Clinical, radiographic and HLA associations as markers for different patterns of psoriatic arthritis

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Abstract

Objective. The aim of this study was to examine whether the five clinical forms of psoriatic arthritis (PsA) identified by Moll and Wright (Semin Arthritis Rheum 1973;3:55–78) could be clearly distinguished, especially as the disease evolved over time, to analyse whether radiographic features or HLA associations could define subsets with greater precision and to identify predictors of disease outcome.

Methods. Seventy-three patients (37 males and 36 females) were followed for a median time of 8 yr (range 1–16 yr). A standard clinical protocol was used to assess patients at each visit and two clinical scores, based on the joint areas involved, were defined to evaluate the mode of onset and the evolution of arthritis. X-ray films of the hands, feet and sacroiliac joints were taken and the patients were divided into two categories according to the presence or absence of erosions and an X-ray erosion score was also used. Three classification methods were used to define the different clinical subsets. HLA-A, B and DR antigens were tested by standard microlymphocytotoxicity assays. A multiple linear regression model was used in the statistical analysis.

Results. The five classical clinical subsets defined by Moll and Wright did not remain since distinct peripheral arthritis patterns tended to evolve over time. Only two discrete groups were identified, axial disease (AD) (sacroilitis with or without peripheral arthritis) in 29% of cases and peripheral disease (PD) without sacroilitis in 71%. AD was positively associated with the duration of arthritis (P < 0.04), presence of mutilation (P < 0.02) and the joint area score over disease evolution (JASE) (P < 0.02). There were erosions in 71% of the patients. Erosions correlated with the presence of mutilation (P < 0.007) and with the JASE (P < 0.0005). HLA-B27 was found in 43% of patients with AD, but only in 11% of PD patients (P < 0.01). No other clear HLA correlations were found.

Conclusions. Despite the relatively small number of patients, this longitudinal study suggests that only two clinical subsets can be clearly defined in PsA, AD and PD; these are primarily determined on clinical grounds although HLA-B27 is strongly associated with AD. The evolution of PD pattern with time means that narrower peripheral arthritis subsets are of little clinical use.

Key words: Psoriatic arthritis, HLA antigens, Radiology, Sacroiliac joint, Prognosis.

Although there are some common features that allow us to define psoriatic arthritis (PsA) as a single entity [1], the disease does not express itself in the same way in all patients. This variability in clinical presentation resulted in the description of five clinical subsets [2], which have been generally accepted [3]. However, the criteria defining the Moll and Wright clinical forms [2] were not clearly established, leading other authors to suggest alternative classifications; again, the markers for each subset were not clearly defined in some of these classifications [4–8]. Furthermore, many classification studies examined patients at only one single time point which may be misleading if disease patterns change over time.

In other diseases, HLA associations have been used to classify disease subsets accurately. There is a strong association between psoriasis and the histocompatibility
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antigens HLA-B13, B17, Cw6 and DR7 [9] which is no longer found when arthritis is present. An association between HLA-B27 and sacroiliitis (SI) has been found [10, 11], but this disappears when only the spine is affected and the sacroiliac joints are normal [12]. In some series, a positive correlation has been observed between HLA-B27 and arthritis of the distal interphalangeal joints [13], and between Cw6 and the oligoarticular subset [14]. Other antigens have been studied, including HLA-B16 [15], HLA-DR4 [13] and HLA-DR7 [15], but clear associations with the different clinical subsets have not been found. In fact, other than the association between HLA-B27 and SI, HLA associations in PsA are very variable.

The aim of the present study was to identify clinical subsets of PsA and their evolution over time, to analyse associations between HLA antigens and clinical subsets, and to identify predictors of disease outcome.

Patients and methods

Patient population and clinical assessment

Seventy-three patients [age 56 (35–69) yr, median (range); 37 males and 36 females; male/female ratio 1.1] with PsA according to the criteria of Moll and Wright [2] were studied prospectively. All patients were seen by a single observer (EL) in a psoriatic arthritis clinic which follows up all the PsA cases seen in our unit without exception. It provides a population of PsA patients covering the full spectrum of the disease. All patients included in this study had been followed up for more than 1 yr. All but 15 patients were followed up for at least 3 yr. The median follow-up was 8 yr (range 1–16) and the median disease duration was 15 yr (range 4–32).

