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SHORT COMMUNICATION

Variants in the 5q31 cytokine gene cluster are associated with psoriasis

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A multitiered genetic association study of 25 215 single-nucleotide polymorphisms (SNPs) in three case–control sample sets (1446 patients and 1432 controls) identified three IL13-linked SNPs (rs1800925, rs20541 and rs848) associated with psoriasis. Although the susceptibility effects at these SNPs were modest (joint allelic odds ratios (ORs): 0.76 to 0.78; P_{comb} : $1.3E-03$ to $2.50E-04$), the association patterns were consistent across the sample sets, with the minor alleles being protective. Haplotype analyses identified one common, susceptible haplotype CCG (joint allelic OR = 1.27; P_{comb} = $1.88E-04$) and a less common, protective haplotype TTT (joint allelic OR = 0.74; P_{comb} = $7.05E-04$). In combination with the other known genetic risk factors, HLA-C, IL12B and IL23R, the variants reported here generate an 11-fold psoriasis-risk differential. Residing in the 5q31 cytokine gene cluster, IL13 encodes an important T-cell-derived cytokine that regulates cell-mediated immunity. These results provide the foundation for additional studies required to fully dissect the associations within this cytokine-rich genomic region, as polymorphisms in closely linked candidate genes, such as IRF1, IL5 or IL4, may be driving these results through linkage disequilibrium.

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Introduction

Psoriasis is the most common autoimmune disease with 1–2% of the general population being affected worldwide. The prevalence of psoriasis varies substantially from near zero in Samoans, Australian Aborigines and South American Amerindians to 3–4% in some European populations, with one report of nearly 12% in Arctic Kazach'ye.^{1–4} It is well-recognized that psoriasis substantially impacts the quality of life for those suffering from its effects, making the disease a principal cause of psychosocial disability.⁵ Variability of clinical features is characteristic of psoriasis, with some patients being affected with, for example, psoriatic arthritis and others with nail involvement or intense pruritus.⁵ Unlike many other common diseases, autoimmune disorders, such as psoriasis, typically strike individuals in the second to fourth decades of life, generating an immense burden on the public health system.

The etiology of psoriasis is thought to arise from the interplay between environmental and genetic factors; however, the specific underlying causes remain poorly understood (for review of our current understanding of

psoriasis pathogenesis, see Griffiths and Barker⁶). Several lifestyle factors have been associated with psoriasis, perhaps the strongest of which include smoking, alcohol use and obesity. Through family-based studies, psoriasis is known to be highly heritable. Linkage and association to psoriasis have been repeatedly demonstrated at the PSOR1 locus within the major histocompatibility complex on chromosome 6p21⁷, and there is mounting evidence that the major histocompatibility complex-class I human leukocyte antigen (HLA)-C variant *0602 is responsible for this strong major histocompatibility complex-linked effect.⁸

In an effort to identify genetic markers underlying the etiology of psoriasis, we have genotyped 25 215 gene-centric, putative functional single-nucleotide polymorphisms (SNPs) in disease-phenotype-based pooled DNA samples from a white North American case–control sample set (467 cases/500 controls), and attempted to replicate significant markers in two additional independent case–control sample sets (979 cases/922 controls) as previously described.⁹ This staged association study confirmed the predisposing effects in the major histocompatibility complex and identified novel psoriasis-risk variants in *IL12B* and *IL23R*. Here we report the identity of three novel susceptibility variants closely linked to *IL13*.

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Results and discussion

Three SNPs within 4 kb of one another in the *IL13* region in 5q31 met our significance criteria in the pooled-genotyping phase of our study: rs1800925 (located 1 kb 5' of the *IL13*-coding region), rs20541 (an *IL13* exon 4 missense SNP, Q144R) and rs848 (located within the 3' untranslated region of *IL13*). Figure 1 shows the location of these SNPs on chromosome 5q31, the neighboring genes and the linkage disequilibrium (LD) structure as determined from r^2 values obtained from the HapMap website (www.hapmap.org).

