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

Pauline YPC Ho¹ (MRCP), Anne Barton¹ (PhD, FRCP), Jane Worthington¹ (PhD), Darren Plant¹ (PhD), Christopher EM Griffiths² (MD, FRCP), Helen S Young² (PhD, MRCP), Peter Bradburn³ (BSc), Wendy Thomson¹ (PhD), Alan J Silman¹ (MD, FRCP), Ian N Bruce¹ (MD, FRCP).

1. arc-Epidemiology Unit, Stopford Building, University of Manchester, Manchester, M13 9PT, UK.
2. Dermatology Centre, Hope Hospital, University of Manchester, Manchester, M6 8HD, UK.
3. Dept of Public Health and Epidemiology, University of Birmingham, B15 2TT, UK.

Address for correspondence and reprint requests: Pauline Ho
arc-EU, Stopford Building, University of Manchester, Oxford Road, Manchester, UK, M13 9PT

  e-mail: Pauline.Ho@manchester.ac.uk

Key words: HLA-Cw*06, HLA-DRB1, HLA-DRB1*07, psoriatic arthritis, genetics.
Abstracts

Objective: Psoriasis of early onset (Type I; age of onset ≤ 40 years) is associated with HLA-Cw*06 whilst the shared epitope (SE) is associated with rheumatoid arthritis (RA) 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 (UIA) 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 = 2.2x10^-21) and with PsA patients having type I psoriasis (OR 5.0, 95% CI 3.2, 7.9, p = 4.39x10^-13), but not with PsA patients having type II psoriasis (age of onset > 40 years). HLA-DRB1*07, in linkage disequilibrium with HLA-Cw*06, was also associated with PsA patients 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 UIA but not with PsA.

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

Psoriatic arthritis (PsA) is commonly defined as “an inflammatory arthritis (IA) associated with psoriasis which is usually negative for rheumatoid factor (RF)” (1). A strong genetic component to susceptibility is suggested by the sibling recurrence risk ratio (λs), which is estimated to be 27 (2;3). Part of the genetic predisposition is likely to be explained by genes within the major histocompatibility complex (MHC) region. For example, human leukocyte 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 ≤ 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 (4-13). 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 DRβ chain) (14). 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 inflammatory arthritis alone is a challenge. There is evidence to suggest that carriage of the HLA-Cw*06 allele is associated with PsA patients with type I psoriasis (12;15-19). Studies of the HLA Class II DRB1 gene have reported that the HLA-DRB1*07 phenotype is associated with peripheral arthritis in PsA whilst HLA-DRB1*04 is associated with a subgroup of PsA patients with polyarthritis mimicking that of RA (20-26). 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-DRB*0401 (which is a SE allele) occurred less frequently (27). Conflicting results have been reported with regard to the HLA-DRB1*02 (HLA-DRB*15 or HLA-DRB*16) and PsA susceptibility with a decrease found in a UK study, but not in a cohort from Toronto (28,29). More recently, a UK study showed no overall difference in the frequency of the SE between PsA cases and controls (28).

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 i.e. 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 carriage in psoriasis patients as previous studies have excluded a role for these genes in the respective conditions (12;30-33). 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 PsA patients into type I and type II psoriasis according to the age at onset of their skin disease (type I = age of onset ≤ 40 years and type II = > 40 years of age). Analyses were also repeated in subsets of PsA patients stratified by the presence of RF.

Subjects:
PsA patients:

The recruitment of PsA patients for this study has been described previously (34). In brief, PsA patients (n = 480) under active follow up by hospital rheumatologists were recruited from throughout the UK with the majority of them coming from the North-West region of 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.

Psoriasis patients:

As described previously (35), patients with Type I psoriasis (age of onset ≤ 40 years) (n = 611) were recruited via the Dermatology Centre at Hope Hospital in Manchester. Some of the psoriasis patients 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 (UIA):

Patients with early UIA were recruited from the Norfolk Arthritis Register (NOAR) as described previously (36). This is a primary-care based inception cohort of subjects with primary UIA. Patients were aged ≥ 16 years with 2 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 inflammatory arthritis 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 sub-typing to define SE alleles were performed using 50ng of genomic DNA amplified with the Dynal RELITM SSO HLA-Cw typing and HLA-DRB1 kits (http://www.dynalbiotech.com/) using a third of the specified volumes for the PCR reagents in a 20µl reaction instead of 60µl as described previously (34). 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 χ² 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 χ² 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 (≤ 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 (LD) analysis:**
Pair wise LD measures (both D’ and r²) were investigated between HLA-Cw*06 and HLA-DRB1*07 using HelixTree (Golden Helix Inc, Montana, USA). This data has been reported previously (34).

