{-7}	9.5×10^{-10}	A/G	0.505	0.484	1.12	*ETS1*	7
rs367569	16	11365500	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	40561579	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	78178893	1.3×10^{-3}	7.0×10^{-6}	3.4×10^{-8}	C/T	0.530	0.502	1.11	*CARD14*	16
rs545979	18	51819750	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	10818092	1.2×10^{-7}	4.5×10^{-11}	3.0×10^{-17}	A/G	0.593	0.558	1.17	*ILF3,CARM1*	37

For previously identified susceptibility loci, the most significantly associated SNP within 500 kb (3 Mb for the MHC region) of the previously published SNP is shown. rs34536443 was the most significantly associated SNP in the *TYK2* region but was found to be independent of the previously published SNP (rs12720356). GWAS *P* value, *P* value from the meta-analysis of the three GWAS data sets; Immunochip *P* value, the result of the meta-analysis of the two Immunochip data sets; combined *P* value, the *P* value from the meta-analysis including all five data sets; RAF, risk allele frequency; notable genes, genes most likely to have an effect on the development of psoriasis; chr., chromosome.

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

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** and **Supplementary Tables 6** and **7**). The strongest signal from the conditional analysis mapped to the major histocompatibility (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 conditional signal at 5q15 was in the *ERAP2* gene (rs2910686: $P = 2.0 \times 10^{-8}$), which did not show any evidence of association in the unconditioned analysis ($P = 0.46$). Further investigation showed 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* was thus masked by *ERAP1* before conditional analysis (**Supplementary Note**). The strongest conditional signal in the 19q13.2 region was rs12720356 in the *TYK2* gene (OR = 1.25; minor allele frequency (MAF) in 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 signal in *TYK2* identified by our meta-analysis (rs34536443: OR = 1.88; MAF in cases = 0.03; $P = 1.5 \times 10^{-39}$). Because rs34536443 was a low-frequency imputed SNP and manifested the greatest effect outside of the MHC region, we directly genotyped this SNP in 3,390 independent samples from Michigan (1,844 cases and 1,546 controls), robustly replicating the association (OR = 2.80; MAF in 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 significantly associated loci (**Supplementary Table 8** and **Supplementary Note**). We identified two significant pairwise interactions after

Box 1 Annotated functions of notable candidate genes within newly identified psoriasis susceptibility loci

***RERE*, *SLC45A1*, *ERRFI1* and *TNFRSF9* (1p36.23):** The signal falls between the *RERE*, *SLC45A1*, *ERRFI1* and *TNFRSF9* genes. *RERE* encodes an arginine–glutamic acid dipeptide repeat–containing protein that controls retinoic acid signaling[38]. *ERRFI1* encodes a feedback inhibitor of the epidermal growth factor (EGF) receptor[39]. *SLC45A1* encodes a solute carrier protein that mediates the uptake of glucose[40]. The *TNFRSF9* gene encodes a costimulatory molecule that has a role in the generation of memory CD8$^+$ T cells.

***RUNX3* (1p36.11):** *RUNX3* encodes 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$^+$ T cells. RUNX3 also has a role in promoting T$_\mathrm{H}$1 differentiation through binding to T-bet[41].

***B3GNT2* (2p15):** *B3GNT2* is a member of the β-1,3-*N*-acetylglucosaminyltransferase family. It catalyzes the initiation and elongation of poly-*N*-acetyllactosamine chains[42]. Deficiency for it has been shown to result in hyperactivation of lymphocytes[43].

***EXOC2* and *IRF4* (6p25.3):** *EXOC2* encodes a component of the multiprotein complex that mediates the docking of exocytic vesicles to the plasma membrane[44]. *IRF4* encodes a transcription factor that regulates *IL17A* promoter activity and controls RORγt-dependent T$_\mathrm{H}$17-mediated colitis *in vivo*[45,46]. *IRF4* also has a role in the stabilization of the T$_\mathrm{H}$17 phenotype through IL-21 (ref. 47) and may regulate CD4 and/or CD8 T-cell differentiation through regulation of *RUNX3* expression[48].

