What Does Human Leukocyte Antigen B27 Have to Do with Spondyloarthritis?

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KEYWORDS

• HLA-B27 • Spondyloarthritis • Diagnosis • Prognosis • Genetics
• Disease phenotype

KEY POINTS

- Human leukocyte antigen (HLA) B27 plays a central role in axial spondyloarthritis (axSpA) diagnosis and constitutes a significant part of previous and current classification criteria.
- HLA-B27 plays a role in the physiopathology of axSpA, although the exact mechanism is not yet fully elucidated.
- HLA-B27 is correlated with spondyloarthritis phenotype, with a consistent positive association with family history, early disease onset, shorter diagnostic delay, and acute anterior uveitis, and a controversial association with disease activity.
- HLA-B27 does not seem to be a poor prognostic factor for radiographic progression and response to treatment.

INTRODUCTION

Spondyloarthritis (SpA) is a common disease, potentially disabling, with a serious socioeconomic burden.[1,2] However, despite this significant impact, particularly in young adults, a substantial diagnostic delay is observed, mostly caused by the ubiquitous and nonspecific primary manifestation of the disease (ie, low back pain), and by the scarcity of diagnostic laboratory markers.[3–5]

Since its first report in 1973,[6,7] human leukocyte antigen (HLA) B27 has been considered the key laboratory parameter for axial SpA (axSpA) and has been used as a supplemental diagnostic test in patients with suspicion of axSpA. Among the typical manifestations of axSpA, HLA-B27 has a sensitivity of 83% to 96% and a

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specificity of 90% to 95% in European white populations with chronic low back pain and an age of onset of less than 45 years.[8]

Its diagnostic importance is reflected by its inclusion in several classification criteria. It is a double-weighted criterion in the 1990 Amor criteria for spondyloarthropathy,[9] and one of 2 major entry criteria in the 2009 Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA, allowing the classification through a clinical arm, even in the absence of radiological manifestations.[8]

In the latter classification criteria, sensitivity and specificity for axSpA were 56.6% and 83.3% respectively, slightly lower than the imaging arm (66.2% and 97.3% respectively). HLA-B27 positivity had a high likelihood ratio of 9, similar to sacroiliitis on MRI.

However, these properties may not be applicable in other populations who have a different HLA-B27 background prevalence than the European white population, in which the ASAS classification criteria were validated.

This article discusses the epidemiologic distribution of HLA-B27, the methods of testing, the relationship with SpA epidemiology, physiopathology, disease phenotype, and prognosis, as well as its role in referral strategies.

WHAT IS THE EPIDEMIOLOGIC DISTRIBUTION OF HUMAN LEUKOCYTE ANTIGEN B27 AROUND THE GLOBE?

Large differences in HLA-B27 prevalence have been described across different geographic areas and ethnicities.[10] In general, the incidence and prevalence of axSpA mirror the frequency of HLA-B27 in the population[11] (**Table 1**).

Axial Spondyloarthritis Prevalence in the Population

Low rates of axSpA have been described in southern Africa, Japan, and Arab countries, compared with higher rates in Europe and very high rates among the native people of circumpolar arctic and subarctic regions of Eurasia and North America. Among Europeans, higher rates of ankylosing spondylitis (AS) were reported in Norway compared with other European countries.[11,12]

Table 1
Human leukocyte antigen B27 and axial spondyloarthritis mirroring prevalence across different populations

	axSpA Prevalence in the General Population (%)	HLA-B27 Prevalence in the General Population (%)	HLA-B27 Prevalence in the axSpA Patients (%)
Africa	0.07	2–9	—
Arab countries	0.30	0.3–6.8	41–84
Asia	0.17–0.18	—	—
Eskimos	0.40–2	25–50	—
Haida Indians	6.10	50	—
Latin America	0.10–0.12	—	—
North America	0.32–0.5	6–8	80–95
Western Europe (Norway)	0.20–0.90 1.10–1.40	8–9 14	75–95

Data from Refs.[2,10,12–20]

Human Leukocyte Antigen B27 Prevalence in the Population

In parallel, in the general population, lower rates of HLA-B27 were reported in Japanese and most Arab populations (0.3%–6.8%) compared with Western European and North American populations (6% to 25%), possibly caused by different genetic backgrounds.[12,13,21,22] The highest rates of HLA-B27 were reported in the population of Papua New Guinea (13%–53%)[23] and Eskimos (25%–50%).[24] In the United States, the prevalence of HLA-B27 in the population was higher in non-Hispanic white Americans (7.5%) compared with other US races/ethnicities combined (3.5%), according to the 2009 US National Health and Nutrition Examination Survey (NHANES) cross-sectional survey.[21]

