EXTENDED REPORT

HLA-Cw6 and *HLA-DRB1*07* together are associated with less severe joint disease in psoriatic arthritis

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Ann Rheum Dis 2007;**66**:807–811. doi: 10.1136/ard.2006.064972

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Accepted 25 December 2006
Published Online First 11 January 2007

Background: Human leucocyte antigen (HLA) genes predict disease severity in psoriasis (*HLA-Cw6*) and rheumatoid arthritis (shared epitope (SE)), but the situation is unclear for psoriatic arthritis (PsA).
Aim: To determine the association of the *HLA-Cw6* and *HLA-DRB1* gene with disease severity in a large UK cohort with PsA.
Methods: Genotyping of the *HLA-Cw* and *HLA-DRB1* loci was undertaken in DNA samples from patients with PsA (n = 480). Stratification and regression analysis were used within the PsA cases to determine whether *HLA-Cw6*, *HLA-DRB1* or the presence of the SE alleles predicted disease severity as measured by the Health Assessment Questionnaire score, the total number of damaged or involved joints adjusted for disease duration and disease-modifying antirheumatic treatments.
Results: *HLA-Cw6* was found to be in linkage disequilibrium with *HLA-DRB1*07* ($r^2 = 0.46$). Patients with PsA who carried both *HLA-Cw6* and *HLA-DRB1*07* had fewer damaged or involved joints (41% fewer damaged (95% CI 23% to 55%, p = 0.02) and 31% fewer involved joints (95% CI 16% to 44%, $p<0.001$)) compared with those who carried neither *HLA-Cw6* nor *HLA-DRB1*07* alleles. Those who carried either *HLA-Cw6* or *HLA-DRB1*07* alleles alone had no evidence of a reduction in joint involvement. The SE, *HLA-DRB1**03 and *HLA-DRB1*04* alleles did not predict severity using these outcome measures.
Conclusion: Patients with PsA carrying both *HLA-Cw6* and *HLA-DRB1*07* alleles have a less severe course of arthritis. This suggests that a protective locus lies on a haplotype marked by these alleles. No association was detected with disease severity and SE status.

Psoriasis affects 1–3% of the adult population, with the plaque form (psoriasis vulgaris) being the most common subtype.[1] Up to 40% of patients with psoriasis have an associated inflammatory arthritis (IA).[2–6] This disease combination, psoriatic arthritis (PsA), is defined as ''an inflammatory arthritis associated with psoriasis which is usually negative for rheumatoid factor (RF)''.[7] Increasing evidence suggests that PsA causes significant morbidity and mortality, with almost 20% of patients developing deforming arthritis.[8–12]

Polymorphisms in genes encoded within the human leucocyte antigen (HLA) region are associated with disease severity in both psoriasis and rheumatoid arthritis (RA). Psoriasis has two common subtypes, type I and type II. The age at onset for type I psoriasis is $\leqslant$40 years, whereas that for type II psoriasis is >40 years. Patients with type I psoriasis have a stronger family history and genetic predisposition. Patients with type I psoriasis who carry the HLA class I allele *HLA-Cw6* have an earlier onset with more extensive and severe skin disease.[13] Patients with RA carrying shared epitope (SE) alleles, particularly two copies, 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) have a more severe phenotype and are more likely to develop extra-articular manifestations.[14–19] The role of the HLA region in determining disease severity in PsA is less clear. *HLA-Cw6* was found to be associated with oligoarthritis in one study,[8] but with polyarthritis in another.[20] In addition, a few small studies have shown that *HLA-DRB1*03* and *HLA-DRB1*04* phenotypes were associated with severe and erosive disease.[21–23] Furthermore, one study showed that the SE was associated with the development of erosions.[24]

The aim of this study therefore was to determine the association of the *HLA-Cw6* and *HLA-DRB1* gene, in particular SE alleles, with disease severity in a large UK cohort with PsA.

METHODS

A within-case study was performed in which all patients with PsA were Caucasians of British Isles descent. Stratification and regression analysis were performed within the PsA cases.