***TAGAP* (6q25.3):** *TAGAP* encodes a RhoGTPase-activating protein that is involved in T-cell activation[49].

***ELMO1* (7p14.2-7p14.1):** *ELMO1* encodes a member of the engulfment and cell motility protein family, which binds to DOCK2 and is essential for Toll-like receptor (TLR7 and TLR9)-mediated interferon (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 (ref. 53) and regulates the production of type I and II IFN[54].

***KLF4* (9p31.2):** *KLF4* encodes 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]. The KLF4 protein also binds to the promoter of *IL17A* and positively regulates its expression.

***ZC3H12C* (11q22.3):** *ZC3H12C* encodes a zinc-finger protein regulating macrophage activation[57].

***ETS1* (11q24.3):** *ETS1* encodes a transcription factor activated downstream of the Ras–mitogen-activated protein kinase (MAPK) pathway and is involved in the homeostasis of squamous epithelia[58]. It is involved in CD8 T-cell differentiation and acts, in part, by promoting RUNX3 expression[59]. It is also a negative regulator of T$_\mathrm{H}$17 differentiation[60].

***SOCS1* (16p13.13):** *SOCS1* is a member of the suppressor of cytokine signaling family of proteins and inhibits signaling events downstream of IFN-γ (ref. 61). It regulates T$_\mathrm{H}$17 differentiation by maintaining STAT3 transcriptional activity[62] and interacts with TYK2 in cytokine signaling[63].

***STAT3*, *STAT5A* and *STAT5B* (17q21.2):** *STAT3*, *STAT5A* and *STAT5B* encode members of the STAT family of transcriptional activators. STAT3 participates in signaling 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 T$_\mathrm{H}$17 cells[65]. STAT5A and STAT5B participate in signaling downstream of the IL-2 family of cytokines, including IL-2, IL-7, IL-15 and IL-21. Both proteins contribute to the development of regulatory T (Treg) cells and inhibit the differentiation of T$_\mathrm{H}$17 cells[66].

***CARD14* (17q25.3):** *CARD14* encodes a member of the family of caspase recruitment domain–containing scaffold proteins, known as CARD- and membrane-associated guanylate kinase–like domain–containing protein (CARMA). CARD14 (also known as CARMA2) is primarily expressed in epithelial tissues and mediates recruitment and activation of the NF-κB pathway[67].

***MBD2*, *POLI* and *STARD6* (18q21.2):** *MBD2* encodes a transcriptional repressor that binds to methylated DNA and has a role in the generation of memory CD8$^+$ T cells[68]. *POLI* encodes an error-prone DNA polymerase, which contributes to the hypermutation 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 STAR-related lipid transfer (START) domain of 200–210 amino acids in length, including STARD6.

***ILF3* and *CARM1* (19p13.2):** *ILF3* encodes a double-stranded RNA–binding protein that complexes with other proteins, double-stranded RNAs, small noncoding RNAs and mRNAs to regulate gene expression and stabilize mRNA. It is a subunit of the nuclear factor of activated T cells (NFAT), a transcription factor required for the expression in T cells of *IL-2*. *CARM1* encodes a transcriptional coactivator of NF-κB and functions as a promoter-specific regulator of NF-κB recruitment to chromatin.

correction for multiple testing ($P < 5 \times 10^{-5}$): *HLA-C* (rs4406273) with *LCE* (rs6677595) and *HLA-C* (rs4406273) with *ERAP1* (rs27432). These interactions confirm the results of previous studies[5,15,16].

To identify potential causal alleles in coding sequence, we looked for missense variants in tight linkage disequilibrium (LD; $r^2 > 0.9$ in 1000 Genomes Project European samples) with the lead SNP at each of the 34 identified loci (**Table 1** and **Supplementary Table 6**). We found ten potentially causal SNPs (**Table 2**), nine of which were included in our meta-analysis. For the known loci near *TRAF3IP2* and *TYK2*, damaging nonsynonymous substitutions were themselves the index SNPs in our initial and conditional analyses. For 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 nonsynonymous variants included the protective polymorphism encoding a p.Arg381Gln alteration in *IL23R*[19], a SNP in the *PRSS53* gene[20], which is also the most highly overexpressed 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].