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

**Patient characteristics:**

**PsA:** The characteristics of the PsA cohort have been described previously (34). 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 (inter-quartile 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 5 or more damaged joints (polyarthritis subgroup) and the median HAQ score was 1.25. As shown previously, PsA patients 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 (19;37). In addition, PsA patients with type I psoriasis had a longer duration of joint disease and more nail involvement, but a lower median HAQ score and fewer involved joints compared to those with type II psoriasis.

**Psoriasis:** All patients had Type I psoriasis with 46% (283/611) 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 psoriasis patients 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 vs. 40% in the remainder, p = 0.44).

**UIA:** 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 ACR criteria for RA (38). 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 was available for 166, whilst HLA-DRB1 data was 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 (15;16;25;26;39-41) (Table 2).

When compared to 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=5.5x10⁻⁹) (Table 2 and Figure 1). Stratification analysis in the PsA cohort by RF status made no difference to the result (OR in RF negative PsA subgroup 3.6, 95% CI 2.3, 5.9, p= 9.6x10⁻⁹). However, the association with HLA-Cw*06 was confined to the subgroup of PsA patients with type I
psoriasis (OR 5.0, 95% CI 3.2, 7.9, p = 4.39x10^{-13}) and was not observed in PsA patients with type II psoriasis (OR 1.1, 95% CI 0.6, 2.1, p = 0.76).

For the psoriasis cohort, as expected, *HLA-Cw*06 was strongly associated with Type I psoriasis compared to controls (OR 6.9 95% CI 4.4 to 11.1, p=2.15x10^{-21}) (Table 2 and Figure 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 PsA patients with type I psoriasis and patients with Type I psoriasis alone. A much weaker association was noted (PsA with type I psoriasis vs. 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 PsA patients with type I psoriasis (OR 2.7, 95% CI 2.1, 3.7 and p<0.00001) compared to controls. Although, *HLA-DRB1*07 occurred significantly more frequently in PsA cases than controls, we have previously reported that this allele exhibits considerable linkage disequilibrium (LD) with *HLA-Cw*06 (correlation ($r^2$) = 0.46) (34). 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 to 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 - 5.3), confirming that the primary association is with *HLA-Cw*06 and not *HLA-DRB1*07.

PsA patients negative for RF were less likely to carry the *HLA-DRB1*04 phenotype compared to population controls (OR 0.74, 95% CI 0.55, 0.99, p=0.03), but no difference was observed between those PsA patients with a positive RF compared to controls (OR 0.96, 95% CI 0.56, 1.61, p=0.88). In addition, the *HLA-DRB1*04 phenotype occurred less frequently in PsA patients with type I psoriasis compared to population controls (p=0.004), but no difference was observed in those PsA patients with type II psoriasis compared to controls (p=0.45). Within PsA patients, when the *HLA-DRB1*04 phenotype was present, it occurred more commonly in PsA patients with type II psoriasis compared to those with type I psoriasis (OR 1.81, 95% CI 1.14, 2.86, p=0.007). No association was detected with those PsA patients having ≥ 5 damaged (poly-damaged) or ≥ 5 involved (poly-involved) joints with the *HLA-DRB1*04 phenotype compared to 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), whilst the *HLA-DRB1*07 phenotype was more common in the PsA cohort compared to population controls (OR 2.15, 95% CI 1.62, 2.84, p = 2.6x10^{-8}). However, when comparing PsA patients with type II psoriasis to 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 to PsA patients 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 PsA patients with type I psoriasis compared to UIA (OR 3.23, 95% CI 2.51, 4.14, p<0.0001).

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

When comparing PsA patients and controls, no association was detected with SE allele carriage and PsA (Table 4 and Figure 2) either in the entire cohort (p = 0.94) or after stratifying the PsA patients by type I or type II psoriasis or by their RF status. For example, no association was detected when comparing SE phenotype between PsA patients with type I psoriasis and population controls (OR 0.90, 95% CI 0.68, 1.19, p = 0.43) or when comparing PsA patients with type II psoriasis to 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 to controls (OR 1.88, 95% CI 1.53, 2.29, p = 3.63x10^-10; Table 4 and Figure 2). When comparing the UIA and PsA subgroups directly, the frequency of the SE phenotype was significantly higher in UIA subjects compared to those PsA patients with type I psoriasis (OR 2.08, 95% CI 1.64, 2.66, p = 7.1x10^-10), but the effect size was lower when comparing UIA subjects to PsA patients with type II psoriasis (OR 1.51, 95% CI 1.02, 2.22, p = 0.03).

