

# Investigating the role of the *HLA-Cw\*06* and *HLA-DRB1* genes in susceptibility to psoriatic arthritis: comparison with psoriasis and undifferentiated inflammatory arthritis

P Y P C Ho,<sup>1</sup> A Barton,<sup>1</sup> J Worthington,<sup>1</sup> D Plant,<sup>1</sup> C E M Griffiths,<sup>2</sup> H S Young,<sup>2</sup> P Bradburn,<sup>3</sup> W Thomson,<sup>1</sup> A J Silman,<sup>1</sup> I N Bruce<sup>1</sup>

<sup>1</sup>arc-Epidemiology Unit, Stopford Building, University of Manchester, Manchester, UK; <sup>2</sup>Dermatology Centre, Hope Hospital, University of Manchester, Manchester, UK; <sup>3</sup>Department of Public Health and Epidemiology, University of Birmingham, UK

Correspondence to: Pauline Ho, arc-EU, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK; Pauline.Ho@manchester.ac.uk

Accepted 21 August 2007  
Published Online First  
29 August 2007

## ABSTRACT

**Objective:** Psoriasis of early onset (type I; age of onset  $\leq 40$  years) is associated with *HLA-Cw\*06* while the shared epitope (SE) is associated with rheumatoid arthritis susceptibility. Our aim was to investigate the role of *HLA-Cw\*06* and *HLA-DRB1* genes (including SE) with psoriatic arthritis (PsA) susceptibility.

**Methods:** In a case-control association study, *HLA-Cw\*06* phenotype frequencies were compared between patients with PsA (n = 480), psoriasis alone (n = 611) and healthy controls (n = 166). Similarly, at the *HLA-DRB1* locus, phenotype and SE frequencies were compared in patients with PsA (n = 480), early undifferentiated inflammatory arthritis alone (n = 1621) and healthy controls (n = 537).

**Results:** The *HLA-Cw\*06* phenotype was associated with type I psoriasis (OR 6.9, 95% CI 4.4, 11.1,  $p = 2.2 \times 10^{-21}$ ) and with patients with PsA having type I psoriasis (OR 5.0, 95% CI 3.2, 7.9,  $p = 4.39 \times 10^{-13}$ ), but not with patients with PsA having type II psoriasis (age of onset  $> 40$  years). *HLA-DRB1\*07*, in linkage disequilibrium with *HLA-Cw\*06*, was also associated with patients with PsA having type I psoriasis (OR 2.7, 95% CI 2.1, 3.7,  $p < 0.00001$ ). *HLA-DRB1\*04* alleles and the SE were associated with undifferentiated inflammatory arthritis but not with PsA.

**Conclusions:** The SE is not a PsA susceptibility locus. *HLA-Cw\*06* and *HLA-DRB1\*07* are associated with patients with PsA having type I psoriasis, suggesting that the primary association is with age of onset of psoriasis. Patients with PsA having type I psoriasis, therefore, have a genetic background different to those with type II psoriasis, and adjustment for this is necessary in future studies that investigate the genetic susceptibility of PsA.

Psoriatic arthritis (PsA) is commonly defined as “an inflammatory arthritis (IA) associated with psoriasis, which is usually negative for rheumatoid factor (RF)”.<sup>1</sup> A strong genetic component to susceptibility is suggested by the sibling recurrence risk ratio ( $\lambda_s$ ), which is estimated to be 27.<sup>2,3</sup> Part of the genetic predisposition is likely to be explained by genes within the major histocompatibility complex (MHC) region. For example, human leucocyte antigen (HLA) associations with psoriasis and IA in the form of rheumatoid arthritis (RA) are well characterised and, in each case, the MHC genes involved are recognised as the major disease susceptibility locus. Psoriasis has two distinct ages of onset: type I, early onset disease

occurring at  $\leq 40$  years of age and type II, late onset occurring at  $> 40$  years of age. Carriage of the HLA class I allele, *HLA-Cw\*06* is associated with type I but not type II psoriasis.<sup>4-15</sup> In contrast, RA is associated with carriage of the shared epitope (SE) of the HLA class II *DRB1* gene (a group of *DRB1* alleles sharing a conserved amino acid motif in the third hypervariable region of the DR $\beta$  chain).<sup>14</sup> *HLA-Cw\*06* is not found on haplotypes encoding the SE.

For PsA disease susceptibility, separating the HLA-related genetic contribution from the contribution to psoriasis and IA alone is a challenge. There is evidence to suggest that carriage of the *HLA-Cw\*06* allele is associated with patients with PsA with type I psoriasis.<sup>12-19</sup> Studies of the HLA class II *DRB1* gene have reported that the *HLA-DRB1\*07* phenotype is associated with peripheral arthritis in PsA while *HLA-DRB1\*04* is associated with a subgroup of patients with PsA with polyarthritis mimicking that of RA.<sup>20-26</sup> In one study of the *HLA-DRB1* locus, *HLA-DRB1\*0402* (which is not a SE allele) was found to occur more frequently in patients with PsA compared with RA or healthy controls, whereas *HLA-DRB1\*0401* (which is a SE allele) occurred less frequently.<sup>27</sup> Conflicting results have been reported with regard to the *HLA-DRB1\*02* (*HLA-DRB1\*15* or *HLA-DRB1\*16*) and PsA susceptibility with a decrease found in a UK study, but not in a cohort from Toronto.<sup>28,29</sup> More recently, a UK study showed no overall difference in the frequency of the SE between PsA cases and controls.<sup>28</sup>

