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ORIGINAL RESEARCH

# Association between HLA-B27 and peripheral spondyloarthritis phenotype: results from the ASAS perSpA study

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## ABSTRACT

**Objective** To analyse the influence of HLA-B27 in the phenotypical expression of peripheral spondyloarthritis (pSpA).

**Method** This is an observational cross-sectional study using data from the Assessment of SpondyloArthritis international Society perSpA registry, including all patients with an available HLA-B27 test result and with a diagnosis of pSpA or psoriatic arthritis (PsA) as per rheumatologist's judgement. Demographic and clinical data, presence of extra musculoskeletal manifestations (EMM) and fibromyalgia were the variables included in a simple and multiple logistic regression model to assess their association to HLA-B27 positivity.

**Results** From the 4465 patients included in the registry, 790 were classified as having either pSpA or PsA and had the HLA-B27 typing available. HLA-B27-positive patients presented a male predominance, had an earlier disease onset and a shorter diagnostic delay compared with the negatives. HLA-B27-positive patients presented a higher frequency of axial involvement, radiographic sacroiliitis, enthesitis and uveitis. Also, root joint involvement, poliarticular joint patern and tarsitis were significantly higher within HLA-B27-positive patients. Furthermore, we did not observe any association between the presence of HLA-B27 and peripheral joint damage, dactylitis, other EMM (psoriasis, inflammatory bowel disease) or fibromyalgia.

The multivariable analysis confirmed the independent association of HLA-B27 positivity with male sex, an earlier onset of the disease, the presence of axial involvement, tarsitis and uveitis.

**Summary** In summary, the presence of HLA-B27 in pSpA patients was associated with earlier disease onset and higher axial involvement, tarsitis and uveitis, but not with other EMM, fibromyalgia or peripheral structural damage.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ HLA-B27 has an important impact on the clinical frame of axial spondyloarthritis. However, the HLA-B27 influence on the peripheral SpA (pSpA) is still unknown.

### WHAT THIS STUDY ADDS

⇒ The relationship of HLA-B27 with axial manifestations and uveitis in pSpA patients is confirmed.

⇒ Peripheral structural damage and fibromyalgia were not associated with HLA-B27 in pSpA patients.

⇒ The potential association between HLA-B27 and peripheral enthesitis or dactylitis is controversial in pSpA patients.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The knowledge of the potential genetic influence of HLA-B27 in phenotypical expression of pSpA may help to improve their management.

## BACKGROUND

Spondyloarthritis (SpA) is a group of rheumatic diseases that share genetic background and a common physiopathology, characterised by an inflammatory process focused on the enthesis that induces a characteristic clinical frame. Classically, the SpA family included different diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease (IBD)-related arthritis and undifferentiated SpA (uSpA). Since the introduction of the Assessment of SpondyloArthritis international Society (ASAS) criteria[1 2] and regarding the most predominant domain affected, patients can be classified as having axial (axSpA) or peripheral SpA (pSpA).

HLA-B27 was discovered in 1973 and remains the best-known genetic factor associated with SpA susceptibility and disease aetiopathogenesis.[3–12] Furthermore, several studies have been previously published evaluating the potential influence of this gen in the axSpA phenotype.[13–17] Recently, our research group has reported that the presence of HLA-B27 in AS is related to several clinical symptoms including a lower frequency of peripheral arthritis.[13] However, to our knowledge, no

previous reports are evaluating the influence of HLA-B27 on pSpA. ASAS perSpA is a worldwide registry of SpA patients that includes anthropometric and clinical characteristics of a high number of patients, so it gives us a unique opportunity to evaluate the role of HLA-B27 in this population.[18 19]

This study aimed to analyse the influence of HLA-B27 in the phenotypical expression of pSpA including PsA, the most well-defined pSpA.

## MATERIAL AND METHOD

This is an observational cross-sectional study using data from ASAS perSpA, a worldwide registry focused on analysing the prevalence and characteristics of peripheral involvement in all subtypes of SpA. Its structure and features have been previously published.[18] In summary, from July 2018 to February 2020, patients of 68 participating centres from 24 countries were recruited consecutively by a rheumatologist, and data were recorded in a specific case report form. Inclusion criteria were: 18 years or older, able to understand and complete questionnaires, and diagnosed of axSpA, pSpA, PsA, ReA, Juvenile SpA, IBD-related arthritis or other type of SpA (uSpA) as judged by the investigator. This study included all patients from this registry who presented an available HLA-B27 test result reported on the form and were classified as pSpA or PsA. We did not include the rest of subtypes in order to avoid heterogenicity or potential biases.