Individual genotyping of these three markers in all three sample sets showed each marker was consistent with Hardy–Weinberg equilibrium in both cases and controls of each sample set (Table 1). Minor allele frequencies for all three SNPs were nearly the same: approximately 18–20% in controls and decreasing to 14–17% in cases. For all three SNPs, combining P -values across the three sample sets using Fisher's combined probability method generated significant values for both allelic and genotypic tests (allelic: $P_{rs1800925} = 2.50E-04$, $P_{rs20541} = 0.0013$ and $P_{rs848} = 0.0017$; genotypic $P_{rs1800925} = 0.0029$, $P_{rs20541} = 0.0022$ and $P_{rs848} = 0.0027$). Notably, the 5' SNP, rs1800925, and the SNP in the 3' untranslated region, rs848, were significant ($P_{allelic} < 0.05$) in all three sample sets.

Pairwise LD values between these three associated SNPs were calculated, using the r^2 measure applied to all individuals in sample set 1 (data not shown). Two of the SNPs, rs20541 and rs848, were in very high LD ($r^2 = 0.98$). The remaining SNP, rs1800925, was not as highly correlated with the other two SNPs ($r^2 = 0.24$ for both comparisons).

Haplotype analyses can often reveal important *cis*-acting effects among alleles at closely linked sites. We used the program Haplo.Stats¹² to estimate haplotypes for these three SNPs and to perform a test of psoriasis association. This program calculates P -values for each haplotype and also a global P -value. Results for the three SNPs (rs1800925, rs20541 and rs848) showed four common haplotypes in each sample set (as expected from the LD patterns), but only the CCG haplotype (carrying the major allele at each site) was significant in all three studies (sample set 1, $P = 0.0288$; sample set 2, $P = 0.0177$; and sample set 3, $P = 0.0037$) (Table 2). A combined analysis showed association for this haplotype ($P_{comb} = 1.84E-04$) and also revealed a second associated haplotype, TTT ($P_{comb} = 7.05E-04$), which carries the minor allele at each site and exhibited protective effects. Overall, the susceptible haplotype, CCG, had a frequency of 72.1% in controls increasing to 76.5% in cases, whereas the protective haplotype, TTT, had a frequency of 11.5% in controls decreasing to 8.8% in cases. As the haplotype frequencies suggest, the effect sizes are modest with the risk CCG haplotype having a joint OR = 1.27 and the protective haplotype having a joint OR = 0.74. The remaining haplotypes did not show significant association.

Interleukin (IL)-13 is an immunoregulatory cytokine, produced primarily by activated Th2 cells, that exerts its effect by binding to its receptor and activating the STAT6-mediated signal-transduction pathway. IL-13 has been most prominently implicated as a critical mediator of an allergic inflammatory response, and genetic variants of *IL13* are known to be associated with susceptibility to asthma in humans.¹³ Genetic variation in *IL13* has also been associated with the risk of atopic

