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Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways

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Psoriasis is a common immune-mediated disorder that affects the skin, nails and joints. To identify psoriasis susceptibility loci, we genotyped 438,670 SNPs in 1,409 psoriasis cases and 1,436 controls of European ancestry. We followed up 21 promising SNPs in 5,048 psoriasis cases and 5,041 controls. Our results provide strong support for the association of at least seven genetic loci and psoriasis (each with combined $P < 5 \times 10^{-8}$). Loci with confirmed association include *HLA-C*, three genes involved in IL-23 signaling (*IL23A*, *IL23R*, *IL12B*), two genes that act downstream of TNF-α and regulate NF-κB signaling (*TNIP1*, *TNFAIP3*) and two genes involved in the modulation of Th2 immune responses (*IL4*, *IL13*). Although the proteins encoded in these loci are known to interact biologically, we found no evidence for epistasis between associated SNPs. Our results expand the catalog of genetic loci implicated in psoriasis susceptibility and suggest priority targets for study in other auto-immune disorders.

Psoriasis is a common inflammatory disease affecting ~1% of individuals. The most obvious cellular features of psoriasis are epidermal hyperplasia, altered keratinocyte differentiation and inflammation[1]. Psoriasis susceptibility has a genetic component, partly explained by association between psoriasis and major histocompatibility complex (MHC) haplotypes bearing HLA-Cw6 (ref. 2) and SNPs near *IL12B* and *IL23R*[3]. Individuals with psoriasis show increased risk for other immune-mediated disorders[4] and some *IL12B* and *IL23R* polymorphisms are associated with Crohn's disease and ulcerative colitis in addition to psoriasis (for an example, see ref. 5).

To identify additional psoriasis susceptibility loci, we carried out a genome-wide association scan of 1,409 psoriasis cases and 1,436 controls in partnership with the Genetic Association Information Network (GAIN)[6] (see **Table 1** and **Supplementary Table 1** online for details of case and control collections). After samples were genotyped at Perlegen Sciences, we used a dataset that passed quality control filters and included 438,670 autosomal SNPs genotyped in 1,359 psoriasis cases and 1,400 controls to impute genotypes for 2.5 million HapMap SNPs (see Methods).

An initial comparison of case-control allele frequencies (genomic control $\lambda = 1.033$) confirmed association at established susceptibility loci *HLA-C* (rs12191877, $P = 4 \times 10^{-53}$), *IL12B* (rs2082412, $P = 5 \times 10^{-10}$) and *IL23R* (rs2201841, $P = 3 \times 10^{-7}$). Encouraged by these results, we selected 21 SNPs (representing 18 independent loci, see Methods) for genotyping in an additional 5,048 cases and 5,051 controls (see **Table 1** and **Supplementary Table 2** online). We found supporting evidence of association at 10 of these 18 loci ($P < 0.05$ in the follow-up sample, direction of effect matches discovery sample; **Table 2**). Evidence for association was particularly compelling at seven of these loci ($P < 0.0005$ in follow-up samples, combined P value $< 5 \times 10^{-8}$). Owing to the 'winner's curse', odds ratios estimated in the discovery sample were larger than those

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Table 1 Summary description of the samples used in this study

	Cases				Controls			
	N	Mean age at onset	Male (%)	Psoriatic arthritis (%)	*N*	Mean age at exam	Male (%)	Total
Discovery samples								
Collection of J.T. Elder	480	23.0	52.1	25.2	702	40.5	49.3	1,182
Collection of G. Krueger	476	28.4	42.9	30.0	473	29.7	42.7	949
Collection of A. Bowcock	453	27.2	49.9	26.5	261	57.4	36.0	714
Discovery sample total	**1,409**	**26.1**	**48.3**	**27.1**	**1,436**	**40.0**	**44.7**	**2,845**
Follow-up samples								
Collection of J.T. Elder	1,642	30.8	46.3	16.4	1,101	48.0	41.0	2,743
Collection of M. Weichenthal	718	25.1	52.1	16.7	1,464	40.4	51.0	2,182
Celera follow-up set 1, A. Begovich	498	29.4	44.6	40.7[a]	498	47.4	44.6	996
Celera follow-up set 2, A. Begovich	483	26.8[b]	53.4	29.3[a]	427	44.3[b]	52.2	910
Collection of D. Gladman	691	29.4	59.9	71.6	217	41.8	47.7	908
Collection of J. Fischer	346	19.0	45.2	13.9	486	n/a[c]	47.2	832
Collection of A. Bowcock	302	28.0	49.0	34.1	500	59.0	48.0	802
Collection of P. Rahman	368	28.3	47.8	81.5	358	54.9	43.0	726
Follow-up sample total	**5,048**				**5,051**			**10,099**

