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HLA-B5 prevalence in patients with spondyloarthritis and impact on disease phenotype: a multicentric case–control study

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Abstract

Objective: The study aimed to estimate the prevalence of HLA-B51 and HLA-B52 in Lebanese patients with spondyloarthritis (SpA) compared with healthy controls (HC). We further aimed to evaluate the impact of HLA-B51 on phenotype and identify the distribution of the alleles in the HLA-B locus.

Methods: A case–control study enrolled consecutive SpA patients from three rheumatology clinics in Lebanon, including axial (axSpA), peripheral SpA (pSpA), and psoriatic arthritis (PsA) and HCs from blood donors. Demographic and disease data were collected through interviews and file reviews, with testing of the entire HLA-B locus using molecular techniques. The prevalence of HLA-B51 and B52 was estimated in SpA patients *vs* controls. Prevalence comparisons were made, and logistic regression identified factors associated with HLA-B51 in patients.

Results: Data from 120 HCs and 86 SpA patients (65 axSpA, 15 pSpA, 6 PsA), mean age 25.6 and 46.4 years, respectively, showed a higher HLA-B51 prevalence in SpA (25.6%), especially axSpA (29.2%) *vs* HC (12.5%) ($P = 0.016$), and a numerically higher HLA-B52 prevalence (8.1% *vs* 4.2%, $P = 0.230$). HLA-B51 correlated with recurrent oral ulcerations (OR 7.99; 95% CI: 2.14, 29.84) and radiographic juxta-articular erosions (OR 7.65; 95% CI: 1.14, 38.03). HLA-B35 was the most dominant allele in both groups (18.7%), followed by HLA-B27 (15.7%) and HLA-B51 (13.4%) in SpA.

Conclusion: HLA-B51 was identified more frequently in patients with SpA compared with HC and was associated with recurrent oral ulcerations and juxta-articular radiographic erosions. Longitudinal studies are needed to determine whether this association indicates a disease overlap or might correlate with a specific SpA phenotype.

Keywords: HLA-B51, HLA-B27, spondyloarthritis, axial spondyloarthritis, peripheral spondyloarthritis, Behçet's syndrome, major histocompatibility complex.

Rheumatology key messages

- HLA-B51 was identified more frequently in Lebanese patients with spondyloarthritis compared with healthy controls.
- HLA-B51 was associated with recurrent oral ulcerations and juxta-articular radiographic erosions.
- HLA-B35 was the most dominant allele, followed by HLA-B27 and HLA-B51 in spondyloarthritis.

Introduction

Spondyloarthritis (SpA) is a group of highly heritable inflammatory diseases primarily associated with the human leucocyte antigen B27 (HLA-B27) of major histocompatibility complex I (MHC I) [1, 2], which explains about 25% of the genetic hereditary factors within the MHC [3]. SpA can be classified into predominantly axial (axSpA) and predominantly peripheral forms encompassing psoriatic arthritis (PsA), arthritis related to inflammatory bowel diseases (IBD-SpA), reactive arthritis and undifferentiated peripheral SpA

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(pSpA) [1, 2, 4–6]. The disease is characterized by a wide range of symptoms, including inflammation in the sacroiliac joints (SIJ), inflammatory back pain (IBP), peripheral arthritis, enthesitis and dactylitis. It may be associated with extramusculoskeletal manifestations (EMMs) such as uveitis, psoriasis and IBD [1]. Currently, there are no universally accepted diagnostic criteria for SpA [7]. However, various sets of classification criteria are currently available, with the Assessment of Spondyloarthritis International Society (ASAS) and the Classification Criteria for Psoriatic Arthritis (CASPAR) being the most commonly utilized [5, 6, 8].

Potential differential diagnoses for SpA encompass chronic conditions with diverse musculoskeletal and extramusculoskeletal manifestations, one of which is Behçet's syndrome (BS). BS is a variable vessel vasculitis that may present with mouth and genital ulcers, skin lesions, arthritis, uveitis, and potential involvement of gastrointestinal and central nervous systems [9, 10]. HLA-B51, a subtype of the extensive B5 antigen and closely related to the B52 serotype, serves as a notable genetic indicator for BS, where an association is found in up to 60% of patients [10–13]. Similarly to SpA, there are no diagnostic criteria for BS. However, two classification criteria are currently in use: the International Study Group (ISG) and the International Criteria for Behçet's Disease (ICBD) [14, 15]. Compared with the ISG criteria, the ICBD demonstrate higher sensitivity (94.8%) but slightly lower specificity (90.5%) [15].

Thus, SpA and BS share numerous clinical features, including articular, ophthalmic and gastrointestinal symptoms, leading to potential diagnostic challenges in the early stages of these conditions [16]. Overall, there seems to be a shared immunopathogenic foundation between the diseases, involving the association of HLA-B51 and HLA-B27, emphasizing the importance of these genetic markers in predicting and managing the disease activity of these conditions [16, 17].

