Celebrating 50 Years of HLA-B27 and Axial Spondyloarthritis: Top 10 Common Questions Answered

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1. What is HLA-B27? What role does HLA-B27 play?

The human leukocyte antigen B27 (HLA-B27), a unique label on the surface of our cells, plays a pivotal role in the immune system. This antigen helps our immune system by showing off pieces (peptides) of pathogenic antigens (like viruses and dying cells) to other immune cells called cytotoxic T cells. When the cytotoxic T cells receive the signal, they swoop in and get rid of the troublemakers, thereby contributing to immune surveillance and response.[1]

2. Which diseases are linked to HLA-B27?

The most striking association is with axial spondyloarthritis (axSpA), where up to 90% of ankylosing spondylitis (AS) and around 70-80% of non-radiographic axSpA patients possess the HLA-B27 allele, respectively.[2,3] Besides axSpA, HLA-B27 is also associated with other diseases within the SpA spectrum, such as acute anterior uveitis, psoriatic arthritis, reactive arthritis, and juvenile idiopathic arthritis.[4-7] Furthermore, there have been reports of an association between inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis and HLA-B27, although conclusive evidence has yet to be established.[8]

3. How does HLA-B27 cause these diseases?

The short answer is that we don't know yet. However, HLA-B27, in combination with other genetic variants, is thought to lead to the chronic activation of downstream immune cells.[9,10] This activation might be mediated by an abnormal gut microbiome, in which HLA-B27 presents disease-associated peptides to downstream T cells. Subsequently, cross-reactive self-attacking T cells migrate to the joints and spine, causing inflammation (Figure 1). It's worth noting that up to 60% of axSpA patients exhibit clinical or subclinical inflammation in the gut.[11] Furthermore, HLA-B27 transgenic mice do not develop SpA symptoms under germ-free conditions.[12] These facts demonstrate a close relationship between the gut and axSpA, and also suggest that specific peptides presented by HLA-B27 in the gut activate downstream T-cell responses leading to SpA-spectrum diseases.

4. Does the HLA-B27 test need to be repeated?

Once a patient has tested positive or negative for HLA-B27 based on established methods such as PCR, the test does not need to be repeated as the presence of this antigen is a stable trait that does not change over time.[13]

Figure 1. Potential Mechanisms of HLA-B27-Mediated Inflammation in Joints and the Spine

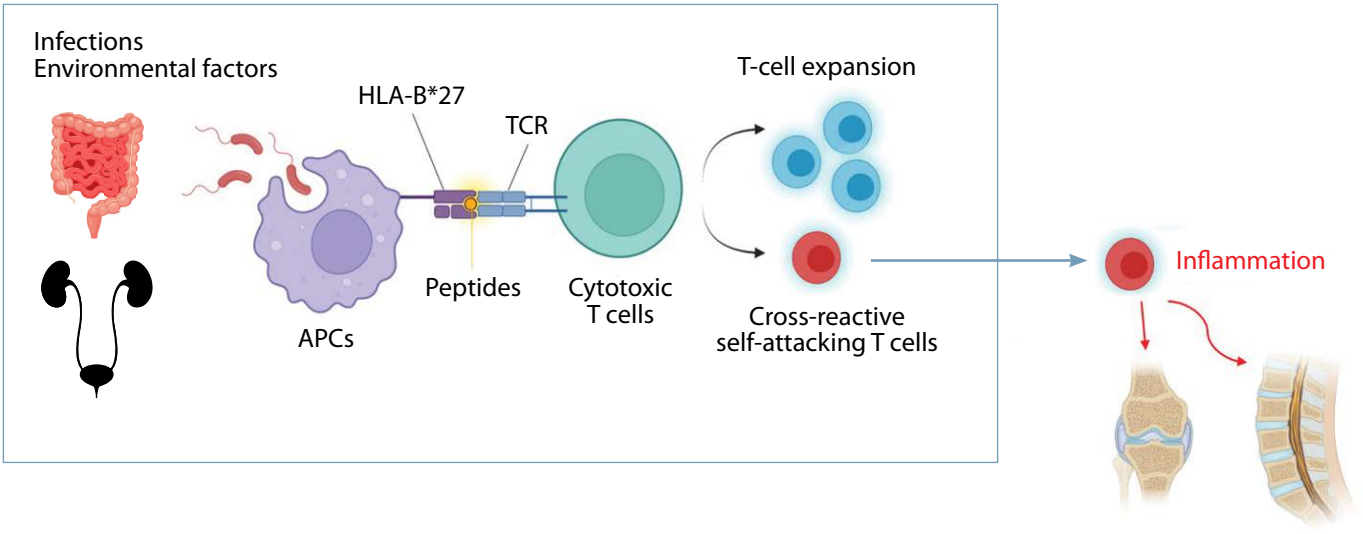
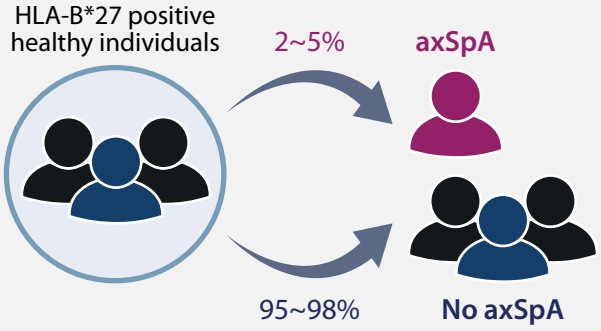
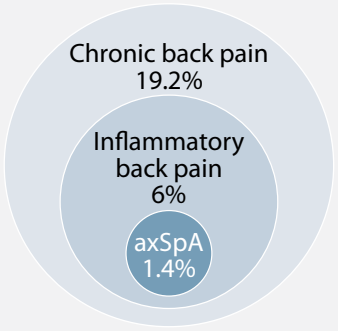