Subjects

Four hundred and eighty patients with PsA attending hospital rheumatologists throughout the UK were recruited after a media campaign and direct referral from consultant rheumatologists. The majority were recruited from the northwest of England. All patients satisfied our inclusion criteria of having both clinically documented inflammatory synovitis and psoriasis regardless of their RF status.

Clinical assessment

A trained research nurse interviewed the patients who also completed a standardised questionnaire. The patient questionnaire included demographic details, age at onset of psoriasis and arthritis, self-reported family history of arthritis and/or psoriasis, and a record of nail or other extra-articular involvement as well as the use of disease-modifying antirheumatic drugs (DMARDs). Functional assessment was performed by using the Stanford Health Assessment Questionnaire (HAQ).[25] The nurse performed a 69-joint examination including the cervical spine, shoulders, elbows, wrists, the metacarpophalangeal joints, proximal interphalangeal joints and distal interphalangeal joints of the hands, the hips, knees, ankles, metatarsophalangeal joints, proximal interphalangeal joints and distal interphalangeal joints of the toes to detect swelling,

Abbreviations: DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HLA, human leucocyte antigen; IA, inflammatory arthritis; LD, linkage disequilibrium; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SE, shared epitope

tenderness and deformity as described previously.[26] A force adequate to blanch the examiner's fingernail bed was used to assess for tenderness, except at the hips where pain on motion constituted tenderness. Joint swelling was recorded if both clinical observation and examination confirmed the finding of soft tissue swelling. A deformed/damaged joint was defined as one of the following: inability to attain the anatomical position, reduction in the range of movement by one-third (unassisted movements) or surgical alteration to the joint.[26]

Current psoriasis severity was graded according to the Psoriasis Area and Severity Index score (range 0–72). The research nurse had been specifically trained to assess this at the Dermatology Centre, Hope Hospital, Salford, Manchester, UK.[27]

Whole blood was obtained for the measurement of RF status (ascertained using a particle agglutination test with a titre >1:40 considered positive) and for DNA extraction.

The study was approved by the North West Multi-centre Research Ethics Committee (MREC 99/8/84) and all subjects provided written informed consent.

HLA typing

For HLA genotyping, 50 ng of genomic DNA was amplified using the Dynal RELI SSO *HLA-Cw* typing and *HLA-DRB1* kits (using one-third of the specified volumes for the PCR reagents) in a 20 µl reaction volume instead of 60 µl. PCR amplicons were identified by a reverse line assay using sequence-specific oligonucleotide probes with the Dynal RELI sequence-specific oligonucleotide strip detection reagent kit (http://www.dynal-biotech.com/). Assay results were interpreted using the Pattern Matching Program provided by Dynal (Invitrogen, Paisley, UK). Broad HLA genotyping and subtyping were performed to identify the presence of the SE in the *HLA-DRB1* locus. 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*.

Statistical analysis

The influence of HLA on a number of disease characteristics was evaluated. The Mann–Whitney U test and χ^2 test were used to compare the characteristics of patients with PsA with type I and type II psoriasis in terms of the extent of skin disease. Allele frequencies of *HLA-Cw6* were compared between these two groups using a χ^2 test. With regard to the major joint aspects, negative binomial regression analysis was used to determine whether *HLA-Cw6*, *HLA-DRB1* or the presence of the SE alleles predicted disease severity as measured by the HAQ, the total number of damaged joints and the total number of involved (tender or swollen or damaged) joints. All analyses were adjusted for duration of joint disease and the use of DMARDs. Subgroup analyses were performed after stratifying the cohort with PsA by RF status, type I or type II psoriasis and whether the DMARD was prescribed by dermatologists or rheumatologists.

Linkage disequilibrium analysis

Pairwise linkage disequilibrium (LD) measures (both D' and r^2) were investigated between *HLA-Cw6* and *HLA-DRB1*07* using HelixTree (Golden Helix, Montana, USA).