Human Leukocyte Antigen B27 Prevalence in Patients with Axial Spondyloarthritis

In patients with axSpA, higher rates of HLA-B27 were found in North America and Western Europe (80%–95%)[10] compared with lower rates in Japan and Arab countries (41%–84%).[12,25]

However, despite the lower background prevalence in these populations, HLA-B27 is characterized by high specificity and a high positive Likelihood Ratio, with a significant strength of association, similar to European and North American studies. These properties make this test highly valuable for axSpA diagnosis, particularly when found positive, but may affect its value in primary screening and referral strategies (see **Table 1**).

HOW IS HUMAN LEUKOCYTE ANTIGEN B27 TESTED?

The strong genetic association between HLA-B27 positivity and SpA after its discovery in 1973 and the role of HLA-B27 testing in the diagnostic work-up of SpA generated a growing increase in the demand for testing worldwide.[6,7] It has been suggested that some of the change of the HLA-B27 prevalence with time may be related to changes in testing methods.

In 1964, Terasaki and McClelland[26] established a complement-dependent cytotoxicity (CDC) test for HLA. Patient lymphocytes are exposed to a panel of sera containing characterized HLA-specific antibodies obtained from multiparous women immunized against HLA-B present on the cells of the fetus. The addition of rabbit serum was used as a source of complement, and the binding of alloantibodies to the HLA triggers complement-dependent cell death detected, at the time, by ethidium bromide positivity and microscopic evaluation.[26] One of the most critical limitations was the lack of specificity toward each HLA-B27 variant, among which only a limited set is associated with SpA.

At present, more than 160 subtypes of HLA-B27 have been identified. These subtypes are distributed according to race and ethnicity and may be associated differently with axSpA.

The most common disease-associated subtypes are B*2702 (Mediterranean population), B*2705 (white people and American Indians), and B*2704 (Asians). Most of the subtypes are disease associated, which makes identifying them in individuals of little utility. However, some subtypes are not associated with disease, such as HLA-B27*09 in Sardinia and HLA-B27*06 in Southeast Asia.[20,27,28]

The CDC test for HLA requires viable cells and poses the risk of false-negative results when the antigen is downregulated or masked. In addition, the assay is extremely sensitive to sample storage conditions and timing.

The development of specific monoclonal antibodies toward HLA-B27 and the increased accessibility of molecular biology techniques allowed the diffusion of flow cytometry and polymerase chain reaction (PCR) in place of the CDC-based assay.

Monoclonal antibodies targeting HLA-B27 (ie, clones ABC-m3, GS145.2, and FD705) conjugated with fluorochromes (fluorescein isothiocyanate) are used to detect the expression of HLA-B27 on T lymphocytes identified by cluster of differentiation 3 (CD3) positivity (phycoerythrin), commonly comparing the mean fluorescent intensity with positive and negative reference microspheres.[29] This approach is widely used worldwide because it is fast and inexpensive and grants acceptable performance in the hands of experienced professionals.[29–31] However, similarly to other immunoassays, flow cytometry is not suitable for the distinction between the HLA-B27 variants and the downregulation of HLA-B27 or the masking by autoantibodies can lead to false-negative results. Note that HLA-B27 belongs to the large cross-reacting group (CREG); thus, the currently used clones can cross react with other CREG members, mainly B7 and B37, leading to false-positivity.[32]

PCR-based genetic testing is a valuable alternative to immunoassays. The HLA-B gene is amplified, and the PCR product is hybridized with multiple sequence-specific oligonucleotides, allowing the detection of the HLA-B27 and providing information on the HLA-B27 variants discriminating the associated SpA.[33] Alternatively, the PCR product can undergo Sanger sequencing, providing the HLA-B sequence at a single-base-pair resolution. More recently, a faster single-step method has been developed involving a specific set of directly conjugated probes for real-time PCR (TaqMan assay).[34]

Overall, the specificity and the resolution of DNA-based assay could replace or at least integrate the flow cytometry data for research purposes or in case of ambiguous results.

DOES HUMAN LEUKOCYTE ANTIGEN B27 HAVE A PHYSIOPATHOLOGIC ROLE AS WELL?

