

## Evidence for Common Genetic Control in Pathways of Inflammation for Crohn's Disease and Psoriatic Arthritis

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**Objective.** Clinical, pharmacologic, and epidemiologic evidence supports the hypothesis that common genetic pathways may underlie inflammatory diseases. In a previous study, a Crohn's disease gene, *CARD15*, was demonstrated to be associated with psoriatic arthritis (PsA). Recently, a functional haplotype of 2 single-nucleotide polymorphisms (SNPs) mapping to the organic cation transporter (*OCTN*) genes, *SLC22A4* and *SLC22A5*, was identified as a second Crohn's disease susceptibility locus. The *SLC22A4* gene has also been associated with rheumatoid arthritis. This study was undertaken to further elucidate associations of PsA with Crohn's disease susceptibility genes.

**Methods.** Association with *CARD15* and *OCTN* was investigated in UK Caucasian patients with PsA (n = 472) and population controls (n = 594), using 5' allelic discrimination assays (TaqMan). Two SNPs in *OCTN*, forming a haplotype previously associated with Crohn's disease, were also tested in patients with psoriasis (n = 218) and patients with early undifferentiated inflammatory arthritis (n = 386). Allele and estimated haplotype frequencies were compared between patients and controls.

**Results.** No association of PsA with *CARD15* was

detected. In contrast, a functional SNP mapping to the promoter region of *SLC22A5* (rs2631367) was associated with PsA (for CC versus GG, odds ratio 1.65, 95% confidence interval 1.13–2.41, uncorrected  $P = 0.005$ ). In addition, the haplotype associated with Crohn's disease was also associated with PsA ( $P = 0.001$ ). No association was detected in the cohort with psoriasis alone or in the cohort with undifferentiated inflammatory arthritis.

**Conclusion.** The *OCTN* haplotype previously associated with Crohn's disease is also associated with PsA, suggesting that these 2 diseases may share some common genetic control in pathways of inflammation.

Psoriasis is a T cell-mediated, chronic, noninfectious skin condition affecting 1–3% of the general population; the plaque form (psoriasis vulgaris) is the most common subtype (1). In hospital series, up to 40% of patients with psoriasis have been reported to have an associated inflammatory arthritis, called psoriatic arthritis (PsA) (2–6). PsA is conventionally defined as an inflammatory arthritis associated with psoriasis, in which patients usually are rheumatoid factor (RF) negative (7). PsA was previously thought to be a benign disease, but increasing evidence suggests that it causes significant morbidity and mortality (8–12). Similar to other chronic inflammatory diseases, PsA is considered to be an etiologically complex disorder involving interactions between an unknown number of genes and as-yet-unidentified environmental factors (13,14). Evidence for a strong genetic contribution comes from family studies showing that the recurrence risk may be as high as 27 for a sibling of a proband with PsA (15), compared with a sibling recurrence risk of ~4 for rheumatoid arthritis (RA). PsA is associated with major histocompatibility complex (MHC) gene haplotypes (16), but no disease susceptibility genes outside the MHC gene region have yet been confirmed.

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The first whole-genome scan of PsA families identified a peak of linkage on chromosome 16q21 (17). The known Crohn's disease susceptibility locus, *CARD15* (MIM no. 605956), maps within 20 Mb of this peak, and it is recognized that patients with Crohn's disease have an increased risk for the development of both PsA and psoriasis (18–23). A previous study of patients with PsA revealed association with functional polymorphisms of this *CARD15* gene (24). In contrast, no association with psoriasis alone has been detected in North American, Italian, or UK cohorts (25–28).

