

The Influence of the HLA-DRB1 Rheumatoid Arthritis Shared Epitope on the Clinical Characteristics and Radiological Outcome of Psoriatic Arthritis

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ABSTRACT. Objective. To investigate the associations of the HLA-DRB1 rheumatoid arthritis shared epitope (SE) with clinical characteristics and radiological outcome in patients with psoriatic arthritis (PsA).

Methods. One hundred fifty-eight patients with well documented PsA and 250 controls were typed for HLA-DRB1 alleles including the SE by polymerase chain reaction. Clinical data collected on the patient group included disease subset, swollen and tender joint counts, the psoriasis area severity index (PASI), and the presence of radiological erosions. Clinical and radiological associations with HLA-DRB1 and SE alleles were determined.

Results. There was an increased frequency of HLA-DR7 (41 vs 25%; $p_{\text{uncorr}} = 0.001$, OR 2.02, $p_{\text{corr}} = 0.01$) and a decreased frequency of HLA-DR2 (19 vs 28%; $p_{\text{uncorr}} = 0.03$, OR 0.59, $p_{\text{corr}} = 0.3$) in the patient population compared with controls. There was no significant difference in the frequency of HLA-DR1 and HLA-DR4 between patient and control populations. There was no significant difference in the prevalence of SE alleles between the patient and control populations (48 vs 54%). There was no increase in the prevalence of the SE in the polyarthritis subgroup, but there was a marginal decrease in those who remained in the oligoarthritis subgroup. There were no differences with respect to sex, age of onset of disease, family history, Health Assessment Questionnaire score, joint score, skin score, or nail score between those patients who were SE positive and those who were SE negative. However, significantly more patients who were SE positive developed radiological erosions (60 vs 43%; $p = 0.03$, OR 2.11).

Conclusion. Overall, the prevalence of the SE in patients with PsA did not differ from our control population. However, it was overrepresented in those who developed radiological erosions. It is possible that the SE does have a role in the clinical severity of PsA. (J Rheumatol 2003;30:96–101)

Key Indexing Terms:

PSORIATIC ARTHRITIS SHARED EPITOPE DISEASE SEVERITY HLA

Genetic susceptibility is likely to be important in the development of psoriatic arthritis (PsA). There will be candidate genes that are associated with susceptibility to psoriasis and others that influence the development of arthritis. There may also be genetic effects on the severity and clinical course of the arthritis. Genome mapping of multiplex families with psoriasis using microsatellite markers has suggested linkage with several chromosomes — 6p¹⁻³, 1q⁴, 4q⁵, and 17q⁶. The situation with PsA is not as clear, although some studies^{7,8} do show significant familial aggregation. The MHC Class I

and II loci on the short arm of chromosome 6 are in an area showing the greatest linkage with psoriasis. It is not known whether these associations are primary or secondary to the presence of another gene within close proximity. It is likely that the development of psoriasis or arthritis or both is associated with the presence of several important genes along an extended haplotype.

Within the MHC Class I locus, the strongest association is between psoriasis and HLA-Cw6, with lesser associations with HLA-B13, HLA-B17, and HLA-B57 that probably reflect linkage disequilibrium on an extended haplotype with HLA-Cw6⁹⁻¹¹. In PsA, the association with Cw6 appears to be less strong than with psoriasis itself^{10,12}. Some Class I alleles have been associated with PsA, namely HLA-B16 and its splits HLA-B38 and HLA-B39, which have been associated with peripheral arthritis^{10,13}, and HLA-B27, which is associated with sacroiliitis and axial disease¹¹. Some of these, namely HLA-B27 and HLA-B39, have been shown to have a role in disease progression¹⁴. The situation with the MHC Class II locus is even less clear. HLA-DR7 has been shown to be increased in both psoriasis and PsA¹⁵, but this is not true in all populations¹². HLA-DR4 has been reported to be associated with peripheral arthritis resem-

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bling rheumatoid arthritis (RA) by some investigators¹⁰, but not others¹², and has been associated with erosive disease¹³.

