The burden of early axial spondyloarthritis

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Chapter 3

Is a positive family history of spondyloarthritis relevant for diagnosing axial spondyloarthritis once HLA-B27 status is known?

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ABSTRACT

Objective

A positive family history (PFH) of spondyloarthritis, in particular a PFH of ankylosing spondylitis (AS) or acute anterior uveitis(AAU), is associated with human leukocyte antigen B27 (HLA-B27) carriership in chronic back pain patients. As it is unknown, the study aimed to investigate if a PFH contributes to diagnosing axial spondyloarthritis (axSpA) once HLA-B27 status is known.

Methods

In axSpA suspected patients from the Assessment of SpondyloArthritis international Society (ASAS), DEvenir des Spondyloarthropathies Indifférenciéés Récentes (DESIR), and SPondyloArthritis Caught Early (SPACE) cohorts logistic regression analyses were performed with HLA-B27 status and PFH according to the ASAS definition (ASAS-PFH) as determinants and clinical axSpA diagnosis as outcome at baseline. Analyses were repeated with a PFH of AS or AAU.

Results

In total, 1818 patients suspected of axSpA were analysed (ASAS n=594, DESIR n=647, and SPACE n=577). In patients from the ASAS, DESIR, and SPACE cohorts, respectively 23%, 39%, and 38% had an ASAS-PFH, 52%, 58%, and 43% were HLA-B27 positive, and 62%, 47%, and 54% were diagnosed with axSpA. HLA-B27 was independently associated with an axSpA diagnosis in each cohort but an ASAS-PFH was not (ASAS cohort: HLA-B27 odds ratio (OR) 6.9 (95% CI 4.7–10.2), ASAS-PFH OR 0.9 (95% CI 0.6–1.4); DESIR: HLA-B27 OR 2.1 (95% CI 1.5–2.9), ASAS-PFH OR 1.0 (95% CI 0.7–1.3); SPACE: HLA-B27 OR 10.4 (95% CI 6.9–15.7), ASAS-PFH OR 1.0 (95% CI 0.7–1.5)). Similar negative results were found for PFH of AS and AAU.

Conclusion

In three independent cohorts with different ethnical backgrounds, ASAS, DESIR, and SPACE, a PFH was not associated independently of HLA-B27 with a diagnosis of axSpA. This indicates that in the vast majority of patients presenting with back pain, a PFH does not contribute to the likelihood of an axSpA diagnosis if HLA-B27 status is known.

INTRODUCTION

Susceptibility for axial spondyloarthritis (axSpA) is thought to be largely genetically determined with human leukocyte antigen B27 (HLA-B27) as the strongest known risk factor for axSpA.[1, 2] With several studies showing an increased prevalence of this disease in relatives of axSpA patients, a positive family history (PFH) of spondyloarthritis (SpA) is thought to be a risk factor for axSpA in patients with chronic back pain.[3, 4] Currently, a PFH of SpA is defined, based on consensus, by the Assessment of SpondyloArthritis international Society (ASAS) as a PFH of ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and/or psoriasis in first- or second-degree relatives.[5] A PFH is a SpA feature in the ASAS classification criteria for axSpA and may contribute to classification independently of HLA-B27 status.[5, 6]

We found in two European cohorts of chronic back pain patients suspected of axSpA that a PFH of AS and a PFH of AAU were positively associated with HLA-B27 carriership. However, such an association was not found for a PFH of ReA, IBD, or psoriasis.[7] Moreover, another study in a worldwide population of patients suspected of axSpA showed that only a PFH of AS had an association with HLA-B27 carriership irrespective of ethnicity or degree of family relationship.[8]

Hence, these two studies show that a PFH according to ASAS (ASAS-PFH), but in particular a PFH of AS, clusters with HLA-B27 positivity in chronic back pain patients.[7, 8] While a PFH can be useful in identifying chronic back pain patients who are more likely to be HLA-B27 positive and therefore may have an increased risk of axSpA, it is currently unknown if a PFH contributes to diagnosing axSpA when HLA-B27 status is known.