Discussion

In this large association study of PsA patients, we have shown that both HLA-Cw*06 and HLA-DRB1*07 are associated with PsA susceptibility in the subgroup of PsA patients 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 2 HLA genes in large cohorts of PsA patients 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 psoriasis patients as previous studies have excluded a role for these genes in the respective conditions (12;30-33). Previous studies on psoriasis patients have shown that both HLA-Cw*06 and HLA-DRB1*07 are associated with Type I psoriasis, but not with Type II psoriasis (12;30;31;42). 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, PsA patients (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 ACR classification criteria for RA by 5 years. In contrast, it occurred less commonly in those PsA patients negative for RF and those PsA patients with type I psoriasis compared to controls. When HLA-DRB1*04 was present in PsA patients, it occurred more frequently in those with type II psoriasis compared to PsA patients 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 PsA patients 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 rheumatoid arthritis 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 PsA patients or those with polyarticular disease but we did not find that to be the case. An advantage of the approach of not excluding RF positive patients is that we have been able to stratify the PsA patients 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 (43).

We have also confirmed the finding of others that the SE was not associated with PsA susceptibility (28;29). Unsurprisingly, the SE was found to be strongly associated with UIA susceptibility and occurred significantly more frequently in UIA subjects compared to PsA patients with type I psoriasis. The smaller number of PsA patients with type II psoriasis may have limited the interpretation of this analysis but the odds of carrying the SE was also significantly higher in UIA subjects compared to PsA patients with type II psoriasis. The findings confirm that, although PsA patients with type II psoriasis appear more genetically similar to UIA subjects than do PsA patients with type I psoriasis, UIA and PsA patients 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 PsA patients with type I psoriasis. We conclude, therefore, that HLA-Cw*06 does not confer additional susceptibility to IA in psoriasis patients. 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 PsA patients with type I and type II psoriasis have different genetic susceptibility factors and that PsA patients with type I psoriasis are more genetically similar to Type I psoriasis patients at least at the HLA-Cw*06 locus. This implies that in future genetic studies, it may be important to stratify PsA patients according to age of onset of psoriasis.
Acknowledgements

This work has been supported by the Arthritis Research Campaign, the Wellcome Trust (Entry Level Fellowships for P Ho and H Young; Advanced Fellowship for A Barton) and the Medical Research Council UK (Clinical Training Fellowship for P Ho).

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in ARD and any other BMJPGL products and sublicense such use and exploit all subsidiary rights, as set out in our license (http://ARD.bmjjournals.com/ifora/licence.pdf).
Reference List


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

<table>
<thead>
<tr>
<th>Subjects</th>
<th>HLA-Cw*06 Information: n</th>
<th>HLA-DRB1 Information: n</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsA whole cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PsA with type I psoriasis</td>
<td>335</td>
<td>342</td>
</tr>
<tr>
<td>• PsA with type II psoriasis</td>
<td>115</td>
<td>120</td>
</tr>
<tr>
<td>Psoriasis (all Type I)</td>
<td>611</td>
<td>NA</td>
</tr>
<tr>
<td>UIA</td>
<td>NA</td>
<td>1621</td>
</tr>
<tr>
<td>Population controls</td>
<td>166</td>
<td>537</td>
</tr>
</tbody>
</table>

UIA = early undifferentiated inflammatory arthritis
NA = not available.
NB. For 3 PsA cases, data was not available as to the type of psoriasis present.
Table 2. Comparison of HLA-Cw*06 in PsA cases, psoriasis and controls

<table>
<thead>
<tr>
<th>HLA-Cw*06</th>
<th>PsA cases</th>
<th>Population controls</th>
<th>Type I psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cohort n = 453</td>
<td>n = 166</td>
<td>n = 611</td>
</tr>
<tr>
<td>0</td>
<td>262 (57.8)</td>
<td>166 (49.6)</td>
<td>94 (81.7)</td>
</tr>
<tr>
<td>1</td>
<td>182 (40.2)</td>
<td>162 (48.4)</td>
<td>19 (16.5)</td>
</tr>
<tr>
<td>2</td>
<td>9 (2)</td>
<td>7 (2)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Phenotype</td>
<td>191 (42.2)</td>
<td>169 (50.4)</td>
<td>21 (18.3)</td>
</tr>
<tr>
<td>p-value*</td>
<td>5.5x10^{-9}</td>
<td>4.39x10^{-13}</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Type I: PsA patients with type I psoriasis
Type II: PsA patients with type II psoriasis