All cases and controls were of white European ancestry.
[a]In the Celera case samples, subjects were only classified as psoriatic arthritis positive or negative ten years after disease onset. In follow-up set 1, 98 of 241 subjects followed-up for >10 years had psoriatic arthritis. In follow-up set 2, 63 of 215 subjects met this criterion. [b]Information on age at disease onset and age at exam was available for 293 cases and 292 controls, respectively. [c]Age information for controls in this sample set was not tracked electronically in the sample database and is not readily accessible.

estimated in the follow-up samples. To minimize this effect, we use follow-up sample odds ratios in the discussion that follows. **Figure 1** summarizes the results of the association scan, with the seven regions of confirmed association detailed in **Figure 2**. Overall, our approach provides ~70% power to detect loci that are well tagged by genotyped SNPs, increase disease risk by >1.35-fold and have a frequency >20%.

The results highlight the role of several key pathways in disease susceptibility. First, three SNPs with strong evidence of association map near *IL12B* (encoding the p40 subunit of IL-23 and IL-12), *IL23A* (encoding the p19 subunit of IL-23) and *IL23R* (encoding a subunit of the IL-23 receptor): rs2082412 (risk allele frequency in controls $f_{control} = 0.80$, odds ratio in follow-up samples $OR_{follow\text{-}up} = 1.44$, combined *P* value $P_{combined} = 2 \times 10^{-28}$), rs2066808 ($f_{control} = 0.93$, $OR_{follow\text{-}up} = 1.34$, $P_{combined} = 1 \times 10^{-9}$) and rs2201841 ($f_{control} = 0.29$, $OR_{follow\text{-}up} = 1.13$, $P_{combined} = 3 \times 10^{-8}$). Genetic variants in the *IL23A* locus are implicated in psoriasis and autoimmune disease susceptibility for the first time by our study. IL-23 signaling promotes cellular immune responses by promoting the survival and expansion of a recently identified subset of T cells expressing IL-17 that protects epithelia against microbial pathogens[7]. Dysregulated IL-23 signaling could predispose certain individuals to inappropriate chronic immune responses that target epithelial cells and ultimately result in psoriasis.

Second, loci including *TNFAIP3* (TNF-α induced protein 3) and *TNIP1* (TNFAIP3 interacting protein 1), whose gene products work downstream of TNF-α to regulate NF-κB, show strong association

Table 2 Loci with strongest evidence of association with psoriasis in the combined sample, including discovery and follow-up samples

				Discovery samples (1,359 cases, 1,400 controls)				Follow-up samples (5,048 cases, 5,051 controls)					
				Frequency[a]				Frequency					
SNP	Chr.	Pos. (Mb)	Alleles risk/nonrisk	Case	Control	OR	*P* value[b]	Case	Control	OR (meta)	*P* value[b] (meta)	Combined *P* value[d]	Notable nearby genes (relative position)[c]
rs12191877	6	31.36	T/C	0.313	0.141	2.79	4×10^{-53}	0.301	0.147	2.64	$<10^{-100}$	$<10^{-100}$	***HLA-C* (–13 kb)**
rs2082412	5	158.65	G/A	0.856	0.792	1.56	5×10^{-10}	0.848	0.798	1.44	3×10^{-20}	2×10^{-28}	***IL12B* (+24 kb)**
rs17728338	5	150.46	A/G	0.093	0.056	1.72	2×10^{-7}	0.087	0.054	1.59	6×10^{-15}	1×10^{-20}	***TNIP1* (–12 kb)**
rs20541	5	132.02	G/A	0.832	0.783	1.37	6×10^{-6}	0.827	0.790	1.27	1×10^{-10}	5×10^{-15}	***IL13* (nonsynonymous)**
rs610604	6	138.24	G/T	0.374	0.318	1.28	1×10^{-5}	0.360	0.320	1.19	7×10^{-8}	9×10^{-12}	***TNFAIP3* (intronic)**
rs2066808[d]	12	55.02	A/G	0.958	0.931	1.68	2×10^{-5}	0.947	0.932	1.34	5×10^{-6}	1×10^{-9}	***IL23A* (+3.7 kb) STAT2 (intronic)**
rs2201841	1	67.47	G/A	0.350	0.286	1.35	3×10^{-7}	0.325	0.295	1.13	4×10^{-4}	3×10^{-8}	***IL23R* (intronic)**
rs1076160	9	134.80	T/C	0.520	0.463	1.26	2×10^{-5}	0.496	0.475	1.09	4×10^{-3}	6×10^{-6}	*TSC1* (intronic)
rs12983316	19	10.98	G/A	0.186	0.144	1.36	2×10^{-5}	0.159	0.147	1.09	0.027	8×10^{-5}	*SMARCA4* (intronic)
rs397211	2	113.60	T/C	0.718	0.677	1.21	1×10^{-3}	0.709	0.696	1.08	0.025	4×10^{-4}	*IL1RN* (+0.5 kb)