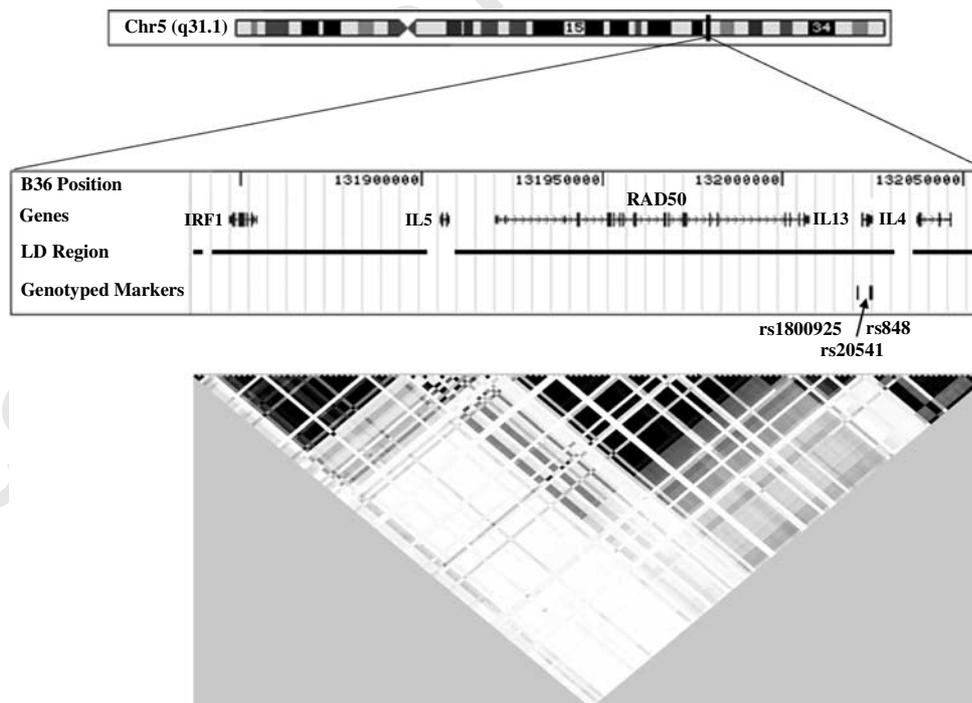


Figure 1 The physical map of the 5q31 region surrounding *IL13* including neighboring genes and LD patterns. The positions of the three SNPs genotyped are provided along with the location of the known genes in this region according to the UCSC Genome Browser build 36 (www.genome.ucsc.edu). The LD heatmap was obtained from the HapMap website (www.hapmap.org) and values were calculated for the pairwise r^2 statistic. LD, linkage disequilibrium.

Table 1 Association of IL13 SNPs with psoriasis

Marker (alleles and position)	Sample set	Status	Genotypes			MAF	HWE	Allelic		Genotypic
			11	12	22			OR (95% CI)	P	P
rs1800925 (T132020708C)	1	Case	338	112	11	0.145	0.577	0.76 (0.59–0.97)	0.0320	0.0781
		Control	303	139	14	0.183	0.756			
	2	Case	335	150	9	0.17	0.111			
		Control	316	158	21	0.202	0.782			
	3	Case	345	119	16	0.157	0.166			
		Control	272	131	21	0.204	0.373			
Combined							0.73 (0.57–0.93)	0.005	0.0205	
rs20541 (T132023863C)	1	Case	326	131	6	0.154	0.106	0.75 (0.59–0.95)	0.0198	0.0092
		Control	298	140	20	0.197	0.462			
	2	Case	339	143	12	0.169	0.63			
		Control	312	170	12	0.196	0.047			
	3	Case	341	131	8	0.153	0.376			
		Control	272	138	12	0.192	0.347			
Combined							0.76 (0.60–0.97)	0.0166	0.0416	
rs848 (T132024399G)	1	Case	323	132	6	0.156	0.076	0.74 (0.58–0.94)	0.0148	0.0113
		Control	294	145	19	0.2	0.884			
	2	Case	338	144	12	0.17	0.527			
		Control	308	171	13	0.2	0.067			
	3	Case	334	138	8	0.16	0.175			
		Control	269	141	13	0.197	0.358			
Combined							0.78 (0.61–0.99)	0.021	0.0503	
							0.78 (0.68–0.89)	0.0017	0.0027	

Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.

All three SNPs were individually genotyped using allele-specific real-time PCR as previously described⁹ (primer sequences are available on request). Positions for each SNP are given according to genomic contig NT_034772.5 (Entrez Nucleotide). The minor allele is listed first, followed by the position in National Center for Biotechnology Information Genome Build 36.2 and then the major allele. All samples were from white population of Northern Europe and are described in detail elsewhere⁹ (sample set 1, 467 cases/460 controls; sample set 2, 498 cases/498 controls; sample set 3, 481 cases/424 controls). Hardy–Weinberg exact *P*-values were calculated according to the formula of Weir.¹⁰ Fisher’s exact *P*-values were calculated for allelic data. Two-tailed *P*-values are presented for sample set 1; one-tailed *P*-values are given for sample sets 2 and 3. Combined *P*-values were calculated using a Fisher’s combined *P*-value, or omnibus method. Genotypic *P*-values for the individual sample sets were calculated using the William’s-corrected G test.¹¹ As with the allelic analysis, *P*-values for sample set 1 are two-tailed; *P*-values for sample sets 2 and 3 are one-tailed. Odds ratios were calculated for the minor allele. Combined or joint ORs were calculated using a Mantel–Haenszel common OR.

dermatitis in a Japanese study¹⁴ and although there has been no prior report on the role of IL-13 in psoriasis, altered expression of the two IL-13 receptor chains, IL4-R α and IL-13 α 1, has been observed in the skin of psoriasis patients.¹⁵ Thus, *IL13* represents a reasonable biological candidate gene for the development of psoriasis.