RESULTS

Patients' characteristics

Tables 1 and 2 describe the characteristics of the cohort with PsA . There is an almost equal gender distribution with a female to male ratio of 1.3:1. Most subjects had type I psoriasis (74%); 57% had at least five damaged joints and RF (titre >1:40) was present in 17%. After stratifying the whole cohort by the presence of RF, no significant difference was observed in the number of tender, swollen, damaged or involved (tender, swollen or damaged) joints between these two subgroups (p = 0.99, 0.38, 0.10 and 0.25, respectively). Patients with PsA with type I psoriasis had a longer duration of joint disease, a stronger family history of both psoriasis and PsA and more nail involvement. In addition, they also tended to develop arthritis after the onset of psoriasis rather than either simultaneously or before the onset of psoriasis. Despite having a longer duration of arthritis, patients with PsA with type I psoriasis had fewer involved and damaged joints as well as lower mean HAQ scores. There was also a trend towards patients with PsA with type II psoriasis being more likely to be RF positive (odds ratio 1.63, 95% CI 0.97 to 2.74, p = 0.06).

HLA-Cw6

Table 3 shows the distribution of *HLA-Cw6* alleles in the cohort with PsA . A total of 191 (42%) patients with PsA carried at least one *HLA-Cw6* allele. The proportion of patients with PsA with type I psoriasis carrying the *HLA-Cw6* phenotype was significantly higher than those with type II psoriasis ($p = 1.2\times10^{-9}$).

Table 1 Characteristics of the cohort with psoriatic arthritis

Characteristics of patients with PsA (n = 480)	
Female gender, n (%)	275 (57)
Plaque psoriasis, n (%)	393 (82)
Type I psoriasis (age at onset ⩽40 years), n (%)	354 (74)
Type II psoriasis (age at onset >40 years), n (%)	123 (26)
Median (IQR) age at onset of psoriasis (years)	26 (15–42.5)
Median (IQR) age at onset of arthritis (years)	36.5 (26–49)
Family history of	
Psoriasis, n (%)	236 (49)
PsA, n (%)	34 (7)
Nail involvement, n (%)	391 (81)
Presence of rheumatoid factor, n (%)	81 (17)
Ever used DMARD, n (%)	389 (81)
MH of dysentery, n (%)	20 (4)
MH conjunctivitis, n (%)	156 (33)
MH uveitis, n (%)	23 (5)
MH recurrent mouth ulcers, n (%)	157 (33)
MH of sexually transmitted disease, n (%)	12 (3)
Median (IQR) PASI	6 (2.5–11.2)
Median (IQR) HAQ	1.25 (0.25–1.875)
Median (IQR) duration of psoriasis (years)	19 (9–33)
Median (IQR) duration of arthritis (years)	10 (5–19)
Onset	
Psoriasis (>1 year) before arthritis, n (%)	304 (63)
Arthritis (>1 year) before psoriasis, n (%)	72 (15)
Psoriasis and arthritis at the same time (±1 year), n (%)	104 (22)
Involved joint *	
Whole cohort, median (IQR)	10 (4.5–21)
Presence of DIP involvement, n (%)	310 (65)
Mono-involved joints, n (%)	22 (5)
Oligo-involved joints (⩽4 joints), n (%)	98 (20)
Poly-involved joints (⩾5 joints), n (%)	360 (75)
Tender joint count	
Whole cohort, median (IQR)	2 (0–6)
Swollen joint count	
Whole cohort, median (IQR)	1 (0–4)
Damaged joints	
Whole cohort, median (IQR)	6 (2–15)
DIP damaged, n (%)	257 (54)
Mono-damaged, n (%)	36 (8)
Oligo-damaged (⩽ 4 joints), n (%)	132 (28)
Poly-damaged joints (⩾5 joints), n (%)	272 (57)

DIP, distal interphalengeal; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; MH, medical history; PsA, psoriatic arthritis.
*Involved joints refer to tender, swollen or damaged joints.