In the present study, we combined data of the above mentioned three cohorts of patients suspected of axSpA: the worldwide ASAS cohort, the French DEvenir des Spondyloarthropathies Indifférenciéés Récentes (DESIR), and the European SPondyloArthritis Caught Early (SPACE) cohort. The main objective of this study was to investigate if an ASAS-PFH, a PFH of AS, or a PFH of AAU contributed to a diagnosis of axSpA in an ethnically diverse group of patients with known HLA-B27 status.

METHODS

The ASAS study is a longitudinal cohort in 29 centres worldwide and has included patients with a suspicion of axSpA (> 3 months' back pain, onset < 45 years, with or without peripheral symptoms) or peripheral SpA (current peripheral arthritis and/or dactylitis and/or enthesitis but without current chronic back pain).[5, 9, 10] Only patients suspected of axSpA

were included in the analysis for this study. The DESIR study (NCT01648907, datalock: April 2015) is a longitudinal cohort study in 25 French centres that included patients aged 18–50 years with inflammatory back pain for ≥ 3 months and < 3 years.[11] The SPACE study is an ongoing inception cohort and includes patients aged ≥ 16 years with chronic back pain (≥ 3 months, ≤ 2 years, onset ≤ 45 years) from rheumatology outpatient clinics in the Netherlands, Italy, Norway, and Sweden.[12] All three studies were approved by local ethical committees and informed consent was obtained before inclusion from all patients. A detailed description of all cohorts is provided elsewhere.[5, 9-12]

All patients underwent a full diagnostic work-up in which clinical, laboratory, and imaging data were collected at baseline, including HLA-B27 testing and radiography of the sacroiliac joints (X-SI). Magnetic resonance imaging of the SI (MRI-SI) was performed in all DESIR and SPACE patients, but in the ASAS cohort the MRI-SI was considered obligatory only for the first 20 patients for each centre. For each patient the clinical diagnosis of axSpA was established by the treating rheumatologist based on the information obtained from the full diagnostic work-up.

The ASAS expert definition of PFH is the presence of AS, AAU, psoriasis, IBD, or ReA in first- or second-degree relatives. Father, mother, sister, brother, daughter, and son are first-degree relatives and grandmother, grandfather, aunt, uncle, niece, and nephew are second-degree relatives in this definition.[5] In the ASAS cohort, information was available concerning which relatives had a SpA-related disease. Therefore, granddaughter, grandson, half-sister, and half-brother were also considered to be second-degree relatives in addition to the ASAS definition.

Data analysis

Baseline data of patients suspected of axSpA in the ASAS, DESIR, and SPACE cohorts were analysed. Descriptive statistics were used to present demographic and clinical characteristics for each cohort. In each cohort, univariable logistic regression models were performed with HLA-B27 status and ASAS-PFH as determinants and a clinical axSpA diagnosis as outcome. The analyses were repeated in multivariable models with both determinants. All analyses were repeated with a PFH of AS and a PFH of AAU. Interactions were tested between HLA-B27 status and each PFH. Interaction terms with $P<0.10$ were considered to be statistically significantly. Age and gender were tested for confounding. Results were stratified for age, gender, and ethnicity in order to test whether results differed between subgroups. Data analyses were performed with Stata SE v.14 software (StataCorp, College Station, TX, USA).