Table 2 Potential causal SNPs for significant loci

Index SNP[a]			Potential causal SNP[b]					Combined *P* value[c]		
Marker[d]	RAF	Annotation	Marker[f]	RAF	Gene with variant	Amino-acid substitution (damaging effect)[g]	r^2	Index SNP	Potential causal SNP	Index SNP (conditioning on causal SNP)
rs9988642	0.93	454 bp downstream of *IL23R*	rs11209026	0.94	*IL23R*	p.Arg381Gln (P)	0.91	1.1×10^{-26}	1.5×10^{-26}	0.13
rs27432	0.29	Intron *ERAP1*	rs27044	0.29	*ERAP1*	p.Gln730Glu	1	1.9×10^{-20}	2.3×10^{-20}	0.14
rs1295685	0.77	3′ UTR *IL13*	rs20541	0.77	*IL13*	p.Arg144Gln	0.97	3.4×10^{-10}	3.5×10^{-10}	0.78
rs33980500	0.09	Missense	Self	0.09	*TRAF3IP2*	p.Asp19Asn (S,P)	1	4.2×10^{-45}	4.2×10^{-45}	NA
rs2066819	0.93	Intron *STAT2*	rs2066807	0.93	*STAT2*	p.Met594Ile	0.9	5.4×10^{-17}	5.1×10^{-16}	0.036
rs12445568	0.36	Intron *STX1B*	rs7199949	0.37	*PRSS53*	p.Pro406Ala	0.9	1.2×10^{-16}	–	–
rs11652075	0.51	Missense	Self	0.51	*CARD14*	p.Arg820Trp (S)	1	3.4×10^{-8}	3.4×10^{-8}	NA
rs34536443	0.97	Missense	Self	0.97	*TYK2*	p.Pro1104Ala (S,P)	1	1.5×10^{-39}	1.5×10^{-39}	NA
rs12720356[e]	0.9	Missense	Self	0.9	*TYK2*	p.Ile684Ser (S,P)	1	3.2×10^{-10}	3.2×10^{-10}	NA
rs4821124	0.19	966 bp downstream of *UBE2L3*	rs2298428	0.18	*YDJC*	p.Ala263Thr	0.96	3.8×10^{-8}	6.2×10^{-8}	0.48

NA, not available, as the index SNP is the potential causal SNP. Shown are data for SNPs that are missense mutations in 1000 Genome Project data that were in LD ($r^2 \geq 0.9$) with primary signals from the known and newly identified loci that achieved genome-wide significance in the meta-analysis or with secondary signals from the conditional analysis (Index SNP). [a]Information for SNPs with the most significant *P* value in our analysis. [b]Information for the SNPs that had high LD with the strongest signal. [c]Meta-analysis *P* value for the index SNP and potential causal SNP and the *P* value for the index SNP while conditioning on the potential causal SNP. Note that the potential causal SNP rs7199949 is not present in our meta-analysis study; therefore its *P* value was not shown. [d]SNPs with the most significant *P* value in our analysis. [e]Meta-analysis *P* value from the conditional analysis. [f]SNPs that are missense mutations that had high LD with our strongest signal. [g]High-confidence damaging effect predicted by SIFT (S) or Polyphen (P).