Of the associations reported, however, it is still unclear whether the primary association is with PsA itself or secondary to one of the two constituent components, ie, IA or psoriasis. In previous studies, all appropriate comparison groups have not been analysed and some studies have also lacked power to address this question. The aim of this study was to compare the association between *HLA-Cw\*06* and *HLA-DRB1*, including the SE, with PsA susceptibility by comparing these phenotypes in patients with PsA, early undifferentiated inflammatory arthritis (UIA) alone, psoriasis alone and healthy controls.

## METHODS

### Overview

For this study, we did not investigate *HLA-Cw\*06* carriage in UIA patients or *HLA-DRB1* allele



This paper is freely available online under the BMJ Journals unlocked scheme, see <http://ard.bmj.com/info/unlocked.dtl>

carriage in patients with psoriasis as previous studies have excluded a role for these genes in the respective conditions.<sup>12, 30–33</sup> A case–control association study was performed to investigate the role of *HLA-Cw\*06* in determining susceptibility to PsA by comparing allele and phenotype frequencies between patients with PsA, psoriasis alone and healthy controls. For the *HLA-DRB1* gene variants, *HLA-DRB1\*04*, *HLA-DRB1\*07*, *HLA-DRB1\*02* (*HLA-DRB\*15* or *HLA-DRB\*16*) and SE phenotype frequencies were compared in patients with PsA, UIA alone and healthy controls. Stratification analyses were performed by subdividing patients with PsA into type I and type II psoriasis according to the age at onset of their skin disease (type I = age of onset  $\leq 40$  years and type II =  $>40$  years of age). Analyses were also repeated in subsets of patients with PsA stratified by the presence of RF.

## Subjects

### Patients with psoriatic arthritis

The recruitment of patients with PsA for this study has been described previously.<sup>34</sup> In brief, patients with PsA ( $n = 480$ ) under active follow-up by hospital rheumatologists were recruited from throughout the UK with the majority of them coming from north-west England. All patients satisfied the inclusion criteria of having both clinically documented inflammatory synovitis and psoriasis regardless of their RF status. A trained research nurse interviewed the patients and completed a standardised clinical history and examination protocol. Detailed demographic and clinical information were obtained and whole blood was taken for the measurement of RF status, DNA extraction and subsequent genetic analysis.

### Patients with psoriasis

As described previously,<sup>35</sup> patients with type I psoriasis (age of onset  $\leq 40$  years) ( $n = 611$ ) were recruited via the Dermatology Centre at Hope Hospital in Manchester. Some of the patients with psoriasis may have an IA, but this was not documented for the majority. A subset ( $n = 229$ ) underwent an examination to exclude inflammatory joint involvement.

### Undifferentiated inflammatory arthritis

Patients with early UIA were recruited from the Norfolk Arthritis Register (NOAR) as described previously.<sup>36</sup> This is a primary-care-based inception cohort of subjects with primary UIA. Patients were aged  $\geq 16$  years with two or more inflamed peripheral joints lasting at least 4 weeks. For the purpose of this study, all patients with *HLA-DRB1* data available were included ( $n = 1621$ ).

### Population controls

Control subjects without a history of IA or psoriasis were recruited from blood donors and general practice registers ( $n = 537$ ).

All patients and controls were white Caucasians of British descent. They were recruited with ethical committee approval (MREC 99/8/84 (PsA samples); LREC 00089 (psoriasis samples), LREC 2003-075 (NOAR samples)) and provided written informed consent.

### HLA typing

Both broad HLA genotyping (*HLA-Cw* and *HLA-DR*) and subtyping to define SE alleles were performed using 50 ng of genomic DNA amplified with the Dynal RELI SSO *HLA-Cw* typing and *HLA-DRB1* kits (<http://www.dynalbiotech.com>)

using a third of the specified volumes for the polymerase chain reaction reagents in a 20  $\mu$ l reaction instead of 60  $\mu$ l as described previously.<sup>34</sup> Alleles were assigned using the Pattern Matching Program provided by Dynal (Invitrogen Ltd, Paisley, UK).

### Statistical analysis

Allele and phenotype frequencies for *HLA-Cw\*06* were compared between PsA cases, psoriasis cases and controls using the  $\chi^2$  test implemented in STATA 8.

For the *HLA-DRB1* gene, *HLA-DRB1\*04*, *HLA-DRB1\*07*, *HLA-DRB1\*02* (*HLA-DRB\*15* or *HLA-DRB\*16*) and SE phenotype frequencies were compared between cases with PsA, UIA and controls using the  $\chi^2$  test implemented in STATA 8. The SE was defined by the presence of any of the following alleles: *HLA-DRB1\*0101*, *HLA-DRB1\*0102*, *HLA-DRB1\*0104*, *HLA-DRB1\*0401*, *HLA-DRB1\*0404*, *HLA-DRB1\*0405*, *HLA-DRB1\*0408* and *HLA-DRB1\*1001*.

