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ORIGINAL INVESTIGATION

Sequence variants in the genes for the interleukin-23 receptor (*IL23R*) and its ligand (*IL12B*) confer protection against psoriasis

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Abstract Psoriasis is an inflammatory skin disorder that is inherited as a multifactorial trait. Genetic analyses have repeatedly identified a primary disease susceptibility locus lying within the major histocompatibility complex (MHC), on chromosome 6p21. A small number of non-MHC susceptibility loci have also been identified. These regions tend to overlap with susceptibility intervals for Crohn's disease and atopic dermatitis, suggesting the possibility that genetic variants affecting inflammatory pathways may contribute to the pathogenesis of multiple disorders. Here, we report a genetic analysis of the interleukin 23 receptor gene (*IL23R*), which was recently identified as a susceptibility determinant for Crohn's disease. We initially examined the results of a whole-genome association scan, carried out on 318 cases and 288 controls. We observed a significant increase of a non-synonymous substitution (p.Arg381Gln) among controls ($P = 0.00036$). We validated this finding by extending our cohort to include a further 519 cases and 528 controls. In the overall sample, the frequency of the 381Gln allele was 3.6% in cases and 7% in controls, yielding a P value of 0.00014. Next, we examined genetic variation at the *IL12RB1*, *IL23A* and *IL12B* genes, respectively, encoding the second subunit of the IL23R receptor and the two subunits of its ligand. This analysis identified independent associations for *IL12B* SNPs rs10045431 (P value for the extended dataset = 0.0001) and rs3212227 ($P = 0.036$). Altogether, these findings indicate that genes participating in IL23 signalling play a significant role in the pathogenesis of chronic epithelial inflammation.

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Introduction

Psoriasis is a chronic skin disorder, characterized by the infiltration of inflammatory effector cells and cytokines into the dermis and the epidermis (Nickoloff and Nestle 2004; Smith and Barker 2006). Familial recurrence of the disorder is well established and psoriasis has long been considered a multifactorial trait (Bowcock and Cookson 2004). Linkage and association analyses have provided overwhelming support for a major susceptibility locus, lying within the major histocompatibility complex (MHC) on chromosome 6p21 (Capon et al. 2002). Conversely, the characterization of non-MHC disease loci has been problematic, owing to the small effects of the underlying genetic variants. Genome-wide scans have mapped no less than nine non-MHC psoriasis susceptibility loci, but only a fraction of these have been validated in independent cohorts (Capon

et al. 2004b). High-resolution genetic analyses have identified putative susceptibility alleles for the PSORS2 locus on chromosome 17q25, but these findings have not been replicated in follow-up studies (Capon et al. 2004a; Helms et al. 2003; Huffmeier et al. 2005; Stuart et al. 2006).

Non-MHC psoriasis susceptibility loci tend to overlap with disease regions for other inflammatory disorders, especially atopic dermatitis (Cookson et al. 2001) and inflammatory bowel disease (Lee et al. 2000; Nair et al. 1997). These observations suggest that genetic variants affecting inflammatory pathways may contribute to the pathogenesis of clinically distinct disorders. This hypothesis is supported by the observation of multiple disease association for genes such as *PTPN22* (Bottini et al. 2006) and *CTLA4* (Ueda et al. 2003), which are involved in inflammatory and autoimmune responses.

Here, we report a detailed analysis of the interleukin-23 receptor (*IL23R)* gene locus, which has been recently identified as a susceptibility gene for Crohn's disease (Duerr et al. 2006). We describe a significant increase for the *IL23R* p.Arg381Gln variant among controls, a finding that we documented in two independently ascertained datasets. We also report a significant association for SNPs rs10045431 and rs3212227, mapping to the *IL12B* gene, which encodes one of the subunits of the IL23 receptor ligand.

Methods

Subjects

The whole-genome association (WGA) scan was carried out on 318 British patients of North-European descent (208 males and 110 females; average age 52.1 years; range 23–86 years) and 288 ethnically matched and unrelated controls (144 males and 144 females; age not known). All patients were recruited at St John's Institute of Dermatology (London, UK), following an examination by an expert clinician (JNB). The control individuals were obtained from the European Collection of Cell Cultures (ECACC; http://www.ecacc.org.uk) Human Random Control Panel, a cohort of healthy Caucasian blood donors whose parents and grand-parents were born in the UK.

