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Clinical Impact of HLA-B27 on Juvenile Idiopathic Arthritis: Eighteen Years of Follow-up in the Population-Based Nordic Juvenile Idiopathic Arthritis Cohort

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Objective. We have previously shown that HLA-B27 was negatively associated with remission status eight years after the onset of juvenile idiopathic arthritis (JIA). We now aimed to study the associations of HLA-B27 with clinical features and disease outcomes 18 years after the onset of JIA.

Methods. We studied 434 patients from the population-based Nordic JIA cohort. Demographic and clinical data, including remission status, were collected consecutively at baseline, eight years after disease onset, and 18 years after disease onset and presented in relation to HLA-B27 status.

Results. The HLA-B27 status was available for 416 of the 434 participants (96%) and was positive for 93 participants (22.4%), more often in men ($P = 0.01$). The sacroiliac, hips, and subtalar joints were more frequently involved in individuals who were HLA-B27 positive than in individuals who were HLA-B27 negative. In almost half of the individuals with HLA-B27 positivity and uveitis, the uveitis was asymptomatic. Uveitis, inflammatory back pain, sacroiliitis, arthritis in hip, tarsal, and subtalar joints, and enthesitis during the disease course were all associated with a lower rate of remission off medication. HLA-B27 positivity was significantly associated with a higher risk of not being in remission off medication after 18 years (odds ratio [OR] 2.6), especially in men (OR 5.6).

Conclusion. Clinical features related to spondylarthropathies were more common in patients who were HLA-B27 positive and associated with worse outcomes and nonremission 18 years after disease onset, particularly in men. Our results underline the adverse impact of having HLA-B27 positivity on long-term outcomes in individuals with JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is not a single disease but a group of disorders having variable courses.[1] It is the most common chronic rheumatic condition in childhood.[2] Long-term studies highlight the diverse trajectories, from mild, self-limiting disease to severe, chronic arthritis.[3] Some categories are definite disease entities with distinct long-term outcomes, whereas others are more heterogenous,[4] making it difficult to predict the disease course both on an individual basis and at group level. A deeper understanding of the disease course is crucial for tailored treatment approaches. The International League of Associations for Rheumatology (ILAR) have agreed on six exclusive JIA categories based on disease manifestations within the first 6 months: systemic arthritis, oligoarticular arthritis (persistent or extended), polyarticular rheumatoid factor (RF) positive, arthritis, polyarticular RF negative arthritis, enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (JPsA) and a seventh category, undifferentiated arthritis, which includes those patients who do not fit any category or fit more than one.[5] Efforts aiming to improve the classification

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and nomenclature used to distinguish forms of chronic arthritis that overlap in adults and children from those unique to childhood are ongoing and under debate,[6,7] one example of which concerns juvenile spondyloarthritis (SpA). Most of the patients with clinical features of SpA in childhood are classified as ERA according to the ILAR criteria, whereas others are categorized as JPsA and undifferentiated arthritis.[8]

The etiology of JIA remains unknown, but, as with most autoimmune disorders, interactions between genetic predisposing factors, immune mechanisms, and environmental exposures are thought to contribute to JIA pathogenesis.[9,10] Results from several studies suggest that specific susceptibility genes can be identified, which can be broadly divided into two groups, HLA genes and non-HLA-related genes.[11] The non-HLA–related genes include, for example, genes encoding tumor necrosis factor and interleukins.[11] The association of JIA with both HLA class I (HLA-A2 and HLA-B27) and HLA class II (HLADRB1 and HLADP) alleles has been reported in various studies, underscoring the supposed importance of aberrant activated immune cells in the disease course.[11,12] There is a well-described association between the cell-surface antigen HLA-B27 and spondyloarthropathies in adults and ERA; HLA-B27 has been reported to be present in 60% to 90% of patients with ERA.[13,14] HLA-B27 positivity is one of the criteria for ERA in the ILAR classification. Additionally, for uveitis, the most common extra-articular manifestation in JIA, there is an association with HLA-B27.[9,15] The exact mechanism linking HLA-B27 to spondyloarthropathies is not fully understood, but protein misfolding leading to activation of cytokine genes is a leading theory.[16]

Large differences in HLA-B27 prevalence have been described across various geographic areas and ethnicities with a prevalence of 8% to 9% in the Western world.[17,18] In general, the incidence and prevalence of ankylosing spondylitis in adults mirror the frequency of HLA-B27 in the population,[19] but so far we have no support for a higher incidence of ERA in the Nordic countries, despite a relatively high occurrence of HLA-B27.[20] Interestingly, a high prevalence of ERA, with the majority being HLA-B27 positive, has been reported from Asia.[21,22]

Predicting disease severity and remission of JIA has long been an aim in research, with the underlying goal of identifying children at high risk of poor outcomes who may benefit from more intensive treatment. Children with ERA are reported to have higher pain intensity and poorer health status in comparison to children with other categories of JIA.[23] In a previous eight-year follow-up study of the Nordic JIA cohort, we demonstrated that HLA-B27 was negatively associated with long-term remission status. This association is likely related to its connection with specific clinical disease characteristics, such as sacroiliitis, rather than serving as a general marker of persistent disease.[24] Additionally, we observed that the pattern of joint involvement in relation to HLA-B27 differs between men and women.[25] In the current study, our objective was to investigate whether these findings remain consistent over a longer disease duration. Specifically, we aimed to further explore HLA-B27 as a marker of clinical manifestations in JIA and to assess its predictive value for disease outcome after 18 years.