It is suggested that the association of SpA and BS with HLA-B27 or HLA-B51 might impact the diseases' phenotype [16, 18]. In axSpA, the presence of HLA-B27 increases the likelihood of early onset and enhances the response to TNF inhibitors (TNFi) [16], a treatment also effective in BS [16, 18, 19]. Moreover, reactive SpA appears to be associated with HLA-B51 [16]. Furthermore, the presence of HLA-B5 in individuals at higher risk for SpA showed an increased prevalence of eye involvement, genital ulcers, and more severe or recurrent uveitis [18, 20]. For SpA patients with both positive HLA-B27 and HLA-B51, an increased risk of developing peripheral joint problems, along with cutaneous symptoms, oral ulcers and uveitis was reported [18], whereas in BS the arthritic type was associated with HLA-B27 and the ocular involvement with HLA-B5 [21]. Notably, Behçet's uveitis in individuals with both HLA-B27 and HLA-B51 may have a more favourable prognosis [20, 22].

Although rare, case reports of the coexistence of BS and SpA are on the rise in the literature [19, 23–26]. Whether this phenomenon represents an incidental occurrence or an overlap of chronic inflammatory diseases is still controversial [24].

In the Middle East region, the diagnostic complexity is further compounded, on one hand, by the low occurrence of HLA-B27 among both the general population and individuals with SpA [27, 28], particularly in Lebanon, where a low prevalence of 41% was reported in patients with axSpA, and, on the other hand, the high prevalence of HLA-B5 and BS [12, 28, 29]. Nevertheless, a proper diagnosis remains mandatory as therapeutic strategies may differ significantly between the two diseases [30–33].

Therefore, the primary objective of this study was to estimate the prevalence of HLA-B51 and HLA-B52 in patients with SpA compared with healthy controls (HC). We further aimed to estimate the proportion of patients with SpA who fulfil the BS classification criteria, evaluate the impact of the presence of HLA-B51 on the SpA phenotype, and identify the general distribution of the alleles found in the HLA-B locus in patients with SpA compared with HC.

Methods

Study design

This case–control study was conducted in 2021–2022.

Participants and setting

Patients diagnosed with axSpA, pSpA and PsA by a rheumatologist were invited to participate in the study during their regular clinic visits. The study involved three centres situated in different regions of Lebanon, including the capital city, Beirut, the northern part and the southern part of Lebanon. Among these centres, two were affiliated with academic institutions, while one was an outpatient clinic.

A control group of healthy participants was recruited from two sources: blood donors at Hotel-Dieu de France hospital, a central hospital in Beirut that serves as a primary collection point for blood donations across the country, and medical students from Saint Joseph University of Beirut during regular donation campaigns.

All participants were Lebanese nationals aged 18 years and older and provided written informed consent.

Variables

Data collection was conducted using an electronic case report form (e-CRF) uploaded on the Google Forms platform (see Supplementary Data, available at *Rheumatology* online) and presented to the patient on an electronic tablet or a smartphone. The form was available in Arabic and English. For the SpA group, data collection was conducted by the three rheumatologists practising in the three distinct rheumatology centres mentioned above. As for the HC group, data collection was carried out by a final-year medical student, using an e-CRF (see Supplementary Data, available at *Rheumatology* online).

Data collected included demographic data: age, gender, nationality, Armenian and Turkish ancestry. In addition, the clinical parameters of the ASAS 2009 and 2011 SpA classification criteria, and of the ISG and ICBD criteria were collected: chronic back pain, IBP, peripheral arthritis, enthesitis, dactylitis, skin and nail psoriasis, IBD, good response to NSAIDs, recurrent oral ulcerations, genital ulcerations, eye lesions (anterior uveitis, posterior uveitis, retinal vasculitis), skin lesions (erythema nodosum-like, papulopustular lesions, pseudofolliculitis), vascular lesions, neurological manifestations and Pathergy test result (if available). Additional data were collected from the patients' files when available: CRP, spinal and SIJ imaging data (X-rays and MRI), and juxtaarticular erosions on X-rays.

HLA genotyping

For patients and controls, all laboratory tests were performed centrally at Hotel-Dieu de France Hospital, where a 5 ml of blood sample was drawn for each patient. The entire B locus was tested using a molecular biology technique based on the reverse SSO DNA typing method. The first step consisted of extraction of the DNA from the blood samples of the patients and of the controls using the GE Healthcare Illustra blood genomic Prep Mini Spin Kit. After extraction, the DNA products were stored at 2–8°C until the tests were performed. The second step of the technique was carried out using the LAB Type SSO Class I B Locus Typing Test (One Lambda, Los Angeles, CA, USA). Patient DNA products were amplified using locus-specific primers coupled to biotin. PCR products are then denatured, allowing their rehybridization to complementary DNA probes fixed on polystyrene microbeads labelled with R-phycoerythrin-conjugated streptavidin. Each microsphere mixture includes negative and positive control microspheres for the subtraction of non-specific background signals. The measurement of the fluorescence intensity of the phycoerythrin fixed on the microbeads was carried out with the Luminex LABScan3D flow analyser (One Lambda). The interpretation of the reactions and the assignment of the corresponding HLA alleles was carried out using HLA Fusion software (One Lambda) and based on the reaction pattern compared with patterns associated with published HLA gene sequences.

The percentage positive value was calculated as: Percentage positive value = 100 × mean fluorescence intensity (MFI) (patient probe) − MFI (probe negative control)/MFI (probe positive control) − MFI (probe negative control). The positive reaction is defined by the percentage of positive values for the probe higher than the pre-set cut-off value for the probe. The negative reaction is defined as the percentage of positive values lower than the cut-off value.