The association between RA and HLA-DR4 has been confirmed in many ethnic populations. Those patients who are not HLA-DR4 positive frequently carry HLA-DR1, HLA-DR6, or HLA-DR10. Closer analysis between these MHC Class II alleles revealed sequence homology between alleles *0101, *0102, *0401, *0404, *0405, *0408, *1001, and *1402 in the area encoding 5 amino acids at positions 70–74 (QKRAA/QRRAA/RRRAA) on the third hypervariable region of the HLA-DR beta chain. Thus the concept of the “shared epitope” emerged¹⁶. Further, there is evidence that these shared sequences may be associated with disease severity in RA^{17,18} rather than disease susceptibility. This is notable if the number of copies of a SE allele is considered; the presence of 2 SE alleles of the same or different type has been linked with more severe erosive disease, implying a synergistic effect^{19–21}.

Thus a detailed study of HLA-DRB1 alleles in PsA has been undertaken to investigate whether previously reported associations particularly with HLA-DR4 may be explained by an increased frequency of a SE allele. Whether such an epitope may identify patients with erosive disease or those with a particular pattern of joint involvement has also been investigated.

MATERIALS AND METHODS

Study population. One hundred fifty-eight patients were recruited from the Bath specialist PsA clinic. This hospital based population included 100 patients from an original inception cohort who have been followed since 1988. All patients were Caucasian, and all had psoriasis either at the time of followup or in the past confirmed by a physician, an inflammatory arthropathy, and were seronegative for rheumatoid factor (RF) at initial assessment (except 3 patients who had low titer positive RF of 60, 64, and 67 IU/ml). There were 80 men and 78 women, the mean age was 56 years, and the mean duration of arthritis was 21 years. The patients were divided into disease subgroups as originally described by Moll and Wright²², except that oligoarthritis was strictly defined as 4 or fewer involved joints and polyarthritis as 5 or more involved joints at the point of assessment. Patients with radiological sacroiliitis and predominant axial symptoms, with or without peripheral arthritis, were designated as having spondyloarthritis (SpA). Patients with classical clinical and radiological features of arthritis mutilans were placed in a separate group. Two patients had involvement of only one knee and were classified as having monoarthritis and one patient had involvement of the distal interphalangeal (DIP) joints only. Thus, the patient subgroups were as follows: polyarthritis (n = 83), oligoarthritis (n = 56), SpA (n = 11), arthritis mutilans (n = 5), monoarthritis (n = 2), and DIP only (n = 1) (Table 1). The control population consisted of 250 healthy Caucasian blood donors from the Bath area. While the controls were subject to the routine screen for blood donors, mild psoriasis, which occurs in about 2% of the population, may have been present.

Outcome measures. Background information was collected on all patients including age of onset of psoriasis and arthritis and a detailed family history. Data were collected annually and recorded on a database. The information collected at each visit included a modified Ritchie tender and swollen joint count (modified to include the terminal interphalangeal joints), the Psoriasis Area Severity Index (PASI), a psoriatic nail severity score, the Health Assessment Questionnaire (HAQ), and inflammatory markers (plasma viscosity or C-reactive protein). If the data had been

Table 1. Demographic and clinical characteristics of the PsA population.

| Characteristic | |
|--|------------------|
| Patients, n | 158 |
| Polyarthritis (≥ 5 involved joints), n | 83 |
| Oligoarthritis (≤ 4 involved joints), n | 56 |
| Spondyloarthritis, n | 11 |
| Arthritis mutilans, n | 5 |
| Monoarthritis, n | 2 |
| DIP joint disease only, n | 1 |
| Sex | 80 men, 78 women |
| Mean age, yrs (SD) | 56 (14) |
| Mean age at onset of psoriasis, yrs (SD) | 29 (15) |
| Mean age at onset of PsA, yrs (SD) | 37 (14) |
| Mean duration of PsA, yrs (SD) | 21 (13) |

collected on more than one occasion, a mean of the values recorded at different visits was used in this analysis. With regard to subgroup allocation, the subgroup that best categorized the patient on the most recent hospital visit was used. Anteroposterior radiographs of the hands and feet taken at the most recent visit were scored for the presence or absence of erosions and this was used as the main radiological outcome measure.