Using the results of a large-scale study of gene expression in psoriatic versus normal skin[24], we found 14 upregulated genes (*IL12RB2*, *LCE3D*, *REL*, *PUS10*, *CDSN*, *PRSS53*, *PRSS8*, *NOS2*, *DDX58*, *ZC3H12C*, *SOCS1*, *STAT3*, *CARD14* and *IFIH1*) and 4 downregulated genes (*MICA*, *RNF114*, *PTRF* and *POLI*) in the 34 associated regions (false discovery rate (FDR) of <0.05; fold change of >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 significance threshold ($P < 1 \times 10^{-7}$) for expression quantitative trait loci (eQTLs) 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 (**Supplementary Note**). 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 individuals of European ancestry to 36, with conditional analysis increasing the number of independent signals to 41. The 39 independent signals associated at $P < 5 \times 10^{-8}$ in the current study collectively account for 14.3% of the total variance in psoriasis risk or approximately 22% of its estimated heritability[29] (**Supplementary Table 10**), 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 found similar patterns of overlap in this study. Notably, ten of the psoriasis susceptibility loci reported here overlapped with those reported in Crohn's disease and ten others associated with celiac disease, diseases that occur at higher frequencies in individuals with psoriasis[30,31] (**Supplementary Fig. 5** and **Supplementary Table 4**). We caution that the statistical significance of these overlapping loci 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] that emerged long before the development of adaptive immunity[34]. In this context, we found it noteworthy 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*; **Box 1** and **Supplementary Table 4**). Among all confirmed psoriasis susceptibility loci, 11 out of 14 psoriasis-specific loci (the 5 new loci involved in the innate immune response 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 that contribute to innate immunity (*REL*, *IFIH1*, *TNIP1*, *TNFAIP3*, *IRF4* and *ELMO1*). 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 IL-17 signaling pathways, which are targeted by highly effective biological therapies[36]. Notably, 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 are needed to identify the underlying causal variants in these psoriasis susceptibility loci and to bring increased understanding of pathogenetic mechanisms.

URLs. WTCCC common controls, http://www.wtccc.org.uk/; 1000 Genomes Project data, ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20100804/; Catalog of Published Genome-Wide Association Studies, 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.

Note: Supplementary information is available in the online version of the paper.

ACKNOWLEDGMENTS

Major support for this study was provided by the US National Institutes of Health, the Wellcome Trust and the German Research Foundation. We thank J.C. Barrett for contribution to the design of the Immunochip and helpful analytical discussion, as well as E. Gray, S. Bumpstead, D. Simpkin and the staff of the Wellcome Trust Sanger Institute Sample Management and Genotyping teams for their genotyping and analytical contributions. We acknowledge use of the British 1958 Birth Cohort DNA collection, funded by the UK Medical Research Council (G0000934) and the

Wellcome Trust (068545/Z/02), and the UK National Blood Service controls, funded by the Wellcome Trust. We acknowledge 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 acknowledge the Genetic repository in Ireland for Psoriasis and Psoriatic Arthritis (GRIPPsA), the Irish blood transfusion service/Trinity College Dublin Biobank and the Dublin Centre for Clinical Research (funded by the Health Research Board and the Wellcome Trust). A detailed list of contributing consortia and relevant funding support is provided in the **Supplementary Note**.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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ONLINE METHODS

Sample collections. The samples used in the three GWAS data sets (Kiel, CASP and WTCCC2) were previously described[3–5]. Samples in the PAGE and GAPC data sets (**Supplementary Tables 1** and **2**) were collected from subjects of European descent at the participating institutions after obtaining informed consent. Enrollment of human subjects for this study was approved by the ethics boards of the participating institutions in adherence with the Declaration of Helsinki Principles. DNA was isolated from blood or Epstein-Barr virus (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 data sets in Strange *et al.*[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, and all samples were provided by the relevant groups listed in **Supplementary Table 2** and by the members of the GAP Consortium listed in the **Supplementary Note**. The UK controls were the WTCCC common control samples that did not overlap with the samples included in the original GWAS (the data set consisted of 6,740 1958 British Birth cohort and 2,900 UK Blood Service samples genotyped at the Wellcome Trust Sanger Institute and the University of Virginia). The German controls were obtained from the PopGen Biobank and genotyped at the Institute of Clinical Molecular Biology at Christian-Albrechts-University of Kiel. The Finland control data were from the DILGOM collection[70]. The Irish controls were provided by the Irish Blood Transfusion Service/Trinity College Dublin Biobank, and Irish cases were collected with the aid of the Dublin Centre for Clinical Research. We did not include specific controls from Austria or Sweden, but principal-components 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 data sets. The German cases (described as a replication data set in Ellinghaus *et al.*[3]) and 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 at Christian-Albrechts-University of Kiel. The respective samples were provided by the groups listed in **Supplementary Table 2** and by the members of PAGE listed in the **Supplementary Note**. The German controls were obtained from a population-based sample from the general population living in the region of Augsburg in southern Germany (KORA S4/F4)[71], which was genotyped at the Helmholtz Zentrum Munich, and from the population-based epidemiological HNR study, for which genotyping was performed 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 at 186 loci were selected from 1000 Genomes Project[72] low-coverage pilot Utah residents of Northern and Western European ancestry (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 regions associated with psoriasis at genome-wide significance (**Table 1**) for fine mapping on the basis of a preliminary meta-analysis of our data, and 1 of the confirmed signals (*IL28RA*) and 9 of the new psoriasis-associated signals (**Supplementary Table 5**, disease overlap) were submitted for fine-mapping by groups studying other diseases (although we also submitted 3 of these as part of our additional SNP allocation: rs11121129, rs10865331 and rs9504361). Six additional signals were detected on the basis of additional SNP allocation in individual groups; 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 data set, genotype calling was performed using Illumina's GenomeStudio Data Analysis software and the custom-generated cluster file of Trynka *et al.*[13]. (which was generated by initial clustering of 2,000 UK samples with the GenTrain2.0 algorithm and subsequent manual readjustment and quality control). Genotype calling for the GAPC data set 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 data set.