The strong association between axSpA and the positivity for HLA-B27 led to speculation about a causative effect of HLA-B27 risk variants in the pathogenesis of the disease. A definitive explanation of the mechanisms behind this association is still lacking, and a detailed systematic review of the molecular mechanisms by which HLA-B27 could increase the susceptibility to AS goes beyond the scope of this article. However, the mechanisms postulated can be summarized in 3 theories, perhaps not mutually exclusive:

- The main highly polymorphic sites associated with SpA are responsible for determining the amino acidic residue in positions 67 and 97 of the HLA-B that takes part in the formation of the peptide-binding domain, involved in both antigen presentation and protein folding.[35,36] The arthritogenic peptide theory postulates a response toward peptides expressed in axSpA joints and other sites of the disease. The HLA-B27 could mediate the presentation of peptides, possibly of microbial origin to cytotoxic CD8+ T cells mounting, because of molecular mimicry, an autoimmune response triggering AS manifestation including spondylitis and arthritis.[37] This theory was partially supported by the detection of CD8+ T cells reactive toward *Chlamydia* in the joints of patients with reactive arthritis.[38] However, many groups failed to identify an arthritogenic peptide in AS and animal models showed that CD8+ T cells are dispensable for the manifestation of the disease.

  [39]The natural function of HLA-B27 in presenting foreign antigens is consistent

with the suggested role for the microbiota in the development or perpetuation of the disease. Different lines of research showed subclinical gut inflammation in patients affected by AS and quantitative and qualitative perturbations of the gut microbiota.[40] Interestingly, the variation in the gut microbial content has been associated with the AS disease activity and is influenced by anti–tumor necrosis factor (TNF) therapy.[41,42] In keeping with the arthritogenic peptide theory, the altered gut microbiome could be a source of multiple autoantigens.[43]

- Typically, the HLA-B27 complex consists of heavy chains forming heterodimers with the with b2-microglobulin (b2m) and, as stated earlier, the complex binds and presents peptides to cytotoxic T cells. The homodimerization theory developed after the observation that the HLA-B27 chains can form homodimers via disulfide bonds through its unpaired cysteine at position 67 without the b2m ($B27_2$).[44] Once at the cell surface, $B27_2$ can be recognized by killer immunoglobulin–like receptors expressed on natural killer cells and CD4+ T cells, possibly triggering the activation and polarization toward a T-helper 17 phenotype.[45] How this process could affect only the target organs such as the joints is still not explained.
- The unfolded protein response (UPR) theory hypothesized that because the HLA-B27 is more prone to misfolding during its assembly in the endoplasmic reticulum (ER), it can form aberrant protein complexes that activate the UPR in the ER.[46] The UPR is known to be associated with a proinflammatory phenotype, leading to the production of inflammatory cytokines, including TNF and interleukin-23. However, the evidence of the increased activation of UPR in AS is so far conflicting.[47]

More recently, nonimmunologic functions of HLA-B27 have been suggested. MRI has shown a link between HLA-B27 positivity and pathologic response to biomechanical stress.[48] However, the cellular mechanisms linking the HLA-B27 to stress-induced inflammation and ossification remain elusive.[49]

DOES HUMAN LEUKOCYTE ANTIGEN B27 INFLUENCE SPONDYLOARTHRITIS PHENOTYPE?

Although the physiopathologic theories are still debated, several studies have established that HLA-B27 positivity can influence the patient clinical phenotype (**Fig. 1**).

Family History

It has long been established that a family history of SpA is common in patients with axSpA. Also, HLA-B27–positive first-degree relatives of HLA-B27–positive patients with axSpA are 16 times more likely to develop axSpA than HLA-B27–positive individuals in the general population.[14,50] In 2 European cohorts of patients with chronic back pain suspected of axSpA, a positive family history (PFH) for axSpA and acute anterior uveitis (AAU) was associated with positive HLA-B27, unlike the PFH for reactive arthritis, inflammatory bowel disease (IBD), or psoriasis.[51] In line with those findings, an analysis of the ASAS cohort, which includes more variable ethnicities, showed that a PFH of axSpA was strongly associated with positive HLA-B27 in both white and Asian patients and in both first-degree and second-degree relatives, but this association was stronger with white ethnicity and with a PFH in first-degree relatives.[52]

A study of Finnish patients with axSpA found higher relative risk of developing axSpA in HLA-B27 homozygotes, with those showing, surprisingly, a less severe disease course.[53] However, 1 Dutch and 1 Korean study found no significant difference between homozygous and heterozygous patients.[14,54]