However, as the initial single-marker results were derived from a screen of a large number of SNPs, false-positive results due to selection bias from multiple testing must be considered. Given the extremely limited number of loci tested in the third sample set (*N* = three loci: *IL12B*, *IL23R* and *IL13*), our results argue against a false-positive error. Using the Dunn–Sidak method of calculating an experimentwise *P*-value¹¹ for the third sample set, analysis of data at the 5’ marker, rs1800925, shows that it retains statistical significance after adjusting for multiple testing (*P*_{adj} = 0.0199). In addition, although simulation results (not shown) indicate that these results could have been generated by a truly associated marker, there is still a reasonable chance that the observed results arose from a null model. Finally, previous analyses of population stratification in these sample sets suggested that the confounding impact on the genetic-association results was marginal.⁹

Three other gene regions with substantial and replicated association evidence, *HLA-C*, *IL12B* and *IL23R*, have been shown to affect the risk of psoriasis. Given the modest effect sizes of these and other gene variants associated with common diseases, multilocus estimates of differential risk are informative measures.¹⁶ In an effort to better elucidate the strength of the psoriasis-predisposing effects from all four loci, we estimated the probability of psoriasis given genotypes at *HLA-C* and the cytokine pathway genes *IL12B*, *IL23R* and *IL13*. Conditional independence between loci was assumed (three independent methods substantiated this assumption; see the legend of Figure 2) and we employed Bayes’ theorem for the calculation. Assuming a psoriasis prevalence of 3%, these calculations show that the differential risk between the very high- and low-risk multilocus genotype groups is over 11-fold (Figure 2; Supplementary Table 1). Greater than 10% of the general North American white population carry gene combinations that increase their risk of psoriasis to over 0.08, whereas 33% of the North American white population are at less than half the risk of disease compared to the general population.

The 5q31 region harboring *IL13* has been identified as a susceptibility locus for psoriasis in a previous family-

Table 2 Three-marker IL13 haplotypes

Haplotype	Sample set 1 (467 cases/460 controls; global P = 0.093)		Sample set 2 (498 cases/498 controls; global P = 0.151)		Sample set 3 (481 cases/424 controls; global P = 0.025)		Combined global P _{comb} = 0.014			
	No. (frequency)		No. (frequency)		No. (frequency)		P _{comb}			
	Case	Control	Case	Control	Case	Control	P	OR	OR _{MH}	
CCG	723 (0.777)	677 (0.736)	749 (0.758)	710 (0.717)	739 (0.77)	606 (0.714)	0.0037	1.34	1.88E-04	1.27
TTT	74 (0.079)	108 (0.117)	97 (0.098)	115 (0.116)	84 (0.087)	96 (0.113)	0.0213	0.75	7.05E-04	0.74
TCG	61 (0.066)	61 (0.066)	70 (0.071)	83 (0.084)	66 (0.069)	72 (0.085)	0.0999	0.80	0.201	0.86
CTT	69 (0.074)	72 (0.079)	69 (0.07)	80 (0.081)	62 (0.065)	66 (0.078)	0.1545	0.82	0.251	0.87
Other	3 (0.003)	3 (0.003)	3 (0.003)	2 (0.002)	9 (0.01)	8 (0.01)	NC	NC	NC	NC

Abbreviations: OR, odds ratio; SNP, single-nucleotide polymorphism.

The HaploStats package¹² was used to estimate haplotype frequencies from unphased data, treating cases and controls separately, and to test for association between haplotypes and disease status. The order of SNPs is rs1800925-rs20541-rs848. Global *P*-values were also calculated and all *P*-values were adjusted for haplotype estimation error. Two-tailed *P*-values are presented for sample set 1; one-tailed *P*-values are presented for sample sets 2 and 3. *P*-values were combined using Fisher's combined probability method. Mantel-Haenszel joint ORs (OR_{MH}) were calculated for each haplotype.