### Variables

We selected the following variables from the registry: sex, age (years), age at onset and at diagnosis (years), diagnostic delay (months), disease duration (years), presence of family history, axial involvement, presence of radiographic sacroiliitis as per New York modified criteria, joint pattern (polyarticular or mono/oligoarticular), presence of root joint involvement (shoulders and/or hips), tarsitis, enthesitis, dactylitis, peripheral structural damage (defined as new bone formation in plain radiograph of hands and foot and/or radiographic destructive arthropathy on the distal interphalangeal joints) and extramusculoskeletal manifestations (EMM): psoriasis, uveitis and IBD. We also recorded the presence of concomitant fibromyalgia as per investigator opinion.

### Statistics

We performed a descriptive analysis of HLA-B27-positive and HLA-B27-negative patients, and a comparative analysis using a simple logistic regression for all variables to assess their association to HLA-B27 positivity. We also analysed separately those patients with pSpA and PsA. Results were considered significant when p<0.05. The missing data in a particular variable were not included in the analysis. We also conducted a multivariable analysis including all significant (p<0.1) and the most relevant clinical variables agreeing with medical criteria.

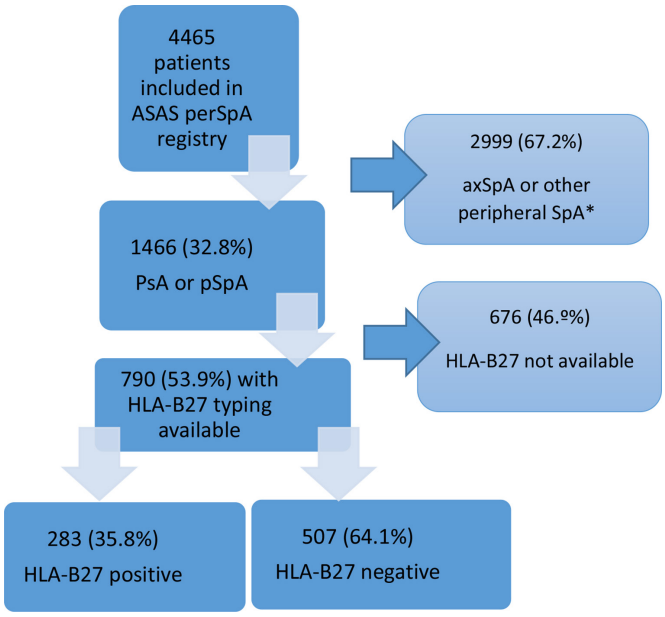


**Figure 1** Flow chart of patients included. SpA: Spondyloarthritis. *Other peripheral SpA: Reactive arthritis, Juvenile arthritis, inflammatory bowel disease arthritis, other type of SpA.

## RESULTS

Among the 4465 patients included in the registry, 1466 (32.8%) were classified as having either pSpA or PsA as per rheumatologist's judgement, of them 790 (53.9%) had the HLA-B27 typing available and 283 (35.8%) were HLA-B27-positive (figure 1).

Results for the global analysis are listed in table 1. 58.3% of the HLA-B27-positive group were male, significantly higher than the negatives (46.5%, p=0.002). No differences between HLA-B27-positive and negative patients were observed regarding family history. HLA-B27-positive patients were significantly younger (42.8 vs 50.6 years old, p<0.001), presented an earlier disease onset (30.7 vs 34.7 years old, p<0.001) and lower age at diagnosis (35.1 vs 43.8 years old, p<0.001), with shorter diagnostic delay (4.5 vs 9.2 years, p<0.001) and also shorter disease duration (12.2 vs 15.9 years, p<0.001).

Mono or oligoarticular joint pattern was lower in the HLA-B27-positive patients without reaching statistical signification (45.3% vs 51.4%, p=0.112). Moreover, tarsitis and enthesitis were more frequent in the HLA-B27-positive group (16.6% vs 10.3%, p=0.01 and 55.4% vs 47.3%, p=0.029, respectively). Dactylitis was less frequent in the HLA-B27-positive group (25.4% vs 33.3%, p=0.021). Peripheral joint damage was also lower in HLA-B27-positive patients (9.9% vs 26.6%, p<0.001).

