RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

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

Marta Arevalo Salaet ,[1] Clementina López-Medina ,[2,3] Mireia Moreno ,[1] Victoria Navarro-Compan,[4] Joan Calvet Fontova,[1] Maria Llop,[1] Maxime Dougados ,[2] Jordi Gratacós[1]

To cite: Arevalo Salaet M, López-Medina C, Moreno M, *et al*. Association between HLA-B27 and peripheral spondyloarthritis phenotype: results from the ASAS perSpA study. *RMD Open* 2022;**8**:e002696. doi:10.1136/rmdopen-2022-002696

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002696).

MAS and CL-M are joint first authors.

Received 29 August 2022
Accepted 17 November 2022

For numbered affiliations see end of article.

Correspondence to
Dr Mireia Moreno;
mmorenoma@gmail.com

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.

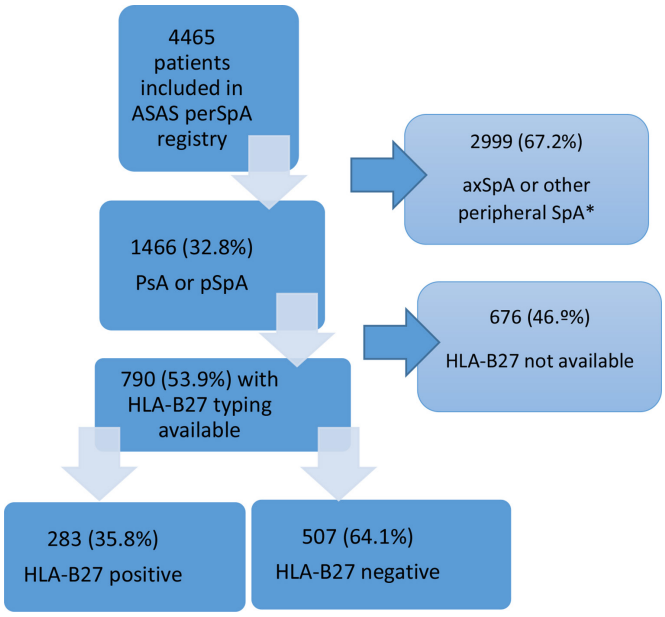

Figure 1 Flow chart of patients included. SpA: Spondyloarthritis. *Other peripheral SpA: Reactive arthritis, Juvenile arthritis, inflammatory bowel disease arthritis, other type of SpA.

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.

Author affiliations
[1]Rheumatology Department, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Medicine Department, Universitat Autònoma de Barcelona, Sabadell, Spain
[2]Department of Rheumatology, Hôpital Cochin. Assistance Publique - Hôpitaux de ParisINSERM (U1153): Clinical epidemiology and biostatistics, PRES Sorbonne Paris-Cité, Université de Paris, Paris, France
[3]Rheumatology Department, Hospital Universitario Reina Sofía/IMIBIC/Universidad de Córdoba, Córdoba, Spain
[4]Rheumatology Department, Hospital Universitario la Paz, IdiPaz, Madrid, Spain

Correction notice This article has been updated since it was first published online. Marta Arevalo Salaet and Clementina López-Medina are joint first authors. Affiliations 1-4 have been updated.

Acknowledgements We would like to thank the Assessment of SpondyloArthritis international Society (ASAS), the patients who participated in the study and the investigators* who included the participants and completed the case report form. We also thank the steering committee members of the ASAS PerSpA (PERipheral involvement in SpondyloArthritis) study.