Table 2 Comparison of patients with psoriatic arthritis with type I and type II psoriasis

	PsA subgroups		
	Type I psoriasis, n = 354	Type II psoriasis, n = 123	Comparison (p value)
Median (IQR) age at onset of psoriasis (years)	20 (12–29)	52 (47–59)	<0.001 (Mann–Whitney U test)
Median (IQR) age at onset of arthritis (years)	31(24–41)	51 (45–59)	<0.001 (Mann–Whitney U test)
Median (IQR) duration of psoriasis (years)	25(15–39)	8 (4–14)	<0.001 (Mann–Whitney U test)
Median (IQR) duration of arthritis (years)	11(5–20)	9 (4–14)	0.03 (Mann–Whitney U test)
PASI score median (IQR)	6.3 (3.1–11.5)	4.85 (1.6–9)	0.003 (Mann–Whitney U test)
Family history of			
Psoriasis, n (%)	196 (55)	37 (30)	<0.001
PsA, n (%)	32 (9)	2 (2)	0.007
Joints			
Involved*, median (IQR)	9 (4–21)	13 (8–22)	0.03 (Mann–Whitney U test)
Damaged, median (IQR)	5 (1–15)	8 (4–17)	0.006 (Mann—Whitney U test)
Tender, median (IQR)	2 (0–6)	2 (0–5)	0.81 (Mann—Whitney U test)
Swollen, median (IQR)	2 (0–4)	1 (0–3)	0.20 (Mann—Whitney U test)
Nail involvement, n (%)	299 (85)	91 (75)	0.02
Onset, n (%)			
Psoriasis before arthritis	268 (76)	36 (29)	Global
Arthritis before psoriasis	28 (8)	41 (33)	<0.001
Same time (±1 year)	58 (16)	46 (38)	
Median (IQR) HAQ	1.13 (0.38–1.75)	1.38 (0.63–2)	0.03 (Mann–Whitney U test)
Ever used DMARD, n (%)	287 (81)	99 (80)	0.89

DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IQR, interquartile range; PsA, psoriatic arthritis.
*Involved joints refer to tender, swollen or damaged joints.

Patients with PsA carrying the *HLA-Cw6* phenotype had fewer damaged or involved (tender, swollen or damaged) joints, (30% less damaged joints (95% CI 13% to 44%, p = 0.001) and 20% less involved joints (95% CI 6% to 33%, p = 0.008)) Restricting the analysis to those with type I psoriasis showed that the presence of *HLA-Cw6* was still associated with a similar reduction in the number of damaged joints (29%, 95% CI 9% to 45%, p = 0.01) and involved joints (20%, 95% CI 2% to 34%, p = 0.04) in this group. Similar trends were seen in those with type II psoriasis; however, the patient numbers were too small to draw robust conclusions.

HLA-DRB1

A total of 188 (40%) patients with PsA carried at least one *HLA-DRB1*07* allele. LD analysis of data generated inhouse from a control population showed that *HLA-Cw6* and *HLA-DRB1*07* were in LD ($r^2 = 0.46$). Therefore, patients with PsA carrying the *HLA-DRB1*07* phenotype also had fewer damaged and involved joints (27% less damaged joints (95% CI 8% to 41%, p = 0.007) and 18% less involved joints (95% CI 2% to 31%, p = 0.029).

In all, 317 (51.9%) patients carried neither the *HLA-Cw6* nor the *HLA-DRB1*07* alleles, whereas 145 (23.7%) carried both (table 4). Further analysis on the combined influence of these two genes (table 4) showed that carrying both *HLA-Cw6* and *HLA-DRB1*07* alleles conferred the protective effect noted, with 41% fewer damaged (95% CI 23% to 55%, p = 0.02) and 31% fewer involved joints (95% CI 16% to 44%, p<0.001) compared with those carrying neither or only one of the alleles in question. Neither *HLA-Cw6* nor *HLA-DRB1*07* predicted clinical severity as measured by the number of tender, swollen joints or theHAQ score. When analysis was confined to patients with PsA with type I psoriasis, similar results were obtained. Individuals carrying both *HLA-Cw6* and *HLA-DRB1*07* had 39% fewer damaged joints (95% CI 16% to 55%, p = 0.08) and 30% fewer involved joints (95% CI 11% to 44%, p = 0.003). The numbers of patients with PsA with type II psoriasis was too small to analyse meaningfully.