The PsA cohort was divided into patients with type I and type II psoriasis by their age at onset of their psoriasis ( $\leq 40$  years or  $>40$  years, respectively) and the analyses were repeated for each subset of PsA. Similar analysis was undertaken after stratifying the PsA cohort by their RF status.

### Linkage disequilibrium analysis

Pairwise linkage disequilibrium (LD) measures (both  $D'$  and  $r^2$ ) were investigated between *HLA-Cw\*06* and *HLA-DRB1\*07* using HelixTree (Golden Helix Inc, Bozeman, MT, USA). These data has been reported previously.<sup>34</sup>

## RESULTS

A summary of the samples used for the *HLA-Cw\*06* and *HLA-DRB1* analysis is provided in table 1.

### Patient characteristics

#### Psoriatic arthritis

The characteristics of the PsA cohort have been described previously.<sup>34</sup> There was an almost equal gender distribution with 57% being female and 74% having type I psoriasis. The median duration of psoriasis was 19 years (interquartile range (IQR) 9–33) and the median duration of joint disease was 10 years (IQR 5–19). A majority (63%) developed psoriasis before the onset of joint disease. RF was present in 17% (titre  $>1:40$ ), 81% had nail involvement, 57% had five or more damaged joints (polyarthritis subgroup) and the median HAQ score was 1.25. As shown previously, patients with PsA with type I psoriasis have a stronger family history of both skin and joint disease and tend to develop arthritis after the onset of psoriasis.<sup>19, 37</sup> In addition, patients with PsA with type I psoriasis had a longer duration of joint disease and more nail

**Table 1** Number of subjects in study (where data are available)

Subjects	<i>HLA-Cw*06</i> information: n	<i>HLA-DRB1</i> information: n
PsA whole cohort	453	465
PsA with type I psoriasis	335	342
PsA with type II psoriasis	115	120
Psoriasis (all type I)	611	NA
UIA	NA	1621
Population controls	166	537

UIA, early undifferentiated inflammatory arthritis; PsA, psoriatic arthritis; NA, not available.

For three PsA cases, data were not available as to the type of psoriasis present.

involvement, but a lower median HAQ score and fewer involved joints compared with those with type II psoriasis.

### Psoriasis

All patients had type I psoriasis with 46% (283 of 611) being female. The median age of onset of psoriasis was 19 years (IQR 13–27). Some of these patients may have an unrecognised IA, but a subset ( $n = 229$ ) have been specifically examined by a dermatologist to exclude an IA. All 611 patients with psoriasis were included in the analysis. No significant differences in clinical, demographic or *HLA-Cw\*06* carriage data were observed between those patients with psoriasis in whom PsA had been specifically excluded and those where it had not (*HLA-Cw\*06* carriage was 43% in those without PsA versus 40% in the remainder,  $p = 0.44$ ).

### Early undifferentiated inflammatory arthritis

Within the UIA cohort, 1053 (65%) were female. At baseline, the median disease duration was 6 months (IQR 3–12); RF was present at a titre  $>1:40$  in 452/1433 (31.5%) and 743 (48.3%) satisfied the American College of Rheumatology criteria for RA.<sup>38</sup> By year 5, 11% of the patients were recorded to have psoriasis in addition to their IA and by year 10 of follow-up, 12% developed psoriasis.

### Controls

In the population control cohort, gender information was available for 268 subjects of whom 119 (44%) were female. *HLA-Cw\*06* data were available for 166, while *HLA-DRB1* data were available for 573 subjects.

### HLA-Cw\*06

The frequency of the *HLA-Cw\*06* phenotype in the population controls tested in the current study was within the range reported previously<sup>15 16 25 26 39–41</sup> (table 2).

When compared with controls, the *HLA-Cw\*06* phenotype was shown to be strongly associated with PsA (odds ratio (OR) 3.6, 95% CI 2.3, 5.8 and  $p = 5.5 \times 10^{-9}$ ) (table 2 and fig 1). Stratification analysis in the PsA cohort by RF status made no difference to the result (OR in the RF-negative PsA subgroup 3.6, 95% CI 2.3, 5.9,  $p = 9.6 \times 10^{-9}$ ). However, the association with *HLA-Cw\*06* was confined to the subgroup of patients with PsA with type I psoriasis (OR 5.0, 95% CI 3.2, 7.9,  $p = 4.39 \times 10^{-13}$ ) and was not observed in patients with PsA with type II psoriasis (OR 1.1, 95% CI 0.6, 2.1,  $p = 0.76$ ).

**Table 2** Comparison of *HLA-Cw\*06* in PsA cases, psoriasis and controls

<i>HLA-Cw*06</i>	PsA cases			Population controls $n = 166$	Type I psoriasis $n = 611$
	Total cohort $n = 453$	Type I $n = 335$	Type II $n = 115$		
0	262 (57.8)	166 (49.6)	94 (81.7)	138 (83.1)	254 (41.6)
1	182 (40.2)	162 (48.4)	19 (16.5)	28 (16.9)	323 (52.9)
2	9 (2)	7 (2)	2 (1.8)	0	34 (5.5)
Phenotype	191 (42.2)	169 (50.4)	21 (18.3)	28 (16.9)	357 (58.4)
p-Value*	$5.5 \times 10^{-9}$	$4.39 \times 10^{-13}$	0.76		$2.15 \times 10^{-21}$

PsA, psoriatic arthritis. Type I, patients with PsA with type I psoriasis; type II, patients with PsA with type II psoriasis.

