

Evidence to support *IL-13* as a risk locus for psoriatic arthritis but not psoriasis vulgaris

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ABSTRACT

Objective There is great interest in the identification of genetic factors that differentiate psoriatic arthritis (PsA) from psoriasis vulgaris (PsV), as such discoveries could lead to the identification of distinct underlying aetiological pathways. Recent studies identified single nucleotide polymorphisms (SNPs) in the interleukin 13 (*IL-13*) gene region as risk factors for PsV. Further investigations in one of these studies found the effect to be primarily restricted to PsA, thus suggesting the discovery of a specific genetic risk factor for PsA. Given this intriguing evidence, association to this gene was investigated in large collections of PsA and PsV patients and healthy controls.

Methods Two SNPs (rs20541 and rs1800925) mapping to the *IL-13* gene were genotyped in 1057 PsA and 778 type I PsV patients using the Sequenom genotyping platform. Genotype frequencies were compared to those of 5575 healthy controls. Additional analyses were performed in phenotypic subgroups of PsA (type I or II PsV and in those seronegative for rheumatoid factor).

Results Both SNPs were found to be highly associated with susceptibility to PsA (rs1800925 $p_{trend} = 6.1 \times 10^{-5}$ OR 1.33, rs20541 $p_{trend} = 8.0 \times 10^{-4}$ OR 1.27), but neither SNP was significantly associated with susceptibility to PsV.

Conclusions This study confirms that the effect of *IL-13* risk locus is specific for PsA, thus highlighting a key biological pathway that differentiates PsA from PsV. The identification of markers that differentiate the two diseases raises the possibility in future of allowing screening of PsV patients to identify those at risk of developing PsA.

INTRODUCTION

Psoriasis vulgaris (PsV) is a chronic inflammatory skin disease in which up to 30% of subjects exhibit additional inflammatory articular disease.¹ This has led to psoriatic arthritis (PsA) being recognised as a distinct clinical entity. Both conditions are considered to be complex diseases that are influenced by environmental and genetic factors. The genetic liability towards the susceptibility to PsA, determined using the sibling recurrence risk (λ_s), is estimated to be much higher ($\lambda_s > 30$) than that of PsV ($\lambda_s = 8-12$).²⁻⁴ These differences are suggestive of additional genetic susceptibility loci for PsA, although it is highly likely that environmental factors also contribute to these differences.⁵

A number of genetic risk loci have now been identified that are associated to both diseases; for example, variants in the *HLA-Cw6*, *IL-12B* and *IL-23R* regions.^{6,7} Interestingly, differences in the genetic basis of the two diseases have been identified; the association to *HLA-Cw6* appears to be stronger for PsV than PsA (OR of 6.9 and 5.0 respectively).⁶ In addition, a German study found variants at the *LCE* locus to be associated with PsV, but not PsA.⁸ However, a subsequent study in a British population found single nucleotide polymorphisms (SNPs) in this region to be associated with PsA.⁹ Given the overlap of known genetic risk factors, and the observed differences of λ_s , there is great interest in the identification of risk factors that are specific for PsA. Once identified, if indeed they do exist, these specific risk factors could highlight aetiological pathways that predispose to the development of PsA and potentially lead to a better understanding of why some patients with PsV develop an inflammatory arthritis.

A number of recent studies investigating the genetic susceptibility to PsV identified association to SNPs on chromosome 5q31.^{10,11} This region is rich in immune-related genes and contains, among others, a cluster of four interleukin (*IL*) genes. There is also prior evidence that the region harbours risk loci for other common autoimmune or inflammatory diseases, including Crohn's disease.^{12,13} The first of the PsV studies was a multitiered case-control study investigating 25 215 gene-centric SNPs, which found association to multiple SNPs in, or in close proximity to, the *IL-13* gene.¹⁰ This study identified association to three SNPs, rs1800925 (5' upstream), rs20541 (exonic missense, Q144R) and rs848 (3' untranslated region), where carriage of the common alleles from any of these SNPs was found to increase the risk of PsV. The second study was a large genome-wide association study (GWAS) in samples of European ancestry, which identified and replicated association to the exonic SNP; rs20541.¹¹ A further large GWAS reported only modest association to rs20541 ($p = 0.023$).¹⁴ All of these studies contained significant proportions of patients identified as also having PsA. Further investigation of this effect in one of the studies found it to be primarily restricted to those individuals with PsA, thus suggesting the discovery of a potential specific genetic risk factor for PsA.¹⁵ However, no such effect was detected in the second study, as association was detected to both diseases, and the third



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study did not attempt a PsA-specific analysis.^{11–14} Furthermore, there is suggestive evidence from a Chinese study supporting the hypothesis that this region is PsA-specific.¹⁶

Given this intriguing suggestion of a PsA-specific effect at the *IL-13* locus, the association to these SNPs was investigated in large sample collections of PsA and PsV patient samples and allele and genotype frequencies were compared to a common set of healthy controls for which genotype data were already available.