HLA-DRB1 typing. DNA was extracted from peripheral blood samples by a standard salting-out technique. HLA-DRB1 typing was performed by polymerase chain reaction (PCR) based sequence-specific oligonucleotide probing as described²³ and subtyped by PCR based sequence-specific primers²⁴. Patients were classified as SE positive if they carried one or more of the SE alleles (*0101, *0102, *0401, *0404, *0405, *0408, *1001, or *1402).

Statistical analysis. The frequencies of the HLA-DRB1 alleles and SE alleles were compared between the patient and control populations using Fisher’s exact test. A result was considered to be significant with $p \leq 0.05$. The Bonferroni correction was used to control for multiple comparisons; p value was multiplied by the number of alleles/subgroups tested in each example. The results were also expressed as odds ratios. In the subgroup analysis, a 3 degrees-of-freedom (3 df) global test was performed in addition to standard pair-wise comparisons between subgroups and controls. The patients from the smaller subgroups were combined to give a third subgroup to the larger oligoarthritis and polyarthritis groups. A 3 df global test was then performed using a 4×2 table and chi-squared test to examine the hypothesis that none of the 3 groups differed from the control population. A further test using a 2×2 table comparing the oligoarthritis subgroup and all other PsA subgroups combined was also performed.

RESULTS

Associations of HLA-DR alleles with PsA (Table 2). There was an increased frequency of HLA-DR7 within the PsA population as a whole compared with controls (41 vs 25%; $p_{\text{uncorr}} = 0.001$, OR 2.02, $p_{\text{corr}} = 0.01$). There was a trend toward an increased frequency of HLA-DR1 in the patient group but this did not reach significance. There was a decreased frequency of HLA-DR2 and HLA-DR4 in the patient group, the former only reaching statistical significance if uncorrected for the number of tests performed ($p_{\text{uncorr}} = 0.03$, OR 0.59).

Associations of HLA-DR alleles with PsA subgroups. There were no significant associations between disease subgroups and the HLA-DR alleles. HLA-DR4 was equally prevalent

Table 2. Frequency of HLA-DR alleles in the PsA patient population compared with controls. Values are the number (%) of patients/controls with at least one copy of the HLA-DR allele.

| Allele | Patients, n = 158 (%) | Controls, n = 250 (%) | P _{uncorr} | OR | P _{corr} |
|----------|--------------------------|--------------------------|---------------------|------|-------------------|
| HLA-DR1 | 47 (30) | 53 (21) | 0.059 | 1.57 | NS |
| HLA-DR2 | 30 (19) | 71 (28) | 0.034* | 0.59 | NS |
| HLA-DR3 | 36 (23) | 52 (21) | 0.71 | 1.12 | NS |
| HLA-DR4 | 44 (28) | 92 (37) | 0.067 | 0.66 | NS |
| HLA-DR5 | 23 (15) | 48 (19) | 0.28 | 0.72 | NS |
| HLA-DR6 | 35 (22) | 59 (24) | 0.81 | 0.92 | NS |
| HLA-DR7 | 64 (41) | 63 (25) | 0.001* | 2.02 | 0.01* |
| HLA-DR8 | 12 (8) | 13 (5) | 0.40 | 1.50 | NS |
| HLA-DR9 | 3 (2) | 4 (2) | 0.99 | 1.19 | NS |
| HLA-DR10 | 2 (1) | 2 (1) | 0.64 | 1.59 | NS |

Both p_{uncorr} and p_{corr} use the Bonferroni correction for the number of tests performed. * p < 0.05.

in both the polyarthritis and oligoarthritis subgroups (present in 25% of each group). HLA-DR1 was slightly more common in the polyarthritis group than the oligoarthritis group (34 vs 20%). HLA-DR3 was the most common allele in the SpA group, present in 5 out of 11 patients (45%), and HLA-DR7 was the most common allele in all subgroups except the SpA group.

Associations of SE alleles with demographic and clinical characteristics (Table 3). There was no association between the sex of the patients and presence of the SE (50% of SE positive patients male, 50% female). There was no difference in the age of onset of psoriasis, age of onset of arthritis, family history of psoriasis/arthritis, HAQ, joint score, PASI, nail score, or mean plasma viscosity between SE positive and SE negative patients.