Recently, a second Crohn's disease susceptibility locus was identified on chromosome 5q31. A functional haplotype in the organic cation transporter (*OCTN*) gene cluster, comprising a single-nucleotide polymorphism (SNP) in exon 9 of *SLC22A4* (rs1050152) and a promoter polymorphism in the adjacent gene, *SLC22A5* (rs2631367), was shown to affect transcription and transporter functions of the genes (29). In addition, carriage of both the associated haplotype and *CARD15* variants substantially increased the risk of developing Crohn's disease, suggesting an interaction between the loci. Interestingly, a different SNP mapping to *SLC22A4* (rs3792876) was shown to be associated with RA in a Japanese study (30). In that study, the associated SNP mapped to intron 1 of *SLC22A4* and affected the binding of a transcription regulator, *RUNX1*.

Crohn's disease, RA, and PsA are all inflammatory disorders that show some overlap of clinical features. They are also cytokine driven, and all respond to anti-tumor necrosis factor  $\alpha$  therapy. We therefore hypothesized that common genetic factors may underlie these 3 chronic inflammatory conditions. The aim of the current study was, first, to investigate the association of *CARD15* and the *OCTN* cluster with PsA in a large UK cohort and, second, to establish whether any associations detected were independent of psoriasis and/or undifferentiated inflammatory arthritis.

## PATIENTS AND METHODS

**Study design.** In this case-control study, allele frequencies of the 3 *CARD15* SNPs causal for Crohn's disease and 10 SNPs spanning *SLC22A4* and *SLC22A5* were determined in cohorts of subjects with PsA, psoriasis alone, and inflammatory arthritis alone and were compared with the frequencies in population controls.

**Patients.** *Patients with PsA.* Patients with PsA who were receiving active followup care by hospital consultant rheumatologists (n = 472) were recruited from throughout the UK following a media campaign and via direct referral from consultant rheumatologists. All patients were Caucasian and had both inflammatory arthritis and psoriasis. Inflammatory

arthritis was defined as inflammation of any joint lasting for at least 6 weeks. All of the patients were examined and interviewed by a metrologist. None had a history of inflammatory bowel disease.

*Patients with psoriasis.* Patients with type I (age at onset <40 years) chronic plaque psoriasis (n = 218) were recruited from the Dermatology Centre of Hope Hospital, Salford, Manchester. All patients were Caucasian and were interviewed and examined by the same physician (HY) to confirm the diagnosis and to exclude any inflammatory joint involvement.

*Patients with early undifferentiated inflammatory arthritis.* The Norfolk Arthritis Register (NOAR) is a community-based study that aims to recruit all patients with early inflammatory arthritis (defined as swelling of at least 2 peripheral joints persisting for a minimum of 4 weeks) in the region covered by the former Norwich Health Authority (31). All patients were interviewed, examined, and reviewed at regular intervals by metrologists from NOAR. Blood was obtained at baseline for rheumatoid factor (RF) testing and DNA extraction. For the purposes of the current study, the first 386 Caucasian patients with inflammatory arthritis who were referred to NOAR, regardless of their final diagnosis, were selected for investigation.

*Population controls.* Ethnically matched control subjects (n = 594) with no history of inflammatory arthritis or inflammatory bowel disease were recruited from among blood donors and general practitioners' registers.

All patients and controls were recruited with the approval of the local research ethics committee, and all provided written informed consent.

**Genotyping.** The 3 *CARD15* SNPs were chosen for testing because they have been shown to be causal for Crohn's disease, and 1 of them (SNP 8) was associated with PsA in the Newfoundland population (24). SNPs 8 (rs2066844), 12 (rs2066845), and 13 (rs2066847) were genotyped using a 5' allelic discrimination assay according to the manufacturer's instructions, except that a 5- $\mu$ l reaction volume rather than a 25- $\mu$ l reaction volume was used (TaqMan; Applied Biosystems, Warrington, UK). The primers and probes were designed using the ABI Assay-by-Design service (<http://www.appliedbiosystems.com>). Each polymerase chain reaction (PCR) mixture contained 15 ng of DNA, 2.5  $\mu$ l of TaqMan MasterMix, and 0.0625  $\mu$ l of 40 $\times$  assay mix. PCR was performed using 384-well plates on an ABI 9700 thermal cycler, with the following reaction conditions: 50°C for 2 minutes, 95°C for 10 minutes followed by 40 cycles at 95°C for 15 seconds and 60°C for 1 minute). A TaqMan 7700 platform (Applied Biosystems) was used to perform plate reading, using the allelic discrimination option.