[a]Frequency of the risk allele. [b]All *P* values are two tailed. [c]Position of each SNP relative to notable nearby genes is given. Plus (+) and minus (–) signs indicate whether the SNP is upstream (–) or downstream (+) of the transcription start site. SNPs that overlap the gene are labeled as 'intronic', 'synonymous' or 'nonsynonymous'. [d]Genotypes for rs2066808 were imputed using MaCH. The distribution of imputed posterior probabilities for each genotype was then compared between cases and controls.
Similar evidence for association was observed at rs2066807 (combined $P = 2 \times 10^{-9}$), which maps nearby and was genotyped in discovery and follow-up samples. Boldface rows indicate loci achieving a genome-wide level of significance ($P < 5 \times 10^{-8}$) in the combined analysis.

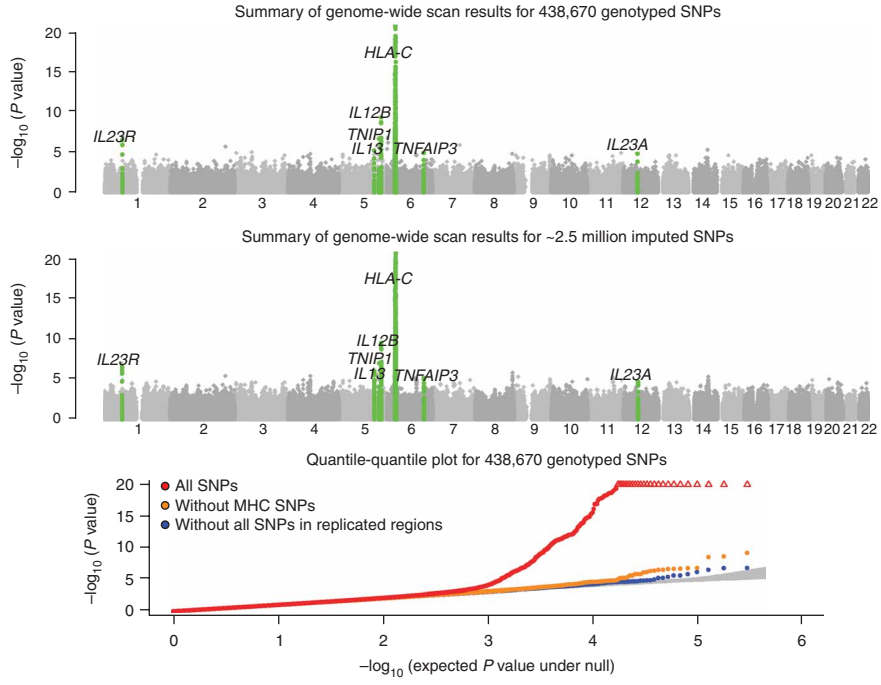

Figure 1 Bird's eye view of association scan results. The top panel summarizes the distribution of test statistics at genotyped SNPs across the genome. We used a simple χ^2 test to compare SNP allele frequencies in cases and controls and plotted the resulting –log *P* values across the genome. Several *P* values $<10^{-20}$ in the MHC region were truncated. Loci where we obtained confirmatory evidence of association in follow-up samples (see **Table 2**) are highlighted in green. The middle panel summarizes the distribution of test statistics across the genome, after genotype imputation. We used a simple *t*-test to compare imputed allele counts in cases and controls and plotted the resulting –log *P* values across the genome. The bottom panel displays a quantile-quantile plot for our test statistics. Results are plotted including all SNPs (in red), after exclusion of SNPs in the MHC (in orange) and after exclusion of all SNPs in regions of replicated association (in blue). The shaded region represents a 90% confidence interval for the test statistics.