Bias

To mitigate the risk of selection bias, we included centres located in various regions of the country, encompassing diverse patient profiles for the recruitment of patients and utilizing the national blood donation hub for the HC group.

Statistical methods

For the prevalence calculations, firstly, we determined the prevalence of HLA-B51 and HLA-B52 in patients with SpA (jointly and separately for each SpA category) and HCs. Secondly, we estimated the prevalence of BS ISG and ICBD parameters and classification criteria among patients with SpA. Thirdly, we identified the factors associated with the presence of HLA-B51 in patients with SpA; we performed a bivariate analysis, specifically the chi-square test for categorical variables (with Fisher's exact test for small samples) and Student's *t*-test or the Mann–Whitney test for continuous variables, as appropriate. The variables associated with HLA-B51 as the dependent variable in the bivariate analysis (*P*-value <0.05) were included in a multivariable binary logistic model. Finally, we assessed the distribution of HLA-B subtypes in SpA patients versus HCs.

Significance was set at $P < 0.05$, and statistical analyses were performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA).

Sample size

For sample size determination, we assumed an HLA-B51/52 prevalence of 12% in the general population and a prevalence of 28% in SpA patients, with a type I error (α) of 0.1 and a type II error (β) of 0.20, leading to a total of 156 subjects (52 SpA patients and 104 healthy controls) required for the study. The sample size calculation was performed using the OpenEpi tool (https://www.openepi.com/SampleSize/SSCC.htm).

Ethical use of human participants' statements

The study was approved by the Ethics Committee of Saint Joseph University, Beirut. Before enrolling in the study, every participant provided written informed consent to participate in the study. All procedures were conducted after receiving signed informed consent from patients and in compliance with our institution's ethical committee guidelines.

Adherence to STROBE guidelines

The study's reporting adhered to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Results

In total, 86 individuals with SpA, among whom 65 (75.6%) had axSpA, 15 (17.4%) had pSpA and 6 (7.0%) had PsA as the main diagnosis and 121 HCs were included in the study (Table 1). One HLA-B51 positive HC was excluded as he was diagnosed with BS during the course of the study, due to oral and genital ulcerations and thrombophlebitis.

The mean (S.D.) age of patients with SpA was 46.4 (13.1) years, higher than the HCs [25.6 (5.8) years], and 66.3% were male (compared with 51.7% for HCs). In patients with SpA, psoriasis was reported in 19.8%, IBD in 18.7% and uveitis in 4.7%, with all EMMs being more frequent in patients compared with HCs.

In patients with SpA, the median disease duration was 11.0 years [interquartile range (IQR) 6.0–19.0] (Table 2).

Table 1. Participants' characteristics (spondyloarthritis patients and healthy controls)

	Patients with spondyloarthritis ($n = 86$)	Healthy controls ($n = 120$)	*P*-value
Age, mean (S.D.), years	46.4 (13.1)	25.6 (5.8)	**<0.001**
Gender, *n* (%)			**0.036**
Males	57 (66.3)	62 (51.7)	
Females	29 (33.7)	58 (48.7)	
Armenian ancestry, *n* (%)	5 (5.8)	7 (5.8)	0.9995
Turkish ancestry, *n* (%)	0 (0.0)	4 (3.3)	0.142
Chronic lower back pain, *n* (%)	77 (89.5)	14 (11.7)	**<0.001**
Inflammatory back pain, *n* (%)	67 (77.9)	6 (5.0)	**<0.001**
Peripheral musculoskeletal manifestation[a], *n* (%)	50 (58.1)	5 (4.2)	**<0.001**
Psoriasis, *n* (%)	17 (19.8)	5 (4.2)	**<0.001**
Crohn's disease, *n* (%)	14 (16.4)	1 (0.8)	**<0.001**
Ulcerative colitis, *n* (%)	2 (2.3)	1 (0.8)	0.572
Uveitis, *n* (%)	4 (4.7)	0 (0.0)	**0.029**
Fulfilment of the ASAS criteria for axSpA, *n* (%)	61 (70.9)	0 (0.0)	**<0.001**
Fulfilment of the ASAS criteria for pSpA, *n* (%)	55 (82.1)	7 (5.8)	**<0.001**

[a] Arthritis, enthesitis or dactylitis. *P*-values shown in bold indicate statistical significance. ASAS: Assessment of Spondyloarthritis International Society; axSpA: axial spondyloarthritis; ICBD: International Classification of Behçet's Disease; pSpA: peripheral spondyloarthriti; SpA: spondyloarthritis.