Collaborators *Hernán Maldonado Ficco (Hospital San Antonio de Padua, Rio Cuarto, Argentina), Rodolfo Pérez Alamino (Hospital Dr Nicolás Avellaneda, Tucumán, Argentina), Emilio Buschiazzo (Hospital Señor del Milagro, Salta, Argentina), Romina Calvo (Hospital Provincial Dr José M. Cullen, Santa Fé, Aregntina), Vanesa Duarte (Clínica Monte Grande, Buenos Aires, Argentina), Maria Victoria Martire (Instituto Médico Platense, La Plata, Argentina), Diego Baenas (Hospital Privado de Córdoba, Córdoba, Argentina), Dora Pereira (Hospital Ricardo Gutiérrez, La Plata, Argentina), Adrian Salas (Consultorio Reumatológico, La Plata, Argentina), Juan Manuel Bande (Hospital General de Agudos Dr E Tornú, Buenos Aires, Argentina), Alberto Berman (Centro Médico Privado de Tucumán, Tucumán, Argentina), Stephanie Belton (University of Alberta, Canada), María Paz Poblete (Facultad de Medicina Clínica Alemana—Universidad del Desarrollo, Santiago de Chile, Chile), Francisca Valenzuela (Facultad de Medicina Clínica Alemana—Universidad del Desarrollo, Santiago de Chile, Chile), Min Xiao (Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China), CS Lau (Hong Kong University, China), Ho Yin Chung (Hong Kong University, China), Sherif Gamal (Cairo University, Cairo, Egypt), Catherine Lebourlout (Cochin Hospital, Paris, France), Daniel Wendling (CHU Besançon, Besançon, France), Clément Prati (CHU Besançon, Besançon, France), Frank Verhoeven (CHU Besançon, Besançon, France), Martin Soubrier (CHU Clermont-Ferrand, Clermont-Ferrand, France), Carine Savel (CHU Clermont-Ferrand, Clermont-Ferrand, France), Trigui Alia (CHU Clermont-Ferrand, Clermont-Ferrand, France), Fan Angélique (CHU Clermont-Ferrand, Clermont-Ferrand, France), Pascal Claudepierre (Henri Mondor Hospital, Créteil, France), Valerie Farrenq (Henri Mondor Hospital, Créteil, France), Kamelia Faramarz (Henri Mondor Hospital, Créteil, France), Isabella Sieber (Rheumazentrum Ruhrgebiet, Herne, Germany), Dories Morzeck (Rheumazentrum Ruhrgebiet, Herne, Germany), Fabian Proft (Charité University, Berlin, Germany), Edit Toth (Flór Ferenc Hospital, Kistarcsa, Hungary), Katalin Nagy (Markhot Ferenc Hospital, Eger, Hungary), Attila Kovacs (MÁV Hospital, Szolnok, Hungary), Liza Rajasekhar (Nizam's Institute of Medical Sciences, Hyderabad, India), Sapan Pandya (Smt NHL Medical College and Sardar Vallabhbhai Patel Hospital and Vedanta Institute of Medical Sciences, Ahmedabad, India), Bhowmik Meghnathi (Sri Sai Siri Hospital and Prathima Institue of Medical Sciences, Karimnagar, India), Carlomaurizio Montecucco (Fondazione IRCCS Policlinico San Matteo, Pavia, Italia), Alessandro Biglia (Fondazione IRCCS Policlinico San Matteo, Pavia, Italia), Akihiko Asahina (The Jikei University School of Medicine, Japan), Masato Okada (St Luke's International University and Hospital, Japan), Tadashi Okano (Osaka City University, Japan), Yuko Kaneko (Keio University School of Medicine, Japan), Haruki Sawada (NTT Medical Center Tokyo, Japan), Yoshinori Taniguchi (Kochi University, Japan), Naoto Tamura (Juntendo University School of Medicine, Japan), Shigeyoshi Tsuji (National Hospital Organization Osaka Minami Medical Center, Japan), Yoichiro Haji (Daido Hospital, Japan), Ayako Hirata (Toho University, Japan), Akimichi Morita (Nagoya City University, Japan), Nelly Salloum (Saint-Joseph University, Beirut, Lebanon), Graciela Meza (CLIDITER), Julio Casasola-Vargas (Hospital General de Mexico, Mexico), César Pacheco-Tena (Hospital General Dr Salvador Zubirán, Chihuahua, Mexico), Greta Reyes-Cordero (Hospital General Dr Salvador Zubirán, Chihuahua, Mexico), César Ramos-Remus (Unidad de Investigación de Enfermedades Crónico Degenerativas, Jalisco, Mexico), J Dionisio Castillo (Unidad de Investigación de Enfermedades Crónico Degenerativas, Jalisco, Mexico), Laura González-López (Universidad de Guadalajara, Jalisco, Mexico), Iván Gámez-Nava (Unidad de Investigación Biomédica 02, Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS Guadalajara, Jalisco, Mexico), Fadoua Allali (University Mohammed V, CHU Ibn Sina, Rabat, Morocco), Hanan Rkain (University Mohammed V, CHU Ibn Sina, Rabat, Morocco), Lahcen Achemlal (University Mohammed V, CHU Ibn Sina, Rabat, Morocco), Taoufik Harzy (University Sidi Mohammed Benabdellah, CHU Hassan II, Fès, Morocco), Santiago Rodrigues-Manica (Universidade NOVA de Lisboa, Portugal), Agna Neto (Universidade NOVA de Lisboa, Portugal), Jose Marona (Universidade NOVA de Lisboa, Portugal), Mª Joao Gonçalves (Universidade NOVA de Lisboa, Portugal), Ana Filipa Mourao (Universidade NOVA de Lisboa, Portugal), Rita Pinheiro Torres (Universidade NOVA de Lisboa, Portugal), Simona Rednic (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Siao-Pin Simon (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Laura Muntean (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Ileana Filipescu (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Maria Tamas (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Laura Damian (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Ioana Felea (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Dana Fodor (Second Medical Clinic, Emergency Conty Hospital, Cluj-Napoca, Romania), Hyun-Yi Kook (Chonnam National University Medical School and Hospital, South Korea), Hyun-Ju Jung (Chonnam National University Medical School and Hospital, South Korea), Tae-Hwan Kim (Hanyang University Hospital for Rheumatic Diseases, South Korea), Mireia Moreno (Hospital Parc Taulí, Barcelona, Spain), Eduardo Collantes-Estévez (Hospital Universitario Reina Sofía de Córdoba, Spain), M. Carmen Castro-Villegas (Hospital Universitario Reina Sofía, Córdoba, Spain), Cristina Fernández-Carballido (Hospital Universitario San Juan de Alicante, Alicante, Spain), Elizabeth Fernández (Hospital Universtario La Paz, Madrid, Spain), Marta Arévalo (Hospital Parc Taulí, Barcelona, Spain), Yeong-Jian Jan Wu (Chang Gung Memorial Hospital at Kee-Lung, Taiwan), Tian-Tsai Cheng (Chang Gung Memorial Hospital at Kao-Hsiung, Taiwan), Cheng-Chung Wei (Chung Sun Medical University, Taiwan), Servet Akar (Izmir Katip Çelebi University School of Medicine, Turkey), Ilhan Sezer (Akdeniz University School of Medicine), Umut Kalyoncu (Hacettepe University School of Medicine, Turkey), Sebnem Ataman (Ankara University School of Medicine, Turkey), Meltem Alkan Melikoglu (Erzurum Atatürk University School of Medicine, Turkey), Sami Hizmetli (Sivas Cumhuriyet University School of Medine, Turkey), Ozgur Akgul (Manisa Celal Bayar University School of Medicine, Turkey), Nilay Sahin (Balikesir University School of Medicine, Turkey), Erhan Capkin (Karadeniz Teknik University School of Medicine, Turkey), Fatima Gluçin Ural (Ankara Yildirim Beyazit University School of Medicine, Turkey), Figen Yilmaz (Istanbul Sisli Etfal Training and Research Hospital), Ilknur Aktas (Istanbul Fatih Sultan Mehmet Training and Research Hospital, Turkey), Anne Boel (Leiden University Medical Center, The Netherlands), Mirian Starmans-Kool (Zuyderland Medical Center, The Netherlands), Sofia Ramiro (Zuyderland Medical Center and Leiden University Medical Center, The Netherlands), Femke Hoekstra-Drost (Zuyderland Medical Center, The Netherlands), Maha Abdelkadir (Maasstad Hospital in Rotterdam, The Netherlands), Angelique Weel (Maasstad Hospital in Rotterdam, The Netherlands), Darerian Schueller (Cases Western Reserve University School of Medicine, Cleveland, Ohio, USA)