Ten SNPs spanning *SLC22A4* and *SLC22A5* were selected for investigation and included the SNP previously associated with RA in a Japanese population (rs3792876), the haplotype associated with RA in the same Japanese population (rs3763112, rs1007602, rs2073838, and rs2269822) (30), and the SNPs forming the haplotype associated with Crohn's disease (*SLC22A4*+1672\*C/T [rs1050152] and *SLC22A5*-207\*G/C [rs2631367]) (29). Three additional SNPs (rs272887, rs2304081, and rs2306772) were included to ensure high-density coverage of this region. All of the SNPs were genotyped using the TaqMan 5' allelic discrimination assay, as described above. SNPs rs2304081, rs2306772, and rs1050152

**Table 1.** Characteristics of the cohorts\*

Characteristic	Controls	PsA	UIA	Psoriasis
Age at arthritis onset, years	–	37 (26–49)	55 (40–67)	–
Age at psoriasis onset, years	–	26 (15–43)	–	18 (12–27)
No. (%) male	198 (42)	200 (42)	159 (41)	120 (55)
No. (%) female	279 (58)	272 (58)	227 (59)	98 (45)
Duration of arthritis, years	–	10 (5–19)	1 (0–1)	–
Duration of psoriasis, years	–	20 (9–33.5)	–	18 (10–29)
No. (%) RF positive	–	101 (22)	99 (27)	–
No. (%) with type I psoriasis	–	348 (74)	–	216 (99)

\* Except where indicated otherwise, values are the median (interquartile range). PsA = psoriatic arthritis; UIA = undifferentiated inflammatory arthritis; RF = rheumatoid factor.

were available from the ABI Assays-on-Demand service (<http://www.appliedbiosystems.com>), while the other 7 SNPs were designed as described above. Details for all primers and probes are available from the authors upon request.

**Statistical analysis.** *Sample sizes.* Sample sizes were calculated based on published allele frequencies (minor allele frequencies of 3.3% for SNP 8 and 2.6% for SNP 13 in *CARD15*; minor allele frequencies of 42% and 49% for the 2 SNPs forming the haplotype associated with Crohn's disease), so that each of the association studies had 80% power to detect a gene conferring a genotype odds ratio (OR) of 2.0 at the 5% significance level (24,29).

*Single-point analysis.* Associations were tested with the chi-square test, using Stata version 8 software (College Station, TX). Formal adjustments were made for multiple testing; a Bonferroni correction of 3 was applied to SNPs mapping to *CARD15*, and a correction of 10 was applied to SNPs mapping to the *SLC22A4* and *SLC22A5* gene locus. Both the uncorrected and corrected *P* values are presented.

*Haplotype analysis.* For the *SLC22A4* and *SLC22A5* genes, pairwise linkage disequilibrium (LD) measures (both *D'* and *r*<sup>2</sup>) were investigated using HelixTree software (Golden Helix, Bozeman, MT). Haplotypes were constructed using the expectation-maximization algorithm implemented in SNP HAP (<http://www-gene.cimr.cam.ac.uk/clayton/software/>) and were assigned to individuals. Haplotype frequencies in patients and controls were compared using the chi-square test. To investigate gene interactions between the Crohn's disease susceptibility haplotype of *SLC22A4* and *SLC22A5* (*SLC22A4+1672\*T SLC22A5-207\*C*) and the Crohn's disease susceptibility variants of *CARD15*, patients with PsA and controls carrying both the TC haplotype and 1 or more *CARD15* variants were compared with those not carrying both variants, as described previously (29).