HLA-B27-positive patients presented higher frequency of axial involvement (64.7% vs 35.3%, p<0.001) and radiographic sacroiliitis (39.1% vs 20.4%, p<0.001). In this group, there was also more shoulder (23.7% vs 15.4%, p=0.004) and hip involvement (36.7% vs 15.2%, p<0.001) as compared with the negatives.

**Table 1** Comparative analysis of all pSpA* patients regarding HLA-B27 status

| | HLA-B27+ (N=283) | | HLA-B27− (N=507) | | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|---|---|---|---|
| | N/mean | %/SD | N/mean | %/SD | OR | P value | OR | P value |
| Men | 165 | 58.3 | 236 | 46.5 | 1.61 (1.20–2.16) | **0.002** | 1.48 (1.03–2.14) | **0.039** |
| Family history | 99 | 33.2 | 163 | 66.8 | 1.14 (0.83–1.54) | 0.418 | | |
| Age (year) | 42.8 | 13.9 | 50.6 | 13.7 | 0.96 (0.95–0.97) | **<0.001** | | n.s.* |
| Age onset (year) | 30.7 | 13.0 | 34.7 | 14.7 | 0.98 (0.97–0.99) | **<0.001** | 0.97 (0.96–0.99) | **<0.001** |
| Age at diagnosis (year) | 35.1 | 13.8 | 43.8 | 13.5 | 0.95 (0.94–0.96) | **<0.001** | | n.s. |
| Diagnostic delay (month) | 4.5 | 7.5 | 9.2 | 11.1 | 0.94 (0.92–0.96) | **<0.001** | 0.95 (0.93–0.97) | **<0.001** |
| Disease duration (year) | 12.2 | 10.7 | 15.9 | 12.5 | 0.97 (0.96–0.98) | **<0.001** | | n.s. |
| Psoriatic arthritis | 86 | 30.4 | 388 | 76.5 | 0.13 (0.10–0.18) | **<0.001** | 0.36 (0.19–0.68) | **0.002** |
| Mono/oligoarticular pattern | 120/265 | 45.3 | 232/451 | 51.4 | 0.78 (0.58–1.06) | 0.112 | | |
| Tarsitis | 47 | 16.6 | 52 | 10.3 | 1.74 (1.14–2.66) | **0.010** | 1.74 (1.05–2.89) | **0.033** |
| Enthesitis | 157 | 55.4 | 240 | 47.3 | 1.39 (1.04–1.86) | **0.029** | | n.s. |
| Dactylitis | 72 | 25.4 | 169 | 33.3 | 0.68 (0.49–0.94) | **0.021** | | n.s. |
| Peripheral structural damage | 28 | 9.9 | 135 | 26.6 | 0.31 (0.19–0.46) | **<0.001** | | n.s. |
| Axial involvement | 183 | 64.7 | 179 | 35.3 | 3.35 (2.48–4.56) | **<0.001** | 2.49 (1.73–3.59) | **<0.001** |
| Radiographic sacroilitis (AS* mNY* criteria fulfilment) | 102/261 | 39.1 | 94/460 | 20.4 | 2.50 (1.79–3.50) | **<0.001** | | n.s. |
| Shoulder involvement | 67 | 23.7 | 78 | 15.4 | 1.71 (1.18–2.46) | **0.004** | | n.s. |
| Hip involvement | 104 | 36.7 | 77 | 15.2 | 3.24 (2.31–4.58) | **<0.001** | | n.s. |
| Psoriasis | 92 | 32.5 | 395 | 77.9 | 0.14 (0.10–0.19) | **<0.001** | 0.48 (0.26–0.92) | **0.025** |
| Uveitis | 61 | 21.6 | 14 | 2.8 | 9.68 (5.45–18.34) | **<0.001** | 5.78 (2.97–12.0) | **<0.001** |
| If uveitis, no of episodes | 7.5 | 9.4 | 2.1 | 1.5 | 1.24 (1.00–1.75) | 0.104 | | |
| IBD | 4 | 1.4 | 14 | 2.8 | 0.50 (0.14–1.42) | 0.232 | | |
| Fibromyalgia | 17 | 6.0 | 62 | 12.2 | 0.46 (0.26–0.78) | **0.006** | | n.s. |

AS, ankylosing spondylitis; IBD, inflammatory bowel disease; mNY, New York modified; n.s., not significant; pSpA, peripheral spondyloarthritis.