Associations of SE alleles with PsA (Table 4). All SE alleles were detected in the patient and control populations except *1402, due to its low frequency in Caucasians. Overall there was no difference in the number of patients who were SE positive compared with controls (48 vs 54%). The most frequent SE allele in the patient group was *0101 (22%), followed by *0401 (17%). The *0404 allele was the only allele to be significantly different in its prevalence between

Table 3. Clinical and demographic features of PsA patients with and without the SE.

| | SE Present | SE Absent |
|---|------------|------------|
| Women, n | 35 | 43 |
| Men, n | 35 | 45 |
| Mean age at onset of psoriasis, yrs (SD) | 29 (15.2) | 29 (15) |
| Mean age at onset of PsA, yrs (SD) | 36 (14.2) | 37 (14) |
| Positive family history of psoriasis (%) | 43 | 45 |
| Mean HAQ at latest followup (SD) | 10.9 (5) | 7.7 (7) |
| Mean joint score at latest followup (SD) | 17.5 (16) | 15.4 (16) |
| Mean PASI at latest followup (SD) | 3.2 (4) | 3.4 (3.4) |
| Mean nail score at latest followup (SD) | 6.0 (7) | 5.4 (5.4) |
| Mean plasma viscosity at latest followup (SD) | 1.81 (0.2) | 1.81 (0.2) |

the patient and control populations, present in only 3.8% of patients with PsA compared with 10% of controls (p_{uncorr} = 0.02, OR 0.34, p_{corr} NS).

Associations of SE alleles with PsA subgroups (Table 5). The SE was present in all disease subgroups although only the oligoarthritis and polyarthritis groups were large enough for analysis. The prevalence of the SE in the polyarthritis subgroup was not increased compared with controls (49 vs 54% in controls). However, there was a reduction in the frequency of the SE in the oligoarthritis subgroup compared with controls (38 vs 54%; p = 0.02, OR 0.32 using a pairwise comparison). This difference failed to reach significance if the oligoarthritis subgroup was compared against all other patients with PsA (p = 0.202) or if a 3 df test was performed comparing the oligoarthritis group with the polyarthritis group, a group combining the SpA, arthritis mutilans, monoarthritis, and DIP only patients and controls (p = 0.134).

Double dose phenomenon. Two copies of a SE allele were found in 9.6% of the control population. There was no significant difference in the number of patients with a double dose compared with controls (6.3 vs 9.6%). The double dose phenomenon was seen more often in the polyarthritis subgroup (8.4%) and less often in the oligoarthritis subgroup (3.6%), but the groups were too small to reach significance.

SE and radiological erosions (Table 6). One hundred fifty-one patients had radiographs of the hands and feet available for scoring for the presence of erosive disease, of whom 76 had erosions and 75 did not. Erosive disease was most prevalent in the polyarthritis subgroup (73%) compared with 30% of the SpA subgroup and 16% of the oligoarthritis subgroup. Those patients who were SE positive were significantly more likely to have erosive disease than those who were SE negative [60% (39/65) vs 43% (37/86); p = 0.03, OR 2.11]. The presence of erosions was not more strongly associated with any particular SE allele than another. There

Table 4. Frequency of SE alleles in the PsA patient population compared with controls. Values shown are the number (%) of patients/controls with at least one copy of the allele.

| SE Allele | Patients, n = 158 (%) | Controls, n = 250 (%) | P _{uncorr} | OR | P _{corr} |
|-----------|-----------------------|-----------------------|---------------------|------|-------------------|
| *0101 | 35 (22) | 46 (18.4) | 0.37 | 1.26 | NS |
| *0102 | 3 (1.8) | 4 (1.6) | 0.99 | 1.19 | NS |
| *0401 | 27 (17) | 54 (21.6) | 0.31 | 0.75 | NS |
| *0404 | 6 (3.8) | 25 (10) | 0.02* | 0.36 | 1.4 (NS) |
| *0405 | 2 (1.3) | 1 (0.4) | 0.56 | 3.19 | NS |
| *0408 | 1 (0.6) | 3 (1.2) | 0.99 | 0.52 | NS |
| *1001 | 2 (1.3) | 2 (0.8) | 0.64 | 1.59 | NS |
| Total | 76 (48.1) | 135 (54) | | | |

p values are shown before and after Bonferroni correction for number of alleles tested. * p < 0.05. NS: p > 0.05.