with psoriasis. In these two regions, markers rs610604 ($f_{control} = 0.32$, $OR_{follow\text{-}up} = 1.19$, $P_{combined} = 9 \times 10^{-12}$) and rs17728338 ($f_{control} = 0.05$, $OR_{follow\text{-}up} = 1.59$, $P_{combined} = 1 \times 10^{-20}$) were sites of replicated association. *TNFAIP3* encodes A20, a TNF-α-inducible zinc-finger protein that temporally limits immune responses by inhibiting NF-κB activation and terminating NF-κB mediated responses[8]. Symptoms in a mouse model of psoriasis induced by administration of IL-23 are ameliorated by blocking of TNF-α[9] and, in a different mouse model, a region of mouse chromosome 10 encompassing *Tnfaip3* promotes psoriasis in a TNF-α–dependent manner[10]. Notably, this same region of the mouse genome has been also associated with atherosclerosis[11], a major co-morbidity of psoriasis[12]. Monoclonal antibodies targeting TNF-α and those targeting the p40 subunit of IL-12 and IL-23 both provide highly efficacious therapeutic regimens for many individuals with psoriasis[13,14]; hence, five of the genes implicated here have key roles in pathways targeted by therapeutic interventions. Further, common polymorphisms near *TNFAIP3* have recently been associated with rheumatoid arthritis (for example, rs6920220, rs10499194; see ref. 15 for an example) and systemic lupus erythematosus (for example, rs5029939, rs13192841, rs2230926 and rs6922466)[16,17]. However, these polymorphisms show no association with psoriasis in our sample (all $P > 0.30$) and are not in linkage disequilibrium (LD, all $r^2 < 0.03$) with the psoriasis-associated alleles (for example, rs610604).

Third, genes in the two other loci implicated here are also key modulators of immune response. One locus encodes the IL-4 and IL-13 cytokines that modulate humoral immune responses mediated by Th2 cells. In this locus, we replicated association at rs20541 ($f_{control} = 0.79$, $OR_{follow\text{-}up} = 1.27$, $P_{combined} = 5 \times 10^{-15}$). Dysregulation of IL-4 and IL-13 might polarize the immune response toward Th1-mediated cellular immune responses such as production of interferon-γ, which supports the marked expansion of IL-17–producing T cells observed in psoriatic lesions[18]. Our findings extend the promising results of a recent study[19] to a genome-wide level of significance. Notably, our *IL4* and *IL13* signal maps within ~200 kb of the *IBD5* Crohn's disease susceptibility locus[5]. The two are not in LD (for example, r^2 between rs20541 and rs10077785 (ref. 5) in HapMap CEU is <0.01), but *IBD5* does show modest evidence for association with psoriasis (rs10077785, $P = 0.03$), suggesting that it could be another locus that contributes to both diseases.

SNP rs12191877, the genotyped marker showing strongest association with psoriasis ($f_{control} = 0.15$, $f_{case} = 0.30$, $OR_{follow\text{-}up} = 2.64$, $P_{combined} \ll 10^{-100}$), was in LD with *HLA-Cw6* ($r^2 = 0.63$). In a subset of cases and controls in which *HLA-Cw6* genotypes were available, *HLA-Cw6* was more strongly associated with psoriasis than any genotyped or imputed SNP, but could not fully account for all observed association signals (data not shown). To assess the evidence for multiple psoriasis susceptibility alleles within the MHC, we implemented a forward-selection procedure to select a set of disease-associated variants in each locus (see Methods). This analysis resulted in a model with three imputed SNPs (**Supplementary Table 3** online). The first two of these (rs12204500 and rs13191343, forward-selection *P* values of 8×10^{-57} and 2×10^{-10}, respectively) are close to and in strong LD with *HLA-Cw6* ($r^2 = 0.78$ and 0.52, respectively), whereas the third one (rs2022544, *P* value $= 10^{-7}$) maps closer to the *HLA-DR* gene cluster and shows only weak LD with *HLA-Cw6* ($r^2 = 0.01$). These results endorse a search for additional psoriasis susceptibility loci within the MHC.