Regarding EMM, uveitis was significantly more frequent in the HLA-B27-positives (21.6% vs 2.8%, p<0.001) and these patients presented a higher number of episodes (7.5 vs 2.1, p=0.104) although this was not statistically significant. In contrast, we did not observe any association between the positivity of HLA-B27 and psoriasis or IBD.

Finally, concomitant fibromyalgia was less frequent in HLA-B27-positive patients compared with the negatives (6% vs 12.2%, p=0.006).

The multivariable analysis confirmed the association of HLA-B27 positivity with male sex (OR 1.48, 95% CI 1.03 to 2.14, p=0.039), an earlier disease onset (OR 0.97, 95% CI 0.96 to 0.99, p<0.001), shorter diagnostic delay (OR 0.95, 95% CI 0.93 to 0.97, p<0.001), axial involvement (OR 2.49, 95% CI 1.73 to 3.59, p<0.001), tarsitis (OR 1.74, 95% CI 1.05 to 2.89 p=0.033) and uveitis (OR 5.78, 95% CI 2.97 to 12 p<0.001).

In the specific comparative study for pSpA (table 2), male sex was also more frequent in the HLA-B27-positive patients (58.8% vs 42.6%, p=0.006), and these patients were also younger (40.4 vs 47 years old, p<0.001), younger at disease onset (30.3 vs 37.2 years old, p<0.001), at diagnosis (33.5 vs 42.3 years old, p<0.001), with less diagnostic delay (3.3 vs 5.1 years, p=0.02). In this group, we observed that differences regarding joint pattern were in line with the global analysis but reaching statistical signification in this subgroup of patients: mono or oligoarticular joint pattern was significantly lower in the HLA-B27-positive patients (46.6% vs 68.8%, p<0.001). Peripheral structural damage was significantly less frequent in the HLA-B27-positive pSpA patients as compared with the negatives (4.1% vs 16.8%, p<0.001). Also in the pSpA subanalysis, we observed higher frequency of axial involvement (65.5% vs 42.9%, p<0.001), radiographic sacroiliitis (38.6% vs 23.7%, p<0.001), shoulder (26.9% vs 13.4%, p=0.006) and hip involvement (44.7% vs 24.4%, p<0.001) and uveitis (25.9% vs 5.9%, p<0.001). On the other hand, IBD (1.5% vs 9.2%, p=0.004) and fibromyalgia (4.6% vs 17.6%, p<0.001) were less frequent within HLA-B27-positive pSpA patients. In the multivariable analysis, we observed the independent association of HLA-B27 positivity with lower age at diagnosis (OR 0.96, 95% CI 0.94 to 0.98, p<0.001), polyarticular joint pattern (OR 0.48,