Table 5. The association of PsA subgroups with the presence of the SE.

| Disease Subgroup | SE Present, n (%) | SE Absent, n (%) |
|-------------------------------|-------------------|------------------|
| Polyarthritis, n = 83 | 41 (49) | 42 (51) |
| Oligoarthritis, n = 56 | 21 (38)* | 35 (63) |
| Spondyloarthritis, n = 11 | 5 (45) | 6 (55) |
| Arthritis mutilans, n = 5 | 1 (20) | 4 (80) |
| Monoarthritis, n = 2 | 1 (50) | 1 (50) |
| DIP joint disease only, n = 1 | 1 (100) | 0 (0) |
| Controls | 135 (54) | 115 (46) |

* p_{uncorr} = 0.027, OR 0.32 following pair-wise comparison between the oligoarthritis group and controls. If the groups are considered as 3 subgroups due to the small sizes of some groups (i.e., polyarthritis, oligoarthritis and "other"), the Bonferroni adjusted p_{corr} value would be 0.081 (3 × 0.027). A global 3 df test to test the hypothesis that none of these 3 groups differs from the control population gives a p value of 0.134. A comparison of the oligoarthritis group with all other PsA patients yields a p value of only 0.202.

was no relationship between any overall HLA-DR subtype (including HLA-DR1 and HLA-DR4) and erosive disease. Of the 76 patients with erosions, 39 (51%) were SE positive compared with only 26 out of 75 (33%) patients with no erosions.

DISCUSSION

This is the first study to investigate the prevalence and role of the SE in PsA. Since PsA can vary dramatically in its clinical course, any factor that may help identify patients who are more likely to develop severe or erosive disease would be of great benefit in patient management. We investigated the influence of the SE on the clinical course of the disease by determining its prevalence in each disease subset and whether it is associated with any particular clinical or radiological characteristic.

More is known about the role of the SE in RA, where it has been studied predominantly in early disease. There is mounting evidence that the SE exerts its effect in RA on disease severity as well as disease susceptibility²⁵. The majority of studies have investigated the role of the SE as a

Table 6. The association between the presence of the SE and the presence of radiological erosions.

| | SE Present, n (%) | SE Absent, n (%) |
|------------------|-------------------|------------------|
| Erosions present | 39 (60)* | 37 (43)* |
| Erosions absent | 26 (40) | 49 (57) |
| Total | 65 | 86 |

* p = 0.03, OR 2.11, comparing the presence of erosions in SE positive and SE negative patients.

predictor of outcome in patients presenting with early synovitis. These studies have provided somewhat conflicting results^{26,27} but, in general, possession of the SE does appear to be associated with more severe disease, particularly in relation to the presence of erosive damage and extraarticular features¹⁸.

In RA, the increased prevalence of HLA-DR4 and HLA-DR1 have been well established and confirmed in many populations²⁸. However, a study of HLA-DR4 in newly diagnosed community based patients with RA did not find any association, suggesting that it is more important in the severity and persistence of RA than in susceptibility²⁵. There have been several reports of HLA-DR associations with PsA and its subgroups. This study has confirmed some of these, but did not find some of the associations reported by others¹¹. There was an increased prevalence of HLA-DR7 compared to a control population. In contrast to some reports of an increased prevalence of HLA-DR4 in PsA, particularly in the polyarthritis subset¹⁰, a nonsignificant reduction of HLA-DR4 was observed in this population. The frequency of HLA-DR2 in the PsA population as a whole was reduced. There was no association of HLA-DR subtypes with any of the disease subsets.