The replication sample included 519 British patients of North-European descent (220 males and 299 females; average age 44.1 years; range 9–91 years) and 528 unrelated controls (264 males and 264 females; all 49 years old). One hundred and seventy one unrelated patients were sampled from a previously described set of multiplex pedigrees (Trembath et al. 1997). The remaining cases were recruited at St John's Institute of Dermatology and Glasgow Western Infirmary. The 528 controls were part of the 1958 Birth Cohort, a nationally representative dataset, which includes individuals born in 1958, in England, Wales and Scotland (Power and Elliott 2006). All patients and controls gave their informed consent to use of their DNA for genetic epidemiological analyses. This study was approved by the Guy's and St Thomas' Hospitals Ethics Committee of Kings College, London.

Genotyping

The WGA scan was carried out on case and control DNA pools, generated as previously described (Steer et al. 2007). Briefly, DNA was diluted to 50 ng/μl based on Quanti-iT Picogreen (Invitrogen) quantitation. The Picogreen analysis was repeated on the diluted DNA and concentrations were adjusted based on these results. This process was repeated until all samples consistently measured 50 ng/μl. Four replicates of each pool were prepared and hybridized to HumanHap300 BeadChips (Illumina, San Diego, USA), according to the manufacturer protocol. Estimates of allele frequencies were obtained based on the hybridization intensities from the two probes corresponding to each SNP allele. The Illumina genotype calling algorithm was modified as previously described (Steer et al. 2007), in order to maximize its accuracy in the context of pooled DNA genotyping.

In the follow up to the whole-genome scan, SNPs rs1004819, rs7517847, rs10489629, rs2201841, rs7709212 and rs3212227 were typed using the Applied Biosystems TaqMan assay, according to the manufacturer protocol. SNPs p.Arg381Gln, rs1343151 and rs10045431 were genotyped by direct sequencing, using the BigDye 3.1 kit (Applied Biosystems).

Direct sequencing

Primers were designed to amplify and sequence all *IL23R* coding exons. Purified PCR products (primer sequences and cycling conditions available on request) were sequenced using the BigDye 3.1 kit and loaded on an ABI 3730*xl* automated sequencer (Applied Biosystems). Nucleotide changes were detected by visual inspection of chromatograms.

Statistical analyses

The differences in allele frequencies between case and control pools were expressed in terms of z-score, a statistic incorporating errors due to imprecise measurements within a DNA pool (Steer et al. 2007). Under the null hypothesis of no association, the z-score is normally distributed, with a mean value of zero and variance of one. Thus, the normal distribution of the z statistic can be used to convert z-scores into P values. For the purpose of this study, a z-score >2.4 (corresponding to $P < 0.01$) was considered as statistically

significant evidence for association. To assess the presence of population stratification within the WGA dataset, we used software written in-house to analyze the observed *z*-score distribution. Our program computes the value of *k*, a multiplier that is used to adjust the *z*-score distribution, in the presence of population stratification. If cases and controls are drawn from the same population, the *z*-score distribution is very close to normality and the value of *k* approaches 1.0 (e.g. when two pools collected from US populations of North-European descent are compared, $k = 0.8$). When cases and controls are drawn from ethnically different populations the *z*-score distribution is much wider than expected and adjusting to normality requires a *k* value that is somewhat different from 1.0 (e.g. when pools collected from North-Europeans and Ashkenazi Jews are compared $k = 0.15$). Thus, the *k* value can be used to measure the presence of population stratification, within a case-control sample.

SNP haplotypes were derived from genotype data, using PHASE 2.1 (Stephens and Scheet 2005). Differences in allele and haplotype frequencies between individually genotyped cases and controls were assessed using a χ^2 test with one degree of freedom. The resulting *P* values were corrected for the number of single markers ($n = 9$) and SNP haplotypes ($n = 4$) that were independently tested. Genotype-conditioned analyses of *IL12B* markers were carried out using the UNPHASED software, which implements a test of equality of odd ratios for haplotypes that are identical at a conditioning locus (Dudbridge 2003).

