Undifferentiated Spondyloarthropathies in Brazilians: Importance of HLA-B27 and the B7-CREG Alleles in Characterization and Disease Progression

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ABSTRACT. ***Objective***. To analyze the profile of the HLA-B27 and B7 cross-reactive group (CREG) alleles and the role of these markers in disease characterization and progression in patients with undifferentiated spondyloarthropathies (uSpA).

Methods. A total of 80 patients with a diagnosis of uSpA (40 HLA-B27 positive and 40 HLA-B27 negative) were prospectively studied for 2 years. The control group consisted of 66 HLA-B27 positive and 112 HLA-B27 negative individuals without a history of seronegative SpA. HLA-B alleles were typed at low (B7-CREG alleles, i.e., B*7, B*54, B*55, B*56, B*40, B*42) or high resolution (B*27 alleles) using polymerase chain reaction-amplified DNA hybridized with sequence-specific oligonucleotide probes.

Results. HLA-B*2705 was the most frequent allele, observed in 92.5% of the patients and in 77% of the controls, followed by the HLA-B*2702, observed in 5% of the patients and in 12% of the controls. HLA-B*2704 was observed in only one patient (2.5%), and was absent in the control population. HLA-B*2703 (6%) and HLA-B*2707 (5%) alleles were observed only in controls. No associations between HLA-B*27 alleles or B7-CREG alleles and any specific manifestation of uSpA were observed. HLA-B27 positive patients more frequently presented juvenile onset SpA ($p = 0.002$) and progression to ankylosing spondylitis (AS) ($p = 0.03$) than did HLA-B27 negative patients. The B7-CREG alleles were observed in 5% of the HLA-B27 positive uSpA group, in 25% of the HLA-B27 negative uSpA group, in 7% of the HLA-B27 positive controls, and in 13% of the HLA-B27 negative controls; a significant association was observed between the presence of the B7-CREG and the HLA-B27 negative uSpA group ($p = 0.012$).

Conclusion. The frequency of the HLA-B*2705 allele among the B27 positive uSpA patients of this series was closely similar to that reported for patients with ankylosing spondylitis (AS). The presence of HLA-B*27 alleles was associated with the progression to AS, and the presence of B7-CREG was associated with uSpA in the HLA-B27 negative group. (J Rheumatol 2003;30:2632–7)

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Seronegative spondyloarthropathies (SpA) constitute a heterogeneous group of disorders with common genetic and clinical characteristics. The strength of disease association with HLA-B27 varies markedly among the various SpA forms as well as among different ethnic populations[1]. The HLA-B27 molecule is encoded by 25 described alleles, named HLA-B*2701 to HLA-B*2725[2], and the occurrence of ankylosing spondylitis (AS) and related SpA has been documented in subjects possessing any one of the first 10 (HLA-B*2701 to HLA-B*2710) alleles[3]. Some B*27 alleles seem not to be associated with AS and related SpA, including HLA-B*2706 in Southeast Asia[4] and HLA-B*2709 in the Italian island of Sardinia[5]. The most recently described alleles (HLA-B*2711 to HLA-B*2725) have not yet been studied in terms of disease association. In addition to B27, the antigens that cross-react with B27 antigens,

including B7, B22, B42, and B60 [called the B7-cross-reactive group (CREG)], are encoded by alleles (B*07, B*54, B*55, B*56, B*42, B*40) that have also been associated with AS[6-8] and Reiter's syndrome[9-11].

Undifferentiated spondyloarthropathies (uSpA) encompass a group of patients with clinical and radiographic features suggestive of a SpA but not fulfilling the diagnostic criteria for any of the currently established diseases in that group[12]. As uSpA present a highly variable expression and disease course, they are frequently characterized as a provisional diagnosis. In the adult population, uSpA have been described in Europeans[13,14], Africans[15,16], Asians[17,18], Eskimos[19,20], and Latin Americans[21].