Figure 2. **A**



(A) Prevalence of axSpA among HLA-B27 positive healthy individuals.

B



(B) Prevalence of chronic back pain, inflammatory back pain, and axSpA in the general population.

5. What is the prevalence of HLA-B27 in the general population?

The prevalence of HLA-B27 in the general population varies significantly across different ethnic groups and geographic regions. On a global average, approximately 6-8% of individuals carry the HLA-B27 antigen, and the Canadian population frequency is also reported to be around 7%. Notably, the prevalence is as low as less than 1% in the Japanese population, to as high as approximately 24% in certain indigenous populations of Alaska.[14-16]

6. If someone is HLA-B27 positive, what is their likelihood of developing axSpA?

It is known that HLA-B27-positive individuals face a lifetime risk of approximately 2-5% for the development of axSpA (Figure 2A), compared to around 1% in the general population.[17] While this risk is higher than that in the general population, it's important to note that more than 95% of HLA-B27-positive individuals do not develop axSpA. However, the risk is higher for individuals who not only carry the HLA-B27 antigen but also have a first-degree relative with axSpA, with estimates at around 20%.[18]

7. Are genetic tests necessary for other family members if one tests positive for HLA-B27?

Despite the hereditary component associated with HLA-B27, genetic testing for HLA-B27 status in asymptomatic family members is not typically recommended or required. Testing is usually reserved for those presenting with suggestive clinical symptoms of an HLA-B27-associated condition.

8. Is it recommended for HLA-B27-positive individuals to consult rheumatologists?

While HLA-B27 alone without any symptoms does not require a rheumatology consultation, when an individual tests positive for HLA-B27 and is experiencing symptoms indicative of a rheumatic condition, it is recommended to consult a rheumatologist for a comprehensive assessment. It is also important to note that although around 20% of the general population has chronic back pain, with 6% being inflammatory back pain, only 1.4% of them have axSpA (Figure 2B).[19]

9. What does a positive HLA-B27 result signify in patients with axSpA?

In the context of axSpA, HLA-B27 positivity is known to be a risk factor for earlier disease onset, a more severe disease course, the development of new bone formation, and a higher incidence of extra-articular manifestations such as anterior uveitis.[20]

10. Does the presence of HLA-B27 affect the response to treatment or the prognosis of axSpA?

Data on the correlation between HLA-B27 status and treatment response in axSpA are diverse and somewhat ambiguous. However, previous studies have reported a better response in HLA-B27-positive patients toward tumor necrosis factor inhibitors (TNFi).[21-24] Regarding prognosis, while axSpA disease may impact life expectancy compared to general populations, carrying HLA-B27 variants itself does not increase mortality risks in either axSpA patients or healthy individuals.[25]

Acknowledgment: Figure 1 and Figure 2 were created with BioRender (*BioRender.com*).

Suggested readings:

1. Ranganathan V, Gracey E, Brown MA, et al. Pathogenesis of ankylosing spondylitis - recent advances and future directions. *Nat Rev Rheumatol.* 2017 Jun; 13(6):359-367. PMID: 28446810.
2. Nakamura A, Boroojeni SF, Haroon N. Aberrant antigen processing and presentation: Key pathogenic factors leading to immune activation in Ankylosing spondylitis. *Semin Immunopathol.* 2021 Apr; 43(2):245-253. PMID:33532928.
3. Yang X, Garner LI, Zvyagin IV, et al. Autoimmunity-associated T cell receptors recognize HLA-B*27-bound peptides. *Nature.* 2022; 612:771–7. PMID: 36477533.

A complete list of references used in the article is available online at *craj.ca*.

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