RESULTS

In total, 1818 patients suspected of axSpA and with complete data on family history at baseline were analysed (ASAS n=594, DESIR n=647, SPACE n=577) (**Table 1**). MRI-SI results were available for 424/594 (71%) ASAS patients, 636/647 (98%) DESIR patients, and 565/577 (98%) SPACE patients. ASAS, DESIR, and SPACE patients, respectively, had a mean ± SD symptom duration of 85.7 ± 108.4, 18.2 ± 10.5, and 13.3 ± 7.1 months; 46%, 47%, and 38% were male; 59%, 89%, and 94% were Caucasian; 52%, 58%, and 43% were HLA-B27 positive; 62%, 47%, and 54% received a clinical diagnosis of axSpA. An ASAS-PFH was reported in 23% of ASAS patients, 39% of DESIR patients, and 38% of SPACE patients. A PFH of AS and a PFH of AAU were reported in 15% and 1% of ASAS patients, 20% and 4% of DESIR patients, and 18% and 6% of SPACE patients, respectively.

In the univariable analysis, HLA-B27 status was significantly associated with an axSpA diagnosis in all three cohorts (**Table 2**). An ASAS-PFH (**Table 2**) and a PFH of AAU (**Supplementary Table S2**) were univariately associated with an axSpA diagnosis in the SPACE cohort, but not in ASAS and DESIR cohorts. A PFH of AS was associated with diagnosis of axSpA in the ASAS cohort, but not in the DESIR and SPACE cohorts (**Supplementary Table S1**).

In the multivariable models, HLA-B27 status was independently and positively associated with a diagnosis of axSpA but such an independent positive association was not found for ASAS-PFH in any cohort (ASAS cohort: HLA-B27 odds ratio (OR) 6.9, 95% CI 4.7–10.2; ASAS-PFH OR 0.9, 95% CI 0.6–1.4; DESIR cohort: HLA-B27 OR 2.1, 95% CI 1.5–2.9; ASAS-PFH OR 1.0, 95% CI 0.7–1.3; SPACE cohort: HLA-B27 OR 10.4, 95% CI 6.9–15.7; ASAS-PFH OR 1.0, 95% CI 0.7–1.5) (**Table 2**). Similar results were found for the multivariable models with a PFH of AS or a PFH of AAU in the ASAS, DESIR, and SPACE cohorts (**Supplementary Tables S1 and S2**) although in the SPACE cohort only a PFH of AS was negatively associated with an axSpA diagnosis.

Statistical interactions between HLA-B27 status and a PFH were tested for each association. No statistically significant interactions were found, except the interaction between HLA-B27 status and a PFH in the SPACE cohort (P=0.016). Compared with the HLA-B27 negative/PFH negative subgroup (n=234) as reference (OR=1), the HLA-B27 negative/PFH positive (n=97) subgroup had an OR of 1.4 (95% CI 0.9–2.3) on a diagnosis of axSpA, the HLA-B27 positive/PFH negative subgroup (n=125) had an OR of 16.8 (95% CI 9.2–30.9), and the HLA-B27 positive/PFH positive subgroup (n=121) had an OR of 8.4 (95% CI 5.0–14.0). This illustrates that PFH does not contribute to a diagnosis of axSpA, not even in the absence of HLA-B27 positivity.

Table 1. Baseline characteristics of the patients suspected of axSpA in the ASAS, DESIR, and SPACE cohort