Analysis of features

A standard clinical protocol was used to assess patients at each visit. Analysis of the clinical features of the patients was performed by a second observer (SM) who examined independently the protocols filled in at all the out-patient visits made by each patient. The data analysed in this study were: sex, date of birth, age at psoriasis and PsA onset, duration of arthritis, mode of onset (defined as the joints involved within the first 3 months of symptoms) [16], nail dystrophy and dactylitis.

Two scores, based on the joint areas involved, were defined to evaluate the mode of onset and the evolution of arthritis. Twenty-four joint areas were recorded: the DIP,PIP and MCP joints of both hands, the wrists, the elbows, the shoulders, the DIP,PIP and MTP joints of both feet, the ankles, the knees and the hips. Areas including more than one joint were defined as involved if a single joint was swollen.

To describe the mode of onset of arthritis, the Joint Area Score at disease Onset (JASO) was used. JASO was taken from the patient’s own description of the extent of their arthritis at its initial manifestation within the first 3 months of symptoms. The score records the number of joint areas in which there was at least one swollen joint plus the presence of pain or limitation of mobility in the shoulders and hips.

To describe the evolution of arthritis, the Joint Area Score over disease Evolution (JASE) was used. JASE records the total number of joint areas ever noted to be swollen by the physician during follow-up plus the presence of pain or limitation of mobility in shoulders and hips.

The final functional status was evaluated according to the American College of Rheumatology revised Steinbrocker criteria [17].

Radiology

X-ray films of the hands, feet and sacroiliac joints were taken in all patients ≤ 1 yr before their last clinical status was analysed. All films were evaluated by two observers. Two approaches to radiological analysis of the peripheral joints were made. In the first, PsA patients were divided into two categories according to the presence or absence of erosions[11]. In the second approach, an erosion score (X-ray score) was defined as the number of joints with at least one erosion.

The sacroiliac joints were evaluated according to the 1966 New York criteria [18]. A score of less than two bilaterally was not considered significant.

Clinical subsets

Three classification methods were used to define the different clinical subsets. In the first method, patients were classified as having axial or peripheral disease. Axial disease (AD) was defined by the presence of radiological SI with or without peripheral arthritis. Peripheral disease (PD) was defined as peripheral arthritis without evidence of radiological SI. In the second method, three subgroups were defined: (1) AD: patients with only axial component defined by the presence of radiological SI without peripheral arthritis; (2) PD: patients with peripheral arthritis without AD; (3) Mixed (MX): patients with axial and peripheral components. In the third classification method, four categories were defined: (1) PD: patients with peripheral arthritis (oligoarthitis or polyarthitis) with or without radiological SI; (2) ankylosing spondylitis (AS) according to the 1966 New York criteria [18], with or without peripheral arthritis; (3) DIP involvement (DIP) DIP joints exclusively involved; (4) arthritis mutilans (AM): patients with arthritis mutilans. This is a modified form of the classification drawn by Moll and Wright [2], because it was not possible to include accurately the patients in the subsets of symmetrical polyarthitis or asymmetrical oligoarthitis. Those patients having AS and AM were recorded as AM, due to the greater specificity of this feature in this particular classification. As no clear definition of mutilation has been given [19], we consider that mutilation was present when a metacarpal or a metatarsal head and the corresponding epiphysis of a phalanx or both epiphyses of an interphalangeal joint of a finger or a toe were completely eroded.
**HLA typing**

HLA-A, B and DR antigens were tested by standard microlymphocytotoxicity assays [20]. All clinical and radiological variables described were correlated with the presence or absence of each HLA-A, B and DR antigen.