## RESULTS

Characteristics of the cohorts are shown in Table 1. Genotype frequencies for all SNPs were in Hardy-Weinberg equilibrium in both patients and controls.

**Single-point analysis.** *CARD15.* Neither allele nor genotype frequencies of the *CARD15* polymorphisms differed between patients with PsA and controls for SNP 8 and SNP 12 (Table 2). SNP 13 of the *CARD15* gene was, however, nominally significantly associated with PsA (*P* = 0.043), but the effect was in the direction opposite to that reported previously (i.e., patients were less likely than controls to carry the variant allele). This association did not remain significant after correction was made for multiple testing (*P* = 0.129). No association was found when PsA patients who had at least 1 variant of the *CARD15* gene were compared with population controls (*P* = 0.09) (Table 3).

*SLC22A4* and *SLC22A5.* Allele frequencies for the *SLC22A4+1672\*C/T* (rs1050152) and *SLC22A5-207\*G/C* (rs2631367) SNPs closely reflected those reported previously in a Canadian population (29) (Table 4). The *SLC22A5-207\*G/C* SNP (rs2631367), previously associated with Crohn's disease, was significantly associated with PsA (*P* = 0.005). This association remained significant even after Bonferroni correction. The effect was only slightly stronger in individuals homozygous for the C allele than for heterozygotes (for CC

**Table 2.** Association of *CARD15* polymorphisms in patients with PsA and population controls\*

Genotype	SNP 8 (rs2066844)				SNP 12 (rs2066845)				SNP 13 (rs2066847)			
	Patients	Controls	<i>P</i>	<i>P</i> <sub>corr</sub>	Patients	Controls	<i>P</i>	<i>P</i> <sub>corr</sub>	Patients	Controls	<i>P</i>	<i>P</i> <sub>corr</sub>
Variant/variant	1 (0.2)	0 (0)			0 (0)	0 (0)			0 (0)	0 (0)		
Variant/wild	35 (7.5)	51 (9.9)			13 (2.8)	16 (3.1)			11 (2.3)	26 (4.8)		
Wild/wild	432 (92.3)	462 (90.1)			452 (97.2)	506 (96.9)			461 (97.7)	515 (95.2)		
Total	468 (100)	513 (100)	0.176	0.528	465 (100)	522 (100)	0.852	1.0	472 (100)	541 (100)	0.043	0.129

\* Values are the number (%). PsA = psoriatic arthritis; SNP = single-nucleotide polymorphism. Uncorrected and corrected *P* (*P*<sub>corr</sub>) values reflect the distribution in patients versus controls.

**Table 3.** *CARD15* variants in patients with psoriatic arthritis and population controls

	Patients, no. (%)	Controls, no. (%)	<i>P</i>
≥1 variant	60 (12.7)	89 (16.5)	0.094
No variants	412 (87.3)	452 (83.5)	–

versus GG, OR 1.65, 95% confidence interval [95% CI] 1.13–2.41; for CG versus GG, OR 1.62, 95% CI 1.16–2.25). The *SLC22A4+1672*\*C/T SNP (rs1050152), which

also was previously associated with Crohn's disease, was not associated with PsA, although carriage of the rare T allele was more common in patients with PsA compared with controls ( $P = 0.086$ ). No association with the 2 SNPs was detected in either the psoriasis cohort or the undifferentiated inflammatory arthritis cohort (Table 4), which suggests that the association is an independent risk factor for PsA. The psoriasis cohort was stratified according to HLA–Cw6 status, but no association was detected in either the HLA–Cw6–positive or the HLA–