Our group has recently described the 2-year followup of a group of 68 Brazilian patients with a diagnosis of uSpA, and analyzed the importance of epidemiological variables (sex, race, HLA-B27, family history, initial symptoms) for disease outcome[21]. As HLA-B27 seems to be an important predictive factor in patients with uSpA in terms of evolution to a definite SpA, we analyzed the HLA-B*27 and the B7-CREG allele profiles in Brazilian patients with uSpA. To further characterize the disease and analyze disease outcome in a 2-year followup, patients were stratified according to the presence or absence of HLA-B*27 alleles. The HLA-B*27 and the B7-CREG allele profiles were also studied in a healthy control group consisting of 66 HLA-B27 positive and 112 HLA-B27 negative individuals.

MATERIALS AND METHODS

Patients. This prospective study was carried out in 80 adult patients with a diagnosis of uSpA who attended the outpatient clinic of the Hospital de Clínicas of the State University of Campinas between 1994 and 2000. Patients not fulfilling the criteria for a definite diagnosis of any of the SpA at the initial visit and who fulfilled both the European Spondylarthropathy Study Group (ESSG)[22] and the Amor[23] sets of criteria for SpA were included in the study.

Forty HLA-B27 positive and 40 HLA-B27 negative patients with uSpA were studied, and were divided into Caucasians and non-Caucasians; the latter included African-Brazilians (Black patients of unmixed ancestry and Mulattos, i.e., originating from the mixture of White and Black populations) and East Asians (Japanese origin). Most patients came from the metropolitan area of Campinas, with a population of roughly 3,000,000 inhabitants, located in an industrial region of the State of São Paulo, in the southeast of Brazil, where the white population includes people of predominantly Portuguese, Italian, and/or Spanish ancestry.

Clinical evaluation included a search for initial symptoms and the presence of axial and peripheral joint involvement, and heel enthesopathies during the 2-year followup. Initial symptoms included inflammatory low back pain (ILBP — without radiographic sacroiliitis)[24], asymmetric oligoarthritis (predominantly affecting large joints of the lower limbs), and heel enthesopathies (Achilles tendinitis and/or plantar fasciitis).

Imaging methods performed at study entry included pelvic and calcaneal radiography. After 2 years of followup, a second pelvic radiography was performed. Each sacroiliac joint was scored according to the modified New York criteria[25]; to be enrolled in the study, patients had to present sacroiliitis ≤ grade 1 at study entry.

After the 2-year followup, patients who fulfilled the modified New York criteria[25] were diagnosed as having AS and patients who presented with characteristic psoriatic skin lesions were diagnosed as having psoriatic arthritis. Disease remission was considered when a complete remission of clinical symptoms for a period of at least one year (without symptomatic medication) associated with a normal pelvic radiography was observed.

Controls. A total of 178 individuals (66 HLA-B27 positive and 112 HLA-B27 negative) were included in the control group. Control individuals were recruited from healthy blood donors and solid organ or hematopoietic stem cell transplant donors, who attended the Transplant Immunogenetic Laboratory of the Department of Clinical Pathology of the State University of Campinas and the Laboratory of Molecular Immunology of the State University of São Paulo at Ribeirão Preto. The control group had no previous history of any SpA and denied familial evidence of SpA.

HLA-B typing. HLA-B alleles were typed at low resolution using polymerase chain reaction-amplified DNA hybridized with sequence-specific oligonucleotide primers (One-Lambda, Canoga Park, CA, USA), and HLA-B*27 alleles were typed using a high resolution HLA-B27 typing kit (Dynal, Oslo, Norway).

Statistical analysis. The chi-square and Fisher exact tests were used to verify the association of the variables of interest; p values ≤ 0.05 were considered to be significant, and $0.10 \leq p < 0.05$ were considered to be a statistical trend.

RESULTS

When comparing the positive and the negative HLA-B27 uSpA groups, we observed a significant association between positive HLA-B27 and the juvenile onset of uSpA (p = 0.002), and a trend association with heel enthesopathy (p = 0.073). Positive HLA-B27 uSpA patients presented a trend towards younger age at disease onset (mean = 24.9 years) compared to negative HLA-B27 uSpA patients (mean =

Table 1. Clinical and epidemiologic characteristics in 80 patients with undifferentiated spondyloarthropathies.