Table 2. Disease characteristics in all patients with spondyloarthritis and by disease category

Type of SpA	All SpA ($n = 86$)	axSpA ($n = 65$)	pSpA ($n = 15$)	PsA ($n = 6$)
Age, mean (S.D.), years	46.4 (13.1)	48.1 (12.4)	39.3 (13.2)	45.7 (15.8)
Gender, *n* (%)				
Male	57 (66.3)	43 (66.2)	9 (60.0)	5 (83.3)
Female	29 (33.7)	22 (33.8)	6 (40.0)	1 (16.7)
Symptom duration, median (IQR), years	11.0 (6.0–19.0)	12.5 (5.0–20.7)	11.0 (5.0–13.5)	2.0 (1.0–15.0)
Diagnostic delay, median (IQR)	5.0 (1.0–10.0)	5.5 (1.0–12.5)	5.0 (1.0–10.0)	6.0 (2.0–10.0)
Disease phenotype				
Chronic lower back pain, *n* (%)	77 (89.5)	63 (96.9)	9 (60.0)	5 (83.3)
Inflammatory lower back pain, *n* (%)	67 (77.9)	60 (92.3)	4 (26.7)	3 (50.0)
Arthritis, *n* (%)	35 (40.7)	23 (35.4)	10 (66.7)	2 (33.3)
Enthesitis, *n* (%)	40 (46.5)	25 (38.5)	12 (80.0)	3 (50.0)
Dactylitis, *n* (%)	8 (9.3)	3 (4.6)	2 (13.3)	3 (50.0)
Any peripheral manifestation, *n* (%)	50 (58.1)	32 (49.2)	14 (93.3)	4 (66.7)
Cutaneous psoriasis, *n* (%)	17 (19.8)	9 (13.8)	3 (20.0)	5 (83.3)
Nail psoriasis, *n* (%)	8 (9.3)	5 (7.7)	1 (6.7)	2 (33.3)
Crohn's disease, *n* (%)	14 (16.3)	11 (16.9)	3 (20.0)	0 (0.0)
Ulcerative colitis, *n* (%)	2 (2.3)	2 (3.1)	0 (0.0)	0 (0.0)
Uveitis, *n* (%)	4 (4.7)	4 (6.2)	0 (0.0)	0 (0.0)
Disease activity				
BASDAI ≥ 4, *n* (%)	28 (36.8)	21 (36.2)	5 (35.7)	2 (50.0)
ASDAS score, median (IQR)	2.4 (1.6–3.1)	2.2 (1.6–3.1)	2.4 (1.3–2.8)	2.5 (1.5–3.4)
Biological markers				
History of elevated CRP, *n* (%)	58 (69.0)	44 (68.8)	11 (73.3)	4 (66.7)
HLA-B27 positivity, *n* (%)	27 (31.4)	24 (36.9)	3 (20.0)	0 (0.0)
Imaging characteristics				
Sacroiliitis on MRI, *n* (%)	48 (55.8)	47 (72.3)	1 (6.7)	0 (0.0)
Sacroiliitis on X-Ray, *n* (%)	42 (48.8)	41 (63.1)	0 (0.0)	1 (16.7)
Sacroiliitis on MRI or X-ray, *n* (%)	56 (65.1)	54 (83.1)	1 (6.7)	1 (16.7)
Syndesmophytes, *n* (%)	23 (11.2)	21 (32.3)	2 (13.3)	0 (0.0)
Juxta-articular lesions on X-rays, *n* (%)	11 (12.8)	7 (10.8)	2 (13.3)	2 (50.0)
Classification criteria				
ASAS criteria for axSpA, *n* (%)	61 (70.9)	54 (83.1)	6 (40.0)	1 (16.7)
ASAS criteria for pSpA, *n* (%)	55 (82.1)	37 (75.5)	15 (100)	4 (66.7)
Family history				
Familial history of SpA, *n* (%)	19 (22.1)	18 (27.7)	1 (6.7)	0 (0.0)
Familial history of uveitis, *n* (%)	5 (5.8)	4 (6.2)	1 (6.7)	0 (0.0)
Familial history of psoriasis, *n* (%)	14 (16.3)	10 (15.4)	2 (13.3)	2 (33.3)
Familial history of IBD, *n* (%)	13 (15.1)	11 (16.9)	2 (13.3)	0 (0.0)
Familial history of BS, *n* (%)	5 (5.8)	4 (6.2)	1 (6.7)	0 (0.0)
Treatment history				
NSAIDs treatment, ever, *n* (%)	80 (93.0)	63 (96.9)	12 (80.0)	5 (83.3)
Response to NSAIDs, *n* (%)	76 (88.4)	57 (87.7)	13 (86.7)	6 (100)
Corticosteroids treatment, ever, *n* (%)	21 (24.4)	17 (26.2)	4 (26.7)	0 (0.0)
csDMARDs treatment, ever, *n* (%)	42 (48.8)	31 (47.7)	8 (53.3)	3 (50.0)
TNFi treatment, ever, *n* (%)	50 (58.1)	43 (66.2)	7 (46.7)	0 (0.0)
tsDMARDs treatment, ever, *n* (%)	19 (22.1)	16 (24.6)	2 (13.3)	1 (16.7)
IL-17i treatment, ever, *n* (%)	11 (12.8)	10 (13.6)	0 (0.0)	1 (15.4)

For the percentage calculation: the denominator is the total of available information (some data is missing, for example when imaging data was not available from the patient's file). ASAS: Assessment of Spondyloarthritis International Society; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BS: Behçet's syndrome; csDMARDs: conventional synthetic DMARDs; HLA: human leucocyte antigen; IBD: inflammatory bowel disease; IL-17i: IL-17 inhibitors; IQR: interquartile range; pSpA: peripheral spondyloarthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; TNFi: TNF inhibitors; tsDMARDs: targeted synthetic DMARDs.