PATIENTS AND METHODS

In this prospective study, we observed patients of newly diagnosed JIA from defined geographic areas of Denmark, Finland, Norway, and Sweden, as has been described previously.[24,26,27] To reflect a population-based study, we included all consecutively referred patients from geographically defined catchment areas in each country between January 1, 1997, and June 30, 2000. The baseline visit was scheduled to take place within the first six months after disease onset. Patients were classified according to the ILAR criteria, primarily at baseline.[5] After eight years, 440 of the original 510 participants were examined again, and data regarding clinical signs and laboratory tests were recorded and children were reclassified.[27] All 510 previously included participants from the Nordic JIA cohort were invited to participate in a follow-up approximately 18 years after disease onset, regardless of medication exposure, disease course, or activity. For participants who were unable to attend a study visit, we offered a standardized telephone interview that included an online completion of the health assessment questionnaire. The study visit (and the telephone interview) included an updated family and medication history. Clinical data were collected, which included joint examination results. To verify the participant-reported data (eg, for assessment of remission status and disease status over the last 10 years), a cross-check of the patient records was performed for many of the patients. Participants were once again reclassified according to the ILAR criteria.

Inactive disease and remission. Remission status was assessed according to the preliminary criteria by Wallace et al.[28] Inactive disease was defined as the absence of active joints, active uveitis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, with normal erythrocyte sedimentation rate (ESR) and, if both were present, also a normal c-reactive protein (CRP) level, as well as the physician's global assessment of disease activity (PhGA) indicating no disease activity. To be in clinical remission while off medication, the patient must have met the criteria for inactive disease for a minimum of 12 continuous months while taking no anti-arthritis and anti-uveitis medications. A joint with active disease was defined as a joint with swelling or a joint with limitation of motion accompanied by pain or tenderness. Inflammatory back pain (IBP) was defined as lumbosacral spinal pain at rest with morning stiffness that improves on movement. Sacroiliitis was defined as the presence of IBP combined with palpatory tenderness over the sacroiliac joints or radiologic evidence of sacroiliitis (magnetic resonance imaging [MRI], computed tomography [CT], or plain x-ray). MRI is currently the gold standard, but because the availability of MRI

during the follow-up has been restricted, we decided to also accept CT and plain x-ray findings indicating sacroiliitis. For the cumulative joint count, temporomandibular joint (TMJ) involvement was based on clinical findings collected at the follow-ups and not on imaging.

We defined a normal ESR as a value of less than 20 mm/h and a normal CRP level as less than 10 mg/L. Scores on a 21-circle visual analog scale used for PhGA, a patient-reported global assessment of well-being, and a patient-reported pain assessment within the previous week were collected. On these scales, 0 indicates no activity, no pain, or best global health, and 10 indicates the maximum activity, worst pain, or poorest global health. Analysis of HLA-B27 was performed using a complement-dependent cytotoxicity assay in Sweden and Denmark, and a flow-cytometric method in the mid-Norway region. A polymerase chain reaction method was used in the North Norway region and in Finland. All three are conventional methods with a high specificity and sensitivity for the HLA-B27 antigen.[29] History of heredity for ankylosing spondylitis, inflammatory bowel disease, JIA, psoriasis, rheumatoid arthritis, and uveitis was collected cumulatively at several time points during the disease course, including at the last study visit. A first-degree relative is defined as a parent or sibling, and a second-degree relative as an aunt, uncle, grandparent, niece, nephew, or half-sibling.

Statistical analysis. Descriptive statistics were used to describe demographic and clinical characteristics. Differences between groups were analyzed using Pearson's chi-square test for dichotomized variables and continuous variables were analyzed using the Mann-Whitney U test. $P < 0.05$ was considered significant. Logistic regression analysis was used to compare remission between genders and clinical results related to HLA-B27. In these analyses, we also added analysis of interaction between odds ratios. SPSS 22 (SPSS Inc.) was used for the statistical analyses. The joint homunculus from the Swedish National Quality Registry for Pediatric Rheumatology was used to design figures.[30] Software