	Positive B27, n = 40 (%)	Negative B27, n = 40 (%)	p
Sex			
Male	33 (82.5)	28 (70)	NS
Female	7 (17.5)	12 (30)	
Race			
Caucasian	31 (77.5)	31 (77.5)	NS
Non-Caucasian	9 (22.5)	9 (22.5)	
Age at onset			
Juvenile [≤ 16 yrs]	11 (27.5)	1 (2.5)	0.002
Adult [> 16 yrs]	29 (72.5)	39 (97.5)	
Mean Age, yrs	24.9	28.5	0.06
Family history	5 (12.5)	3 (7.5)	NS
Initial symptom			
ILBP	18 (45)	19 (47.5)	NS
PA	16 (40)	18 (45)	NS
HE	6 (15)	3 (7.5)	NS
ILBP	26 (65)	31 (77.5)	NS
HE	25 (62.5)	17 (42.5)	0.073
Ankles	29 (72.5)	26 (65)	NS
Knees	22 (55)	22 (55)	NS
Hips	9 (22.5)	7 (17.5)	NS
Wrists	1 (2.5)	5 (12.5)	NS
Shoulders	2 (5)	3 (7.5)	NS
Sternoclavicular	2 (5)	3 (7.5)	NS

ILBP: inflammatory low back pain; PA: peripheral arthritis; HE: heel enthesopathies; NS: non-significant.

28.5 years) (p = 0.06). Clinical and epidemiologic features of both uSpA groups are shown in Table 1.

In decreasing order, the most frequent HLA-B*27 alleles among uSpA patients were: B*2705 allele, detected in 37 (92.5%) patients, B*2702 allele in 2 (5%), and B*2704 in only one (2.5%) patient, the latter being of Japanese ancestry. No significant association was observed between HLA-B*27 alleles and any specific manifestation of the uSpA group.

In the control group, the HLA-B*2705 allele was observed in 51 (77%) individuals, B*2702 in 8 (12%), B*2703 in 4 (6%), and B*2707 in 3 (5%). The HLA-B*2703 and HLA-B*2707 alleles were present only in the control group (p = 0.017). There was a significant association between HLA-B*2703 and African-Brazilians (p = 0.018) in the control group, but no significant association between HLA-B*2707 and race was observed. The distribution of the HLA-B*27 alleles in the uSpA and control groups is shown in Table 2.

The B7-CREG alleles were observed in 2 patients (5%) of the HLA-B27 positive uSpA group, in 10 patients (25%) of the HLA-B27 negative uSpA group, in 5 individuals (7%) of the HLA-B27 positive control group, and in 14 (13%) of the HLA-B27 negative control group. The B7-CREG alleles were overrepresented in the HLA-B27 negative uSpA group in relation to the HLA-B27 positive uSpA group (p = 0.012). No significant association was observed between the B7-CREG and any specific manifestation of uSpA. The disposition of the B7-CREG alleles in the uSpA groups and controls is shown in Table 3.

Table 2. HLA-B27 alleles (uSpA vs control group).

HLA-B27 Alleles	uSpA, n = 40 (%)	Controls, n = 66 (%)	p
HLA-B*2705	37 (92.5)	51 (77)	NS
HLA-B*2702	2 (5)	8 (12)	NS
HLA-B*2704	1 (2.5)	—	NS
HLA-B*2703	—	4 (6)	0.017†
HLA-B*2707	—	3 (5)	0.017†

uSpA: undifferentiated spondyloarthropathies; NS: non-significant. † For statistical purposes, HLA-B*2703 and HLA-B*2707 were considered as one group (7 patients).

Table 3. Alleles that encode the B7-CREG (uSpA vs control group).

	uSpA B27+, n = 40	uSpA B27–, n = 40	Controls B27+, n = 66	Controls B27–, n = 112
B*07	1	7	3	11
B*54, *55, *56	0	0	0	0
B*40	1	2	1	3
B*42	0	1	1	0
Total	2	10	5	14
p	0.012		NS	

uSpA: undifferentiated spondyloarthropathies; NS: non-significant.