When we applied the same forward-selection strategy to the other loci, two independent SNPs ($r^2 < 0.01$) were selected in the *IL12B* and *IL23R* regions. Although only one SNP was selected in the four other regions (**Supplementary Table 3**), it is likely that independent disease-associated alleles exist in additional loci such as *TNIP1* where rs884520 (a SNP only ~6 kb away from the peak of association at rs17728338) was suggestively associated with psoriasis ($P = 9 \times 10^{-5}$ unadjusted, $P = 0.051$ after conservative adjustment for 565 independent tests) in our conditional analyses. Fully characterizing the impact of these loci on psoriasis susceptibility will require characterization of the full spectrum of allelic variation at each locus in large case-control samples.

As all the loci implicated here are involved in regulation of immune responses, and several of the proteins they encode interact physically (for example, IL-12B/p40 and IL-23/p19 form a heterodimer that binds to IL-23R, and TNIP1 interacts with TNFAIP3) we assessed evidence of epistasis in our data. We considered all 21 possible pairings of the seven lead SNPs, testing for deviation from a log-additive risk

model. Only the pairing involving rs12191877 near *HLA-C* and rs610604 near *TNFAIP3* showed any evidence for epistasis under this model ($P = 0.02$ in combined sample). It is possible that tests of interaction will be more powerful once the causal variants at each loci have been identified, but it is notable that even when proteins encoded by the associated loci interact physically no significant evidence for epistasis was detected (a similar situation occurs for height[20], among other traits).

To evaluate evidence for heterogeneity in the effect sizes at each of the seven replicated loci, we calculated I^2 and Q statistics for a meta-analysis of follow-up samples (**Supplementary Table 4** online). We observed no evidence for heterogeneity at non-MHC loci, and only