Contributors MAS and CL-M share the same participation. MAS did the research work and first draft of the manuscript, CL-M did all the statistics and research work, MM wrote and reviewed the manuscript, JCF, VN-C, MD, JG and ML reviewed the final work. The guarantor of the present work is JG.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Marta Arevalo Salaet http://orcid.org/0000-0002-1863-7494
Clementina López-Medina http://orcid.org/0000-0002-2309-5837
Mireia Moreno http://orcid.org/0000-0002-4365-4341
Maxime Dougados http://orcid.org/0000-0003-3009-6229

REFERENCES

1 Rudwaleit M, van der Heijde D, Landewé R, *et al*. The assessment of spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25–31.
2 Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development of assessment of spondyloarthritis International Society classification criteria for axial spondyloarthritis (Part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
3 Brewerton DA, Hart FD, Nicholls A, *et al*. Ankylosing spondylitis and HL-A 27. *Lancet* 1973;1:904–7.
4 Caffrey MF, James DC. Human lymphocyte antigen association in ankylosing spondylitis. *Nature* 1973;242:121.
5 Allen RL, O'Callaghan CA, McMichael AJ, *et al*. Cutting edge: HLA-B27 can form a novel beta 2-microglobulin-free heavy chain homodimer structure. *J Immunol* 1999;162:5045–8.
6 Allen RL, Bowness P, McMichael A. The role of HLA-B27 in spondyloarthritis. *Immunogenetics* 1999;50:220–7.
7 Barnea E, Melamed Kadosh D, Haimovich Y, *et al*. The Human Leukocyte Antigen (HLA)-B27 Peptidome. *Mol Cell Proteomics* 2017;16:642–62.
8 Bowness P. Hla-B27, antigen presentation and ERAP1. *Clinical and Experimental Rheumatology* 2014;32:768.
9 Colbert RA, Tran TM, Layh-Schmitt G. Hla-B27 misfolding and ankylosing spondylitis. *Mol Immunol* 2014;57:44–51.
10 Colbert RA, Navid F, Gill T. The role of HLA-B*27 in spondyloarthritis. *Best Pract Res Clin Rheumatol* 2017;31:797–815.
11 Colmegna I, Cuchacovich R, Espinoza LR. HLA-B27-associated reactive arthritis: pathogenetic and clinical considerations. *Clin Microbiol Rev* 2004;17:348–69.
12 Arévalo M, López-Medina C, Moreno Martinez-Losa M, *et al*. Role of HLA-B27 in the comorbidities observed in axial spondyloarthritis: data from COMOSPA. *Joint Bone Spine* 2020;87:445–8.
13 Arévalo M, Gratacós Masmitjà J, Moreno M, *et al*. Influence of HLA-B27 on the ankylosing spondylitis phenotype: results from the REGISPONSER database. *Arthritis Res Ther* 2018;20:221.
14 Akkoç N, Yarkan H, Kenar G, *et al*. Ankylosing spondylitis: HLA-B*27-Positive versus HLA-B*27-Negative disease. *Curr Rheumatol Rep* 2017;19:26.
15 Feldtkeller E, Khan MA, van der Heijde D, *et al*. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003;23:61–6.
16 Khan MA, Kushner I, Braun WE. Comparison of clinical features in HLA-B27 positive and negative patients with ankylosing spondylitis. *Arthritis Rheum* 1977;20:909–12.
17 Chung HY, Machado P, van der Heijde D, *et al*. Hla-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with recent onset axial spondyloarthritis. *Ann Rheum Dis* 2011;70:1930–6.