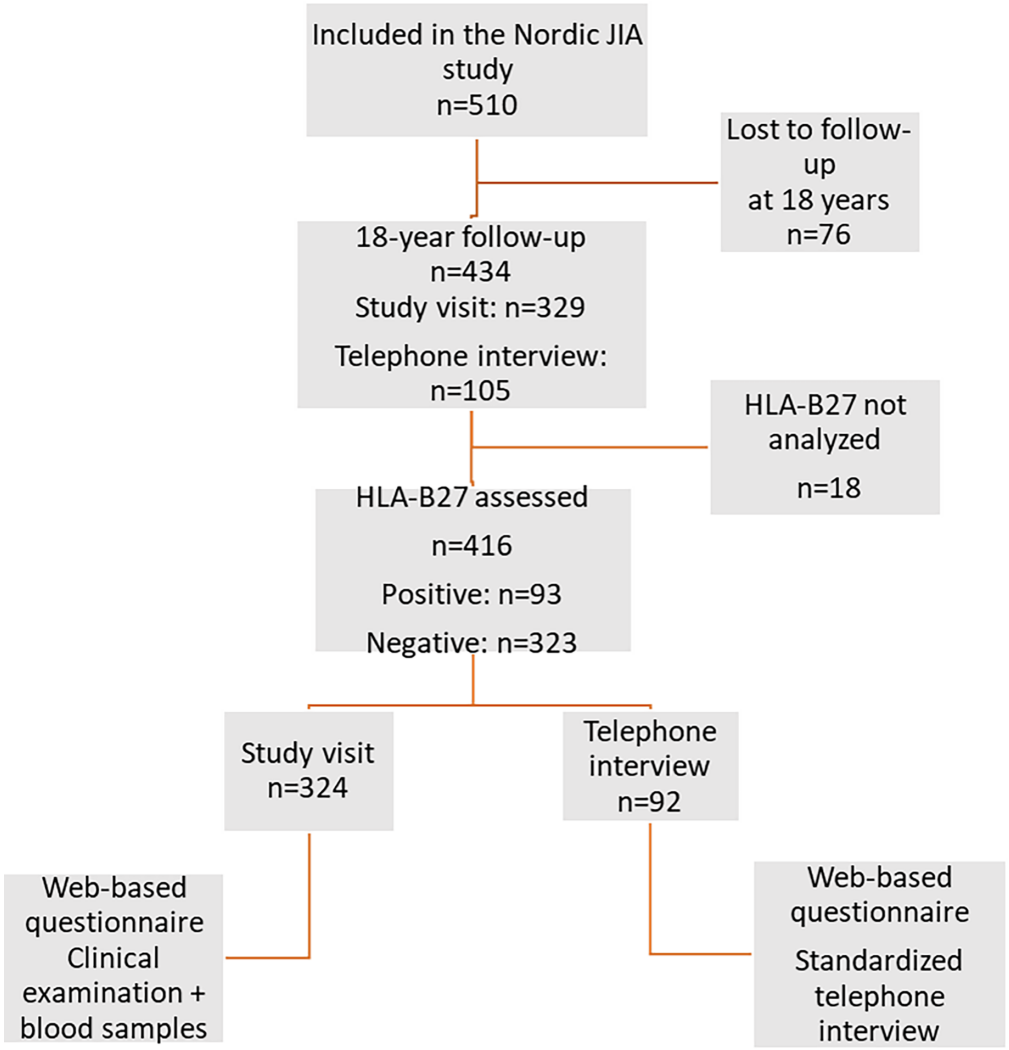

Figure 1. Flow chart of the study population throughout the 18-year observation period. JIA, juvenile idiopathic arthritis.

Table 1. Demographic data of 416 patients assessed for HLA-B27 in the Nordic JIA cohort*

JIA Category	Total Cohort (N = 416), n (%)	HLA-B27 Positive (n = 93), n (%)
Systemic	14 (3.3)	2 (1.4)
Oligo persistent	111 (26.7)	12 (10.8)
Oligo extended	79 (19.0)	10 (12.6)
Poly RF−	69 (16.6)	10 (14.5)
Poly RF+	6 (1.4)	1 (16.7)
Juvenile psoriatic	27 (6.5)	5 (18.5)
ERA	44 (10.6)	35 (79.5)
Undifferentiated	66 (15.9)	18 (27.3)

*ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; oligo, oligoarticular; poly, polyarticular; RF− = rheumatic factor negative, RF+, rheumatic factor positive.

R (version 4.3.2) with packet *ggmap* (version 4.0.0) was used for analyses of the site involvement frequencies.

Ethical approval. Approval from medical research ethics committees and data protection authorities and written informed consent from all participants were obtained according to the regulations of each participating country.

RESULTS

Clinical characteristics. Of the 510 eligible patients, 434 (85%) participants attended the 18-year follow-up visit, for which 329 (76%) attended a visit in person and 105 (24%) received a telephone interview (Figure 1). HLA-B27 status was registered for 416 (95.6%) of the participants, of whom 283 were women, and 133 were men (Table 1). HLA-B27 status was positive for 93 participants, 18.7% of the women and 30.1% of the men, and was significantly more common in men (P = 0.01). The individuals with HLA-B27 positivity were spread over all seven JIA categories, but as expected, found most frequently in the ERA category (79.5%) and in the undifferentiated category (27.3%) (Table 1). We found no significant difference in occurrence between genders in the different categories (data not shown).