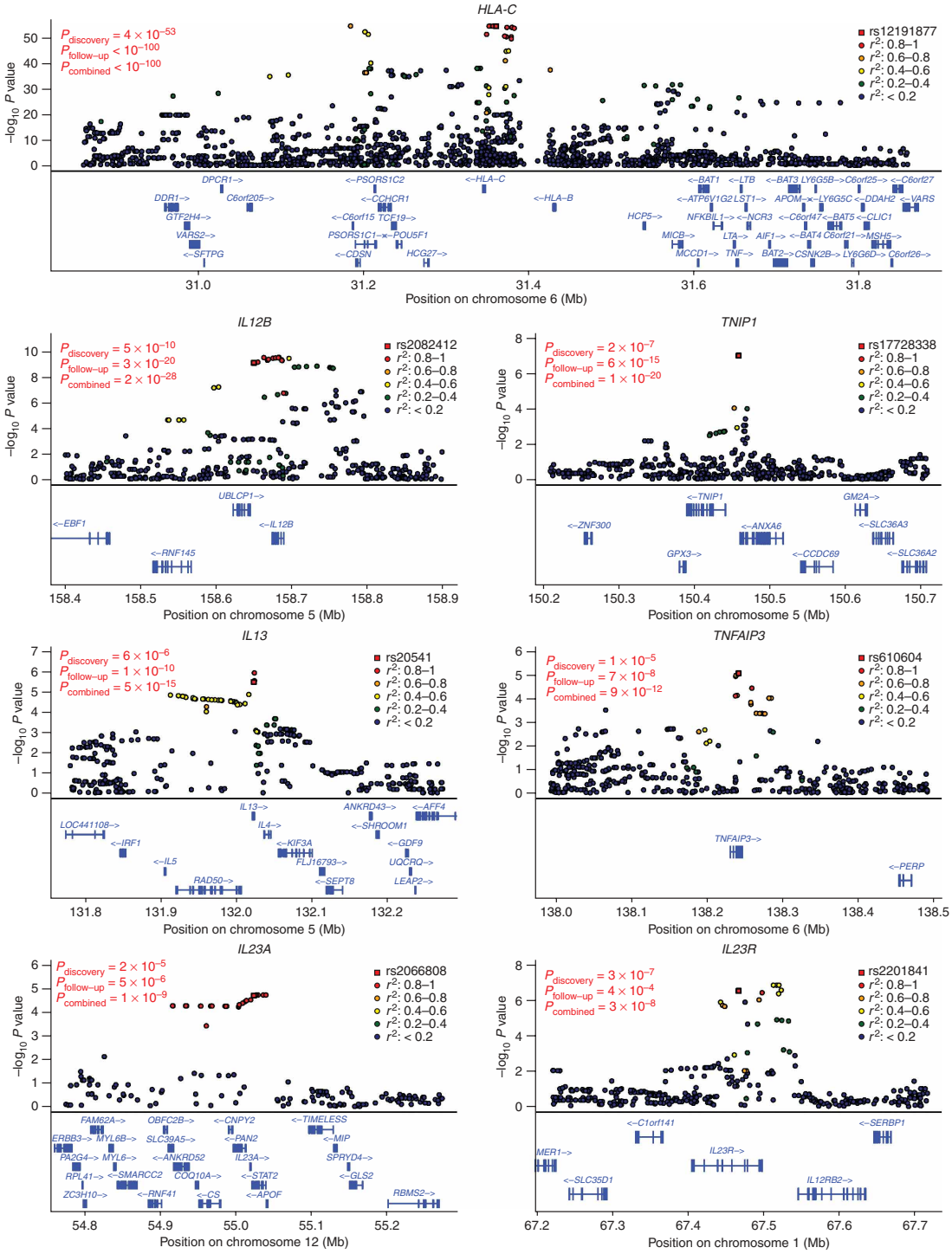

Figure 2 Evidence for association in confirmed loci. The figure summarizes evidence of association (in the discovery sample) in each region of confirmed association. Test statistics at the SNP selected for follow-up (typically, the genotyped SNP showing strongest evidence for association in each locus) are highlighted with a square. Test statistics for other SNPs are drawn as circles and color coded according to the degree of linkage disequilibrium with the SNP selected for follow-up.

modest evidence for heterogeneity at rs12191877 in the MHC ($P = 0.007$, **Supplementary Table 4**)—potentially reflecting sample differences in the proportion of familial cases and psoriatic arthritis. At several of the confirmed loci, we found modest differences in association signal strength for psoriatic arthritis compared to purely cutaneous psoriasis (**Supplementary Table 5** online), supporting epidemiologic evidence for differences in genetic architecture of the two conditions[21]. In other stratified analyses, we found no evidence for heterogeneity between males and females (all $P > 0.15$) or between younger and older individuals (all $P > 0.15$, cases and controls stratified around median ages).

Psoriatic and uninvolved skin show significantly different expression for hundreds of genes, involved in both immune response and in the regulation of cellular differentiation and proliferation[22]. We reasoned that altered expression of genes in the loci implicated by our study might also be a molecular trigger in disease progression. Therefore, we examined expression of the genes in the loci showing replicated evidence of association in skin biopsies from 64 GWAS controls and in biopsies of involved and uninvolved skin from 58 GWAS cases (**Supplementary Table 6** and **Supplementary Fig. 1** online). Together, these results show that four of the genes investigated (*HLA-C, IL12B, TNIP1* and *IL23A*) show highly significant differences in expression between involved and uninvolved skin (all with $P < 10^{-9}$). Two of these (*IL23A*, *TNIP1*) also showed differences in expression when we compared normal skin from controls and uninvolved skin from cases ($P < 0.0003$). The results are consistent with the hypothesis that the expression of particular *HLA-C* alleles and of *IL23A* and *IL12B* (encoding the two subunits of IL-23) in psoriatic skin are key events in disease progression. However, the dosage of risk alleles at the seven psoriasis-associated SNPs did not correlate with transcript levels for nearby genes in either involved, uninvolved or normal skin. It remains possible that association between these SNPs and gene expression patterns is stronger at specific time points during development, disease progression or in specific cell types.