**Table 4.** Genotype frequencies in patients with PsA, population controls, psoriasis controls, and UIA controls\*

SNP/genotype	Controls, no. (%)	PsA		Type I psoriasis		UIA	
		No. (%)	<i>P</i> ( $P_{\text{corr}}$ )†	No. (%)	<i>P</i> ( $P_{\text{corr}}$ )‡	No. (%)	<i>P</i> ( $P_{\text{corr}}$ )‡
rs3763112							
GG	108 (18.9)	68 (14.6)					
GA	283 (49.6)	218 (46.8)					
AA	179 (31.4)	180 (38.6)	0.028 (0.28)				
rs1007602							
AA	254 (45.0)	227 (48.6)					
AG	248 (44.0)	199 (42.6)					
GG	62 (11.0)	41 (8.8)	0.359 (1.0)				
rs3792876§							
TT	6 (1.0)	2 (0.4)					
TC	87 (14.7)	61 (13.3)					
CC	501 (84.3)	396 (86.3)	0.481 (1.0)				
rs2073838							
AA	6 (1.0)	3 (0.6)					
AG	86 (14.8)	60 (12.9)					
GG	490 (84.2)	403 (86.5)	0.544 (1.0)				
rs272887							
CC	294 (50.5)	266 (56.5)					
CT	241 (41.3)	179 (38.0)					
TT	48 (8.2)	26 (5.5)	0.073 (0.73)				
rs2304081							
CC	493 (84.6)	401 (86.4)					
CT	84 (14.4)	60 (12.9)					
TT	6 (1.0)	3 (0.7)	0.633 (1.0)				
rs2306772							
AA	6 (1.1)	3 (0.6)					
AG	82 (14.5)	61 (13.1)					
GG	477 (84.4)	403 (86.3)	0.620 (1.0)				
rs1050152¶							
TT	112 (20.5)	93 (21.0)		41 (20.5)		74 (19.3)	
TC	260 (47.6)	231 (52.1)		96 (48.0)		172 (44.9)	
CC	174 (31.9)	119 (26.9)	0.214 (1.0)	63 (31.5)	0.995 (1.0)	137 (35.8)	0.466 (0.93)
rs2631367#							
CC	135 (24.0)	114 (27.3)		54 (25.6)		90 (23.3)	
CG	263 (46.6)	218 (52.3)		98 (46.4)		179 (46.4)	
GG	166 (29.4)	85 (20.4)	0.005 (0.05)	59 (28.0)	0.842 (1.0)	117 (30.3)	0.955 (1.0)
rs2269822							
TT	10 (1.9)	10 (2.2)					
TC	116 (22.3)	97 (21.1)					
CC	395 (75.8)	352 (76.7)	0.885 (1.0)				

\* PsA = psoriatic arthritis; UIA = undifferentiated inflammatory arthritis.

† Distribution in patients with PsA versus controls.

‡ Distribution, versus patients with PsA.

§ Single-nucleotide polymorphism (SNP) associated with rheumatoid arthritis (30).

¶ SNP forming the haplotype associated with Crohn's disease (29). For carriage of T allele,  $P = 0.086$ .

# SNP forming the haplotype associated with Crohn's disease. For CC versus GG, odds ratio (OR) 1.65, 95% confidence interval (95% CI) 1.13–2.41; for CG versus GG, OR 1.62, 95% CI 1.16–2.25.

**Table 5.** Haplotype frequencies for SNPs rs1050152 and rs2631367\*

Haplotype	Controls	PsA	Type I psoriasis	UIA
TC†	503 (44.0)	393 (47.9)	196 (42.1)	324 (41.8)
CG	604 (52.9)	376 (45.9)	252 (54.0)	417 (53.7)
CC	34 (3.0)	49 (6.0)	18 (3.9)	35 (4.5)
TG	1 (0.1)	2 (0.2)	0	0

\* Values are the number (%). SNP = single-nucleotide polymorphism. †  $P = 0.001$  in patients with psoriatic arthritis (PsA),  $P = 0.66$  in patients with type I psoriasis, and  $P = 0.23$  in patients with undifferentiated inflammatory arthritis (UIA), for the percentage of patients with the TC haplotype compared with the percentage of patients with the other haplotypes.