The most frequent symptom was chronic low back pain (89.5%), followed by IBP (77.9%), enthesitis (46.5%), arthritis (40.7%) and dactylitis (9.3%). In general, 58.1% had any peripheral musculoskeletal manifestations, including 49.1% of patients with axSpA. A family history of SpA was reported in 22.1% of patients. Also, 69.0% had a history of elevated CRP, 31.4% tested positive for HLA-B27, 55.8% had sacroiliitis on MRI, 48.8% had radiographic evidence of sacroiliitis and 23.6% had syndesmophytes. Juxta-articular erosions on X-rays were reported in 12.8%. At the time of data collection, 36.8% had active disease [reflected in a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) above 4], 58.1% were treated with TNF inhibitors (TNFi), 22.1% with targeted synthetic DMARDs, and 12.8% with IL-17 inhibitors (IL-17i). According to the ASAS classification criteria, 70.9% fulfilled the axSpA criteria and 82.1% fulfilled the pSpA criteria.

HLA-B51 was identified more frequently in patients with SpA (25.6%) compared with HCs (12.5%; $P = 0.016$), and particularly in patients with axSpA (29.2%; $P = 0.005$) compared with HCs (Table 3). The odds ratio (OR) of having an HLA-B51 positive allele in patients with axSpA was 2.89 (95% CI: 1.35; 6.19). HLA-B51 was numerically more frequent in patients with axSpA who fulfilled the ASAS axSpA classification criteria (13/54, 24.1%) compared with HCs ($P = 0.055$). Also, HLA-B52 was numerically more frequent in

Table 3. Prevalence of HLA-B5 and HLA-B27 genes in patients with spondyloarthritis and healthy controls

	Healthy controls ($n = 120$)	SpA ($n = 86$)	axSpA ($n = 66$)	pSpA ($n = 16$)	PsA ($n = 7$)	*P*-value[a]	*P*-value[b]
HLA-B51$^+$, *n* (%)	15 (12.5)	22 (25.6)	19 (29.2)	2 (13.3)	1 (16.7)	**0.016**	**0.005**
HLA-B52$^+$, *n* (%)	5 (4.2)	7 (8.1)	4 (6.2)	2 (13.3)	1 (16.7)	0.230	0.722
HLA-B51$^+$ or HLA-B52$^+$, *n* (%)	20 (16.7)	27 (31.4)	21 (32.3)	4 (26.7)	2 (33.3)	**0.013**	**0.014**
HLA-B27$^+$, *n* (%)	4 (3.3)	27 (31.4)	24 (36.9)	3 (20.0)	0 (0.0)	**<0.001**	**<0.001**

P-values shown in bold indicate statistical significance.
[a] *P*-value calculated for the difference between all patients with spondyloarthritis and healthy controls.
[b] *P*-value calculated for the difference between patients with axial spondyloarthritis and healthy controls. axSpA: axial spondyloarthritis; HLA: human leucocyte antigen; pSpA: peripheral spondyloarthritis; PSA: psoriatic arthritis.

patients with SpA (8.1%) compared with HCs (4.2%), but the difference did not reach statistical significance ($P = 0.230$).

Among the reported BS symptoms in the SpA patients, recurrent oral ulcerations were reported in 40.7% of patients (*vs* 20.8% in HCs), skin lesions in 16.3% (*vs* 9.2% in HCs), genital ulcerations in 1.2% (*vs* 0.8% in HCs), uveitis in 4.7% and vascular lesions in 2.3% (*vs* none in HCs) (Table 4). No patient with SpA fulfilled the International Study Group (ISG) classification criteria for BS, whereas nine (10.5%) fulfilled the ICBD classification criteria, compared with six (5.0%) in HCs.

In patients with axSpA, in the bivariate analysis, the presence of HLA-B51 was associated with recurrent oral ulcerations (77.3% in patients with SpA *vs* 28.1% in HC, $P < 0.001$), juxta-articular lesions on X-rays (31.8% *vs* 6.5%, $P = 0.066$), skin lesions (31.8% *vs* 10.9%, $P = 0.022$), and fulfilling the ICBD classification criteria (22.7% *vs* 6.3%, $P = 0.044$) (Table 5).

In the multivariable analysis, after adjusting for all the parameters mentioned above, the presence of HLA-B51 remained associated with recurrent oral ulcerations (OR 7.99; 95% CI: 2.14, 29.84) and juxta-articular lesions on X-rays (OR 7.65; 95% CI: 1.14, 38.03) (Table 5).

Other disease features were numerically associated with the presence of HLA-B51, although a statistically significant difference was not reached. In particular, uveitis was more frequent in HLA-B51-positive patients (9.1% *vs* 3.1%), as well as psoriasis (22.7 *vs* 18.8%) and dactylitis (13.6% *vs* 7.8%), whereas Crohn's disease was less frequent (9.1% *vs* 18.8%). Also, disease activity was slightly higher in HLA-B51-positive patients (45.5% had a BASDAI above 4 *vs* 33.3%).

The most predominant allele in both SpA patients and HCs was *HLA-B35* (18.7% and 18.6%, respectively) (Fig. 1). As expected, the second most frequent allele in patients with SpA was *HLA-B27* (15.7% of all alleles, 31.4% of patients), and *HLA-B51* was the second most frequent allele (13.4% of all alleles, 26.6% of patients). Both alleles were significantly more frequent in patients with SpA compared with HCs (1.67% and 6.25%, $P < 0.001$ and $P = 0.024$, respectively), whereas *HLA-B18*, *HLA-B49* and *HLA-B38* were more frequent in HCs. The co-occurrence of *HLA-B51* and *HLA-B27* was observed in 4 out of 86 patients (4.6%), all of whom were patients with axSpA (4 out of 65 patients or 6.1%).