Although this study represents a significant advance in our understanding of the genetic underpinnings of psoriasis, much work remains to be done. The association signals identified here account for a sibling recurrence risk (λ_s) of <1.35 (including ~ 1.25 due to HLA); consequently, much of the overall sibling recurrence risk for psoriasis, which has been estimated at approximately three- to sixfold[23], remains unexplained. Still, the rapid pace of advance in psoriasis genetics is encouraging. In the past 18 months, the number of independent genetic loci confidently associated with psoriasis has increased from one (*HLA-Cw6* and other MHC variants) to at least ten, including the seven association signals reported in this paper, copy number variants in the beta-defensin[24] and late cornified envelope (LCE) gene regions[25], and a signal near *RNF114*, a potential regulator of T-cell activation[26]. The *RNF114* signal is supported by our data (see **Supplementary Table 7** online for analysis of previously reported GWAS[26,27] signals in our data). Although we did not systematically characterize copy number variation, we note that rs4112788, a SNP proxy for the LCE deletion[25,27], is associated with disease in our discovery sample ($P = 0.001$). In each of the loci identified here, fine-mapping and resequencing efforts together with further functional studies are required to pinpoint and characterize causal variants, confirm the identity of the implicated genes, and accurately quantify the contribution of the locus to disease susceptibility. In parallel, follow-up analyses with larger numbers of SNPs, execution of genome-wide association scans in larger sample sets, meta-analyses of genome-wide scan results, and large scale analyses of rarer variants should lead to identification of additional susceptibility loci.

METHODS

Informed consent. All participating subjects gave informed consent and protocols were reviewed and approved by local institutional review boards.

Genotyping. Perlegen Sciences genotyped discovery samples using four proprietary, high-density oligonucleotide arrays. SNPs on the arrays were selected to tag common variation in samples of European ancestry. Cases and controls from the same collection were genotyped together, and arranged to ensure similar proportions of cases and controls in each plate. Follow-up samples were genotyped using either Applied Biosystems Taqman assays, Sequenom single base extension assays, or allele-specific kinetic PCR. The 21 SNPs selected for follow-up included 19 SNPs selected to represent loci with strongest evidence for association in our initial scan (including 2 SNPs per locus for hits near *IL13*, *IL23A* and *PRKRIP1*) and two SNPs in loci that included strong functional candidates (*IL1RN* and *CNTN5*) but more modest evidence of association (rs397211, $P = 1 \times 10^{-3}$, and rs12807920, $P = 1 \times 10^{-4}$).

Sample quality control. Eighteen samples failed genotyping for technical reasons. Among the remaining samples, we excluded those with call rates $<95\%$ (8 samples) and with outlier heterozygosities of $<31\%$ or $>34\%$ (24 samples; the average heterozygosity for all samples was 32.6% with s.d. of 0.4%). We also excluded one individual from each pair of unexpected duplicates, first- or second-degree relatives (36 individuals). This resulted in a dataset with 1,359 cases and 1,400 controls.

Quality control of genotype data. Perlegen Sciences called $>50\%$ of genotypes for 556,383 SNPs. Before analysis, we excluded markers with $<95\%$ genotype call rates (99,963 SNPs), with minor allele frequency $<1\%$ in the combined dataset (6,106 SNPs), with HWE P value $<10^{-6}$ (2,962 SNPs), with >2 mismatches among 48 duplicate pairs (62 SNPs) or with >2 mendelian inconsistencies among 27 trios (41 SNPs). In total, 447,249 SNPs passed the quality control filters (average call rate of 99.2%). Here, we present analyses of 438,670 autosomal SNPs.

Genotype imputation. As previously described[28], we used information on patterns of haplotype variation in the HapMap CEU samples (release 21)[29] to infer missing genotypes '*in silico*'. We only analyzed SNPs that were genotyped or could be imputed with relatively high confidence (estimated r^2 between imputed SNP and true genotypes >0.3, so that patterns of haplotype sharing between sampled individuals and HapMap samples consistently indicated a specific allele).