Characteristics	ASAS (n=594)	DESIR (n=647)	SPACE (n=577)
Age (years) at baseline, mean ± SD	33.7 ± 11.7	33.6 ± 8.6	30.8 ± 8.1
Male	276 (46%)	305 (47%)	221 (38%)
Caucasian	348 (59%)	577 (89%)	454/484 (94%)
Duration of back pain (months), mean ± SD	85.7 ± 108.4[a]	18.2 ± 10.6[a]	13.3 ± 7.1
IBP	301/532 (57%)	647 (100%)[b]	396/576 (69%)
Good response to NSAIDs[c]	274 (46%)	515/644 (80%)	263/563 (47%)
Peripheral arthritis	197 (33%)	363 (56%)	97/575 (17%)
Enthesitis	241 (41%)	312 (48%)	121 (21%)
Dactylitis	23 (4%)	83 (13%)	35 (6%)
AAU	53 (9%)	51 (8%)	47 (8%)
Psoriasis	22 (4%)	97 (15%)	77 (13%)
IBD	8 (1%)	23 (4%)	38 (7%)
Positive family history according to ASAS definition	135 (23%)	249 (39%)	218 (38%)
A positive family history of			
AS	87 (15%)	127 (20%)	104 (18%)
AAU	7 (1%)	29 (4%)	34 (6%)
ReA	8 (1%)	6 (1%)	19/563 (3%)
IBD	12 (2%)	32 (5%)	32/570 (6%)
Psoriasis	36 (6%)	129 (20%)	95/571 (17%)
HLA-B27 positivity	310 (52%)	376/646 (58%)	246 (43%)
Elevated CRP / ESR	185 (31%)	254 (39%)	188 (33%)
Radiographic sacroiliitis[d]	119/593 (20%)	172 (27%)	80/570 (14%)
Sacroiliitis on MRI[d]	189/424 (45%)	207/636 (33%)	207/565 (37%)
Clinical diagnosis of axSpA[e]	368 (62%)	302 (47%)	313 (54%)

Results are presented as n (%) unless specified otherwise. [a] <5% missing values. [b] Inclusion criterion. [c] Back pain not present anymore or is much better 24-48 hours after a full dose of NSAID. [d] Imaging based on local reading of the sacroiliac joints. [e] Level of confidence regarding the diagnosis is ≥ 6 in ASAS and SPACE, ≥ 8 in DESIR. AAU; acute anterior uveitis; AS; Ankylosing Spondylitis; ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; IBD, inflammatory bowel disease; IBP, inflammatory back pain; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; ReA; Reactive Arthritis.

Table 2. Results of the contribution of a PFH and HLA-B27 to a clinical diagnosis of axSpA

	axSpA+	axSpA-	OR (95% CI)	P-value
ASAS cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**254 (43%)**	**56 (9%)**	**6.7 (4.7-9.8)**	**<0.001**
HLA-B27-	114 (19%)	170 (29%)	1.0 (ref)	(ref)
Univariable analysis: ASAS-PFH				
ASAS-PFH+	91 (15%)	44 (7%)	1.4 (0.9-2.0)	0.138
ASAS-PFH-	277 (47%)	182 (31%)	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and ASAS-PFH				
HLA-B27+	**254 (43%)**	**56 (9%)**	**6.9 (4.7-10.2)**	**<0.001**
ASAS-PFH+	91 (15%)	44 (7%)	0.9 (0.6-1.4)	0.561
DESIR cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**204 (32%)**	**172 (27%)**	**2.1 (1.5-2.9)**	**<0.001**
HLA-B27-	98 (15%)	172 (27%)	1.0 (ref)	(ref)
Univariable analysis: ASAS-PFH				
ASAS-PFH+	117 (18%)	132 (20%)	1.0 (0.7-1.4)	0.900
ASAS-PFH-	185 (29%)	213 (33%)	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and ASAS-PFH				
HLA-B27+	**204 (32%)**	**172 (27%)**	**2.1 (1.5-2.9)**	**<0.001**
ASAS-PFH+	117 (18%)	132 (20%)	1.0 (0.7-1.3)	0.772
SPACE cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**205 (36%)**	**41 (7%)**	**10.3 (6.9-15.5)**	**<0.001**
HLA-B27-	108 (19%)	223 (39%)	1.0 (ref)	(ref)
Univariable analysis: ASAS-PFH				
ASAS-PFH+	**132 (23%)**	**86 (15%)**	**1.5 (1.1-2.1)**	**0.018**
ASAS-PFH-	181 (31%)	178 (31%)	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and ASAS-PFH				
HLA-B27+	**205 (36%)**	**41 (7%)**	**10.4 (6.9-15.7)**	**<0.001**
ASAS-PFH+	132 (23%)	86 (15%)	1.0 (0.7-1.5)	0.921

Statistically significant associations are printed in bold. ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leucocyte antigen B27; OR, odds ratio; PFH, positive family history.