Results

IL23R association analysis

In the initial phase of this study, we assessed the presence of association at the *IL23R* locus by examining the raw data from a stage I whole-genome association (WGA) scan, carried out on pools of case ($n = 318$) and control ($n = 288$) DNAs. The scan generated genotypes for 99% of the analysed markers ($n = 313{,}830$ SNPs). The distribution of the resulting *z*-scores was close to normality, matching the pattern expected for two samples drawn from the same population ($k = 0.81$). Importantly, this demonstrates the absence of stratification within the WGA case-control sample.

As expected, the most significant association scores generated by the scan corresponded to MHC markers. The highest ranking SNP was rs3134792 ($z = 6.08$; $P = 3.77 \times 10^{-9}$), mapping centromeric to HLA-C. In the *IL23R* region, the scan generated allele frequencies for 17 tag SNPs. We observed evidence for disease association for two markers: rs11465804 in intron 8 ($z = 3.1$; $P = 0.0009$; rank 722) and rs11209026 in exon 9 ($z = 2.9$; $P = 0.002$; rank 1,311). Of note, rs11209026 is a non-synonymous SNP, resulting in an Arg to Gln substitution (p.Arg381Gln).

To validate the association with *IL23R* markers, we individually genotyped the case and control samples from the WGA pools for the p.Arg381Gln substitution and five neighbouring SNPs (rs1004819, rs7517847, rs10489629, rs2201841, rs1343151). The disease associated SNP in intron 8 (rs11465804) was not further genotyped, since we found that it is in high linkage disequilibrium with p.Arg381Gln ($D' = 1$; $r^2 = 0.9$). Individual genotyping of case and control samples showed that all examined markers were in Hardy–Weinberg equilibrium ($P > 0.05$). Genetic analyses confirmed the association with the p.Arg381Gln substitution, with the Gln allele showing a significant increase among control subjects ($\chi^2 = 16.8$; after correction for multiple testing, $P_c = 0.00036$). None of the neighbouring SNPs showed any evidence for disease association (Table 1).

The association with the p.Arg381Gln variant was subsequently validated by expanding our dataset to include a further 519 cases and 528 controls. In the combined sample, including a total of 837 cases and 816 controls, the association with p.Arg381Gln yielded a P_c value of 0.00014 (OR 0.49; 95% CI 0.35–0.68).

To investigate the possibility that the association may be secondary to linkage disequilibrium with other *IL23R*

Table 1 Association analysis of *IL23R* SNPs

Pools *z*-score		Minor allele frequency (allele counts)		Odd ratio	P_c value
		Individual cases	Individual controls		
rs1004819	1.1	0.33 (204/610)	0.32 (184/572)	1.05	N/S
rs7517847	1.2	0.44 (282/636)	0.43 (248/574)	0.96	N/S
rs10489629	0.66	0.45 (277/620)	0.45 (254/570)	1.00	N/S
rs2201841	0.65	0.35 (218/624)	0.32 (186/574)	1.10	N/S
rs1343151	2.0	0.34 (199/624)	0.33 (187/560)	0.93	N/S
p.Arg381Gln (WGA)	2.9	0.022 (14/620)	0.072 (41/562)	0.29	0.00036
p.Arg381Gln (replication)	–	0.045 (45/996)	0.069 (72/1034)	0.63	0.17
p.Arg381Gln (combined)	–	0.036 (59/1616)	0.07 (113/1596)	0.49	0.00014

N/S not significant

variants, we re-sequenced the gene coding exons in 16 patients carrying the p.Arg381Gln substitution. This analysis did not identify any coding variant that was in linkage disequilibrium with the 381Gln allele.