**Statistical analysis**

Statistical analysis was performed with the help of a statistician (LA). In the descriptive study, the statistical associations were assessed by $\chi^2$, Fisher’s exact and Mann–Whitney non-parametric tests. The significance of results was controlled at the $\alpha = 0.05$ level using the simple sequentially rejective multiple test procedure to adjust for multiple comparisons [21]. Differences in X-ray scores in PD and in AD subsets were studied with analysis of variance. Analysis of covariance was used to adjust these differences for JASE and for the time since first clinical manifestation. Results are presented as significance tests for the coefficients for the SI variable (AD vs PD) and for JASE in the implicit multiple linear regression model [22]. In order to compare the annual average increase in the number of erosions between AD and PD subsets, an interaction term between SI and time since first manifestation was tested.

In order to identify the best predictors of mutilation, its association with SI, sex, duration of arthritis (<16 yr and >16 yr) and JASE (<10 and >10) were assessed with multiple logistic regression. Forward stepwise modelling was used to identify the predictors of mutilation.

An indicator variable was defined for every HLA antigen present in the sample. In order to assess whether any antigen was associated with erosive disease, we planned the inclusion of such HLA variables in the multiple linear regression model for number of erosions. Indicator variables would enter the model in a forward stepwise strategy, provided their associated partial $F$-test was significant ($P < 0.05$).

**Results**

**Demographic and clinical features**

The median age of onset of psoriasis was 32 yr (range 8–55). The median age of onset of PsA was 42 yr (range 18–60) and the median duration of arthritis was 15 yr (range 4–32). Nail dystrophy was ever present in 52 patients (71%), dactylitis in 39 (53%) and mutilation in 17 (23%).

**Mode of onset and classification**

Thirty-eight patients (52%) had less than four swollen joints at initial presentation (26 patients with monoarthritis, eight patients with two swollen joints and four patients with three affected joints), but only five patients (6.8%) still had less than four affected joints at the time of this study. In further support of the concept that disease patterns changed with time, the median (range) of the JASO was 2 (0–8), but the JASE increased to 10 (2–19).

Mutilation was associated with higher JASE [presence of mutilation 12 (5–21) vs absence 9 (2–18) ($P < 0.01$)], whereas the presence of dactylitis did not correlate with the number of involved joints either at onset or during disease evolution.

The patterns of PsA were classified into different clinical subsets using the three methods of classification described in Patients and methods. Using classification 1, there were 52 (71%) patients with PD and 21 (29%) patients with AD. Using classification 2, there were 52 (71%) patients with PD, 20 (27%) with MX and only one (2%) with axial disease alone. Using classification 3, 17 (24%) patients had arthritis mutilans and three (4%) had involvement of DIP joints exclusively (DIP). There were 10 (14%) patients fulfilling the New York criteria for AS of whom four also had arthritis mutilans. The other 47 (64%) patients had PD. Because of the small number of patients in the AS and DIP groups (classification 3) and AD group (classification 2), they were not included in further statistical analysis and only classification 1 has been analysed. Table 1 shows the associations observed between the clinical subsets defined using classification 1 and other parameters.

**Radiology**

The radiological features of the PsA patients are shown in Table 2. The evolution to erosive disease was independent of duration of arthritis, but the presence of mutilation and a higher JASE were associated with erosive disease.

The median X-ray score was 3 (range 0–27). The presence of mutilation was significantly associated ($P < 0.0001$) with a higher X-ray score, as was the presence of SI (AD subset). The median (range) X-ray score in the AD subset was 9 (0–49) and in the PD subset it was 2 (0–24) ($P < 0.05$).

**HLA associations**

The presence of mutilation, SI, and JASO, JASE and X-ray score were analysed in relation to HLA typing (data not shown). We found no significant association between mutilation and any HLA antigen. HLA-B12(+) patients had lower JASE [median 8 (range 0.2–17) ($n = 21$)] than B12(−) patients [median 11 (range 2–21)] ($P < 0.05$). HLA-B13(+) patients showed a lower X-ray score [median 0 (range 0–6) ($n = 8$)] than B13(−) patients [median 4 (range 0–28)] ($P < 0.01$). HLA-B27 was positive in nine of 21 patients (43%) with SI and in six of 52 patients (11%) without SI ($P < 0.01$). HLA-DR4-positive patients had higher JASO [median 2.5 (range 1–8) ($n = 18$)] than DR4-negative patients [median 1 (range 0–10)] ($P < 0.05$) and no significant differences were observed in JASE between DR4-positive and DR4-negative patients.