No confounding by age or gender was found and similar results were found when data were stratified for mean age or gender (data not shown). Results were also stratified for Caucasian vs non-Caucasian patients and we found similar results for Caucasian and non-Caucasian patients (data not shown).

DISCUSSION

In all three cohorts with different ethnical backgrounds, HLA-B27 carriership was associated with a clinical diagnosis of axSpA whereas conflicting results were found in the association between a PFH and an axSpA diagnosis in univariable analyses, irrespective of the definitions tested. In multivariable analyses, HLA-B27 was independently associated with an axSpA diagnosis in each cohort but an ASAS-PFH, a PFH of AS, and a PFH of AAU were not (positively) associated with an axSpA diagnosis.

In the multivariable analysis, in the SPACE cohort but not in the ASAS or DESIR cohort, a PFH of AS had a negative association with an axSpA diagnosis after adding HLA-B27 positivity. This is likely a spurious finding as only positive associations (statistically significant or not) with an axSpA diagnosis were found in all three cohorts. Moreover, no interaction was found between HLA-B27 status and a PFH of AS in any of the three cohorts.

A PFH had, at best, only a modest association with a clinical diagnosis of axSpA before adjustment of HLA-B27 and only in the SPACE cohort was this association statistically significant. It was previously shown that HLA-B27 and imaging are key elements for making a diagnosis of axSpA, with other SpA features, including a PFH, playing a more modest role.[13] This can explain the modest association between a PFH and the clinical diagnosis, although a PFH is related to HLA-B27 positivity.[7, 8]

We have repeatedly demonstrated that a PFH of SpA helps in identifying chronic back pain patients at increased risk of axSpA as a PFH of SpA is positively associated with HLA-B27 carriership.[7, 8] However, the effect of this positive association is apparently entirely taken over by a positive test for HLA-B27. Although in all three cohorts a few patients who were HLA-B27 negative but had a PFH were considered to have axSpA, our data show at group level that when knowledge about HLA-B27 status is available, a positive PFH does not have further influence on a diagnosis in an ethnically diverse group of patients. Thus, this finding casts doubt about the relative weight of PFH in the classification criteria for axSpA, in which PFH and HLA-B27 have independent contributions.

Nevertheless, our findings are in line with previous studies in which a PFH is a feature of HLA-B27 positive but not of HLA-B27 negative axSpA.[14, 15] In literature HLA-B27 negative

familial axSpA was found in only a few cases suggesting that HLA-B27 negative familial axSpA may exist. However, these patients were typed using currently obsolete methods with higher risks of mistypings.[16, 17]

Given the potential implications for clinical practice it is important to stress several limitations. The DESIR cohort had inflammatory back pain as an inclusion criterion, while the ASAS and SPACE cohorts included patients with chronic back pain. Nevertheless, similar results were found in all three cohorts. Although data of three cohorts were analysed, there was an under-representation of patients with for instance an African or South American ethnicity. The ASAS cohort included predominantly patients with a Caucasian or Asian ethnicity and the DESIR and SPACE cohorts included predominantly Caucasian patients, which corresponds to the two largest populations of axSpA patients worldwide.[18] Another limitation is the self-reported family history by patients and this could have led to an over- or underestimation of the investigated effects. Nevertheless, this is similar in most clinical settings where the physician usually has to depend on patient-reported information about the family history. Further, HLA-B27 status was known for each patient in each cohort, just as in the clinical setting, and thereby a similar amount of bias was present in each case.