The frequency of the SE in a population with established RA (mean disease duration 15.4 years) was recently found to be 76%²⁰. The frequency has been reported to be as high as 95%²⁹. However, as roughly 50% of the normal population carry at least one SE allele, its use as a predictive test is

limited by low specificity and low positive predictive value. The test is probably better applied to patients known to have RA to help identify those at increased risk of severe disease³⁰. The frequency of the SE in this population of patients with PsA was 48%, with a control frequency of 54%. The most frequent SE allele in the patient population was *0101, followed by *0401. The frequency of *0404 was lower in patients than in controls, and was clearly different from the frequencies reported in RA, where it is often the most common allele. There was no association between different SE alleles and disease subgroup or markers of severity, unlike RA, where *0401 and *0404 have been linked with more severe disease³¹. Another point of interest is that the SE was equally prevalent in male and female patients with PsA, whereas in RA it has been reported to be more frequent in men³².

It could be hypothesized that the SE may be found at a higher frequency in those patients who develop a polyarthritis resembling RA. However, the frequency of the SE in the polyarthritis subset was found to be no different from the normal population. There was a reduction in the frequency of the SE in patients who remained in the oligoarthritis subset. This may suggest that, in the absence of the SE, patients are less likely to progress to polyarticular disease or that other genetic influences are more important in oligoarthritis. This study is based on patients with well established disease with a mean duration of arthritis of 21 years. Although it is recognized that patients do move between subsets³³, the majority of patients in this study are likely to be correctly classified in view of the length of their disease process. The genetic associations with disease subsets in this study are therefore less prone to classification difficulties than in studies where the disease duration is shorter.

The influence of the SE on the development of radiological erosions in patients with PsA is another important finding of this study. Seventy-three percent of patients in the polyarthritis group had erosive disease of the hands and feet, compared with only 16% of the oligoarthritis group and 30% of the SpA group. When considering the proportions of patients in each subgroup with erosions, the influence of the SE was not so significant, but looking at the population as a whole, patients who were SE positive were significantly more likely to develop erosions than those who were SE negative (60 vs 43%). This suggests that the SE may influence disease severity in PsA as well as RA. It is interesting that there is mounting evidence that the predominant influence of the SE on erosive disease in RA appears to be in patients who are seronegative for rheumatoid factor (RF). This has been found in both early synovitis^{34,35} and established RA populations³⁶. In one of these studies³⁴ it was found that the SE had no influence on the likelihood of disease persistence in an early synovitis population and only a modest effect on functional disability. The most obvious

effect was on the development of erosions [relative risk (RR) 1.9] and it was restricted to those who were seronegative for RF. No effect on the severity of radiological damage defined by the total Larsen score or number of eroded joints was noted.

It is possible that SE allele copy number influences disease severity in RA^{31,37}. The presence of 2 identical or 2 different SE alleles is known as the double dose phenomenon. A study in RA found an increased RR for RA in patients who were compound heterozygous for SE alleles (RR 11.7) over those who were homozygous (RR 4.3) for the same SE allele²⁰. Some 25% of the patients with RA had a double dose of the SE. In this study, only 6.3% of the PsA population as a whole carried 2 copies of a SE allele compared with 9.6% of the control population. There were no clear associations between the dose of the SE, homozygosity, or compound heterozygosity and the disease subset or development of erosions, although fewer patients in the oligoarthritis subgroup had a double dose (3.6 vs 9.6% in controls; NS).

In summary, the frequency of SE alleles in this population of patients with PsA was similar to that in a control population. There was no increase in the frequency of the SE in the polyarthritis subset. There was a lower frequency of the SE in patients who remained in the oligoarthritis subset. As only 16% of the oligoarthritis subset were erosive, the lower frequency of the SE in this subset may simply reflect the association of the SE with erosive disease. It would seem that the greatest influence of the SE in PsA is in the development of erosions. It is possible the SE influences severity in RA via the development of erosions, and this may be a feature in common between the 2 arthritis populations. However, the clear differences in the prevalence of the SE in our population and its subgroups and published data in RA further delineate the differences between patients with PsA and RA. The data presented here add to the genetic evidence that PsA is a distinct clinical entity, and argues against the view of the polyarthritis subgroup as simply a form of RA with psoriasis. Further genetic studies, both within and outside the HLA region, will hopefully provide more information on genetic classification and severity markers in psoriatic arthritis.

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