Discussion

In this cross-sectional multicentric study, the prevalence of HLA-B51 was significantly higher in patients with SpA (25.6%), particularly axSpA (29.2%), compared with HCs (12.5%). There was also a numerically increased prevalence of HLA-B52 in patients with SpA (8.1%) compared with HCs (4.2%), but this difference did not reach statistical significance, probably due to the lower prevalence of this allele in general.

Data regarding the prevalence of HLA-B51 in patients with SpA are scarce but seem to mirror the HLA-B51 prevalence in the population. A study on 408 patients with axSpA from the Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) cohort, a multiethnic study, and from The North American Spondylitis Consortium (NASC) identified HLA-B51 in only 2.7% of patients with axSpA and 3.8% controls [2]. Also, in 442 Han Chinese patients with axSpA and 346 controls from Shanghai and Gansu, China, HLA-B51 was found in 4.4% of patients and 8.8% of controls [2]. However, other studies from Korea identified HLA-B51 in 15.9% (24/151) [16] and 21.4% (12/56) patients with SpA [34].

In the current study, the HLA-B51 prevalence in the general population (12.5%), represented here by healthy blood donors, was comparable to studies conducted in countries across the Middle East and Eastern Asia regions, which revealed a prevalence ranging from 8.5% to 15.3% among healthy groups [18, 35]. In contrast, findings from the USA, Northern and Eastern Europe indicated a pooled percentage of HLA-B51/B5 carriage (3.5% to 8.8%) that was lower than that observed in the Middle East, Eastern Asia, and Southern Europe regions [2, 12].

Despite the association of SpA with HLA-B51, only 10.5% of patients with SpA fulfilled the ICBD BS classification criteria (*vs* 5.0% in HCs), and none fulfilled the ISG BS classification criteria. These results are in line with the known high specificity of the ISG criteria and confirm the higher sensitivity but lower specificity of the ICBD criteria, which may lead to overdiagnosis, particularly in patients with conditions like SpA [14, 15, 36].

Actually, overlap between SpA and BS seems to be rare, as indicated by limited literature reports [19, 22, 25]. While the number of documented cases is on the rise, it remains unclear whether this coexistence is coincidental or suggestive of a true overlap [24, 25]. Notably, in the current study, the association of HLA-B27 and HLA-B51 was identified only in 6.1% of patients with axSpA and 4.6% of patients with SpA.

Also, in the current study, the presence of HLA-B51 was associated with recurrent oral ulcerations and juxta-articular radiographic lesions. The association with oral ulcerations might raise questions about an association of BS in these patients, the possibility of an association of SpA with Crohn's disease or the consequence of frequent NSAID use in SpA. This finding is in line with previous reports indicating

Table 4. Prevalence of Behçet's syndrome symptoms in patients with spondyloarthritis and healthy controls

	Healthy controls ($n = 120$)	SpA ($n = 86$)	axSpA ($n = 65$)	pSpA ($n = 15$)	PsA ($n = 6$)
Recurrent oral ulcerations, *n* (%)	25 (20.8)	35 (40.7)	30 (46.2)	4 (26.7)	1 (16.7)
Genital ulcerations, *n* (%)	1 (0.8)	1 (1.2)	1 (1.5)	0 (0.0)	0 (0.0)
Cutaneous lesions, *n* (%)	11 (9.2)	14 (16.3)	13 (20.0)	0 (0.0)	1 (16.7)
Vascular lesions, *n* (%)	0 (0.0)	2 (2.3)	2 (3.1)	0 (0.0)	0 (0.0)
Neurological lesions, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uveitis or retinal vasculitis, *n* (%)	0 (0.0)	4 (4.7)	4 (6.2)	0 (0.0)	0 (0.0)
Pathergy's test positivity, *n* (%)	N/A	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ISG criteria, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ICBD criteria, *n* (%)	6 (5.0)	9 (10.5)	9 (13.8)	0 (0.0)	0 (0.0)

axSpA: axial spondyloarthritis; ICBD: International Criteria for Behçet's Disease; ISG: International Study Group; N/A: not applicable; pSpA: peripheral spondyloarthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis.

Table 5. Factors associated with HLA-B51 in patients with spondyloarthritis (bivariate and multivariable analyses)