\*Comparison of phenotype (carriage of one or two alleles) with population controls using the  $\chi^2$  test.

Data shown in n (%). Data were not available for three patients as to the type of psoriasis present.

For the psoriasis cohort, as expected, *HLA-Cw\*06* was strongly associated with type I psoriasis compared with controls (OR 6.9 95% CI 4.4 to 11.1,  $p = 2.15 \times 10^{-21}$ ) (table 2 and fig 1). To determine whether *HLA-Cw\*06* is associated with PsA itself or primarily with psoriasis, we compared the *HLA-Cw\*06* phenotype frequencies in those patients with PsA with type I psoriasis and patients with type I psoriasis alone. A much weaker association was noted (PsA with type I psoriasis versus type I psoriasis, OR 0.72, 95% CI 0.55, 0.96,  $p = 0.02$ ), suggesting that the primary association of *HLA-Cw\*06* is with type I psoriasis and not PsA *per se*.

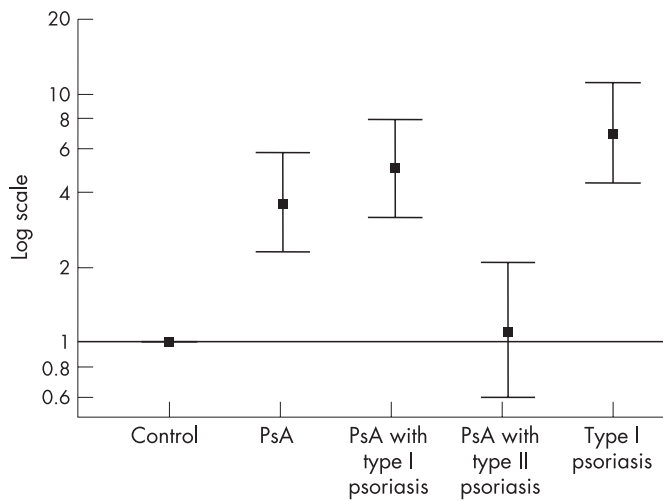
### HLA-DRB1

Stratification analysis showed that the *HLA-DRB1\*07* phenotype was strongly associated in those patients with PsA with type I psoriasis (OR 2.7, 95% CI 2.1, 3.7 and  $p < 0.00001$ ) compared with controls. Although, *HLA-DRB1\*07* occurred significantly more frequently in PsA cases than controls, we have previously reported that this allele exhibits considerable LD with *HLA-Cw\*06* (correlation ( $r^2$ ) = 0.46).<sup>34</sup> Therefore, it was not unexpected that, after adjusting for the presence of *HLA-Cw\*06* phenotype, the association of *HLA-DRB1\*07* with PsA as a whole group (OR 1.38, 95% CI 0.88, 2.17,  $p = 0.16$ ) or in the subgroup with type I psoriasis compared with controls (OR 1.63, 95% CI 0.96, 2.78,  $p = 0.07$ ) was no longer statistically significant. However, the association of PsA with *HLA-Cw\*06* remained similar after adjusting for the presence of the *HLA-DRB1\*07* (OR 3.2, 95% CI 2.0 to 5.3), confirming that the primary association is with *HLA-Cw\*06* and not *HLA-DRB1\*07*.

Patients with PsA negative for RF were less likely to carry the *HLA-DRB1\*04* phenotype compared with population controls (OR 0.74, 95% CI 0.55, 0.99,  $p = 0.03$ ), but no difference was observed between those patients with PsA with a positive RF compared with controls (OR 0.96, 95% CI 0.56, 1.61,  $p = 0.88$ ). In addition, the *HLA-DRB1\*04* phenotype occurred less frequently in patients with PsA with type I psoriasis compared with population controls ( $p = 0.004$ ), but no difference was observed in those patients with PsA with type II psoriasis compared with controls ( $p = 0.45$ ). Within patients with PsA, when the *HLA-DRB1\*04* phenotype was present, it occurred more commonly in patients with PsA with type II psoriasis compared with those with type I psoriasis (OR 1.81, 95% CI 1.14, 2.86,  $p = 0.007$ ). No association was detected with those patients with PsA having  $\geq 5$  damaged (poly-damaged) or  $\geq 5$  involved (poly-involved) joints with the *HLA-DRB1\*04* phenotype compared with population controls (OR 0.87, 95% CI 0.6, 1.2,  $p = 0.39$  and OR 0.81, 95% CI 0.60, 1.08,  $p = 0.14$ , respectively).