**Functional status**

In the analysis of functional status, there were 22 patients in grade I, 10 patients in grade II and 31 patients with more severe disability, grades III/IV (with only three patients in grade IV). We found that no
Table 1. Clinical features of PsA subgroups according to classification 1

<table>
<thead>
<tr>
<th>Features</th>
<th>Axial (AD)</th>
<th>Peripheral (PD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 21) (28.8%)</td>
<td>(n = 52) (71.2%)</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>1.6</td>
<td>0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56 (35–71)</td>
<td>56 (35–69)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at PsA onset (yr)</td>
<td>36 (12–58)</td>
<td>42 (23–61)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of arthritis (yr)</td>
<td>17 (3–51)</td>
<td>14 (4–28)</td>
<td>0.04</td>
</tr>
<tr>
<td>Dactylitis\textsuperscript{a} (n = 39)</td>
<td>13 (61.9)</td>
<td>26 (50.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Mutation\textsuperscript{a} (n = 17)</td>
<td>9 (42.9)</td>
<td>8 (15.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>JASO (number of joint areas)</td>
<td>1 (0–6)</td>
<td>2 (0.6–10)</td>
<td>0.02</td>
</tr>
<tr>
<td>JASE (number of joint areas)</td>
<td>12 (0.3–22)</td>
<td>9 (2–18)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\textsuperscript{a}JASO, Joint Area Score at disease Onset; JASE, Joint Area Score over disease Evolution.
Axial disease, presence of sacroiliitis with or without peripheral arthritis; peripheral disease, peripheral arthritis without evidence of axial disease.
Statistical significance after adjustment for multiple comparisons; median (range); \textsuperscript{a}n (%).

Table 2. Clinical features of 73 PsA patients in relation to erosive and non-erosive disease

<table>
<thead>
<tr>
<th>Features</th>
<th>Erosive disease (n = 52) (71%)</th>
<th>Non-erosive disease (n = 21) (29%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at PsA onset (yr)</td>
<td>39 (16–59)</td>
<td>44 (22–61)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of arthritis (yr)</td>
<td>16 (4–33)</td>
<td>11 (2–33)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dactylitis\textsuperscript{a} (n = 39)</td>
<td>33 (63.4)</td>
<td>6 (28.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mutation\textsuperscript{a} (n = 17)</td>
<td>17 (32.7)</td>
<td>0 (0.0)</td>
<td>0.007\textsuperscript{a}</td>
</tr>
<tr>
<td>Sacroiliitis\textsuperscript{a,b} (n = 21)</td>
<td>17 (32.7)</td>
<td>4 (19.0)</td>
<td>NS</td>
</tr>
<tr>
<td>JASO (number of joint areas)</td>
<td>2 (0–8)</td>
<td>2 (0–20)</td>
<td>NS</td>
</tr>
<tr>
<td>JASE (number of joint areas)</td>
<td>11 (4–19)</td>
<td>6 (0.2–23)</td>
<td>0.0005\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}JASO, Joint Area Score at disease Onset; JASE, Joint Area Score over disease Evolution.
\textsuperscript{b}Statistical significance after adjustment for multiple comparisons; median (range); \textsuperscript{a}n (%).
\textsuperscript{a}Axial disease subgroup, presence of sacroiliitis with or without peripheral arthritis.