Association analysis of the *IL12RB1*, *IL23A* and *IL12B* genes

Having established an association with an *IL23R* sequence variant, we proceeded to investigate the other members of the interleukin-23 receptor complex. We examined the *IL12RB1*, *IL23A* and *IL12B* genes, which respectively encode the second subunit of the IL23R receptor and the two subunits of its ligand. The whole-genome association scan provided us with allele frequencies for 29 tag SNPs spanning these three genes (15 markers in *IL12RB1*, 2 in *IL23A* and 12 in *IL12B*). None of the *IL12RB1* and *IL23A* markers showed any evidence for association. Conversely, SNP rs7709212, which maps 6 kb upstream of the *IL12B* coding region, yielded a *z*-score of 3.2 ($P = 0.0007$; rank 528). An examination of rs7709212 neighbouring markers revealed a *z*-score of 3.5 for SNP rs10045431 ($P = 0.0002$; rank 197), lying 60 kb upstream of *IL12B*. Individual genotyping of the entire data set confirmed the presence of an association with both rs7709212 ($\chi^2 = 11.5$; $P_c = 0.006$; OR = 0.76; 95% CI 0.65–0.89) and rs10045431 ($\chi^2 = 18.8$; $P_c = 0.0001$; OR = 1.41; 95% CI 1.21–1.64) (Table 2).

During the late stages of our study, Cargill et al. reported a significant association between psoriasis and *IL12B* marker rs3212227 (Cargill et al. 2007). We analysed this SNP in our dataset and were able to confirm a marginal protective effect for the rs3212227 locus ($\chi^2 = 8.24$; $P_c = 0.036$; OR = 0.76; 95% CI 0.63–0.92).

All examined markers were found to be in Hardy–Weinberg equilibrium ($P > 0.05$).

We carried out haplotype-based association analyses, using PHASE. This showed that the rs7709212 disease associated allele is found on both risk-bearing and neutral haplotypes (Table 3). Conversely the risk allele of marker rs10045431 is only found on a single, disease-associated haplotype (A T A). Likewise, the protective allele of SNP rs3212227 is only found on one haplotype (C C C), whose frequency is significantly increased among controls (Table 3).

Table 3 Association analysis of *IL12B* haplotypes

Haplotype	Frequency (counts)		P_c value
	Cases	Controls	
A T A	0.31 (525/1694)	0.25 (407/1630)	0.0004
C C C	0.14 (237/1694)	0.18 (293/1630)	0.007
C C A	0.12 (203/1694)	0.14 (228/1630)	N/S
C T A	0.39 (661/1694)	0.39 (636/1630)	N/S

Only haplotypes whose frequency was >1% in both cases and controls were included in the Table; locus order: rs10045431, rs7709212, rs3212227

In order to assess whether association at the rs10045431 locus was secondary to linkage disequilibrium with rs3212227, we implemented genotype-conditioned analyses, using the UNPHASED program. We observed significantly different odd ratios for the two rs10045431-rs3212227 haplotypes that were identical at the rs3212227 locus ($\chi^2 = 10.7$; 2 *df*; $P = 0.005$), indicating that the rs10045431 association cannot be ascribed to linkage disequilibrium with rs3212227.

Statistical interaction analysis

In order to assess the presence of epistasis between *IL23R* and *IL12B* disease associated alleles, we implemented a case-only test for the detection of gene–gene interaction (Yang et al. 1999). Under the null hypothesis of no epistasis, the genotype frequencies of unlinked markers are expected to be independent from each other. We therefore analysed the distribution of *IL12B* and *IL23R* patient genotypes by carrying out χ^2 tests on 3×3 contingency tables. We observed non significant χ^2 values for both the rs10045431 versus p.Arg381Gln ($\chi^2 = 3.71$; 4 *df*; $P = 0.43$) and rs3212227 vs. p.Arg381Gln comparison ($\chi^2 = 2.91$; 4 *df*; $P = 0.57$), indicating the absence of an epistatic interaction between *IL12B* and *IL23R* disease associated SNPs.