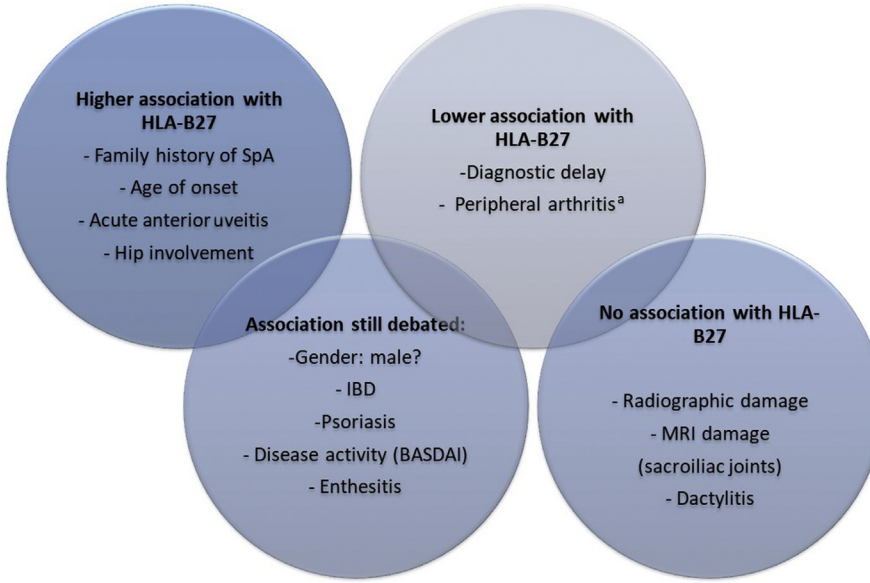

Fig. 1. Classification of axSpA parameters based on their association with HLA-B27. [a] Association between HLA-B27 and peripheral SpA is significant, but it is lower than the association with axSpA. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IBD, inflammatory bowel disease.

Moreover, in HLA-B27–positive first-degree relatives of patients with axSpA, the risk of developing axSpA is 12%, whereas the risk in HLA-B27–negative relatives is very low ($\leq$1%).[55]

Age of Onset

Several studies have reported that HLA-B27 was associated with earlier onset of disease,[3,56,57] a finding that was confirmed in the more recent DEvenir des Spondylarthropathies Indifférenciées Récentes cohort.[58] This association is an interesting feature of axSpA, because it may play a predictive role in evaluating the disease evolution and prognosis.

Diagnostic Delay

In early axSpA cohort studies, HLA-B27 positivity was associated with shorter delay to diagnosis.[3,58] Therefore, its presence, as an objective marker, may prompt earlier diagnosis.

Gender

Several studies showed a higher male prevalence in HLA-B27–positive patients with axSpA, but the data are conflicting on this point.[59–62]

Disease Activity

HLA-B27–positive patients with axSpA showed no higher clinical burden of the disease. On the contrary, 1 study found significantly higher Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index

(BASFI) scores in HLA-B27–negative patients, even without differences in biological parameters (erythrocyte sedimentation rate and C-reactive protein [CRP]).[53]

Other cohort studies reported similar BASDAI and BASFI scores in HLA-B27–positive and HLA-B27–negative patients,[53,54,63] except for the DESIR cohort, which found slightly worse BASDAI, BASFI, and Bath Ankylosing Spondylitis Metrology Index scores in the HLA-B27–negative population.[58] Findings of a positive correlation with high CRP level were not confirmed.[64,65]

Joint Topography Pattern

Hip arthritis was more frequently reported in HLA-B27–positive patients with AS in most of the studies.[54,60,63]

Association with peripheral disease pattern is less than for axial SpA.[56,58,61] In cohorts with psoriatic arthritis, HLA-B27 was positive in only 29.3% of patients.[65]

From 30% to 80% of patients with reactive arthritis and 20% to 35% of patients with psoriatic arthritis were HLA-B27 positive.[66,67]

Regarding enthesitis, few studies showed their significantly higher prevalence among patients with AS with positive HLA-B27,[58,68] but this pattern was not observed in other studies.[54,60,63]

For dactylitis, no significant differences were noted between HLA-B27–positive and HLA-B27–negative patients with AS in the few studies mentioning it.