We were able to complete the 2-year followup for all patients. After this time, 59 patients (74%) remained with the diagnosis of uSpA, 10 (12%) presented disease remission, and 11 (14%) turned out to have a definite SpA (9 with AS and 2 with psoriatic arthritis). Patients presenting with uSpA who possessed any of the HLA-B*27 alleles developed AS in much higher frequency than did uSpA patients without these alleles (p = 0.03). A summary of the 2-year outcome in all uSpA patients of this series is shown in Table 4.

DISCUSSION

Our study showed that HLA-B*27 and B7-CREG alleles may have relevant implications in terms of disease outcome in uSpA patients, even over short-term followup (2 yrs). In addition, this is the first study evaluating HLA-B*27 alleles in Brazilian uSpA patients, a population whose gene bank represents the contribution of individuals of various racial and ethnic backgrounds, including Caucasian immigrants from many regions of Western Europe, African-American populations from the Niger-Congo of Equatorial Africa, native Amerindian populations[26], and more recently Asian immigrants, particularly from Japan.

Although no consensus has been reached regarding the diagnosis of uSpA, in our study the selection of patients was primarily based on symptomatic uSpA, i.e., patients with clinical complaints of inflammatory low back pain (without radiographic sacroiliitis), asymmetric oligoarthritis (affecting predominantly large joints in the lower limbs), and heel enthesopathies (Achilles tendinitis or plantar fasciitis, or both). Since asymptomatic radiographic sacroiliitis or recurrent attacks of acute anterior uveitis have been considered to represent distinct uSpA subgroups[12], patients presenting with these features were excluded. In addition, patients who did not fulfill both the ESSG and the Amor sets of criteria for SpA were also excluded. Although there are some uSpA patients who do not fulfill 6 points in the Amor set of criteria[21,27], these patients were not included in this study, because we intended to include only patients with a "definite" uSpA; the usefulness of these criteria for SpA was stressed by Prof. Amor in a recent editorial[28]. The selection of patients aged between 18 and 50 years was because we intended to study the outcome of uSpA in an adult population, as the disease in children[29] and in the elderly[30]

Table 4. Outcome after 2 years of followup.

	HLA-B27+, n = 40	HLA-B27–, n = 40	p
uSpA	28	31	NS
AS	8	1	0.03
PsA	1	1	NS
Remission	3	7	NS

uSpA: undifferentiated spondyloarthropathies; AS: ankylosing spondylitis; PsA: psoriatic arthritis; NS: non-significant.

frequently presents different patterns from those seen in adults.

There is substantial evidence favoring a direct role for HLA-B*27 alleles in enhancing genetic susceptibility to AS and other related SpA, although the underlying molecular basis of disease association has not yet been completely identified[3,31]. B*2705 and B*2702 were the most frequent alleles seen in Brazilian patients presenting with uSpA, similar to the observations reported for other Caucasian populations. HLA-B*2705 is the most widespread B*27 allele, being considered the ancestral gene from which others have evolved[3,31]. This allele is clearly associated with SpA in about 90% of the B27 positive population of northern Europe[3,32], and is virtually the only allele observed among the native populations of Siberia[32] and North America[3,33]. Although the B*2705 allele is observed in 68% of the B27 positive individuals of the Fula ethnic group in Gambia, the relative risk of these individuals to develop AS is extremely low in relation to B27 positive Caucasians, suggesting the presence of some non-B27 protective factor reducing the prevalence of AS in this African Black population[34]. The HLA-B*2702 allele is also clearly disease associated in the SpA group and is present in 4 to 10% of the B27 positive individuals of Northern Europe[3,33], increasing to 20% in the Iberian Peninsula (Spain and Portugal)[35], and rising to 55% in Semitic B27 positive populations[36]. In our study, the HLA-B*2704 allele was observed in only one uSpA patient, of Japanese ancestry; indeed, this is the most frequent allele in Asian patients, strongly associated with SpA in Chinese, Indonesians, and Japanese[3,4,37,38].