Disease characteristics in individuals who were HLA-B27 positive compared with individuals who were HLA-B27 negative are listed in Table 2. Age at disease onset (8.3 years) was higher in individuals who were HLA-B27 positive compared with individuals who were HLA-B27 negative (5.3 years), irrespective of gender. Uveitis, IBP, sacroiliac (SI) joint tenderness, sacroiliitis on imaging, as well as enthesitis during the course of the disease were significantly more common among individuals who were HLA-B27 positive. There was no significant difference in occurrence of psoriasis and dactylitis between the individuals who were HLA-B27 positive and individuals who were HLA-B27 negative. IBP, SI joint tenderness, sacroiliitis on imaging, as well as enthesitis during the disease course were significantly more common among men who were HLA-B27 positive compared with women who were HLA-B27 positive. Notably, 14 of the 30 individuals who were HLA-B27 positive and developed uveitis had asymptomatic uveitis.

Heredity. The individuals who were HLA-B27 positive had more often a first- or second-degree relative with ankylosing spondylitis compared with individuals who were HLA-B27 negative (Table 3). Also, individuals who were HLA-B27 positive more often had a first- or second-degree relative with symptomatic uveitis compared with the individuals who were HLA-B27 negative. Conversely, there was no significant

Table 2. Clinical characteristics of participants in the Nordic JIA cohort in relation to gender and HLA-B27*

Clinical Characteristics	Total cohort, n (%)	HLA-B27 Negative, n (%)	HLA-B27 Positive, n (%)	P value[a]	HLA-B27 Positive, Female, n(%)	HLA-B27 Positive, Male, n (%)	P value[a]
N (%)	416 (100)	323 (77.6)	93 (22.4)		53	40	0.008
Age at onset, Md (IQR), y[b]		5.3 (2.3,9.2)	8.3 (3.5,11.7)	0.002	7.4 (3.1,11.5)	9.0 (4.2,11.8)	0.42
Cumulative joints, Md (IQR)	7 (3.0,13.0)	7 (3.0,13.0)	8 (4.0,14.5)	0.15	7 (4,17.0)	8 (3.25,14.0)	0.45
Uveitis	96 of 416 (23.1)	66 of 323 (20.4)	30 of 93 (32.2)	0.005	15 of 53 (28.3)	15 of 40 (37.5)	0.10
Uveitis, symptomatic	26 of 416 (6.2)	10 of 323 (3.1)	16 of 93 (17.2)	<0.001	7 of 53 (13.2)	9 of 40 (22.5)	0.24
IBP[c]	69 of 411 (16.8)	36 of 323 (9.6)	33 of 93 (35.5)	<0.001	11 of 53 (20.8)	22 of 39 (56.4)	0.003
SI tenderness[d]	53 of 416 (12.7)	31 of 323 (9.6)	22 of 93 (23.6)	<0.001	6 of 53 (11.3)	16 of 40 (40.0)	<0.001
Sacroiliitis on imaging[e]	27 of 416 (6.5)	9 of 323 (2.8)	18 of 93 (19.4)	<0.001	6 of 53 (11.3)	12 of 40 (30.0)	0.024
Enthesitis	80 of 416 (19.2)	49 of 323 (15.2)	31 of 93 (33.3)	<0.001	12 of 53 (22.6)	19 of 40 (47.5)	0.012
Psoriasis	38 of 416 (9.1)	28 of 323 (8.7)	10 of 93 (10.8)	0.54	5 of 53 (9.4)	5 of 40 (12.5)	0.64
Dactylitis	21 of 414 (5.1)	18 of 323 (5.6)	3 of 93 (3.2)	0.38	2 of 53 (3.8)	1 of 40 (2.5)	0.71

*CT, computed tomography; IBP, inflammatory back pain; IQR, interquartile range; JIA, juvenile idiopathic arthritis; MRI, magnetic resonance imaging; SI, sacroiliacal joint.
[a]Independent sample Mann-Whitney U test was used for comparison of continuous variables and Pearson chi-square test for comparison of categorical variables.
[b]Age at onset was missing for one of the 93 participants who was HLA-B27 positive.
[c]IBP is defined as lumbosacral spinal pain at rest with morning stiffness that improves on movement.
[d]SI tenderness is defined as palpatory tenderness over the SI joint.
[e]Sacroiliitis on imaging is including conventional x-ray, CT and MRI.

Table 3. Heredity associated with HLA-B27 for 434 participants in the Nordic JIA cohort*

Characteristic	Total, n (%)	HLA-B27 negative, n (%)	HLA-B27 positive, n (%)	*P* value[a]
Ankylosing spondylitis				
First degree[b]	20 of 384 (5.2)	7 of 301 (2.3)	13 of 83 (15.7)	<0.001
Second degree[c]	30 of 384 (7.8)	15 of 301 (5.0)	15 of 83 (18.1)	<0.001
Uveitis				
First or second degree	20 of 364 (5.5)	10 of 280 (3.6)	10 of 84 (11.9)	0.008
Symptomatic	16 of 358 (4.5)	7 of 276 (2.5)	9 of 82 (11.0)	0.003
Asymptomatic	4 of 342 (1.2)	3 of 266 (1.1)	1 of 76 (1.3)	0.89
IBD, first or second degree	16 of 362 (4.4)	14 of 280 (5.0)	2 of 82 (2.4)	0.44
JIA				
First degree	26 of 370 (7.0)	20 of 286 (7.0)	6 of 84 (7.1)	0.13
Second degree	31 of 370 (8.4)	26 of 286 (9.1)	5 of 84 (5.9)	0.65
First or second degree	57 of 370 (15.4)	46 of 286 (16.1)	11 of 84 (13.1)	0.34
Rheumatoid arthritis				
First degree	22 of 376 (5.8)	17 of 292 (5.8)	5 of 84 (5.9)	0.67
Second degree	79 of 376 (21.0)	64 of 292 (21.9)	15 of 84 (17.8)	0.64
First or second degree	101 of 376 (26.9)	81 of 292 (27.7)	20 of 84 (23.8)	0.50

*IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis.
[a]Pearson chi-square test comparing the individuals who were HLA-B27 positive with the individuals who were HLA-B27 negative.
[b]First-degree relative is defined as parent or sibling; information collected during the first 15 to 18 years of disease onset.
[c]Second degree relative is aunt, uncle, grandparent, niece, nephew, or half-sibling; information collected during the first 18 years of disease onset.

difference between individuals who were HLA-B27 positive or individuals who were HLA-B27 negative regarding heredity for JIA or rheumatoid arthritis (RA) in first- or second-degree relatives.

Joint patterns. Active joints were assessed at each study visit, including information about cumulatively active joints up until the 18-year visit (Supplementary Table 1). The differences in joint involvement by HLA-B27 status over time are shown in

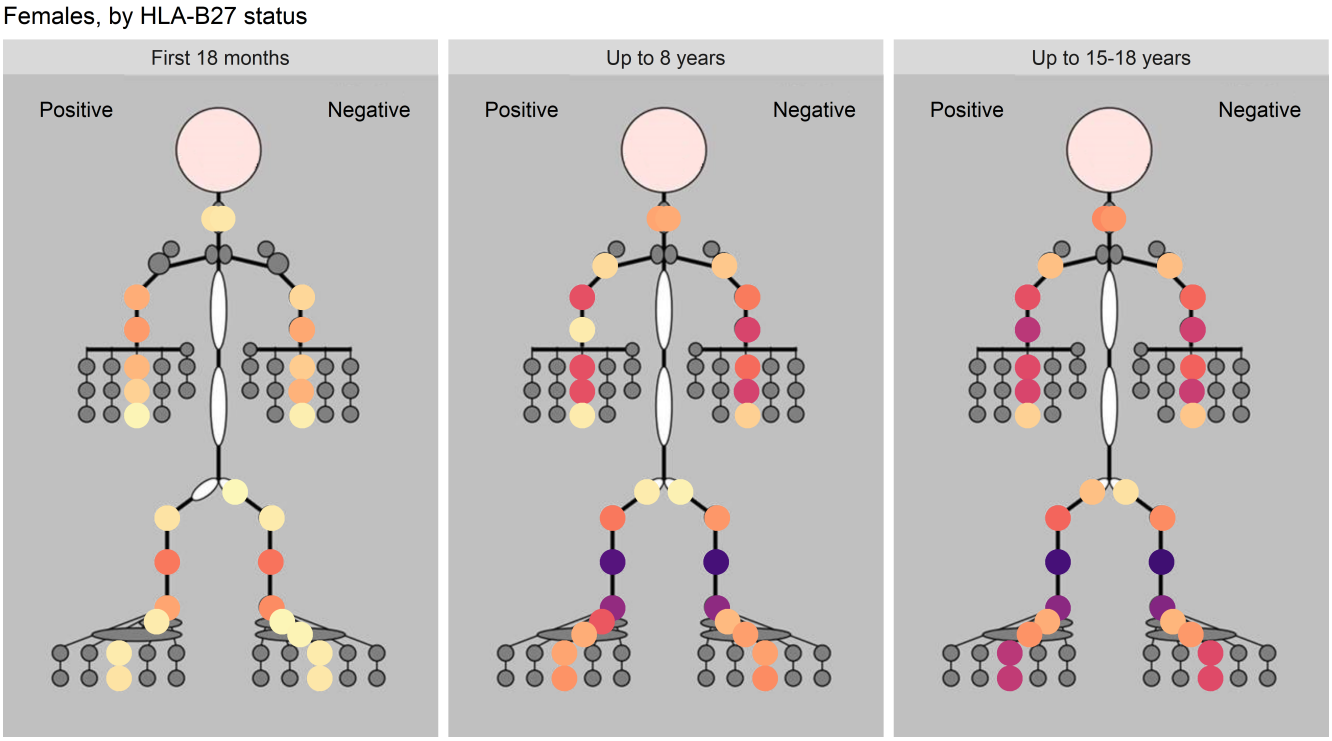

Figure 2. Cumulatively active joints at the follow-ups among women, by HLA-B27 status. The percentages of individuals with activity in a particular joint are shown in a color spectrum. The TMJ involvement was based on clinical findings at the 18-year follow-up study visit, and not on imaging. TMJ, temporomandibular joint.