Imputation. To increase the number of overlapping SNPs between data sets, we performed imputation on the 3 GWAS data sets using minimac[74] (Kiel and CASP) and IMPUTE2 (refs. 75,76) (WTCCC2) using data from 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 and info score < 0.5 for IMPUTE2) were removed. For all 3 data sets, cases and controls were imputed together.

Sample and genotype quality control. For the Immunochip data sets, we first excluded SNPs with a call rate below 95% or with a Hardy-Weinberg equilibrium P value of $<1 \times 10^{-6}$. Samples with less than SNP call rates below 98% 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 that have P values >0.5 from the meta-analysis of the three GWAS data sets as a quality control tool for each individual Immunochip data set. Using the HapMap 3 samples as reference[77], we performed principal-component 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 data sets, principal-components analysis was also performed in each of the Immunochip data sets 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 did separate the samples well by country of origin. The use of the top ten eigenvectors as covariates in the analysis did not completely correct for stratification, and, therefore, a linear mixed-model method (efficient mixed-model association expedited (EMMAX)) was instead used for the association analysis. These methods have been shown to outperform principal components in correcting for this type of population stratification and cryptic relatedness[79], which is becoming more common as sample sizes increase and studies comprise more collaborative efforts.

To identify duplicate pairs or highly related individuals among data sets, 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], requiring Pi-HAT of ≥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 because of duplication in the WTCCC2 GWAS sample. For GWAS samples that were duplicated in the Immunochip data sets (the majority of duplicates), we removed the samples from the Immunochip data sets to keep the previously published data sets intact.

The GWAS data sets underwent quality control as previously described and were analyzed for association using the top principal components from the previous analyses as covariates[3–5].

We visually inspected the signal intensity cluster plots for all SNPs with associations reaching genome-wide significance to confirm high-quality genotype calling.

Genomic control. Genomic control inflation factors for the five data sets 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 data sets. Because the Immunochip was designed for deep replication and fine mapping of loci associated with autoimmune

doi:10.1038/ng.2467

diseases[12], using all independent SNPs from the chip would not give an accurate estimate of the genomic control[80] value (λ_{GC}). Therefore, we selected common SNPs (with minor allele frequency (MAF) of >0.05) from the Immunochip that had association *P* values of >0.5 on the basis of a meta-analysis combining the Kiel, CASP and WTCCC2 GWAS, and then performed LD pruning to identify an independent SNP set to compute λ_{GC} for the association results from the Immunochip data sets. As a result of SNP selection bias, the genomic control value for the final meta-analysis was computed using a set of independent SNPs associated with reading and writing ability (J.C. Barrett, personal communication). We further removed SNPs that were within 500 kb of previously detected psoriasis-associated loci (within 3 Mb in the MHC region), and the remaining 1,426 SNPs yielded λ_{GC} of 1.11 for the meta-analysis overall. Using λ_{1000} (ref. 81), the genomic control inflation factor for an equivalent study of 1,000 cases and 1,000 controls, the rescaled λ equaled 1.01.

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doi:10.1038/ng.2467