Table 3. Clinical features and radiology in 73 PsA patients in relation to functional status

<table>
<thead>
<tr>
<th>Functional status</th>
<th>I + II (n = 42 (57.5%))</th>
<th>III + IV (n = 31 (42.5%))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female ratio</td>
<td>1.00</td>
<td>1.06</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53 (34–70)</td>
<td>58 (43–72)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age at PsA onset (yr)</td>
<td>42 (18–57)</td>
<td>40 (18–61)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of arthritis (yr)</td>
<td>13 (3–31)</td>
<td>16 (4–41)</td>
<td>0.04</td>
</tr>
<tr>
<td>Dactylitis\textsuperscript{a} (n = 39)</td>
<td>26 (66.7)</td>
<td>13 (33.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Mutation\textsuperscript{a} (n = 17)</td>
<td>8 (47.1)</td>
<td>9 (52.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Sacroiliitis\textsuperscript{a,b} (n = 21)</td>
<td>9 (42.9)</td>
<td>12 (57.1)</td>
<td>NS</td>
</tr>
<tr>
<td>JASO (number of joint areas)</td>
<td>2 (0–7)</td>
<td>1 (0–14)</td>
<td>NS</td>
</tr>
<tr>
<td>JASE (number of joint areas)</td>
<td>8 (2–18)</td>
<td>12 (2–22)</td>
<td>0.001\textsuperscript{a}</td>
</tr>
<tr>
<td>Erosive disease (n = 21)\textsuperscript{a}</td>
<td>10 (47.6)</td>
<td>11 (52.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\textsuperscript{a}JASO, Joint Area Score at disease Onset; JASE, Joint Area Score over disease Evolution.
\textsuperscript{b}Statistical significance after adjustment for multiple comparisons; median (range); \textsuperscript{a}n (%).
\textsuperscript{a}Axial disease subset, presence of sacroiliitis with or without peripheral arthritis.

clinal or radiological features predicted poor functional outcome except the JASE score (Table 3).

**Predictors of outcome**

More erosions were present in the AD subset: the adjusted mean difference was 5.72 (P = 0.0195). The number of erosions increased with JASE (regression coefficient: β = 0.17, P = 0.0156).

In the multiple logistic regression (MLR) model, the association between mutilation and AD remained statistically significant (P = 0.009), as did the association between mutilation and sex (P = 0.003), even after adjustment for duration of arthritis (whose coefficient was marginally significant) (P = 0.017). The association between mutilation and JASE became non-significant when the former variables entered the MLR model.

**Discussion**

Our main aim in this study has been to analyse the clinical subsets of PsA. No precise criteria allowing the clear definition of every one of their five subsets were used by Moll and Wright [2], other than the presence of SI in the AS subset. Moreover, the fact that with time the various peripheral forms develop into the polyarticular subset was not considered. In PsA, the oligoarticular subset (less than four joints affected [23]) cannot be defined as a clinical form since there are no
markers that allow us to classify a patient as having an oligoarticular subset of disease, unlike in juvenile chronic arthritis. Considering that the vast majority of peripheral forms of PsA evolve into polyarthritis, we believe that it is not appropriate to define several separate PD subsets. The classical classification of Moll and Wright should, therefore, now be abandoned, as has already been suggested in some publications [6, 16, 24, 25] despite a recognition of its past usefulness in leading to a better understanding and study of PsA.

The main handicap when analysing the mode of onset of PsA in studies performed at a single time point is that the data come from the patient’s history. This may provide incorrect information, since patients often do not recall important data. This problem is likely to be diminished when the patient is seen shortly after the start of the disease. We have considered the number of joints affected in the first 3 months of evolution of the disease in order to establish a classification of the modes of onset of PsA. We found that 38 patients (52%) had less than four joints affected, of whom 26 (35% of the total) presented with a monoarthritis as the first clinical manifestation. These proportions are similar to those observed by Jones et al. [16], who also considered the joints involved within the first 3 months of symptoms. However, only five of our patients (6.8%) continued to have less than four joints affected at the time of the study due to the progressive involvement of different joints during the course of disease. It is thus impossible to differentiate clinically between mono/oligoarticular arthritis, polyarticular arthritis and subsets limited to the DIP joints, as is currently general practice [19], since the oligoarticular subset and the subset limited to the DIP joints tend to become polyarticular in due course [16].