The presence of *HLA-DRB*03*, *HLA-DRB*04* or one or two copies of the RA SE alleles did not predict the HAQ score, total number of damaged joints or total number of involved joints (data not shown).

Analysis was repeated in subgroups stratified by RF status and by whether the DMARD was prescribed by a dermatologist or a rheumatologist (data not shown), but the conclusions were not meaningfully changed. For example, in RF-negative patients with PsA, *HLA-Cw6* remained associated with fewer damaged and involved joints (28% fewer damaged joints (95% CI 9% to 43%, p = 0.006) and 17% fewer involved joints (95% CI 1% to 31%, p = 0.04)

Table 3 *HLA-Cw6* in patients with psoriatic arthritis

	PsA cases		
HLA-Cw6 alleles	Total cohort, n = 453	Type I, n = 335	Type II, n = 115
0	262 (57.8)	166 (49.6)	94 (81.7)
1	182 (40.2)	162 (48.4)	19 (16.5)
2	9 (2)	7 (2)	2 (1.8)
p Value*		1.2×10^{-9}	

PsA, psoriatic arthritis; Type I, patients with PsA with type I psoriasis; Type II, patients with PsA with type II psoriasis.
Values are represented as n (%).
*Global comparison between patients with type I and type II PsA using χ^2 analysis.

DISCUSSION

As far as we are aware, this is the largest genetic association study of patients with PsA reported to date. We found that patients with PsA carrying both the *HLA-Cw6* and *HLA-DRB1*07* phenotypes have less severe joint disease, but carrying either *HLA-Cw6* or *HLA-DRB1*07* alleles alone did not confer protection. Our data confirm previous reports that the *HLA-Cw6* and *HLA-DRB1*07* alleles are in LD with each other.[28 29] In addition, we have found an interaction between these two loci. However, in contrast with previous reports, the presence of SE, *HLA-DRB1*04* or *HLA-DRB1*03* alleles did not predict clinical severity as measured by the HAQ score, the number of damaged joints or the number of involved joints. Stratification analysis by the presence of RF status did not alter these conclusions.

Table 4 Interaction of *HLA-Cw6* with *HLA-DRB1*07* in damaged and involved joints

HLA-Cw6	HLA-DRB1*07	n (%)	Damaged joints OR (95% CI)	Involved joints OR (95% CI)	Tender joints OR (95% CI)	Swollen joints OR (95% CI)
−	−	317 (51.9)	Referent	Referent	Referent	Referent
+	−	71 (11.6)	0.96 (0.69 to 1.33) p=0.82	1.12 (0.87 to 1.44) p=0.37	1.46 (0.98 to 2.18) p =0.07	1.26 (0.83 to 1.90) p = 0.28
−	+	78 (12.8)	1.10 (0.79 to 1.54) p=0.57	1.21 (0.93 to 1.57) p=0.15	1.52 (1 to 2.31) p=0.05	1.07 (0.70 to 1.64) p=0.75
+	+	145 (23.7)	0.59 (0.45 to 0.76) p=0.02	0.69 (0.56 to 0.84) p<0.001	1.02 (0.75 to 1.41) p=0.86	0.96 (0.69 to 1.33) p=0.28

+, presence of one or two alleles; −, absence of alleles.
p Value calculated using negative binomial regression analysis.