Among Brazilian control individuals, the B*2705 and B*2702 alleles were also the most frequently observed alleles, presenting with frequencies closely similar to those observed for uSpA patients. Besides these alleles, the B*2703 and B*2707 alleles were observed in the control group and were not detected in the uSpA patients. HLA-B*2703 allele was over-represented in African-Brazilians in relation to the Caucasian population of the present study. The B*2703 allele has been reported to be common in Western Africans; however, it is very rare in African-Americans, and the association of this allele with AS and related SpA is rare[3]. The HLA-B*2707 allele has been described in association with SpA in patients from Asia[4,17,38] and Europe[3]; however, no patient with this allele was observed in the present study.

The finding of 5 different HLA-B*27 alleles (B*2702, B*2703, B*2704, B*2705, B*2707) does reflect the genetically highly diverse feature of the Brazilian population, as mentioned. Elsewhere, high B*27 allele diversity has been shown in Azorians, a population that also presents 5 distinct alleles (B*2702, B*2703, B*2705, B*2707, B*2708), and represents the genetic contribution of individuals from European, Asian, and African ancestry[39]. Recently, the highest variability of HLA-B*27 alleles (B*2702, B*2703, B*2705, B*2707, B*2708, B*2713) was described in patients with AS and related SpA in Northern Spain[40].

Although the frequency of HLA-B*27 alleles did not differ significantly between uSpA patients and controls, a significant association with juvenile onset was observed in uSpA presenting with these alleles (11 patients in the B27 positive group had disease onset before age 16 years vs only one in the B27 negative group). In addition, the presence of HLA-B*27 alleles presented an important association with the evolution to AS after 2 years of followup (8 vs 1), compared to uSpA patients who did not possess the B*27 alleles. These results support the idea that the presence of HLA-B*27 alleles represents an important prognostic factor, indicating younger onset and more aggressive outcome in uSpA patients. In our previous study evaluating 147 AS patients followed at the same institution, HLA-B27 was positive in 78.2% of the patients with AS[41]. HLA-B27 did not show an association with race in Brazilian patients (in the former[41] or the present study), probably due to the mixed nature of the Brazilian non-Caucasian population; none of the 80 uSpA patients in the present study presented pure African ancestry.

Another important association in this study was between B7-CREG and the B27 negative uSpA group. Antigens that cross-react with HLA-B27 have been considered to have an important role in the etiopathogenesis of SpA. The frequency of HLA-B7 antigen in AS has been reported to be increased in African-American Blacks[6] or European Caucasian[7] patients, frequently in the absence of HLA-B27. HLA-B60 (encoded by the B*40 alleles) can enhance the susceptibility to AS onset in HLA-B27 positive patients[8]. The CREG-B7 antigen group (predominantly B7) can also be found in patients with Reiter's syndrome in Caucasian North Americans[9], Israelis[10], and African Blacks[11]. In the present study, HLA-B*07 was the most prevalent allele of the B7-CREG group, predominating in the HLA-B27 negative patients; it presented no statistical association to any clinical or epidemiological variables.

One can speculate about the etiopathogenic factors involved in the 75% of the uSpA patients that are HLA-B27 negative and CREG-B7 negative. Gene mapping studies have implicated non-B27 genes both within the MHC and elsewhere as being involved in the susceptibility of the SpA[3,31,42,43]. Another important concern in these patients is the association with an infectious triggering microorganism, characterizing a reactive arthritis[44]. Although all the uSpA patients in our study denied previous or current symptoms compatible with reactive arthritis/Reiter's syndrome, recent data have outlined the importance of serologic and microbiologic tests, together with the clinical setting, in the diagnosis and management of undifferentiated oligoarthritis[45-47]. In conclusion, in Brazilian uSpA patients, HLA-B*2705 was the most frequently observed allele, presenting closely

similar frequencies to normal and AS Caucasian populations. The presence of HLA-B*27 alleles was associated with progression from uSpA to AS, and the presence of B7-CREG alleles was associated with the HLA-B27 negative uSpA group.

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