Cw6–negative subgroup ( $P = 0.26$  and  $P = 0.73$ , respectively). When the cohorts were stratified according to the presence or absence of RF, no association was detected in RF-negative patients with undifferentiated inflammatory arthritis (for CC versus GG, OR 0.96, 95% CI 0.6–1.5), although the association remained statistically significant in RF-negative patients with PsA (for CC versus GG, OR 1.66, 95% CI 1.2–2.5).

**Haplotype analysis.** For the *SLC22A4* and *SLC22A5* locus, strong LD was observed across this region, with  $D'$  measurements of  $>0.9$  between all SNPs. The same haplotype previously associated with Crohn's disease (29) was also shown to be associated with PsA ( $P = 0.001$ ). However, no association was detected in the psoriasis cohort or the undifferentiated inflammatory arthritis cohort (Table 5). In addition, patients with PsA carrying the TC haplotype and  $\geq 1$  of the *CARD15* Crohn's disease susceptibility variants were compared with healthy controls also carrying these variants. No difference in the frequencies was demonstrated ( $P = 0.33$ ).

## DISCUSSION

Clinical, pharmacologic, and epidemiologic evidence provides support for the hypothesis that Crohn's disease, RA, and PsA have common genetic pathways. In the current study, we investigated the association of PsA with the Crohn's disease susceptibility genes, *CARD15*, *SLC22A4*, and *SLC22A5*. In contrast to a previous study in a Newfoundland population (24), we observed no association between PsA and functional *CARD15* polymorphisms in our UK cohort. However, we did observe an association between PsA and a functional haplotype consisting of an SNP in exon 9 of *SLC22A4* (rs1050152) and a promoter SNP in *SLC22A5* (rs2631367) that previously was shown to be associated with Crohn's disease (29). Furthermore, we have shown

that this association is unique to PsA, being independent of both psoriasis and undifferentiated inflammatory arthritis.

*CARD15* was considered to be a strong candidate gene for PsA susceptibility, for 2 reasons. First, it is involved in regulating many proinflammatory and immune-related genes. Second, it maps close to a peak of linkage on chromosome 16q that was identified in a whole-genome scan of PsA families (17). Finally, a Canadian study (in a Newfoundland population) revealed association with PsA in a series of 187 patients with PsA and 136 healthy controls (OR 2.97, 95% CI 1.61–5.47) (24). However, in our larger study in a UK population of patients with PsA, we did not show association. This finding is unlikely to be a false-negative result, because our study had adequate power to detect the OR for the individual associated SNPs reported in the Canadian study. Genotype frequencies did not differ from Hardy-Weinberg expectations, and the allele frequencies for the 3 SNPs were similar to those observed in previous studies in UK populations (27,32–34).

There was association between SNP 13 of the *CARD15* gene and PsA, but the direction of association was opposite to that reported previously (i.e., patients were less likely to carry the variant allele); this did not remain statistically significant after correction for multiple testing.

The difference between our results and those observed in the Newfoundland study may reflect differences in the 2 populations. The population in Newfoundland is genetically isolated and therefore is predicted to have extended LD (24). Thus, an SNP could act as a marker in the Newfoundland population and not in the UK population. However, there is substantial evidence that the SNPs tested in *CARD15* are disease-causal polymorphisms, and differences in patterns of LD would therefore be irrelevant. Interestingly, in the whole-genome scan for PsA, *CARD15* does not map directly under the peak of linkage on chromosome 16q or within the 1–logarithm of odds support interval (17). Previous studies of cohorts of Italian and German patients also failed to show association of the locus with PsA (35,36). One reason why *CARD15* may be associated with a Newfoundland but not a UK population is that the gene may play a role in PsA susceptibility only in the setting of environmental factors that are present in Newfoundland but not in the UK.