Research in PsA has been hampered by the lack of an agreed validated single classification system for PsA and an ambiguous definition of ''an inflammatory arthritis associated with psoriasis which is usually negative for rheumatoid factor''.[7] A major strength of our study is that our large cohort enables us to explore within-case comparisons to identify genetic factors for disease severity. The clinical characteristics of this cohort with PsA are very similar to those described elsewhere.[8 24 30–32] This suggests that they are typical of other hospital-based series of patients with PsA—for example, 81% had nail involvement.[6 31 33 34] Our cohort had a higher proportion of patient with a positive RF (17%) than others (ranging from 3% to 10%).[3 6 31 34 35] We define a positive RF as a titre >1:40 rather than >1:160 used in some studies. If, however, we use the more stringent cut-off value, the frequency of RF would be 11%.[31] A strength of using broad inclusion criteria for PsA is that we could perform stratification analysis-based RF to explore whether RF is an important cofactor in PsA. However, in no situation did either stratification analysis or adjustment for RF status alter the conclusions. Clinically, we have confirmed that patients with PsA with type I psoriasis have a stronger familial tendency and a predilection for psoriasis to occur before arthritis.[36 37] However, in contrast with Rahman *et al*,[36] who found no difference between those with type I or type II psoriasis in terms of the number of swollen, clinically damaged or radiographically damaged joints, we found that despite having a longer duration of joint disease, patients with PsA with type I psoriasis had less severe disease as measured by the HAQ score, number of damaged joints or involved joints.

One key limitation of our dataset is the reliance on clinical, as opposed to radiographic, evidence of joint involvement. Subjects for this study were recruited from a large number of clinical departments and *x* rays were not specifically taken by a standard protocol for this study. This investigation focused on the number of involved (tender or swollen or damaged) or damaged joints and HAQ score as clinical markers of severity. It has been shown that clinical inflammation occurs before radiological damage and that radiological damage occurs before clinical damage.[38] The number of involved joints was used as a marker of inflammation. Hence, we have tested severity using indicators that occur both before and after radiological damage to compensate for the fact that we do not have these data. Furthermore, it may be argued that using damaged joints as a marker for disease severity is more clinically relevant. Using damaged joint counts also allows an assessment of more joint areas than would have been possible with the conventional radiographs. Interestingly, when an association with either of the two surrogate indicators (involved or damaged joints) was found, the direction and strength of the association was consistent for both.

We have shown for the first time that patients with PsA carrying a combination of *HLA-Cw6* and *HLA-DRB1*07* alleles have milder disease with fewer damaged or involved joints. A potential explanation is that patients with PsA who carry the *HLA-Cw6* alleles may have been treated with a DMARD before the arthritis because of severe skin disease. However, excluding patients with PsA who had been prescribed a DMARD by their dermatologists (n = 41) did not change the associations found (data on file). The interaction between the two loci may indicate that alleles of both genes have a function in conferring protection from severe joint disease but only in combination. More likely is the hypothesis that these alleles are part of a haplotype on which the true protective allele is carried. The *HLA-C* and *HLA-DRB1* genes are separated by a number of genes such as *TNF*, *LTB*, *LTA* and *MICB*. Dissecting this association will require further work using high-density mapping of the region to identify the true protective variant.

A previous study in a UK cohort reported that the presence of the SE alleles was associated with radiological erosions, suggesting that the SE may play a role in PsA severity.[24] We did not demonstrate an association of SE alleles with other indicators of clinical severity such as the HAQ score, the number of damaged joints or the number of involved joints. Similarly, we did not confirm the results of other small studies that reported associations of *HLA-DRB*03* or *HLA-DRB1*04* with clinical severity in patients with PsA.[21–23] However, an association of SE with radiological erosions specifically cannot be excluded.

In conclusion, we have found that patients with PsA carrying both the *HLA-Cw6* and *HLA-DRB1*07* alleles have a less severe course of arthritis, as measured by the number of damaged and involved joints. This suggests an interaction between these two loci, but further work is required to determine whether the *HLA-Cw6* and *HLA-DRB1*07* themselves or a variant in LD with the associated haplotype is the real protective locus. Furthermore, despite having a large number of patients with PsA with a positive RF, we found no association between clinical disease severity markers and SE status.

ACKNOWLEDGEMENTS

This work has been supported by the Arthritis Research Campaign, the Wellcome Trust (Entry Level Fellowships for PYPCH and Advanced Fellowship for AB) and the Medical Research Council UK (Clinical Training Fellowship for PYPCH).
We thank Peter Bradburn for his help with patient recruitment.

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Competing interests: None declared.

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