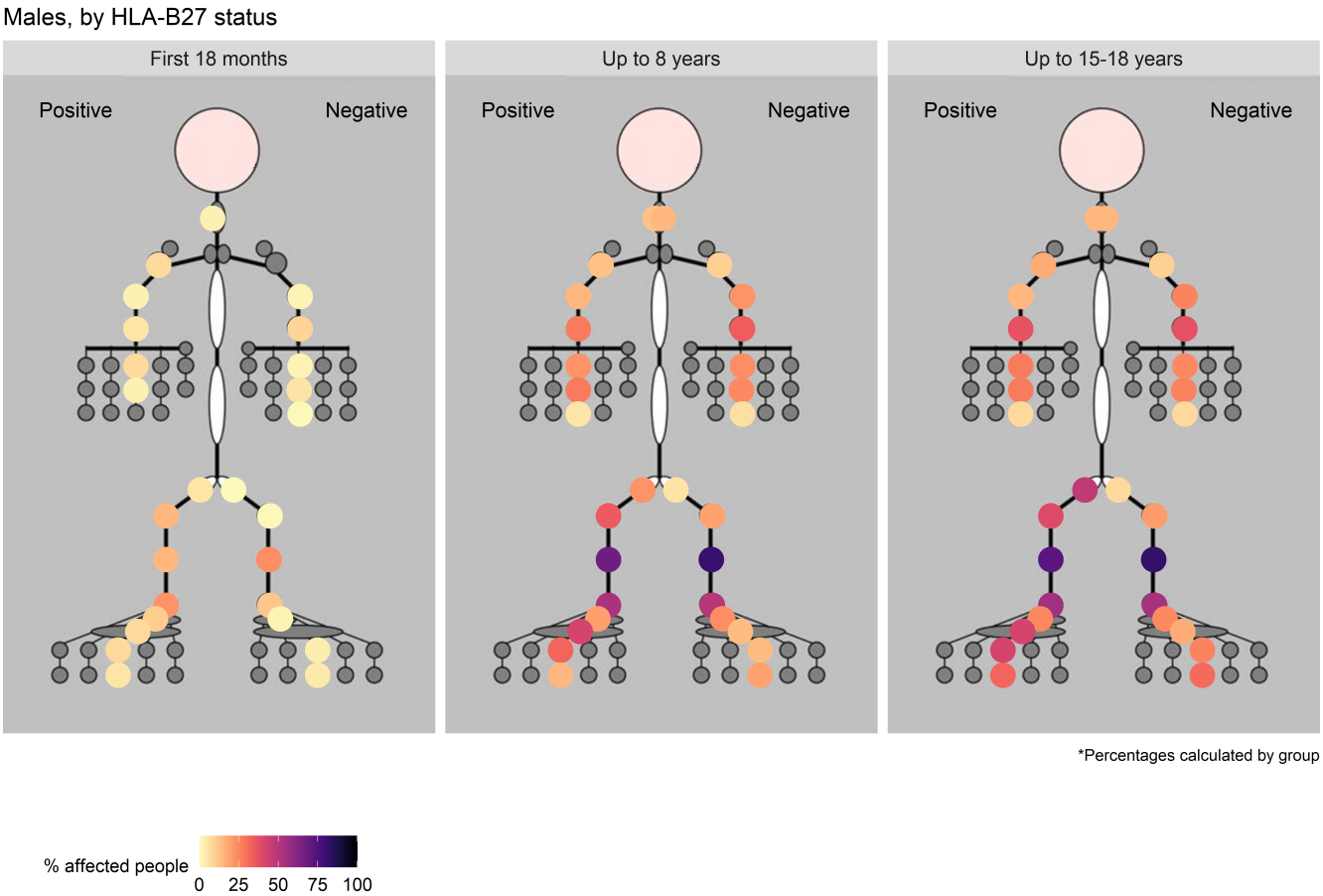

Figure 3. Cumulatively active joints at the follow-ups among men, by HLA-B27 status. The percentages of individuals with activity in a particular joint are shown in a color spectrum. The TMJ involvement was based on clinical findings at the 18-year follow-up study visit, and not on imaging. TMJ, temporomandibular joint.

Figure 2 for women and Figure 3 for men. The SI, hip, and subtalar joints were more frequently involved in individuals who were HLA-B27 positive compared with individuals who were HLA-B27 negative (Supplementary Table 1, Figure 2, and Figure 3). Involvement of the SI, hip, subtalar, and metatarsophalangeal (MTP) joints was more common among men who were HLA-B27 positive compared with women who were HLA-B27 positive.

Remission. Remission data were obtained for 406 individuals assessed for HLA-B27 (Table 4). For individuals who were HLA-B27 positive, the overall odds ratio (OR) for not being in remission after 18 years was 2.6 (95% confidence interval [CI] 1.5–4.3), using data from individuals who were HLA-B27 negative as reference. OR for not being in remission was significantly higher for men (OR 5.6; 95% CI 2.3–13.7) than for women (OR 1.7; 95% CI 0.9–3.3). We also found that sacroiliitis, enthesitis, hip, tarsal, and subtalar arthritis, as well as uveitis, were associated with a significantly higher OR for not being in remission off medication after 18 years. In the HLA-B27 positive individuals, an increased risk of not being in remission was only significant for IBP, enthesitis, and uveitis (Table 4).