METHODS

Patient samples

Caucasian PsA patients were recruited from three UK rheumatology centres and one centre in Ireland, providing a total of 1057 genomic DNA samples (885 UK and 172 Ireland), the details of which have been described previously.^{17–19} PsA classification was defined as the presence of both psoriasis and inflammatory arthritis, regardless of rheumatoid factor status and all had peripheral arthritis. The majority of samples satisfied the CASPAR (CIASsification criteria for Psoriatic ARthritis) classification system, although some were collected prior to the introduction of this classification system.²⁰ This study was approved by the North West Multicentre Research Ethics Committee (MREC 99/8/84), and all subjects provided informed consent.

A total of 778 unrelated patients with type I psoriasis (age of disease onset ≤ 40 years) were recruited from the Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester, UK. All patients gave written informed consent and the study was approved by the Salford and Trafford Local Research Ethics Committee.

SNP selection

Two of the three previously identified risk SNPs, rs1800925 and rs20541, were selected for genotyping. The remaining SNP, rs848, was not included due to very high linkage disequilibrium (LD) with rs20541 ($D' = 1.00$, $r^2 = 0.96$ CEU HapMap release 22).

Control samples

Data for both SNPs were available for healthy controls from the Wellcome Trust Case-Control Consortium 2 project (<http://www.wtccc.org.uk>). This dataset consists of samples from the 1958 British Birth Cohort and the UK Blood Service Collection genotyped on the Illumina Human1M-Duo. In addition, 375 control samples were available from Ireland.

Genotyping

SNP genotyping of the PsA, PsV and Ireland control samples was performed using Sequenom's MassARRAY system (San Diego,

California, USA) according to the manufacturers' specifications for the iPLEX chemistry using 10 ng of genomic DNA. Genotype cluster plots were evaluated prior to analysis to ensure satisfactory assay performance.

Statistical analysis

Data handling, quality control, association and haplotype analyses were performed using the PLINK software package.²¹ The dataset was filtered to exclude samples and SNPs with a missing data rate $>10\%$, in conjunction with 50 other SNPs in the same sample collections. Test statistics were calculated for deviation from Hardy–Weinberg equilibrium (HWE) using an exact test, the Cochran–Armitage trend test, OR (including 95% CI) and LD (r^2 and D'). Multiple logistic regression was performed to test for independent effects of the two SNPs using Stata (version 10.1). The primary PsA analysis consisted of the combined analysis of UK and Ireland cases and controls as a single population. The PsV analysis compared the UK cases to the UK controls only. In addition, the genotypes of both SNPs were directly compared between the two disease groups using the Armitage test for trend.

Subphenotype analysis was performed within the PsA dataset based on, first, the age at onset of psoriasis (type I psoriasis has an onset <40 years of age, whereas type II psoriasis is defined as an onset >40 years of age) and, second, seronegativity for rheumatoid factor in an attempt to exclude those patients who may have PsV and coexistent rheumatoid arthritis. All subphenotype analyses were performed in UK samples only, where age at onset was available for 784 patients and rheumatoid factor status was available for 480 patients. Each subphenotype group was compared against UK controls and evidence for association was tested using the Armitage test for trend. No information was available regarding the extent of psoriasis or the presence of spondyloarthritis.

In the interests of exploring whether heterogeneity exists between the UK and Ireland PsA datasets and the potential confounding it may introduce, data from each population were next analysed independently. This was followed by joint analysis using an inverse-variance meta-analysis under the assumption of fixed effects. Allelic heterogeneity between the two groups was estimated using the Cochran Q and I^2 statistics.

RESULTS

Genotyping

Both SNPs demonstrated satisfactory clustering of genotypes with clear and distinct clusters. Following exclusion of samples failing the minimum threshold for missing data, there were 937 PsA cases, 743 type I PsV cases and 5533 healthy controls (5199 UK and 334 Ireland), with a genotyping success rate of $>99\%$ in the remaining samples.