Assessment of genotyping and imputation quality. A single plate containing 90 study samples was re-genotyped for 906,600 SNPs using the Affymetrix 6.0 chip. Comparison of 15,844,334 genotypes for 218,039 SNPs overlapping between the Perlegen and Affymetrix platforms resulted in an observed discrepancy rate of 0.25% per genotype (0.12% per allele). Comparison of 57,747,244 imputed and experimentally derived genotypes for 661,881 non-Perlegen SNPs present in both our imputed SNP set and the Affymetrix 6.0 array resulted in a discrepancy rate of 1.80% per genotype (0.91% per allele). Overall, the average r^2 between imputed genotypes and their experimental counterparts, which provides an estimate of the relative power of analysis relying on imputation instead of direct genotyping, was 0.93. This r^2 statistic exceeded 0.80 for $>90\%$ of SNPs, suggesting excellent coverage of common variation in the genome.

Association analyses. To evaluate the evidence for association between each genotyped or imputed SNP and psoriasis, we first calculated a single χ^2 statistic that contrasted observed or imputed allele counts between cases and controls. The 832 follow-up samples collected by J. Fischer (**Table 1**) and colleagues were analyzed using a family-based approach[30]. To combine statistics across different samples, we first selected an arbitrary reference allele for each marker and then calculated a z statistic characterizing the evidence for association in each study (summarizing both the P value, in its magnitude, and the direction of effect, in its sign). We then calculated an overall z statistic as a weighted average of the individual statistics and calculated the corresponding P value. Weights were proportional to the square root of the number of individuals examined in each sample and were selected such that the squared weights sum to 1.0.

Forward selection procedure. We first selected the SNP that showed strongest association in each region. Then, conditioning on this SNP, we searched for the

next most strongly associated SNP. If evidence for association at this second SNP was stronger than expected by chance (after adjusting for the number of SNPs tested), we sought a third strongly associated SNP and so forth.

Gene expression. We obtained 6 mm punch skin biopsies at the University of Michigan Department of Dermatology. One biopsy of normal skin was obtained from the buttock of 64 control individuals. Two biopsies (one involved, one uninvolved) were obtained from 58 psoriatic subjects. Involved skin biopsies were taken from psoriasis plaques, and uninvolved skin biopsies were taken from the buttocks, at least 10 cM away from the nearest plaque. RNA from each biopsy was isolated using the RNeasy kit (Qiagen). Samples were run on Affymetrix U133 Plus 2.0 arrays to evaluate expression of ~54,000 probes according to the manufacturer's protocol. The raw data from 180 microarrays was processed using the Robust Multichip Average (RMA) method. Prior to analysis, we adjusted RMA expression values to account for batch and sex effects. To obtain a single expression value for each gene, we calculated the average of expression values of multiple probe sets on the microarray that were mapped to the same gene. Gene expression was contrasted between different groups of samples using two sample *t*-tests (for comparisons involving skin from normal controls and individuals with psoriasis) or paired *t*-tests (for comparisons involving involved and uninvolved skin from affected individuals). Comparisons of normal skin from controls and psoriatic skin from cases gave similar results (but slightly more significant *P* values) to paired comparisons of involved and uninvolved skin from the same affected individual and are not shown. Reanalysis of a previously published dataset[22] including paired biopsies of involved and uninvolved skin from 16 individuals gave results consistent with those reported here, suggesting that *IL23A*, *IL12B* and *TNIP1* are overexpressed in involved skin. This independent dataset did not suggest differential expression of *HLA-C*.

Accession codes. dbGAP: genotype and phenotype data described in this manuscript have been deposited with accession code phs000019.v1.p1. NCBI GEO: microarray data have been deposited under accession number GSE13355.

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

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AUTHOR CONTRIBUTIONS

J.T.E., G.G.K., A.M.B. and G.R.A. designed and directed the study. J.D., C.H., P.E.S., D. Goldgar, B.J.F., Y.L. and G.R.A. designed and carried out the main genome scan analysis. R.P.N., K.C.D., C.H., J.D., P.E.S., J.E.G., T.T., S.P., S.L.G., W.L., P.-Y.K., A.M., C.A.W., J.J.V., J.T.E, G.G.K. and A.M.B. provided samples for the initial genome-wide association scan and replication and executed the experiments. A.R., S.S., M.W., D. Gladman, P.R., S.J.S., J.F., G.M.L. and A.B.B. provided additional replication data. J.D., J.T.E. and G.R.A. generated the first draft of the paper. Additional major edits were done by K.C.D., P.E.S., A.B.B., G.G.K. and A.M.B. All authors reviewed and approved the paper.

COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturegenetics/.

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