18 López-Medina C, Molto A, Sieper J, *et al*. Prevalence and distribution of peripheral musculoskeletal manifestations in spondyloarthritis including psoriatic arthritis: results of the worldwide, cross-sectional ASAS-PerSpA study. *RMD Open* 2021;7:e001450.
19 Benavent D, Plasencia C, Poddubnyy D, *et al*. Unveiling axial involvement in psoriatic arthritis: an ancillary analysis of the ASAS-perSpA study. *Semin Arthritis Rheum* 2021;51:766–74.
20 Yang M, Xu M, Pan X, *et al*. Epidemiological comparison of clinical manifestations according to HLA-B*27 carrier status of Chinese ankylosing spondylitis patients. *Tissue Antigens* 2013;82:338–43.
21 Linssen A. B27+ disease versus B27- disease. *Scand J Rheumatol Suppl* 1990;87:111–8. discussion 8-9.
22 Rudwaleit M, Haibel H, Baraliakos X, *et al*. The early disease stage in axial spondylarthritis: results from the German spondyloarthritis inception cohort. *Arthritis Rheum* 2009;60:717–27.
23 Poddubnyy D, Jadon DR, Van den Bosch F, *et al*. Axial involvement in psoriatic arthritis: an update for rheumatologists. *Semin Arthritis Rheum* 2021;51:880–7.
24 Gladman DD. Axial disease in psoriatic arthritis. *Curr Rheumatol Rep* 2007;9:455–60.
25 Chandran V, Tolusso DC, Cook RJ, *et al*. Risk factors for axial inflammatory arthritis in patients with psoriatic arthritis. *J Rheumatol* 2010;37:809–15.
26 Castillo-Gallego C, Aydin SZ, Emery P, *et al*. Magnetic resonance imaging assessment of axial psoriatic arthritis: extent of disease relates to HLA-B27. *Arthritis Rheum* 2013;65:2274–8.
27 Ziadé N, El Hajj J, Rassi J, *et al*. Root joint involvement in spondyloarthritis: a post hoc analysis from the International ASAS-PerSpA study. *Rheumatology* 2022;61:667–78.
28 Valls Pascual E, Fontanilla Ortega P, Vicens Bernabeu E, *et al*. Clinical characteristics, treatment and ocular complications of HLA-B27-related anterior uveitis and HLA-B27-non related anterior uveitis. *Reumatol Clin* 2016;12:244–7.
29 Llop M, Gratacós J, Moreno M, *et al*. Uveitis in peripheral spondyloarthritis patients: an ancillary analysis of the ASAS-PerSpA study. *Ther Adv Musculoskelet Dis.* 2022;14:1759720X:221119246.
30 Michelena X, Poddubnyy D, Marzo-Ortega H. Axial psoriatic arthritis: a distinct clinical entity in search of a definition. *Rheum Dis Clin North Am* 2020;46:327–41.
31 Alunno A, Carubbi F, Stones S, *et al*. The impact of fibromyalgia in spondyloarthritis: from classification criteria to outcome measures. *Front Med* 2018;5:290.

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

Arevalo Salaet M, López-Medina C, Moreno M, *et al*. Association between HLA-B27 and peripheral spondyloarthritis phenotype: results from the ASAS perSpA study. *RMD Open* 2022;8:e002696. Doi: 10.1136/rmdopen-2022-002696

This article has been updated since it was first published online. Marta Arevalo Salaet and Clementina López-Medina are joint first authors. Affiliations 1–4 have been updated.

RMD Open 2022;**8**:e002696corr1. doi:10.1136/rmdopen-2022-002696corr1