*Comparison of phenotype (carriage of 1 or 2 alleles) with population controls using χ² test

Data shown in n (%)

Data was not available for 3 patients as to the type of psoriasis present.
Table 3. *HLA-DRB1* phenotypes in PsA cases, UIA and controls (where data available)

<table>
<thead>
<tr>
<th>HLA-DRB1</th>
<th>PsA cases</th>
<th>Controls n = 537</th>
<th>p value (PsA whole cohort compared to controls)</th>
<th>UIA n=1621</th>
<th>P value (UIA compared to controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole cohort n = 465</td>
<td>Type I n = 342</td>
<td>Type II n = 120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRB1*02</td>
<td>118 (25)</td>
<td>81 (24)</td>
<td>36 (30)</td>
<td>145 (27)</td>
<td>0.57</td>
</tr>
<tr>
<td>DRB1*04</td>
<td>142 (31)</td>
<td>92 (27)</td>
<td>48 (40)</td>
<td>195 (36)</td>
<td>0.06</td>
</tr>
<tr>
<td>DRB1*07</td>
<td>188 (40)</td>
<td>159 (46)</td>
<td>29 (24)</td>
<td>129 (24)</td>
<td>3.09x10^-8</td>
</tr>
</tbody>
</table>

PsA: psoriatic arthritis
UIA: Early undifferentiated inflammatory arthritis
Type I: PsA patients with type I psoriasis
Type II: PsA patients with type II psoriasis
Data shown in n (%) unless stated otherwise
Table 4. Shared epitope frequency in PsA cases, UIA and controls

<table>
<thead>
<tr>
<th>Shared epitope</th>
<th>UIA n=1621</th>
<th>PsA cases Whole cohort n=467</th>
<th>Type I n=344</th>
<th>Type II n=120</th>
<th>Population controls n=537</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>634 (39.1)</td>
<td>256 (54.8)</td>
<td>197 (57.3)</td>
<td>59 (49.2)</td>
<td>293 (54.6)</td>
</tr>
<tr>
<td>1</td>
<td>740 (45.7)</td>
<td>184 (39.4)</td>
<td>126 (36.6)</td>
<td>55 (45.8)</td>
<td>203 (37.8)</td>
</tr>
<tr>
<td>2</td>
<td>247 (15.2)</td>
<td>27 (5.8)</td>
<td>21 (6.1)</td>
<td>6 (5.0)</td>
<td>41 (7.6)</td>
</tr>
<tr>
<td>Phenotype</td>
<td>987 (60.9)</td>
<td>211 (45.2)</td>
<td>147 (42.7)</td>
<td>61 (50.8)</td>
<td>244 (45.4)</td>
</tr>
<tr>
<td>p-value*</td>
<td>3.63x10^{-10}</td>
<td>0.94</td>
<td>0.43</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

UIA: early undifferentiated inflammatory arthritis
Type I: PsA patients with type I psoriasis
Type II: PsA patients with type II psoriasis
*Comparison of phenotype (carriage of 1 or 2 alleles) with population controls
Data shown in n (%) unless stated otherwise
Figure 1. Comparison of *HLA-Cw*06 phenotype in PsA cases, psoriasis and controls
(Figure shows odds ratios and 95% confidence intervals on a log scale).
Figure 2. Shared epitope phenotype in PsA cases, undifferentiated inflammatory arthritis and controls
(Figure shows odds ratios and 95% confidence intervals on a log scale).
Investigating the role of the HLA-Cw*06 and HLA-DRB1 genes in susceptibility to psoriatic arthritis: comparison with psoriasis and undifferentiated inflammatory arthritis

Pauline YPC Ho, Anne Barton, Jane Worthington, Darren Plant, Christopher EM Griffiths, Helen S Young, Peter Bradburn, Wendy Thomson, Alan J Silman and Ian N Bruce

Ann Rheum Dis published online August 29, 2007

Updated information and services can be found at:
http://ard.bmj.com/content/early/2007/08/29/ard.2007.071399

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Open access (634)
- Degenerative joint disease (4641)
- Musculoskeletal syndromes (4951)
- Connective tissue disease (4253)
- Genetics (969)
- Immunology (including allergy) (5144)
- Rheumatoid arthritis (3258)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/