**Table 2** Comparative analysis of pSpA* patients regarding HLA-B27 status (excluding PsA*)

| | Total pSpA* (N=316) | | HLA-B27+ (N=197) | | HLA-B27– (N=119) | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N/mean | %/SD | N/mean | %/SD | N/mean | %/SD | OR | P value | OR | P value |
| Men | 167 | 52.8 | 116 | 58.8 | 51 | 42.6 | 1.91 (1.21–3.04) | **0.006** | | n.s.* |
| Family history | 84 | 26.6 | 55 | 27.9 | 29 | 24.4 | 1.20 (0.72–2.04) | 0.489 | | |
| Age (year) | 42.9 | 14.6 | 40.4 | 13.7 | 47.0 | 15.2 | 0.97 (0.95–0.98) | **<0.001** | | n.s. |
| Age onset (year) | 32.8 | 14.3 | 30.3 | 13.4 | 37.2 | 14.9 | 0.97 (0.95–0.98) | **<0.001** | | n.s. |
| Age at diagnosis (year) | 36.8 | 14.9 | 33.5 | 14.1 | 42.3 | 14.7 | 0.96 (0.94–0.97) | **<0.001** | 0.96 (0.94–0.98) | **<0.001** |
| Diagnostic delay (month) | 4.0 | 6.3 | 3.3 | 6.1 | 5.1 | 6.5 | 0.96 (0.92–0.99) | **0.020** | | n.s. |
| Disease duration (year) | 10.1 | 9.2 | 10.2 | 9.7 | 9.8 | 8.2 | 1.01 (0.98–1.03) | 0.669 | | |
| Mono/oligoarticular pattern | 164/300 | 54.7 | 89/191 | 46.6 | 75/109 | 68.8 | 0.40 (0.24–0.64) | **<0.001** | 0.48 (0.27–0.84) | **<0.001** |
| Tarsitis | 46 | 14.6 | 34 | 17.3 | 12 | 10.1 | 1.86 (0.95–3.89) | 0.083 | | n.s. |
| Enthesitis | 172 | 54.4 | 113 | 57.4 | 59 | 49.6 | 1.37 (0.87–2.16) | 0.179 | | |
| Dactylitis | 69 | 21.8 | 42 | 21.3 | 27 | 22.7 | 0.92 (0.53–1.61) | 0.775 | | |
| Peripheral structural damage | 28 | 8.9 | 8 | 4.1 | 20 | 16.8 | 0.21 (0.08–0.48) | **<0.001** | 0.31 (0.11–0.79) | **0.019** |
| Axial involvement | 180 | 57.0 | 129 | 65.5 | 51 | 42.9 | 2.53 (1.59–4.05) | **<0.001** | | n.s. |
| Radiographic sacroilitis (AS* mNY* criteria fulfilment) | 98/298 | 32.9 | 71/184 | 38.6 | 27/114 | 23.7 | 3.52 (2.13–5.87) | **<0.001** | | n.s. |
| Shoulder involvement | 69 | 21.8 | 53 | 26.9 | 16 | 13.4 | 2.4 (1.31–4.49) | **0.006** | 2.18 (1.06–4.71) | **0.039** |
| Hip involvement | 117 | 37.0 | 88 | 44.7 | 29 | 24.4 | 2.50 (1.53–4.19) | **<0.001** | | n.s. |
| Uveitis | 58 | 18.4 | 51 | 25.9 | 7 | 5.9 | 5.58 (2.60–13.92) | **<0.001** | 3.37 (1.48–8.72) | **0.006** |
| If uveitis, no of episodes | 6.4 | 8.6 | 7.1 | 9.0 | 1.9 | 1.5 | 1.13 (1.00–2.51) | 0.227 | | |
| IBD* | 14 | 4.4 | 3 | 1.5 | 11 | 9.2 | 0.15 (0.03–0.50) | **0.004** | | n.s. |
| Fibromyalgia | 30 | 9.5 | 9 | 4.6 | 21 | 17.6 | 0.22 (0.09–0.49) | **<0.001** | 0.32 (0.12–0.81) | **0.020** |

AS, ankylosing spondylitis; IBD, inflammatory bowel disease; mNY, New York modified; n.s., not significant; PsA, Psoriatic Arthritis; pSpA, peripheral spondyloarthritis.

95% CI 0.27 to 0.84, p<0.001), shoulder involvement (OR 2.18, 95% CI 1.06 to 4.71, p=0.039) and uveitis (OR 3.37, 95% CI 1.48 to 8.72, p=0.006).

In the specific analysis for PsA (table 3), HLA-B27-positive patients were younger at inclusion (48.2 vs 51.6 years old, p=0.028), and at diagnosis (38.7 vs 44.3 years old, p<0.001), presented higher family history (51.2% vs 34.5%, p=0.004), less diagnostic delay (7.1 vs 10.4 years, p=0.017) and higher frequency of axial involvement (62.8% vs 33%, p<0.001), radiographic sacroiliitis (40.3% vs 19.4%, p<0.001) and uveitis (11.6% vs 1.8%, p<0.001) as compared with the negatives. In the multivariable analysis, family history (OR 2.1, 95% CI 1.26 to 3.52, p=0.004), axial involvement (OR 3.48, 95% CI 2.1 to 5.84, p<0.001) and uveitis (OR 8.03, 95% CI 2.73 to 25.03, p<0.001) were the variables independently associated to HLA-B27 positivity.

In online supplemental material, we included a comparative analysis of the 790 patients included in the study and the 676 patients not included for not having HLA-B27 test available.

## DISCUSSION

To our knowledge, this is the first study assessing the role of HLA-B27 on the phenotype of pSpA. Our study supports an association between the presence of the gen with an earlier onset of the disease and the presence of axial involvement, tarsitis and uveitis in patients with pSpA, including those with a diagnosis of PsA.