DISCUSSION

In this 18-year prospective study in a population-based setting, the age at onset of JIA in participants with HLA-B27 positivity was found to be high in both men and women. The presence of HLA-B27 was significantly more common in men. Features such as IBP, SI joint tenderness sacroiliitis on imaging, and enthesitis were more common in men who were HLA-B27 positive compared with women who were HLA-B27 positive. The joint pattern related to HLA-B27 differed between genders. Clinical characteristics of juvenile spondyloarthropathy were associated with worse outcomes after 18 years, and HLA-B27 was a negative prognostic factor for men but not for women.

In our cohort, 22.4% of the individuals were HLA-B27 positive, which is close to the frequency of 25% reported in a study from Finland.[31] Individuals who were HLA-B27 positive were found in all JIA categories with the highest occurrence of HLA-

Table 4. Odds ratio for not being in remission off medication 18 years after disease onset in relation to gender and HLA-B27 for participants in the Nordic JIA cohort*

Characteristic		Not in Remission Off Medication at 18 Year Follow-up (231 of 406, 56.9%)			Gender or Clinical Characteristic Interactions	
	n	Prevalence, n (%)	OR (95% CI)	*P* value[a]	OR (95% CI)	*P* value[b]
Patients assessed, HLA-B27 positive	91 of 406	67 of 91 (73.6)	2.6 (1.5–4.3)	0.001	–	–
Male, HLA-B27 positive	39 of 130	31 of 39 (79.5)	5.6 (2.3–13.7)	<0.001	3.3 (1.1–9.8)	0.033
Female, HLA-B27 positive	52 of 276	36 of 52 (69.2)	1.7 (0.9–3.3)	0.10	–	–
IBP	68 of 402	51 of 68 (75.0)	2.7 (1.5–4.8)	<0.001	–	–
HLA-B27 positive	33	29 of 33 (87.9)	4.1 (1.3–13.5)	0.018	2.5 (0.6–10.0)	0.19
HLA-B27 negative	35	22 of 35 (62.8)	1.6 (0.8–3.4)	0.17	–	–
SI tenderness	53 of 406	42 of 53 (79.2)	3.3 (1.6–6.6)	<0.001	–	–
HLA-B27 positive	22	19 of 22 (86.4)	2.8 (0.7–10.4)	0.13	1.0 (0.2–4.5)	1.0
HLA-B27 negative	31	23 of 31 (74.2)	2.9 (1.3–6.7)	0.012	–	–
Enthesitis	77 of 406	61 of 77 (79.2)	3.6 (2.0–6.4)	<0.001	–	–
HLA-B27 positive	30	27 of 30 (90.0)	4.7 (1.3–17.4)	0.020	1.7 (0.4–7.4)	0.48
HLA-B27 negative	47	34 of 47 (72.3)	2.8 (1.4–5.5)	0.003	–	–
Sacroiliitis on imaging	27 of 406	26 of 27 (96.3)	22.1 (3.0–164.3)	0.003	–	–
HLA-B27 positive	18	18 of 18 (100)	NA	–	NA	–
HLA-B27 negative	9	8 of 9 (88.9)	7.7 (1.0–62.2)	0.056	–	–
Hip arthritis	105 of 397	68 of 105 (64.7)	1.6 (1.0–2.5)	0.045	–	–
HLA-B27 positive	33	25 of 33 (75.8)	1.4 (0.5–3.6)	0.55	0.9 (0.3–2.9)	0.86
HLA-B27 negative	72	43 of 72 (59.7)	1.5 (0.9–2.6)	0.14	–	–
Tarsal arthritis	74 of 398	55 of 74 (74.3)	2.6 (1.5–4.6)	<0.001	–	–
HLA-B27 positive	19	17 of 19 (89.5)	4.1 (0.9–19.2)	0.076	1.7 (0.3–9.2)	0.52
HLA-B27 negative	55	38 of 55 (68.1)	2.3 (1.3–4.4)	0.007	–	–
Subtalar arthritis	92 of 400	68 of 92 (59.8)	2.6 (1.6–4.4)	<0.001	–	–
HLA-B27 positive	29	22 of 29 (75.9)	1.2 (0.4–3.4)	0.68	0.4 (0.1–1.3)	0.14
HLA-B27 negative	63	46 of 63 (73.0)	3.0 (1.6–5.6)	<0.001	–	–
Uveitis	95 of 406	71 of 95 (74.7)	2.8 (1.7–4.7)	<0.001	–	–
HLA-B27 positive	29	28 of 29 (96.6)	16.5 (2.1–129)	0.008	8.3 (1.0–70.7)	0.051
HLA-B27 negative	66	43 of 66 (65.2)	2.0 (1.1–3.5)	0.018	–	–
Uveitis, symptomatic	26 of 423	21 of 26 (80.8)	3.5 (1.3–9.5)	0.013	–	–
HLA-B27 positive	13	12 of 13 (92.3)	13.7 (1.7–109)	0.013	8.3 (0.8–91.4)	0.008
HLA-B27 negative	13	9 of 13 (69.2)	1.6 (0.5–5.5)	0.42	–	–

*SI tenderness is defined as palpatory tenderness over the SI joint. IBP is defined as lumbosacral spinal pain at rest with morning stiffness that improves on movement. SI on imaging includes conventional x-ray, CT, and MRI. CI, confidence interval; CT, computed tomography; IBP, inflammatory back pain; JIA, juvenile idiopathic arthritis; MRI, magnetic resonance imaging; NA, not applicable; OR, odds ratio; SI, sacroiliac joint.
[a]Logistic regression analysis.
[b]Interaction of odds ratios in relation to gender and HLA-B27 respectively.

