Human Leukocyte Antigens in Undifferentiated Spondyloarthritis

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Objectives: Undifferentiated spondyloarthritis (USpA) is a major member of the spondyloarthritis family. Ankylosing spondylitis (AS), the prototype of the family, is a largely genetic disease, with human leukocyte antigens (HLA)-B27 being the essential gene. Other genes in the HLA region have also been implicated. The purpose of this study was to identify the alleles of the HLA-A, -B, -C, -DR, and -DQ, which are present at higher frequencies in USpA patients compared with an ethnically matched control population.

Methods: Sixty-three Taiwanese patients with USpA were compared with 75 matched healthy controls. HLA typing was performed by polymerase chain reaction-sequence specific oligo-nucleotide genotyping.

Results: The frequencies of HLA-B27, -B60, -C3, and -DR12 were strikingly higher in USpA patients compared with healthy subjects, with odds ratios of 75.4, 14.0, 9.6, and 7.0, respectively. When USpA patients with axial involvement were compared with those with peripheral arthritis, the following were more marginally frequent in those with axial involvement: HLA-B27 and -DR12 (odds ratios, 4.0 and 4.0, respectively). There was no association of HLA typing with other variables, including enthesitis, uveitis, erythrocyte sedimentation rate, and serum C-reactive protein. Interestingly, in 12 HLA-B27-negative USpA patients, HLA-B60, -C3, and -DR12 were more frequent compared with controls (odds ratios, 35, 16.2, and 8.1, respectively).

Conclusions: Similar to AS, USpA is also linked to HLA-B27. A linkage to other HLA alleles observed here, even in our HLA-B27-negative USpA patients, strongly suggests that USpA in general is a genetic disease.

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Spondyloarthritis (SpA) is a family of arthritis conditions with inflammatory lesions in the axial as well as peripheral joints. The prototype is ankylosing spondylitis (AS), which is a largely genetic disease, human leukocyte antigen (HLA)-B27 being an essential gene. Other members of the family are Reiter's syndrome, reactive arthritis (ReA), psoriatic arthritis (PsA), and inflammatory bowel diseases (IBD)-related arthritis (1,2).

The definition of this SpA family has been rather confusing until 1991, when a group of SpA specialists generated a set of classification criteria known as the European Spondyloarthropathy Study Group (ESSG) classification criteria (1). Based on this set of criteria, there are many SpA patients who cannot be assigned to any of the diagnoses listed above. These are called undifferentiated spondyloarthritis (USpA) (3-10). Since then, USpA has become the second most frequent type of SpA following AS, and its prevalence has been estimated to be between 1 and 2% (3-5). Unlike AS, the cause of USpA has been rather

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neglected by investigators (3,7-13). There are very few studies that address even the prevalence of HLA-B27 among USpA in different ethnic groups (2,6,14). However, genetics clearly play a role.

A pilot study is needed to identify the candidate markers to focus on in future large-scale studies. Since it is suspected that several of the AS-causing genes are in the MHC region, this particular pilot study focused on the frequencies of HLA alleles in USpA patients compared with control subjects of the same ethnic background of Han people in Taiwan. The results demonstrate that, in addition to HLA-B27, several other candidate HLA markers should also be tested in future large-scale studies.

METHODS

Patients and Controls

This retrospective study recruited 63 patients (44 male, 19 female) with USpA who visited the rheumatology outpatient clinic in Taipei-Veterans General Hospital from June 2003 to April 2005. SpA was diagnosed according to the ESSG criteria (1). Patients were diagnosed with USpA when they had SpA but did not meet the criteria for AS, ReA, PsA, or other SpAs. The control group included 75 healthy blood donors, and their demographic data were well matched with those of the USpA patients.

In this study, all USpA patients and controls were Han Chinese. To explore the role of HLA genes between USpA patients and the control group, we divided these USpA patients into subgroups, including male and female, axial and peripheral arthritis, and HLA-B27-negative and HLA-B27-positive USpA. Other features evaluated included enthesitis, uveitis, levels of blood erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and immunoglobulin A (IgA). Pelvic radiographs and lumbar or cervical spine lateral views were performed in all patients. Written informed consent was obtained from all participants, and the protocol was approved by the local institutional review board.

Laboratory Examinations

HLA (including 506 HLA-A alleles, 851 HLA-B alleles, 276 HLA-C alleles, 476 HLA-DR alleles, and 81 HLA-DQ alleles) typing was performed by using polymerase chain reaction sequence-specific oligo-nucleotide genotyping methods (Dynal, UK Ltd., Bromborough, UK). ESR was done using the Westergren method, and the serum levels of IgA and CRP were measured by nephelometry (Behring Nephelometer Analyzer-II Dade Behring, Marburg, Germany). In some cases, only 1 allele was identified, which may indicate that the individual was either homozygous for that allele or carried an unidentified allele. As the number of unidentified alleles was likely to be very low, these cases were considered to be homozygous for the genotyped allele in all further analyses.

Statistical Analysis

Statistical analysis was performed using the SPSS statistical software package. Demographic data and clinical characteristics were summarized as the mean ± standard deviation for continuous variables, and as proportions for categorical variables. The Mann-Whitney *U*-test and Fisher's exact test were used, as appropriate, to analyze group differences. The Bonferroni correction for multiple testing was applied where indicated. *P* values were provisionally regarded as significant if they were less than 0.05.

RESULTS

Demographic Data and Clinical Characteristics of USpA Patients

Among the 63 patients with USpA, the ratio of male to female was 2.3. The age at disease onset was 28.9 ± 11.3 years, and the disease duration was 4.7 ± 2.9 years (range, 7 months to 12 years). The pattern of arthritis was predominantly axial in 38 (60%), predominantly peripheral in 29 (46%), and mixed in 4 (Table 1).

Comparison of HLA Typing between USpA Patients and Control Subjects

The comparison of the frequencies of HLA alleles (HLA-A, -B, -C, -DR, -DQ) between the 63 USpA patients and the 75 healthy controls are shown in Table 2. The most significant finding is that HLA-B27 was present in 81% of USpA patients but only 5% of the control subjects (OR = 75.4). Unexpectedly, HLA-DR12 was also present in as high as 68% of USpA patients, but only 20% of control subjects (OR = 7.0). We also observed in USpA patients statistically significant higher frequencies of HLA-C3 and -B60. However, their frequencies among patients were only 29 and 16%, respectively. Of the HLA alleles that were higher in control subjects compared with USpA patients, the most interesting was HLA-C10, which was present in 45% of control subjects but only 8% of USpA patients (OR = 0.1).

Table 1 Demographic Data and Clinical Characteristics of 63 USpA Patients

Demographics/Clinical Characteristics	Number (%)
Male	44 (70)
Female	19 (30)
Age at onset of disease (y)	28.9 ± 11.3
Disease duration (y)	4.7 ± 2.9
Axial involvement	38 (60)
Peripheral arthritis	29 (46)
HLA-B27+	51 (81)
Uveitis	15 (24)
Enthesitis	23 (37)

HLA, human leukocyte antigen.