Extra-Articular Manifestations

Acute anterior uveitis

AAU prevalence in HLA-B27–positive individuals is estimated at around 1%. This risk is 2.6 to 4.2 times higher in HLA-B27–positive patients with SpA.[69,70] In contrast, the prevalence of HLA-B27 in patients presenting with AAU is around 50%. Moreover, in HLA-B27–positive patients with axSpA, the prevalence of AAU increases to 40%, whereas it is between 26% and 30% in general axSpA studies.[71] Also, Juanola and colleagues[72] recently found that SpA existed in 41% of patients presenting with more than 1 episode of AAU separated by at least 3 months.

Taken from the AAU angle, in patients with AAU who are HLA-B27 positive, the risk of developing SpA is between 35% and 66%, in contrast with HLA-B27-negative patients with AAU, in whom it is between 3.8% and 6%.[73]

Even HLA-B27–positive AAU seems to have a unique clinical presentation: unilateral; sudden in onset; and symptomatic, with blurred vision, photophobia, ocular redness, and pain. On examination it presents a significant anterior segment inflammation, often including hypopyon, posterior synechiae, and fibrin; it is typically nongranulomatous, episodic, and can alternate between eyes.[74]

Moreover, it has different characteristics than the negative one, independent of its association with axSpA: earlier onset (32–35 years), male preponderance (1.5:1–2.5:1), familial aggregation.[74,75]

Also, the incidence of ocular complications seems to be frequent in HLA-B27–associated uveitis: posterior synechiae and posterior subcapsular cataracts at presentation, ocular hypertension and posterior subcapsular cataract during follow-up, epiretinal membrane, cystoid macular edema, and band keratopathy more rarely.[76]

Whether the incidence of those complications and the visual outcomes differ between patients with HLA-B27–positive and HLA-B27–negative uveitis remains controversial, with some studies finding a higher rate of visual loss with HLA-B27–positive uveitis,[77] and others, including a large meta-analysis, showing no differences.[78]

Therefore, counseling about the risk of development of SpA should be undertaken in patients found to have HLA-B27–associated uveitis, because the ability to identify and

treat HLA-B27–associated uveitis and concomitant SpA can limit the ocular and systemic morbidity.

Inflammatory bowel diseases

The gastrointestinal inflammation associated with axSpA ranges from microscopic (subclinical but found on ileocolonoscopic and histologic studies) to clinically overt IBD, with a prevalence, respectively, of 25% to 69% and 3% to 10%.[20] In contrast, stratifying patients by the level of gastrointestinal involvement, HLA-B27 positivity was observed in 35% to 95% of individuals with subclinical inflammation and in 27% to 78% of patients with a diagnosis of IBD.

However, no clear evidence has been found to prove that, in HLA-B27–positive patients with axSpA, the risk of developing IBD or subclinical IBD is higher.

In contrast, in patients with IBD, many data show that there is an increasing trend of HLA-B27 prevalence, ranging from 9.6% in inflammatory back pain (IBP), to 40% in radiographic sacroiliitis, to 73% in axSpA.[79] These data suggest that being HLA-B27 positive can be taken as a predisposing factor for sacroiliitis or axSpA in patients with IBD.[80]

However, some studies suggest a negative association with IBD, which deserves further investigation regarding the gene-environment interaction hypothesis.[67,81]

In addition, in patients with IBD, the presence of HLA-B27 is associated with a higher risk of developing extraintestinal disease manifestations, including sacroiliitis, spondylitis, peripheral arthritis, and enthesitis.[82]

Psoriasis

In a multivariate analysis of an early SpA cohort, psoriasis data showed a negative association with HLA-B27 (odds ratio, 0.59; 95% confidence interval, 0.39, 0.90; $P = .01$),[58] which suggests a 22% to 58% reduction in the odds of having psoriasis when HLA-B27 is positive in patients with axSpA.

However, a contradictory trend is found in some other studies, with an increasing prevalence of HLA-B27 in psoriasis, psoriatic arthritis (PsA), and axial PsA/psoriatic SpA at 5%, 20%,[66] and 23.4% to 34.5%,[83,84] respectively.

The recent review by Queiro and colleagues[66] also suggested that HLA-B27 is a genetic biomarker of joint disease in patients with psoriasis, and a marker for disease expression in PsA. It is also associated with a shorter interval between the development of skin eruptions and musculoskeletal symptoms; a higher risk of enthesitis, dactylitis, and uveitis; and a tendency toward peripheral and axial joint damage over time.[66,84–86]

A recent study also showed that, in patients with PsA, positive HLA-B27 was associated with more severe sonographic enthesitis, particularly in patients with longer disease duration.[87] However, there is an ongoing debate over the definition of psoriatic axial disease and axSpA with associated psoriasis.