B27 in the ERA and the undifferentiated category. We assume that the relatively high prevalence of HLA-B27 positivity in the general population in the Nordic countries could contribute to the high prevalence of JIA in these countries. This is known from the adult population in which prevalence of spondyloarthropathy is generally higher in populations with a higher background prevalence of HLA-B27 positivity.[32] On the other hand, we found no association between HLA-B27 positivity and heredity for JIA.

Over time, an increasing number of joints were affected in our cohort, with no difference in the number of cumulative joints between HLA-B27 positive and HLA-B27 negative individuals. At the eight-year follow-up, we found HLA-B27 associated with clinical signs of sacroiliitis and enthesitis in men, but not in women.[24] After 18 years, features of sacroiliitis and enthesitis, in addition to involvement of the hip, subtalar, and MTP joints, were more common in men who were HLA-B27 positive compared with women who were HLA-B27 positive. This result concerning gender difference is difficult to relate to other study cohorts because we have not found any studies that have conducted a gender comparison. Involvement of these joints and enthesitis are supported by studies focused on ERA, with the majority of patients being HLA-B27 positive, but still without gender comparison.[33–35] To our knowledge, there are no other studies on the development of joint pattern over time in HLA-B27 positive compared to HLA-B27 negative individuals. In studies of ERA, we have found a few presentations of joint pattern which, to varying degrees, support the involvement of sacroiliacal joints, hips, knees, tarsal, and subtalar joints.[36–38]

In spondylarthropathy in adults, it is more common for men to be HLA-B27 positive than for women, which in some studies has been related to a diagnostic delay.[39,40] In follow-up studies, HLA-B27 is shown to be a risk factor for the development of

sacroiliitis.[41] Interestingly, in our cohort as many as one third of individuals with imaging-proven sacroiliitis 18 years after onset were HLA-B27 negative.

HLA-B27-associated uveitis is usually considered to be acute and symptomatic.[42] In our study, uveitis, with or without symptoms, was significantly more common among individuals who were HLA-B27 positive. The results from a study by Walsheid et al support our results; in their study of patients with ERA, 40% had an asymptomatic uveitis.[43] In conclusion, uveitis in individuals with HLA-B27 positivity is not always symptomatic, an important fact that clinicians need to be aware of.

Not surprisingly, individuals who were HLA-B27 positive were significantly more likely to have a first- or second-degree relative with ankylosing spondylitis. In the ASAS-criteria, both first- and second-degree heredity of spondyloarthtropathy is recognized.[44] In publications strictly presenting heredity of HLA-B27, first-degree heredity is well-known, but second-degree heredity is more seldom described.[45,46] Interestingly, we found no link between HLA-B27 and a family history of JIA or RA in first- or second-degree relatives, indicating that HLA-B27 does not influence the occurrence of these conditions. The reliability of our data is further supported by the fact that the anamnestic data on heredity were collected repeatedly during the study.

Previous studies have shown a more severe and long-standing disease associated with HLA-B27.[47–49] This is in line with our results in which HLA-B27 positivity was associated with a higher risk of not being in remission off medication after 18 years, although with a significantly higher risk in men but without significance in women. Nevertheless, it is still important to acknowledge the women with signs of spondyloarthropathy. In a study by Minden et al, lower probability of remission was found for patients who were HLA-B27 positive compared with patients who were HLA-B27 negative; however, gender differences were not studied.[47] The different clinical characteristics associated with spondyloarthropathy during the course of the disease in our study were associated with lower remission rate off medication, which has not been possible to compare with any other cohort.

A strength of our study is the population-based design and the long follow-up time; however, some limitations should be addressed. The number of individuals with sacroiliitis is small as is the number of imaging examinations, which restrict the conclusions that can be drawn. Our composite variable, defined as sacroiliitis and visualized in the homunculus of cumulatively active joints, could be questioned. We chose to combine patients with IBP with SI palpatory tenderness to be regarded as clinical sacroiliitis. The patients with sacroiliitis on imaging without clinical symptoms were included in this variable. We acknowledge that the different imaging techniques are not interchangeable, but our study is a clinical longitudinal study cumulatively collecting arthritis in different joints. In that aspect, an arthritis should be considered either if it is shown to be active on an MRI or shows chronic changes on plain x-ray. Another limitation is that the inclusion period for our study was at the very beginning of the introduction of biologic drugs, which might impede comparison with outcome studies performed today. Although not all patients were examined on every occasion, the majority underwent assessment on three separate occasions.

In conclusion, this study contributes valuable insights into the long-term adverse implications of HLA-B27 positivity in JIA, highlighting gender differences and persistent clinical challenges. The results raise the question of whether screening for HLA-B27 should be considered for all patients with JIA.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ekelund confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg. not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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