Discussion

Interelukin-23 (IL-23) is an IL12-related cytokine, which plays an important role in the regulation of cell-mediated

Table 2 Association analysis of *IL12B* SNPs

	Pools *z*-score	Minor allele frequency (allele counts)				Odd ratio	Combined P_c value
		WGA cases	WGA controls	Replication cases	Replication controls		
rs7709212	3.2	0.30 (181/596)	0.32 (178/562)	0.26 (218/836)	0.35 (348/1004)	0.76	0.006
rs10045431	3.5	0.36 (198/556)	0.29 (161/558)	0.33 (327/978)	0.26 (247/954)	1.41	0.0001
rs3212227	n/a	0.15 (88/604)	0.18 (101/562)	0.16 (166/1034)	0.20 (198/982)	0.76	0.036

immune responses (Kastelein et al. 2007). IL-23 stimulates the differentiation and proliferation of Th17 cells, a subset of T helper cells that are critical mediators of inflammation in several mouse models of autoimmune disease (Kikly et al. 2006).

In this study, we used the raw data from a WGA scan to show that variants in the genes for the IL-23 receptor (*IL23R*) and the p40 IL-23 subunit (*IL12B*) are significantly associated with psoriasis. Our scan readily identified a very strong association between the disease and MHC markers. The association results at the *IL23R* and *IL12B* loci were markedly less significant, with ranks ranging from 197 to 1,311. These findings are consistent with the expectation that non-MHC loci have a modest effect on disease risk.

The observation of a significant protective effect for the p.Arg381Gln *IL23R* variant is in agreement with the recent findings by Duerr et al. who reported a similarly strong effect in multiple Crohn's disease case-control datasets (Duerr et al. 2006). In our study, we observed that the replication dataset generated a weaker association at the *IL23R* locus (we found a *P* value of 0.019, which lost significance after correction for multiple testing), compared to the WGA sample. Since the replication resource includes a large number of patients that were sampled from pedigrees with multiple affected individuals, our results suggest that the p.Arg381Gln substitution could have a weaker protective effect when high-penetrance susceptibility alleles are segregating within a family.

During the late stages of this study, Cargill et al. also documented a significant association between psoriasis and a number of SNPs mapping to the *IL23R* (p.Leu310Pro and p.Arg381Gln) and *IL12B* genes (rs7709212, rs3212227 and rs6887695) (Cargill et al. 2007). Such a high degree of reproducibility is uncommon in the analysis of complex traits and suggests that variation affecting the IL23 receptor complex plays a key role in the pathogenesis of chronic epithelial inflammation.

We cannot exclude the possibility that the associations that we observed may be secondary to linkage disequilibrium (LD) with as yet undiscovered causal alleles. Our analysis of the *IL12B* locus identified independent association signals for two non-coding SNPs, mapping to the upstream region (rs10045431) and the 3′ UTR of the gene (rs3212227). Further investigations, including patient re-sequencing and genotyping, will be necessary to identify the specific variants underlying these associations.

Conversely, our patient re-sequencing effort failed to identify any *IL23R* coding variants that were in LD with the protective allele p.Arg381Gln. Arg381, which is strongly conserved among higher vertebrates, is located within the binding domain for the JAK2 kinase, the first mediator of the IL23R signalling cascade (Parham et al. 2002). In this context, it is tempting to speculate that p.Arg381Gln may confer protection against inflammatory disease by inhibiting downstream signalling.

Our analyses failed to detect any evidence of epistatic interaction between *IL12B* and *IL23R* disease associated alleles. A lack of epistasis between associated alleles of substantial effect has previously been reported for age-related macular degeneration (Maller et al. 2006) and type 2 diabetes (Weedon et al. 2006), suggesting that gene–gene interactions may have more subtle effect on the pathogenesis of complex traits, than previously thought.

In conclusion, we have shown significant association between *IL23R* and *IL12B* variation and psoriasis. The therapeutic relevance of our observations is highlighted by the positive results of recent clinical trials where anti IL12-p40 antibodies have been used for the treatment of psoriasis (Krueger et al. 2007). In this context, our association findings confirm the pathogenic relevance of the IL23 signalling cascade and provide further support for therapeutic strategies targeting this pathway in the treatment of chronic epithelial inflammation.

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