Table 3 shows that in the UIA cohort, the *HLA-DRB1\*04* phenotype was more common than population controls (OR 1.40, 95% CI 1.14, 1.72 and  $p = 0.001$ ), while the *HLA-DRB1\*07* phenotype was more common in the PsA cohort compared with population controls (OR 2.15, 95% CI 1.62, 2.84,  $p = 2.6 \times 10^{-8}$ ). However, when comparing patients with PsA with type II psoriasis with UIA subjects, no difference was observed between these two cohorts for either the *HLA-DRB1\*04* or the *HLA-DRB1\*07* phenotypes ( $p = 0.35$  and  $p = 0.45$  respectively). When compared with patients with PsA with type I psoriasis, the frequency of the *HLA-DRB1\*04* phenotype was significantly higher in UIA subjects (OR 2.17, 95% CI 1.66, 2.84,  $p < 0.0001$ ). Conversely, the *HLA-DRB1\*07* phenotype was significantly higher in patients with PsA with type I psoriasis compared with UIA (OR 3.23, 95% CI 2.51, 4.14,  $p < 0.0001$ ).





**Figure 1** Comparison of HLA-Cw\*06 phenotype in psoriatic arthritis (PsA) cases, psoriasis and controls. Odds ratios and 95% confidence intervals are shown on a log scale.

Previous studies have reported conflicting results with regard to the *HLA-DRB1\*02* (*HLA-DRB1\*15* or *HLA-DRB1\*16*) and PsA susceptibility with a decrease found in a UK study, but not in a cohort from Toronto.<sup>28, 29</sup> We did not observe a difference in our cohort.

**Shared epitope**

When comparing patients with PsA and controls, no association was detected with SE allele carriage and PsA (table 4 and fig 2) either in the entire cohort ( $p = 0.94$ ) or after stratifying the patients with PsA by type I or type II psoriasis or by their RF status. For example, no association was detected when comparing SE phenotype between patients with PsA with type I psoriasis and population controls (OR 0.90, 95% CI 0.68, 1.19,  $p = 0.43$ ) or when comparing patients with PsA with type II psoriasis with population controls (OR of 1.24, 95% CI 0.82, 1.88,  $p = 0.28$ ).

As expected, the SE was significantly associated with UIA compared with controls (OR 1.88, 95% CI 1.53, 2.29,  $p = 3.63 \times 10^{-10}$ ; table 4 and fig 2). When comparing the UIA and PsA subgroups directly, the frequency of the SE phenotype was significantly higher in UIA subjects compared with those patients with PsA with type I psoriasis (OR 2.08, 95% CI 1.64, 2.66,  $p = 7.1 \times 10^{-10}$ ), but the effect size was lower when comparing UIA subjects to patients with PsA with type II psoriasis (OR 1.51, 95% CI 1.02, 2.22,  $p = 0.03$ ).

**DISCUSSION**

In this large association study of patients with PsA, we have shown that both *HLA-Cw\*06* and *HLA-DRB1\*07* are associated with PsA susceptibility in the subgroup of patients with PsA

with type I psoriasis but not in those with type II psoriasis, suggesting that the primary association is with type I psoriasis. Our data also confirms that the association with the *HLA-DRB1\*07* is because this allele is in LD with *HLA-Cw\*06*. We can find no evidence for association of the SE with PsA susceptibility.

The simultaneous investigation of two HLA genes in large cohorts of patients with PsA and appropriate control groups has enabled us to try and dissect out the contribution to PsA over and above that to UIA alone and psoriasis alone. We did not investigate *HLA-Cw\*06* in UIA patients or *HLA-DRB1* in patients with psoriasis as previous studies have excluded a role for these genes in the respective conditions.<sup>12, 30-33</sup> Previous studies on patients with psoriasis have shown that both *HLA-Cw\*06* and *HLA-DRB1\*07* are associated with type I psoriasis, but not with type II psoriasis.<sup>12, 30, 31, 42</sup> We have confirmed that, although both phenotypes show association, the *HLA-DRB1\*07* result has arisen due to LD with *HLA-Cw\*06*. Furthermore, analysis of *HLA-Cw\*06* phenotype in patients with type I psoriasis, patients with PsA (stratified according to their types of psoriasis) as well as population controls has allowed us to conclude that the association is primarily with type I psoriasis rather than PsA itself.

Unsurprisingly, *HLA-DRB1\*04* was found to occur more frequently in the UIA cohort, the majority of whom satisfied American College of Rheumatology classification criteria for RA by 5 years. In contrast, it occurred less commonly in those patients with PsA who were negative for RF and those patients with PsA with type I psoriasis compared with controls. When *HLA-DRB1\*04* was present in patients with PsA, it occurred more frequently in those with type II psoriasis compared with patients with PsA with type I psoriasis. This may suggest that the *HLA-DRB1\*04* allele is protective for type I PsA. Alternatively, it may simply reflect the fact that if one allele is increased in frequency (*HLA-DR\*07* allele frequency increased in patients with PsA with type I psoriasis) then the frequency of others must be reduced.