Radiologic Signs

Despite a common perception that HLA-B27 is associated with disease severity in AS, its role in structural progression and disease severity has not been sufficiently proved.

The first study to compare clinical features of HLA-B27–positive versus HLA-B27–negative patients with AS was that of Khan and colleagues[88] in 1977, finding no significant differences.

In the setting of early IBP cohorts, an association with the persistence of MRI-identified inflammation at the sacroiliac joints (SIJs) and lumbar spine in early IBP

was reported.[58,89] In this kind of setting, HLA-B27 represented a predictive value for axSpA in patients with IBP.

Association with Behçet Disease

Although major histocompatibility complex class I, especially HLA-B5/B51, is the most associated gene with Behçet disease (BD), HLA-B27 has also been studied.

A recent meta-analysis found that the risk of HLA-B27 positivity for BD progression is increased by a factor of 1.55, which is weak compared with the odds ratio of 5.78 in carriers of HLA-B5/B51.[90]

Paradoxically, uveitis occurring in BD is milder in patients with both the HLA-B5/B51 and HLA-B27 genes, probably because of less posterior segment involvement and complications, and a less chronic course of the disease.[91]

IS HUMAN LEUKOCYTE ANTIGEN B27 ASSOCIATED WITH SPONDYLOARTHRITIS PROGNOSIS?

Some recent data suggested that HLA-B27 is a marker associated with more severe axial bone-forming phenotypes of the SpA disease spectrum (AS and axial PsA/peripheral spondyloarthritis (psSpa)).[20]

These data are contradicted by other studies suggesting that HLA-B27 does not seem to be associated with radiographic progression.[92] Data from the DESIR cohort did not find an association between HLA-B27 and MRI structural lesions of the SIJ.[58]

Moreover, the prevalence of HLA-B27 does not seem to be different between AS and nonradiographic axSpA.[93]

Furthermore, in early axSpA, data from the DESIR cohort showed that HLA-B27 is associated with less delay in diagnosis, which may indirectly affect disease prognosis positively.[58] In contrast, the presence of the HLA-B27 antigen does not seem to be associated with response to biologic treatment.[94]

HOW DOES HUMAN LEUKOCYTE ANTIGEN B27 AFFECT REFERRAL STRATEGIES FROM THE PRIMARY CARE SETTING?

In the past couple of decades, referral strategies were developed for primary care settings, with the aim of reducing the diagnostic delay, thus ensuring adequate management in the early stage of the disease and improving disease prognosis. These strategies have a common clinical starting point: chronic and/or inflammatory chronic low back pain. In addition, HLA-B27 is considered a major criterion in most of these strategies, whether in the primary screening step or in the second line, after documenting clinical criteria.[95]

Globally, in a target population consisting of patients with chronic low back pain and onset before 45 years of age, referring a patient based on HLA-B27 positivity yields in axSpA diagnosis in one-third of the cases in European white populations. Adding HLA-B27 positivity to IBP increases the diagnosis of axSpA from 34% to 62%.[95]

HLA-B27 is an interesting screening parameter because it is easy to prescribe, clear to interpret (positive or negative), and has a moderate 1-time cost. However, its value depends largely on its prevalence in the general population and the strength of its association with SpA across geographic regions and ethnicities. However, most of the published strategy studies were conducted in European populations and their results cannot be extrapolated to other populations, particularly where HLA-B27 prevalence is lower.

SUMMARY

HLA-B27 plays a central role in axSpA diagnosis and constitutes a significant part of previous and current classification criteria.

It has a certain role in the physiopathology of axSpA, although the exact mechanism is not yet fully elucidated. HLA-B27 is correlated with SpA phenotype, with a consistent positive association with family history, early disease onset, shorter diagnostic delay, and AAU. However, it does not seem to be associated with either higher disease activity or with a poor prognostic factor for radiographic progression and response to treatment.

Because of its strong association with axSpA, HLA-B27 can be a pivotal parameter in referral strategies. However, in countries with lower background HLA-B27 prevalence, these strategies should be studied further, and data for other sensitive and specific markers in populations with low prevalence are needed.

DISCLOSURE

The authors have nothing to disclose.

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