	Bivariate analysis			Multivariable analysis
	HLA-B51$^-$($n = 64$)	HLA-B51$^+$($n = 22$)	*P*-value	OR (95% CI)
Age, mean (S.D.), years	45.3 (11.1)	46.7 (13.7)	0.647	
Disease duration, median (IQR), years	11.0 (5.0–18.5)	14.0 (5.5–19.0)	0.817	
Diagnostic delay, median (IQR)	5.0 (1.0–10.5)	6.0 (1.0–10.0)	0.966	
Sex, *n* (%)				
Male	43 (67.2)	14 (63.6)	0.761	
Female	21 (32.8)	8 (36.4)		
Armenian ancestry, *n* (%)	2 (9.1)	3 (4.7)	0.599	
Chronic low back pain, *n* (%)	58 (90.6)	19 (86.4)	0.688	
Inflammatory back pain, *n* (%)	50 (78.1)	17 (77.3)	0.934	
Arthritis, *n*, (%)	26 (40.6)	9 (40.9)	1.000	
Enthesitis, *n* (%)	30 (46.9)	10 (45.5)	1.000	
Dactylitis *n* (%)	5 (7.8)	3 (13.6)	0.416	
Skin psoriasis, *n* (%)	12 (18.8)	5 (22.7)	0.686	
Nail psoriasis, *n* (%)	5 (7.8)	3 (13.6)	0.416	
Crohn's disease, *n* (%)	12 (18.8)	2 (9.1)	0.504	
Ulcerative colitis, *n* (%)	1 (1.6)	1 (4.5)	0.448	
Uveitis or retinal vasculitis, *n* (%)	2 (3.1)	2 (9.1)	0.269	
History of high CRP, *n* (%)	45 (71.4)	14 (63.8)	0.495	
Good response to NSAIDs, *n* (%)	57 (89.1)	19 (86.4)	0.711	
Family history of SpA, *n* (%)	13 (20.6)	6 (27.3)	0.497	
Family history of uveitis, *n* (%)	3 (4.7)	2 (9.1)	0.599	
Family history of psoriasis, *n* (%)	12 (18.8)	2 (9.1)	0.504	
Family history of IBD, *n* (%)	10 (15.6)	3 (13.6)	1.000	
Family history of BS *n* (%)	2 (3.1)	3 (13.6)	0.103	
Recurrent oral ulcerations, *n* (%)	**18 (28.1)**	**17 (77.3)**	**<0.001**	**7.99 (2.14, 29.84)**
Genital ulcerations, *n* (%)	1 (1.6)	0 0	1.000	
Skin lesions, *n* (%)[a]	**7 (10.9)**	**7 (31.8)**	**0.022**	2.56 (0.51, 12.87)
Sacroiliitis on MRI, *n* (%)	37 (57.8)	11 (50.0)	0.524	
Sacroiliitis on X-rays, *n* (%)	31 (48.4)	11 (50.0)	0.899	
Syndesmophyte, *n* (%)	16 (25.0)	7 (31.8)	0.533	
Juxta-articular lesion on X-rays, *n* (%)	**4 (6.5)**	**7 (31.8)**	**0.006**	**7.65 (1.14, 38.03)**
BASDAI ≥ 4	18 (33.3)	10 (45.5)	0.320	
BASDAI score, median (IQR)	2.9 (1.9–4.6)	3.6 (1.8–4.9)	0.559	
ASDAS score, median (IQR)	2.2 (1.4–3.1)	2.5 (1.7–2.8)	0.993	
ICBD criteria, *n* (%)	**4 (6.3)**	**5 (22.7)**	**0.044**	1.06 (0.16, 6.79)

Significant associations are shown in bold.
[a] Skin lesions included erythema nodosum-like, papulopustular lesions, and pseudofolliculitis. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BS: Behçet's syndrome; HLA: human leucocyte antigen; IBD: inflammatory bowel disease; ICBD: International Criteria for Behçet's Disease; IQR: interquartile range; OR: odds ratio; SpA: spondyloarthritis.

such associations, as 9/21 HLA-B51-positive patients with SpA (42.9%) had oral ulcerations in a mini-review of four studies [18]. As for the association with juxta-articular radiographic lesions, it might indicate an association of HLA-B51 with a more severe phenotype of peripheral joint involvement, which was also suggested in the above mini-review [18]. However, we did not identify previous reports of peripheral radiographic damage associated with HLA-B51 positivity.

Unlike previous studies [18, 20], we did not identify an association between HLA-B51 and uveitis. This was probably related to the lower-than-expected prevalence of uveitis in the current study (4.7% in SpA, 6.2% in axSpA) compared with