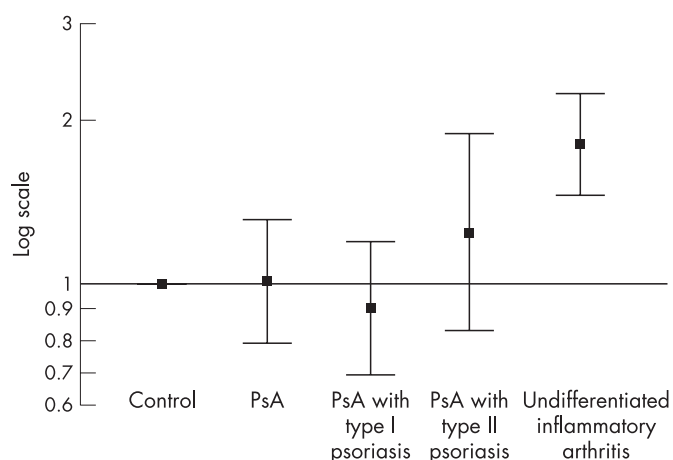
The broad inclusion criteria for PsA used in this study may have led to the misclassification of some patients who have true RA and coincidental psoriasis being classified as PsA. In this situation, one may have expected to see an association with *HLA-DRB1\*04* in either the RF-positive subgroup of patients with PsA or those with polyarticular disease but we did not find that to be the case. An advantage of not excluding RF-positive patients is that we have been able to stratify the patients with PsA by their RF status to explore whether RF is an important co-factor in PsA susceptibility. However, in no situation did this stratification change the conclusions of an analysis, suggesting that it is not. Our genetic findings, therefore, accord with recent clinical data suggesting that polyarticular PsA is more similar to oligoarticular PsA than to RA.<sup>43</sup>

We have also confirmed the finding of others that SE was not associated with PsA susceptibility.<sup>28, 29</sup> Unsurprisingly, SE was

**Table 3** *HLA-DRB1* phenotypes in PsA cases, UIA and controls (where data available)

HLA-DRB1	PsA cases			Controls n = 537	p value (PsA whole cohort compared with controls)	UIA n = 1621	p Value (UIA compared with controls)
	Whole cohort n = 465	Type I n = 342	Type II n = 120				
DRB1*02	118 (25)	81 (24)	36 (30)	145 (27)	0.57	342 (21)	0.006
DRB1*04	142 (31)	92 (27)	48 (40)	195 (36)	0.06	719 (44)	0.001
DRB1*07	188 (40)	159 (46)	29 (24)	129 (24)	$3.09 \times 10^{-8}$	344 (21)	0.21

PsA, psoriatic arthritis; UIA, early undifferentiated inflammatory arthritis; type I, patients with PsA with type I psoriasis; type II, patients with PsA with type II psoriasis. Data shown in n (%) unless stated otherwise.



**Figure 2** Shared epitope phenotype in psoriatic arthritis (PsA) cases, undifferentiated inflammatory arthritis and controls. Odds ratios and 95% confidence intervals are shown on a log scale.

found to be strongly associated with UIA susceptibility and occurred significantly more frequently in UIA subjects compared with patients with PsA with type I psoriasis. The smaller number of patients with PsA with type II psoriasis may have limited the interpretation of this analysis but the odds of carrying SE was also significantly higher in UIA subjects compared with patients with PsA with type II psoriasis. The findings confirm that, although patients with PsA with type II psoriasis appear more genetically similar to UIA subjects than do patients with PsA with type I psoriasis, UIA and patients with PsA with type II psoriasis are sufficiently different, in terms of their genetic susceptibility, to be viewed as distinct entities.

In summary, our study confirms the established strong association of *HLA-Cw\*06* with type I psoriasis susceptibility. The association of PsA with *HLA-Cw\*06* is of similar strength and is confined to those patients with PsA with type I psoriasis. We conclude, therefore, that *HLA-Cw\*06* does not confer additional susceptibility to IA in patients with psoriasis. We also note that the association between *HLA-DRB1\*07* and PsA is due to its significant LD with *HLA-Cw\*06*. No independent association was detected with *HLA-DRB1\*02*, *HLA-DRB1\*04*, *HLA-DRB1\*07* or with the SE and PsA. Our study suggests that the genetic susceptibility of PsA cannot be explained by the *HLA-Cw\*06* or *HLA-DRB1* loci and confirms the importance of choosing the appropriate control populations when studying this condition. The findings also suggest that adjustment for *HLA-Cw\*06* is of central importance when attempting to dissect the genetic susceptibility of IA in patients with psoriasis. Finally, our findings suggest that patients with PsA with type I and type II psoriasis have different genetic susceptibility factors and that patients with PsA with type I psoriasis are more genetically similar to type I patients with psoriasis at least at the *HLA-Cw\*06* locus. This implies that in future genetic studies, it may be important to stratify patients with PsA according to the age of onset of psoriasis.

**Acknowledgements:** This work has been supported by the Arthritis Research Campaign, the Wellcome Trust (Entry Level Fellowships for PYPCH and HSY; Advanced Fellowship for AB) and the Medical Research Council UK (Clinical Training Fellowship for PYPCH).