The association between presence of HLA-B27 and an earlier disease onset in pSpA patients is in the line with previous data published in patients with axSpA.[13–15 20] In this sense, there is substantial previous evidence in axSpA patients showing an association of the gen with susceptibility and family aggregation.[14 15 17 20–22] However, in contrast with previous data published about axSpA we did not observe a clear association between the presence of family aggregation and HLA-B27 positivity. In this sense, 66.8% of HLA-B27-negative patients had also a family history of SpA. These data suggest that other factors different from HLA-B27 may also have an important role in heritability in pSpA patients. The diagnostic delay was significantly higher in HLA-B27-negative patients, both in the global and the specific analysis for PsA and pSpA, which is supported by previous published studies in axSpA.[15] A possible explanation might be a higher clinical suspicion of SpA in HLA-B27-positive patients given that the presence of the gen is a variable included in ASAS classification criteria.[1]

In our study, the presence of HLA-B27 was associated with higher axial involvement and sacroiliitis, both in the global and the stratified analysis. In this sense, the data are in accordance with prior studies in SpA, showing substantial evidence of the role of the gen in axial domain implication.[13 17 23–26]

To analyse the influence of HLA-B27 in the clinical frame of pSpA is a challenge, especially due to the heterogeneity of these patients. In the global analysis, we did not observe statistically significant differences regarding articular pattern (oligoarticular vs polyarticular) associated with the presence of the gen HLA-B27, however, in the specific analysis for pSpA, polyarticular joint pattern was more frequent in the HLA-B27-positive patients. Also, the presence of tarsitis and both the shoulder and hip involvement were significantly more frequent in the HLA-B27-positive group of patients. In this sense, the observed results from hip involvement are in accordance with a recent study suggesting for hip involvement a distinct phenotype similar to axSpA (including younger age at onset and HLA-B27 positivity).[27] Enthesis are the main target of SpA inflammation, and according to our global results this was more frequent in HLA-B27-positive patients only in the univariable model, not significant in the multivariable analysis. However, we did not observe any association between the presence of HLA-B27 and dactylitis. Given the study characteristics and the difficulty to assess the real involvement of peripheral enthesis in these patients, we point out the need of more extensive studies assessing this point.

On the other hand, we did not observe any association between the presence of the HLA-B27 and peripheral radiographic damage. In fact, we observe an association between the absence of HLA-B27 and the peripheral structural damage in pSpA patients. In a recent study, we neither observed any association between HLA-B27 and structural spinal damage in AS patients.[13] In summary, these data suggest the presence of other factors different from HLA-B27 may play a major role in the process of structural damage in SpA.

Regarding EMM, uveitis was independently associated with the presence of HLA-B27 in pSpA patients, which is in accordance with previously reported studies in the subset of axSpA.[12 14 16 20 28 29] Our results also support the lack of association between HLA-B27 and the rest of EMM (IBD and psoriasis). These data are in accordance with prior literature.[12–14 16 20 30]

We performed a specific analysis separatedly for pSpA and PsA patients (tables 2 and 3, respectively) in order to analyse any specific clinic associations. However, the main results are in the line of those observed in the global set of pSpA patients, except for the positive association between the presence of HLA-B27 and family history of SpA in PsA patients.

Finally, a brief comment about fibromyalgia, which is a common comorbidity in SpA patients observed in around a quarter of patients.[31] The presence of this comorbidity highly complicates the management of these patients, so the study of the potential factors implicated in its presence becomes a priority. Our data did not show any association of HLA-B27 and fibromyalgia. In fact, the presence of fibromyalgia was significantly higher in the HLA-B27-negative patients in pSpA patients. In this sense, there is evidence in prior literature about the presence of higher scores of pain and disability in AS patients