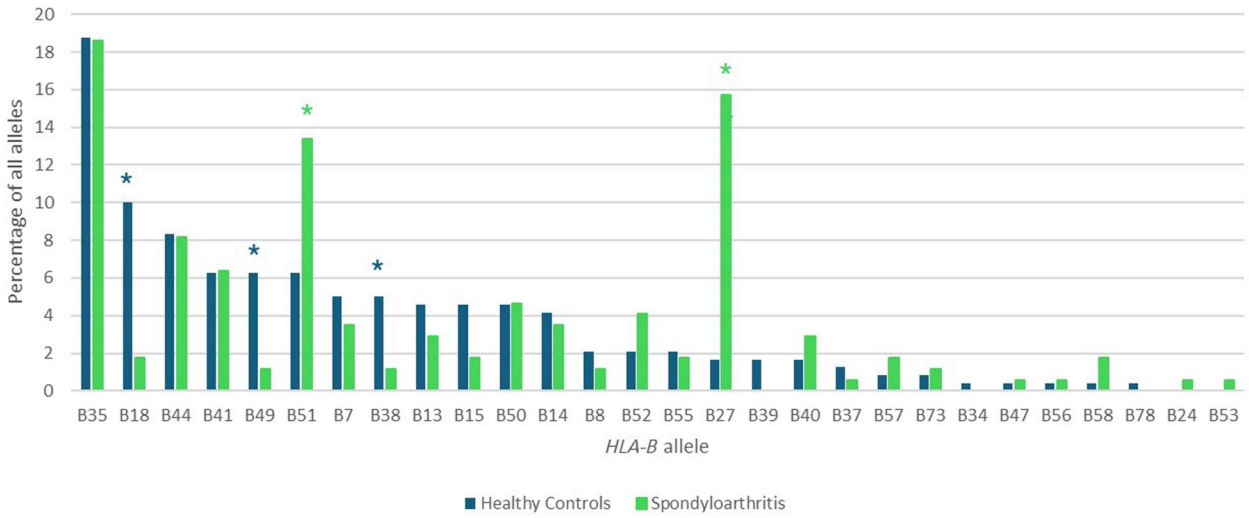

Figure 1. Distribution of *HLA-B* alleles in patients with spondyloarthritis and healthy controls. *Statistically significant differences between patients and controls. Alleles are presented from the most to the least frequent in healthy controls

international studies. For example, data from the recent international PerSpA study found a prevalence of uveitis in 21.6% of patients with axSpA and 17.3% of patients with pSpA [37]. Nevertheless, the prevalence of other EMMs, namely IBD and psoriasis in axSpA (20.0% and 13.8%, respectively), was higher in the current study compared with the PerSpA cohort (4.4% and 12.2%, respectively), which might indicate genetic specificities or different referral patterns.

Nevertheless, some disease features were numerically associated with the presence of HLA-B51, namely uveitis (9.1%), psoriasis (22.7%) and dactylitis (13.6%), whereas Crohn's disease tended to be less associated (9.1%); these associations could reach the statistical significance threshold if the sample size was larger.

Finally, the study of the distribution of the alleles found in the *HLA-B* locus identified *HLA-B35* as the predominant allele (18.7%). This result is similar to previous reports from Lebanon. In a large study in 1994 Lebanese individuals, screened as potential bone marrow or kidney donors, the *HLA-B35* allele was identified in 18.4% of individuals and *HLA-B51* in 8.5% [35]. Another study on *HLA* typing done in 426 Lebanese subjects in 2012 found a prevalence of 19.0% of the *HLA-B35* allele [38]. Also, the results are similar to data from the Middle East region, with frequencies ranging from 14.9% to 18.7%). Comparatively, in the USA, Europe, Japan and China, *HLA-B35* appears to be less common, ranging from 4.2% to 6.8% [2, 35, 39]. *HLA-B41*, which seems to be specific to the Lebanese population [40], was found in 6.25% of alleles in the current study. As for *HLA-B51*, it was identified as the sixth most prevalent allele in HCs in the current study (6.25% of alleles and 12.5% of HC). Comparatively, the *HLA-B51* allele seems to be most found in Saudi Arabia at 19%, Qatar at 17.35% [41] and Greece at 15.3% [39]. In Syria and Jordan, its occurrence is less common, at 8.1% and 10.3% respectively [41]. On the other hand, *HLA-B52* exhibits a more consistent distribution, with a relatively low frequency in the current study (2.08% of alleles, 4.2% of HCs) compared with a range from 2% in Tunisia to 7.1% in Syria [41].

The low prevalence of *HLA-B27* in HCs (1.67% of alleles in HCs, 3.3% of HCs) and in patients with axSpA (36.9%) confirms previous data from Lebanon, as the latest data on 106 HCs and 141 patients with axSpA found a prevalence of 3.8% and 41.1%, respectively [28].

The current study has some limitations. A classification bias might occur as HCs who have not yet developed symptoms of SpA or BS might be erroneously classified as controls. This bias might be especially considered here since the HCs are relatively young (mean age 25.6 years). However, HLA-B51 positivity appears to correlate with an earlier onset and younger age at the onset of BS, along with pseudofolliculitis and a reduced occurrence of arterial aneurysms [42–44], indicating that most HLA-B51-positive HCs are probably real controls. Future studies should consider including age-matched controls, although these would be difficult to identify in the general population. In addition, in the HC arm, the symptoms were self-reported by the blood donors during an interview with a medical student and were not authenticated by a rheumatologist.

Despite the limitations, the current study has major strengths. To the best of our knowledge, this is one of the few to extensively analyse the prevalence of HLA-B51 and the entire HLA-B locus, in patients with axSpA, particularly in patients from the Middle East region. Also, the current study evaluated the phenotypic impact of the presence of HLA-B51.

In summary, HLA-B51 was identified in a quarter of patients with SpA, a statistically higher frequency compared with HCs, whereas HLA-B52 was less prevalent in general and only numerically higher in SpA *vs* HCs. Moreover, the proportion of patients who fulfilled the ICBD BS classification criteria was numerically higher in patients with SpA compared with HCs. Furthermore, the presence of HLA-B51 in patients with SpA did impact the disease phenotype, with more recurrent oral ulcerations and juxta-articular radiographic erosions. Finally, in patients with SpA as well as in HCs, *HLA-B35* was the most prevalent allele at the *HLA-B* locus and was followed by *HLA-B51* and *HLA-B27* in

patients with SpA. Larger studies in the future can help validate these results, particularly in certain SpA subgroups. In addition, longitudinal studies are needed to determine whether the association of HLA-B51 with SpA indicates a true disease overlap or might be associated with a specific SpA phenotype.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Access to the full database can be granted based on reasonable request from the corresponding author.

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