The *OCTN* gene cluster appears to be a second Crohn's disease susceptibility locus and has also been associated with RA in a Japanese population, although a different polymorphism was implicated in that study

(29). We have shown that the same *SLC22A4* exon 9 and *SLC22A5* promoter polymorphisms that form a haplotype associated with Crohn's disease are also associated with PsA. Functional studies have demonstrated that the 2 polymorphisms can affect function independently of one another (29). Single-point analysis suggests that the association with PsA is primarily with the promoter polymorphism of *SLC22A5*.

The effect size of the *SLC22A5*-207\*C/G (rs2631367) promoter polymorphism in susceptibility to PsA is modest (for CC versus GG, OR 1.65, 95% CI 1.13–2.41; for CG versus GG, OR 1.62, 95% CI 1.16–2.25) and lower than that reported in Crohn's disease (29). This may reflect the fact that 2 functional polymorphisms are associated with Crohn's disease, compared with a primary effect of the *SLC22A5*-207\*C/G (rs2631367) promoter SNP in PsA. Alternatively, it may reflect the phenomenon of upward bias, in which effect sizes in initial studies are often overestimated (37).

In this study, several SNP markers were tested in order to conduct a systematic investigation of association with the Crohn's disease susceptibility genes. Association with the *SLC22A5*-207\*C (rs2631367) allele may have occurred due to chance alone (false-positive result). In order to account for this, it has been proposed that associations should be corrected for the multiple tests undertaken. However, this approach would reduce the power to detect association and may result in an elevated false-negative rate (Type II error) (38). Furthermore, we demonstrated that the SNP genotypes are not independent, because *D'* and correlation values between SNPs mapping to the *SLC22A4* and *SLC22A5* gene locus are high. Hence, applying a Bonferroni correction is overly conservative, but it should be noted that the *SLC22A5*-207\*C (rs2631367) allele remained significantly associated despite this ( $P = 0.05$ ).

Previous studies of PsA have been hampered by the fact that it was unclear whether reported associations were primarily with arthritis, psoriasis, or PsA itself. One of the major strengths of the current study is that it included all 3 patient groups. Although sample sizes in the cohorts comprising patients with psoriasis and undifferentiated inflammatory arthritis were smaller than those in either the PsA or control cohorts, the study had adequate power to exclude effect sizes of 1.65 and 1.55, respectively, in these 2 groups. By using this study design, we established that association of the *SLC22A4*+1672\*T (rs1050152) and *SLC22A5*-207\*C (rs2631367) haplotype with PsA is independent of both psoriasis and inflammatory arthritis.

The promoter SNP associated with PsA in the

current study has been shown to disrupt a heat-shock element, and the presence of the variant *SLC22A5*-207\*C allele results in lower promoter activity upon stimulation in different cell lines (29). The polymorphism in exon 9 of *SLC22A4* causes a nonconservative amino acid substitution (leucine to phenylalanine) and results in reduced transporter function of the gene (29). Although the organic cation transporters are widely expressed in different tissues in the body and are major components of the human xenobiotic excretion machinery (39), their precise function remains to be elucidated. Exactly how altered function of these genes contributes to susceptibility to PsA but not psoriasis requires further investigation.

In summary, we did not observe an association of *CARD15* with PsA, but other genes mapping under the peak of linkage on chromosome 16q remain strong candidate susceptibility genes for PsA. We did, however, observe an association between PsA and a functional haplotype consisting of a nonconservative amino acid substitution in exon 9 of *SLC22A4* (rs1050152) and a promoter SNP of *SLC22A5* (rs2631367) previously shown to be associated with Crohn's disease. The association was independent of both psoriasis and undifferentiated inflammatory arthritis. This finding was not replicated in a recent study in Newfoundland (40), despite very similar genotype frequencies in the control populations. It should be noted, however, that the Newfoundland study was underpowered to detect the effect size reported here. Hence, studies in other PsA cohorts are required to determine whether this association exists in other populations. Our results suggest that, at least in the UK population, common inflammatory pathways underlie both Crohn's disease and PsA.

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