It is important to emphasize that the current study investigated only patients with chronic back pain suspected of axSpA. Therefore, the results are not applicable to patients with predominantly peripheral symptoms. In these patients a PFH of other SpA-related diseases, such as psoriasis, could be valuable in diagnosing patients with peripheral SpA.[9]

Furthermore, we have investigated the association between a PFH and a diagnosis of axSpA when the HLA-B27 status is known. However, rheumatologists or other clinicians might have limited access to HLA-B27 testing. In this case, we would like to recommend assessing the presence of a PFH, especially a PFH of AS. A PFH of AS is associated with HLA-B27 positivity and could therefore be used to identify patients with an increased risk of axSpA.[7, 8]

In conclusion, in three independent cohorts including one worldwide cohort, a PFH was not associated independently of HLA-B27 with a diagnosis of axSpA in patients suspected of axSpA. These results may have implications for diagnosis and classification.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Results of the contribution of a PFH for AS and HLA-B27 to an axSpA diagnosis

	axSpA+	axSpA-	OR (95% CI)	P-value
ASAS cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**254**	**56**	**6.7 (4.7-9.8)**	**<0.001**
HLA-B27-	114	170	1.0 (ref)	(ref)
Univariable analysis: PFH of AS				
PFH of AS+	**65**	**22**	**2.0 (1.2-3.3)**	**0.009**
PFH of AS-	303	204	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AS				
HLA-B27+	**254**	**56**	**6.9 (4.6-10.2)**	**<0.001**
PFH of AS+	65	22	0.9 (0.5-1.7)	0.800
DESIR cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
HLA-B27-	98	172	1.0 (ref)	(ref)
Univariable analysis: PFH of AS				
PFH of AS+	63	64	1.2 (0.8-1.7)	0.461
PFH of AS-	239	281	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AS				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
PFH of AS+	63	64	1.0 (0.6-1.4)	0.829
SPACE cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**205**	**41**	**10.3 (6.9-15.5)**	**<0.001**
HLA-B27-	108	223	1.0 (ref)	(ref)
Univariable analysis: PFH of AS				
PFH of AS+	63	41	1.4 (0.9-2.1)	0.153
PFH of AS-	250	223	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AS				
HLA-B27+	**205**	**41**	**13.4 (8.4-21.4)**	**<0.001**
PFH of AS+	**63**	**41**	**0.4 (0.2-0.8)**	**0.004**

Statistically significant associations are printed in bold. AS, Ankylosing Spondylitis; ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leucocyte antigen B27; OR, odds ratio; PFH, positive family history.

Supplementary Table S2. Results of the contribution of a PFH for AAU and HLA-B27 to an axSpA diagnosis

	axSpA+	axSpA-	OR (95% CI)	P-value
ASAS cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**254**	**56**	**6.7 (4.7-9.8)**	**<0.001**
HLA-B27-	114	170	1.0 (ref)	(ref)
Univariable analysis: PFH of AAU				
PFH of AAU+	4	3	0.8 (0.2-3.7)	0.792
PFH of AAU-	364	223	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AAU				
HLA-B27+	**254**	**56**	**6.9 (4.7-10.1)**	**<0.001**
PFH of AAU+	4	3	0.4 (0.08-1.8)	0.224
DESIR cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
HLA-B27-	98	172	1.0 (ref)	(ref)
Univariable analysis: PFH of AAU				
PFH of AAU+	16	13	1.4 (0.7-3.0)	0.350
PFH of AAU-	286	332	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AAU				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
PFH of AAU+	16	13	1.1 (0.5-2.3)	0.863
SPACE cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**205**	**41**	**10.3 (6.9-15.5)**	**<0.001**
HLA-B27-	108	223	1.0 (ref)	(ref)
Univariable analysis: PFH of AAU				
PFH of AAU+	**25**	**9**	**2.5 (1.1-5.4)**	**0.024**
PFH of AAU-	288	255	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AAU				
HLA-B27+	**205**	**41**	**10.7 (7.0-16.3)**	**<0.001**
PFH of AAU+	25	9	0.8 (0.3-1.8)	0.540

Statistically significant associations are printed in bold. AAU, acute anterior uveitis; ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leucocyte antigen B27; OR, odds ratio; PFH, positive family history.