Table 1 Summary of genotype and association results for the two SNPs mapping to the *IL-13* gene vicinity for UK/Ireland cases and controls

SNP	Genotype	Controls (n = 5533)			PsA cases (n = 937)			
		Count/Frq	RAF	HWE	Count/Frq	RAF	ptrend	OR (CI)
rs1800925	CC	3715 (67.1)			690 (73.6)			1.33 (1.16 to 1.53)
	CT	1619 (29.3)	0.82	0.82	224 (23.9)	0.86	6.1×10^{-5}	
	TT	180 (3.3)			20 (2.1)			
rs20541	GG	3749 (67.8)			679 (72.5)			1.27 (1.10 to 1.45)
	GA	1604 (29.0)	0.82	0.82	234 (25.0)	0.86	8.0×10^{-4}	
	AA	175 (3.2)			18 (1.9)			

Genotype counts are presented with frequencies in parentheses.

HWE, Hardy–Weinberg equilibrium (reported in controls only); RAF, risk allele frequency.

Table 2 Summary of genotype and association results for the two SNPs mapping to the *IL-13* gene vicinity for PsV and UK controls samples

SNP	Genotype	Controls (n = 5199)			PsV cases (n = 743)			
		Count/Frq	RAF	HWE	Count/Frq	RAF	ptrend	OR (CI)
rs1800925	CC	3480 (66.9)	0.82	0.96	511 (68.8)	0.83	0.34	1.07 (0.92 to 1.24)
	CT	1531 (29.4)			211 (28.4)			
	TT	169 (3.3)			21 (2.8)			
rs20541	GG	3506 (67.4)	0.82	0.85	498 (67.0)	0.82	0.72	0.97 (0.85 to 1.12)
	GA	1521 (29.3)			217 (29.2)			
	AA	168 (3.2)			27 (3.6)			

Genotype counts are presented with frequencies in parentheses.

HWE, Hardy-Weinberg equilibrium (reported in controls only); n, number; RAF, risk allele frequency.

Table 3 Summary of subphenotype analysis performed in the UK PsA and controls samples

SNP	Genotype	Type I psoriasis (n = 496)			Type II psoriasis (n = 169)			Seronegative (n = 313)		
		Count/Frq	ptrend	OR (CI)	Count/Frq	ptrend	OR (CI)	Count/Frq	ptrend	OR (CI)
rs1800925	CC	345 (72.8)	0.0096	1.28 (1.06 to 1.54)	121 (74.2)	0.05	1.37 (1.00 to 1.89)	222 (74.0)	0.017	1.33 (1.05 to 1.69)
	CT	119 (25.1)			39 (23.9)			71 (23.7)		
	TT	10 (2.1)			3 (1.8)			7 (2.3)		
rs20541	GG	347 (73.1)	0.0077	1.29 (1.07 to 1.56)	116 (7.20)	0.13	1.27 (0.93 to 1.74)	221 (74.2)	0.008	1.38 (1.09 to 1.76)
	GA	119 (25.1)			43 (26.7)			73 (24.5)		
	AA	9 (1.9)			2 (1.2)			4 (1.3)		

Genotype counts are presented with frequencies in parentheses.

n, number.

Statistical analysis

Neither SNP demonstrated deviation from HWE in the combined control group. Both SNPs demonstrated similar genotype frequencies; however, only moderate LD was observed ($r^2 = 0.23$, $D' = 0.49$). Significant association with susceptibility to PsA was found for both SNPs (rs1800925 p -trend = 6.1×10^{-5} , rs20541 p -trend = 8.0×10^{-4}), where the major allele increased the risk of disease susceptibility (table 1). No significant association was found to type I PsV with either SNP (table 2). Direct comparison of the two disease groups demonstrated significant differences for both SNPs (rs1800925 $p = 0.015$; rs20541 $p = 0.004$).

Association to rs1800925 remained significant after adjusting for rs20541 ($p = 0.0065$; OR 0.80 (0.69 to 0.94)) in the multiple logistic model. However, association to rs20541 did not reach significant statistical significance on adjustment for rs1800925 genotypes ($p = 0.10$; OR 0.88 (0.75 to 1.03)). The haplotype formed by the two risk alleles (CG) was significantly enriched in cases compared to controls (79.4% vs 74.6%) and is more significantly associated than single-point analysis of either SNP ($p = 7.55 \times 10^{-6}$; OR 1.32) (supplementary table 2).

Finally, the association was investigated within phenotypic and population-based subgroups within the PsA samples. Both SNPs were found to be associated in the type I and seronegative subgroups (table 3). There were no qualitative differences between the effect sizes observed in any of the subgroups, although the statistical evidence for association was weakened due to the smaller sample sizes.