The most robust distinction at the present time is the presence of radiographic SI which has both clinical and HLA correlates. For this reason, rather than abandoning the concept of PsA subsets altogether, we have described two clinical subsets: peripheral disease without sacroiliac involvement (PD) and axial disease (AD). Nevertheless, we must note that, in patients with AD, radiographic SI may develop during disease evolution, and not be present at the onset. In patients with AD, the arthritis was of a longer duration, arthritis mutilans was more frequent and the JASE was higher than in PD, although the JASSO was lower (Table 1). AD appears, therefore, more aggressive than PD, although it is not associated with a worse functional status (Table 3). SI behaves similarly in other spondyloarthropathies such as in reactive arthritis where HLA-B27-positive patients have more specific spondyloarthropathic features, such as SI, enthesitis and iritis [26].

We have observed erosions in hands or feet in 71% of the patients. Veale et al. [7] found erosions in 35% of their patients and Torre-Alonso et al. [8] in 57%. These apparent differences may be explained by the diverse patient selection in those series, and in the X-ray scoring methods used. Although in the final statistical analysis we have not been able to prove a definite correlation between the duration of arthritis and the appearance of erosions (Table 2), we have found a correlation between JASE and the presence or absence of erosions.

Both the presence of arthritis mutilans and of radiographic SI are associated with a higher X-ray score. Although the presence of SI is not correlated with the presence or absence of erosions, it is associated with a higher X-ray score in those patients who have erosions.

Mutilation is an enigma in PsA. It is not rare, since we have observed it in 17 (23.3%) of our patients. It seems that it may be an intrinsic aspect of psoriatic disease that is observed in both the AD and PD forms, but it is seen rarely in other forms of arthritis such as rheumatoid disease. It is associated with SI, female sex, and with a duration of disease >16 yr, although when we apply the MRL model, the association with JASE becomes non-significant. It remains unclear what mechanisms determine the development of such severe osteolysis.

It has been suggested that the analysis of MHC antigens would allow a more precise and accurate classification of PsA, but this has proved not to be the case. The most relevant piece of data in our study is the correlation between HLA-B27 and SI, as it has been already published [8, 10–12, 28]; 42.9% of our patients with SI were HLA-B27 positive. This percentage is rather lower than in other series, but this difference cannot be explained for variations in HLA-B27 frequency in the general population around Barcelona. A local frequency of 6.3% has been described, which does not differ substantially from the other populations where most of these studies have been carried out. We believe that this discrepancy is due to the fact that the meaning of axial disease or even the inclusion criteria of SI are not the same in the different studies.

In one study it was found that the presence of HLA-B13 could correlate with a milder form of disease [14]. In this sense, we have observed that the HLA-B13-positive patients had a lower X-ray score. The data that suggest HLA-B12, B13 and DR4 as outcome predictors must certainly be confirmed, and do not parallel the results of Gladman and Farewell [29] who performed an analysis of 276 patients with a different methodology than ours. It is very likely that there are genetic markers, other than MHC, that determine the clinical expression of PsA; unfortunately, the results of the research in other fields have been negative and no associations have been found.

We have performed an analysis of the different variables in relation to functional status. However, the statistically significant association with age and duration of arthritis disappears after adjustment for multiple comparisons. We have only observed a positive correlation with JASE. We have used a different methodology than the one used by Gladman et al. [27], who found that a high number of effusions and of past medications predict progression of joint damage, whereas a low sedimentation rate ‘protects’ from such progression.

In summary, we propose a differentiation into two
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Clinical subsets, PD and AD, which are defined by the presence or absence of radiographic SI. Since the joints involved in the peripheral arthritis change as the disease evolves, we can currently find no justification for a rigid separation of distinct PD subsets as previously proposed by Moll and Wright. The only significant predictor of poor functional outcome we have found is the presence of an increasing number of involved joints as assessed by the JASE. Finally, the only HLA association confirmed in our study is that between HLA-B27 and SI, supporting the concept that the only distinct disease subset is that defined by SI.

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References