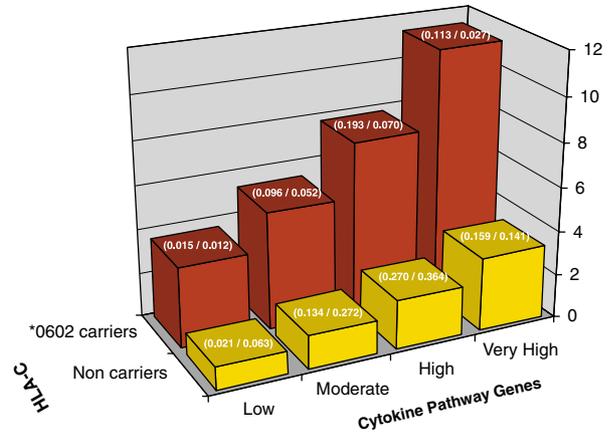


Figure 2 Human leukocyte antigen-cytokine pathway psoriasis relative risk plot. The scaled relative risk of each multilocus genotype combination is graphed using the data from sample set 1. *HLA-C* genotypes were determined as previously described⁹ and aggregated into *0602 carriers and noncarriers. Psoriasis-associated diplotypes at *IL12B* (rs3212227 and rs6887695) and *IL23R* (rs753511 and rs11209026)⁹ were combined with genotypes at rs1800925 (5' of *IL13*) and partitioned into four cytokine pathway categories: very high risk, high risk, moderate risk and low risk, as described in Supplementary Table 1. Psoriasis prevalence of 0.03 was assumed. Conditional independence between the loci was also assumed (three separate analyses—a genotype-based squared correlation coefficient, the multifactor dimensionality reduction (MDR) program¹⁷ and a Monte Carlo simulation—substantiated this assumption and provided no evidence for significant interaction effects between these markers). Expected frequencies of the multilocus genotype combinations are presented for both affected and unaffected populations and are listed above each bar (affected/unaffected). The relative risk estimates were scaled with respect to the lowest risk category, which was set at 1.00.

based linkage study of psoriasis,¹⁸ as well as for other inflammatory conditions including Crohn's disease^{19–22} and bronchial hyperresponsiveness/atopy/asthma phenotypes.^{13,23,24} It is becoming increasingly clear that the same genes can be involved in the molecular pathophysiology of several autoimmune diseases. Variants in *CARD15/NOD2* are associated with Crohn's disease as well as Blau syndrome^{25,26} whereas the same missense SNP in the intracellular phosphatase, *PTPN22*, is associated with multiple autoimmune diseases including rheumatoid arthritis and type I diabetes.^{27,28} The link between psoriasis and Crohn's disease appears to be particularly strong, as evidenced by (i) a similar aberrant response in T-helper cells,²⁹ (ii) familial clustering of the two diseases²⁹ and (iii) the observation that the same allele in the *IL23R* SNP, rs11209026, is associated with risk for both diseases.^{9,30} Genes contributing to asthma and psoriasis risk, such as *ADAM33*, also appear to overlap.³¹

It should be stressed, however, that 5q31 region contains several other cytokine and immunoregulatory genes such as *IL3*, *IL4*, *IL5*, *CSF2* and *IRF1* that span ~700 kbp on chromosome 5q. More importantly, this region shows extensive LD, where haplotype blocks of limited diversity are interrelated.³² Consequently, in studies of other diseases showing association with the 5q31 region, multiple genetic markers across this region show nearly equivalent statistical significance,³³ rendering it difficult to identify the true disease-associated gene(s). As for the *IL13* polymorphisms identified in this

report, they share moderate correlation ($r^2 > 0.2$) with multiple SNPs in these other immune-related genes (www.hapmap.org). Thus, it remains to be determined whether other immune-related gene markers in the 5q31 region are associated with the risk of psoriasis in our sample sets. In addition, as several unrelated genetic variants in a locus may contribute to disease susceptibility, as is the case for variants in *CARD15/NOD2* and Crohn's disease,²⁵ it is imperative that comprehensive association testing of all tagging markers in this region be carried out to determine whether other polymorphisms in *IL13* or other genes influence the risk of psoriasis.

In conclusion, we have presented results of three *IL13* SNPs exhibiting suggestive psoriasis-association patterns. These variants were found in the same multi-tiered-association study, which led to the identification of the psoriasis-associated genes *IL12B* and *IL23R*,⁹ independently verified by other investigators.³⁴ A common susceptibility haplotype, CCG, carried by 92% of controls produced a consistent, albeit moderate effect (joint OR = 1.27) that achieved statistical significance ($P_{\text{comb}} = 1.88E-04$). Conversely, a less-frequent haplotype, TTT, generated protective effects in our study (joint OR = 0.74) with fairly similar significance ($P_{\text{comb}} = 7.05E-04$). Further, combining the genotypic effects at the SNP directly 5' of *IL13* (rs1800925) with previously reported susceptibility variants at *HLA-C*, *IL12B* and *IL23R* demonstrates a range of psoriasis relative risk from 0.34, increasing 11-fold to 3.83. This report provides the foundation for additional genetic studies and focused functional inquiries necessary to fully characterize the 5q31 involvement in psoriasis.

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Supplementary Information accompanies the paper on Genes and Immunity website (<http://www.nature.com/gene>)