**Table 3** Comparative analysis of PsA* patients regarding HLA-B27 status

| | Total PsA* (N=474) | | HLA-B27+ (N=86) | | HLA-B27– (N=388) | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N/mean | %/SD | N/mean | %/SD | N/mean | %/SD | OR | P value | OR | P value |
| Men | 234 | 49.4 | 49 | 57.0 | 185 | 47.7 | 1.45 (0.91–2.34) | 0.120 | | n.s.* |
| Family history | 178 | 37.6 | 44 | 51.2 | 134 | 34.5 | 1.99 (1.24–3.20) | **0.004** | 2.10 (1.26–3.52) | **0.004** |
| Age (year) | 51.0 | 13.0 | 48.2 | 12.7 | 51.6 | 13.0 | 0.98 (0.96–0.99) | **0.028** | | n.s. |
| Age onset (year) | 33.5 | 14.1 | 31.5 | 12.0 | 34.0 | 14.5 | 0.99 (0.97–1.00) | 0.152 | | |
| Age at diagnosis (year) | 43.3 | 13.1 | 38.7 | 12.5 | 44.3 | 13.1 | 0.97 (0.95–0.98) | **<0.001** | | n.s |
| Diagnostic delay (month) | 9.8 | 11.5 | 7.1 | 9.5 | 10.4 | 11.8 | 0.97 (0.94–0.99) | **0.017** | 0.96 (0.93–0.99) | **0.005** |
| Disease duration (year) | 17.6 | 12.7 | 16.6 | 11.6 | 17.8 | 12.9 | 0.99 (0.97–1.01) | 0.443 | | |
| Mono/oligoarticular pattern | 188/416 | 45.2 | 31/74 | 41.9 | 157/342 | 45.9 | 0.85 (0.51–1.41) | 0.530 | | |
| Tarsitis | 53 | 11.2 | 13 | 15.1 | 40 | 10.3 | 1.55 (0.76–2.98) | 0.203 | | |
| Enthesitis | 225 | 47.5 | 44 | 51.2 | 181 | 46.6 | 1.20 (0.75–1.92) | 0.449 | | |
| Dactylitis | 172 | 36.3 | 30 | 34.9 | 142 | 36.6 | 0.93 (0.56–1.50) | 0.765 | | |
| Peripheral structural damage | 135 | 28.5 | 20 | 23.3 | 115 | 29.6 | 0.72 (0.41–1.22) | 0.237 | | |
| Axial involvement | 182 | 38.4 | 54 | 62.8 | 128 | 33.0 | 3.43 (2.12–5.62) | **<0.001** | 3.48 (2.10–5.84) | **<0.001** |
| Radiographic sacroilitis (AS* mNY* criteria fulfilment) | 98/423 | 23.2 | 31/77 | 40.3 | 67/346 | 19.4 | 3.03 (1.69–5.40) | **<0.001** | | **n.s.** |
| Shoulder involvement | 76 | 16.0 | 14 | 16.3 | 62 | 16.0 | 1.02 (0.52–1.88) | 0.945 | | |
| Hip involvement | 64 | 13.5 | 16 | 18.6 | 48 | 12.4 | 1.62 (0.85–2.96) | 0.129 | | n.s. |
| Uveitis | 17 | 3.6 | 10 | 11.6 | 7 | 1.8 | 7.16 (2.67–20.29) | **<0.001** | 8.03 (2.73–25.03) | **<0.001** |
| If uveitis, no of episodes | 6.7 | 9.5 | 9.7 | 11.6 | 2.4 | 1.6 | 1.23 (0.99–2.22) | 0.270 | | |
| IBD* | 4 | 0.8 | 1 | 1.2 | 3 | 0.8 | 1.51 (0.07–11.96) | 0.723 | | |
| Fibromyalgia | 49 | 10.3 | 8 | 9.3 | 41 | 10.6 | 0.87 (0.37–1.83) | 0.728 | | |

AS, ankylosing spondylitis; IBD, inflammatory bowel disease; mNY, New York modified; ns, not significant; PsA, psoriatic arthritis.

HLA-B27-negatives compared with those with HLA-B27-positive.[12 16 17]

We need to mention some limitations of our study. As this is a study with data from a clinical practice registry, there is a clear potential selection bias because some phenotypical manifestations of patients would make it more or less likely that HLA-B27 was determined. So, we added an analysis comparing HLA-B27 availability to have a more precise focus of this point (online supplemental table 1). The study was developed around the diagnosis of SpA supported by the expert physician's judgement. The absence of objective data to definitively establish a diagnosis suggests this method as the best gold standard in these cases. We also included a specific analysis for pSpA and PsA, however, it reduces significantly the sample size and difficult to draw definitive conclusions.

In summary, the presence of HLA-B27 in pSpA patients was associated with an earlier disease onset and higher axial involvement, tarsitis and uveitis. We did not observe any association between HLA-B27 and other EMM (psoriasis and IBD), fibromyalgia or peripheral structural damage. Several other pSpA manifestations such us enthesitis, dactylitis or even family aggregation show in our study controversial results, highlighting the need of more extensive and specific studies to shed light on this point.

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