**Competing interests:** None.

**Table 4** Shared epitope frequency in PsA cases, UIA and controls

Shared epitope	UIA n = 1621	PsA cases			Population controls n = 537
		Whole cohort n = 467	Type I n = 344	Type II n = 120	
0	634 (39.1)	256 (54.8)	197 (57.3)	59 (49.2)	293 (54.6)
1	740 (45.7)	184 (39.4)	126 (36.6)	55 (45.8)	203 (37.8)
2	247 (15.2)	27 (5.8)	21 (6.1)	6 (5.0)	41 (7.6)
Phenotype	987 (60.9)	211 (45.2)	147 (42.7)	61 (50.8)	244 (45.4)
p Value*	$3.63 \times 10^{-10}$	0.94	0.43	0.28	

UIA, early undifferentiated inflammatory arthritis; PsA, psoriatic arthritis; type I, patients with PsA with type I psoriasis; type II, patients with PsA with type II psoriasis.

\*Comparison of phenotype (carriage of one or two alleles) with population controls. Data shown in n (%) unless stated otherwise.

## REFERENCES

- Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;**3**:55–78.
- Moll JM, Wright V. Familial occurrence of psoriatic arthritis. *Ann Rheum Dis* 1973;**32**:181–201.
- Gladman DD, Farewell VT, Pellett F, Schentag C, Rahman P. HLA is a candidate region for psoriatic arthritis. Evidence for excessive HLA sharing in sibling pairs. *Hum Immunol* 2003;**64**:887–9.
- Nair RP, Henseler T, Jenisch S, Stuart P, Bichakjian CK, Lenk W, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. *Hum Mol Genet* 1997;**6**:1349–56.
- Trembath RC, Clough RL, Rosbotham JL, Jones AB, Camp RD, Frodsham A, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet* 1997;**6**:813–20.
- Burden AD, Javed S, Bailey M, Hodgins M, Connor M, Tillman D. Genetics of psoriasis: paternal inheritance and a locus on chromosome 6p. *J Invest Dermatol* 1998;**110**:958–60.
- Leder RO, Mansbridge JN, Hallmayer J, Hodge SE. Familial psoriasis and HLA-B: unambiguous support for linkage in 97 published families. *Hum Hered* 1998;**48**:198–211.
- Capon F, Novelli G, Semprini S, Clementi M, Nudo M, Vultaggio P, et al. Searching for psoriasis susceptibility genes in Italy: genome scan and evidence for a new locus on chromosome 1. *J Invest Dermatol* 1999;**112**:32–5.
- Balendran N, Clough RL, Arguello JR, Barber R, Veal C, Jones AB, et al. Characterization of the major susceptibility region for psoriasis at chromosome 6p21.3. *J Invest Dermatol* 1999;**113**:322–8.
- Samuelsson L, Enlund F, Torinsson A, Yhr M, Inerot A, Enerback C, et al. A genome-wide search for genes predisposing to familial psoriasis by using a stratification approach. *Hum Genet* 1999;**105**:523–9.
- Lee YA, Ruschendorf F, Windemuth C, Schmitt-Egenolf M, Stadelmann A, Nurnberg G, et al. Genomewide scan in German families reveals evidence for a novel psoriasis-susceptibility locus on chromosome 19p13. *Am J Hum Genet* 2000;**67**:1020–4.
- Enerback C, Martinsson T, Inerot A, Wahlstrom J, Enlund F, Yhr M, et al. Evidence that HLA-Cw6 determines early onset of psoriasis, obtained using sequence-specific primers (PCR-SSP). *Acta Derm Venereol* 1997;**77**:273–6.
- Tiilikainen A, Lassus A, Karvonen J, Vartiainen P, Julin M. Psoriasis and HLA-Cw6. *Br J Dermatol* 1980;**102**:179–84.
- Barton A, Ollier W. Genetic approaches to the investigation of rheumatoid arthritis. *Curr Opin Rheumatol* 2002;**14**:260–9.
- Al Heresh AM, Proctor J, Jones SM, Dixey J, Cox B, Welsh K, et al. Tumour necrosis factor-alpha polymorphism and the HLA-Cw\*0602 allele in psoriatic arthritis. *Rheumatology (Oxford)* 2002;**41**:525–30.
- Gladman DD, Cheung C, Ng CM, Wade JA. HLA-C locus alleles in patients with psoriatic arthritis (PsA). *Hum Immunol* 1999;**60**:259–61.
- Espinoza LR, Vasey FB, Oh JH, Wilkinson R, Osterland CK. Association between HLA-BW38 and peripheral psoriatic arthritis. *Arthritis Rheum* 1978;**21**:72–5.
- Armstrong RD, Panayi GS, Welsh KI. Histocompatibility antigens in psoriasis, psoriatic arthropathy, and ankylosing spondylitis. *Ann Rheum Dis* 1983;**42**:142–6.
- Rahman P, Schentag CT, Gladman DD. Immunogenetic profile of patients with psoriatic arthritis varies according to the age at onset of psoriasis. *Arthritis Rheum* 1999;**42**:822–3.
- McHugh NJ, Laurent MR, Treadwell BL, Tweed JM, Dagger J. Psoriatic arthritis: clinical subgroups and histocompatibility antigens. *Ann Rheum Dis* 1987;**46**:184–8.
- Gonzalez S, Brautbar C, Martinez-Borra J, Lopez-Vazquez A, Segal R, Blanco-Gelaz MA, et al. Polymorphism in MICA rather than HLA-B/C genes is associated with psoriatic arthritis in the Jewish population. *Hum Immunol* 2001;**62**:632–8.
- Espinoza LR, Vasey FB, Gaylord SW, Dietz C, Bergen L, Bridgeford P, et al. Histocompatibility typing in the seronegative spondyloarthropathies: a survey. *Semin Arthritis Rheum* 1982;**11**:375–81.
- Kantor SM, Hsu SH, Bias WB, Arnett FC. Clinical and immunogenetic subsets of psoriatic arthritis. *Clin Exp Rheumatol* 1984;**2**:105–9.