Both SNPs remained associated upon independent analysis of the UK PsA dataset, with effect sizes similar to those observed in the primary analysis, and no significant deviation from HWE in the controls (supplementary table 1). Only rs1800925 was significantly associated in the Ireland dataset. The failure to detect association to rs20541 may well be attributable to decreased power due to the small sample numbers in this dataset. Neither SNP significantly deviated from HWE in the Ireland controls. Effect estimates for the meta-analysis were consistent with those reported for the primary analysis, with no evidence for allelic heterogeneity between the two populations (rs1800925

$Q = 0.22$, $I^2 = 32.2$; rs20541 $Q = 0.68$, $I^2 = 0$) (supplementary table 1).

DISCUSSION

The results presented here confirm the findings of Duffin *et al*, who described association of the *IL-13* locus with PsA, but not with PsV. This represents one of the first replicated examples of a differential association between these two closely related phenotypes.

Although the present results support the observation made by Duffin *et al* that the effect of rs1800925 is limited to PsA,¹⁵ they contradict the findings reported by Nair *et al*.¹¹ That PsV GWAS contained a significant proportion of PsA cases in the primary scan and validation stages, where upon subgroup analysis there was significant association to both PsA and PsV.

The discrepancy in findings could exist for a number of reasons; first, it could result from a false-negative (type II error) in the PsV arm of the present study. However, the study has greater than 80% power to detect an effect of similar magnitude to that reported by Nair *et al*. A type II error is therefore unlikely, but not impossible. Second, it is conceivable that a false-positive (type I error) occurred in the PsV arm of the study performed by Nair *et al*. Although this is a well-powered study, its samples are drawn from multiple populations (USA, Canada, Germany and France) and collections (contributions from nine research groups) that may well lead to population stratification and confound results. In support of this possibility, it is interesting to note that the control allele frequencies across the nine individual cohorts genotyped varied from 0.76 to 0.81 for the rs20541 and rs848 SNPs. Indeed, the paper does not report association to rs1800925, the main effect observed in this study and that performed by Duffin *et al*.^{11 15} The effect of possible confounding may be further exacerbated by the presence of unidentified PsA cases as most of the PsV patients included were not reported as having had a rheumatological assessment. However, in spite of these limitations, this remains the best powered study to date and, as such, its results should not be dismissed casually. On the contrary, the authors should

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be commended for organising a consortium with sufficient power to detect novel susceptibility loci. In light of the contradicting results, further studies in independent sample collections will be required to validate the differential association of the locus with PsA but not PsV.

The presence of unclassified PsA patients within a PsV sample collection represents a significant source of confounding for studies attempting to identify PsA-specific risk loci. This could lead to false-positive associations in PsV samples at PsA specific loci and potentially invalidate any attempts to identify such loci. Such studies would greatly benefit from a PsV sample collection screened by a rheumatologist to exclude PsA as a comparator group. In the study presented here, the PsV samples were not screened by a rheumatologist; however, the lack of association with PsV would suggest that only a limited proportion of these samples have unclassified PsA.

From the data presented here and in other published studies, it is unclear as to which variant is causal or if there are multiple independent effects. The present results confirm a strong association to rs1800925; however, the results for an independent effect at rs20541 are inconclusive. Only rs1800925 remained significant in the multiple logistic model, suggesting that this represents the main effect. However, an independent effect at rs20541 cannot be ruled out when the effect estimates are taken into consideration, indeed the data are suggestive of independent effect at this locus. It is likely that a statistically significant association to rs20541 was not achieved in this model due to a lack of power. Haplotype analysis found the CG haplotype to be more associated than either SNP individually. However, the haplotype results should be considered with caution given the observed evidence for historical recombination between the two SNPs ($D' = 0.49$). Larger sample sizes than available for this study would be required to robustly confirm or rule out any potential independent effect for rs20541.

The three SNPs implicated to date each have potential functional impact: rs20541 is a missense SNP that maps to exon 4 of *IL-13* and results in the substitution of a glycine for arginine (Q144R), rs1800925 maps to 1 kb of the 5' of the coding region and rs848 is located within the 3' untranslated region. However, it is possible that these SNPs could tag an unknown causal variant, therefore fine mapping will be required to identify a suitable short-list of candidate SNPs to take forward for functional evaluation.

In conclusion, the present study supports the PsA-specific association to SNPs at chromosome 5q31 and potentially highlights a key pathway that is distinct for joint inflammation in psoriatic disease.

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