24. **Sakkas LI**, Loqueman N, Bird H, Vaughan RW, Welsh KI, Panayi GS. HLA class II and T cell receptor gene polymorphisms in psoriatic arthritis and psoriasis. *J Rheumatol* 1990;**17**:1487–90.
25. **Gerber LH**, Murray CL, Perlman SG, Barth WF, Decker JL, Nigra TA, *et al*. Human lymphocyte antigens characterizing psoriatic arthritis and its subtypes. *J Rheumatol* 1982;**9**:703–7.
26. **Gladman DD**, Anhorn KA, Schachter RK, Mervart H. HLA antigens in psoriatic arthritis. *J Rheumatol* 1986;**13**:586–92.
27. **Gladman DD**, Farewell VT, Rahman P, Schentag CT, Pellett F, Ng CM, *et al*. HLA-DRB1\*04 alleles in psoriatic arthritis: comparison with rheumatoid arthritis and healthy controls. *Hum Immunol* 2001;**62**:1239–44.
28. **Korendowych E**, Dixey J, Cox B, Jones S, McHugh N. The influence of the HLA-DRB1 rheumatoid arthritis shared epitope on the clinical characteristics and radiological outcome of psoriatic arthritis. *J Rheumatol* 2003;**30**:96–101.
29. **Gladman DD**, Farewell VT. HLA studies in psoriatic arthritis: current situation and future needs. *J Rheumatol* 2003;**30**:4–6.
30. **Henseler T**. Genetics of psoriasis. *Arch Dermatol Res* 1998;**290**:463–76.
31. **Kastelan M**, Gruber F, Cecuk E, Kerhin-Brkljacic V, Brkljacic-Surkalovic L, Kastelan A. Analysis of HLA antigens in Croatian patients with psoriasis. *Acta Derm Venereol Suppl (Stockh)* 2000;**211**:12–13.
32. **Newton JL**, Harey SM, Wordsworth BP, Brown MA. A review of the MHC genetics of rheumatoid arthritis. *Genes Immun* 2004;**5**:151–7.
33. **Gibert M**, Balandraud N, Touinssi M, Mercier P, Roudier J, Reviron D. Functional categorization of HLA-DRB1 alleles in rheumatoid arthritis: the protective effect. *Hum Immunol* 2003;**64**:930–5.
34. **Ho PY**, Barton A, Worthington J, Thomson W, Silman AJ, Bruce IN. HLA-Cw6 and HLA-DRB1\*07 together are associated with less severe joint disease in psoriatic arthritis. *Ann Rheum Dis* 2007;**66**:807–11.
35. **Plant D**, Lear J, Marsland A, Worthington J, Griffiths CE. CARD15/NOD2 single nucleotide polymorphisms do not confer susceptibility to type I psoriasis. *Br J Dermatol* 2004;**151**:675–8.
36. **Ho P**, Bruce IN, Silman A, Symmons D, Newman B, Young H, *et al*. Evidence for common genetic control in pathways of inflammation for Crohn's disease and psoriatic arthritis. *Arthritis Rheum* 2005;**52**:3596–602.
37. **Fernandez-Sueiro Sr JL**, Willisch A, Pinto J, Pertega S, Galdo F, Blanco FJ. Clinical features of psoriatic arthritis according to the type of cutaneous psoriasis. *Arthritis Rheum* 2005;(9):supplement, abstract 504.
38. **Arnett FC**, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
39. **Lopez-Larrea C**, Torre Alonso JC, Rodriguez PA, Coto E. HLA antigens in psoriatic arthritis subtypes of a Spanish population. *Ann Rheum Dis* 1990;**49**:318–19.
40. **Gladman DD**, Farewell VT, Kopciuk KA, Cook RJ. HLA markers and progression in psoriatic arthritis. *J Rheumatol* 1998;**25**:730–3.
41. **Woodrow JC**, Ilchysyn A. HLA antigens in psoriasis and psoriatic arthritis. *J Med Genet* 1985;**22**:492–5.
42. **Allen MH**, Ameen H, Veal C, Evans J, Ramrakha-Jones VS, Marsland AM, *et al*. The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. *J Invest Dermatol* 2005;**124**:103–6.
43. **Helliwell PS**, Porter G, Taylor WJ. Polyarticular psoriatic arthritis is more like oligoarticular psoriatic arthritis, than rheumatoid arthritis. *Ann Rheum Dis* 2007;**66**:113–17.

### Keep up to date: sign up for our alerting services

Find out automatically when an article is published on a specific topic or by a particular author. We can also alert you when an article is cited or if an eLetter or correction is published. You can also choose to be alerted when a new issue is published online [and when we post articles Online First]. Check out the New Content Alerts and Citation tracker from the Online tools section on the home page.