World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

# Geographical variations in HLA-B27 prevalence and its relationship with rheumatological disorders: A systematic review and meta-analysis

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World Journal of Biology Pharmacy and Health Sciences, 2024, 20(02), 691–695

Publication history: Received on 24 September 2024; revised on 13 November 2024; accepted on 16 November 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.20.2.0856

## Abstract

This systematic review and meta-analysis tries to examines the geographic and methodological variation in HLA-B27 prevalence and its association with rheumatological disorders such as rheumatoid arthritis or Ankylosing Spondylitis in different countries using data from seven studies in screening between 1977 and 2022, including cross-sectional, This study, as well as a prospective cohort study, reveals considerable heterogeneity in HLA-B27 prevalence Japan (78 %) found a high prevalence, which was significantly linked with ankylosing spondylitis. In contrast, lower prevalence was found in Colombia (4.5%) and France (9.6% of patients with RA), suggesting a clinically variable importance (based on our selected article). These findings highlight the influence of geographic and ethnic factors on the role of HLA-B27 in rheumatoid arthritis and highlight the need for regionally specific screening and management strategies. Future research should investigate the interactions between HLA-B27 and other genetic and environmental factors to refine diagnostic and therapeutic strategies. It is important to note that some studies were published earlier but became online available recently in years and decade.

**Keywords:** HLA-B27; Prevalence; Arthritis; Ankylosing spondylitis; Reactive arthritis; Ethnic factors; Diagnostic strategies; Management

## 1. Introduction

Human leukocyte antigen B27 (HLA-B27) is the most widely and extensively studied genetic marker due to its strong association with several rheumatic diseases, particularly (AS) and spondyloarthropathies (SpA). The prevalence of HLA-B27 varies broadly across geographical locations and ethnic groups, showing different genetic backgrounds and pathways across studies. Understanding these variables is important for accurate diagnosis, treatment, and epidemiology of rheumatoid arthritis. This systematic review with meta-analysis aimed to try to integrate existing data on geographic and technical variation in HLA-B27 prevalence. By conducting several studies between 1977 and 2022, such as cohort studies, retrospective studies, and prospective studies, we aim to provide a broad overview of the fallout of HLA-B27 prevalence variety in terms of where they are in the world which countries and the factors that influence these differences. This review will also focus on the implications of these changes for clinical practice and future research in medical and specially in Rheumatology.

## 2. Methodology

This meta-analysis includes Seven studies from various countries, focusing on the prevalence and relationship of HLA-B27 in patients with different forms of arthritis and other rheumatological diseases utilizing methodologies such as

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cross-sectional studies, retrospective analyses, and prospective cohort studies. Detection methods for HLA-B27 varied, including serological techniques, PCR-SSP, and flow cytometry. A comprehensive literature search was done across databases like PubMed, Google Scholar, web of science and Scopus identified studies published between 1977 and 2022, with inclusion criteria requiring studies to report HLA-B27 prevalence in humans arthritis patients and other rheumatologic diseases, while excluding non-human studies, reviews, editorials, and those lacking sufficient methodological detail. This approach ensured the inclusion of high-quality research, allowing for a robust analysis of HLA-B27 prevalence across diverse populations and arthritis types and other rheumatic diseases. It highly important to note that some studies were published earlier but became online available recently in years and decade. For example, some studies of 1980 Sweden got online in 2009, help of ai taken for text generation with corrections.

## 3. Results

**Table 1** Summary of Studies on HLA-B27 Prevalence in different Countries.

| No. | Study | Country | HLA-B27 Prevalence | Methodology | Specific Findings |
|---|---|---|---|---|---|
| 1 | Żuber et al., 2015 | Poland | 27.2% in JIA patients | Cross-sectional study of 431 JIA. | Common in enthesitis-related arthritis (71%), older onset, higher resistance to DMARDs and corticosteroids. |
| 2 | Dequeker et al., | Belgium | 40% in seronegative RA, 5.6% in seropositive RA | Retrospective analysis of 246 arthritis patients using serological methods. | Significant association HLAB27 with seronegative arthropathies. |
| 3 | Villota et al., 2015 | Colombia | 4.5% in transplant patients | Cross-sectional study of 465 transplant recipients | Higher prevalence in males (6.5% vs. 2%), joint pain in 19% of HLA-B27 positive patients without autoimmune diseases. |
| 4 | Nasrallah et al., | Lebanon | 23% in seronegative peripheral arthritis | Prospective study of 109 patients | HLA-B27 prevalence in early-diagnosed patients with rheumatoid arthritis was 23% in the total group and 71% in those initially diagnosed as having rheumatoid arthritis. |
| 5 | Bjelle et al., | Sweden | 16.6% in blood donors | - | Higher frequency linked to a higher incidence of rheumatic diseases southern Sweden |
| 6 | Saraux et al., | France | 9.6% in RA patients | retrospectively from the standardized clinical records of 311 RA | No significant association between HLA-B27 and RA characteristics; not useful for RA diagnosis. |
| 7 | Tada et al., 2022 | Japan | 78% in ankylosing spondylitis patients | Multicentre study of 111 ankylosing spondylitis patients | HLA-B27-positive patients younger and diagnostic delay |

The summary of this metanalysis on HLA-B27 prevalence across various countries reveals diverse patterns of association between this genetic marker and different forms of arthritis, reflecting both geographic and methodological differences. “In Poland, Żuber et al. (2015) conducted a cross-sectional study involving 431 patients with Juvenile Idiopathic Arthritis (JIA). They found that HLA-B27 was present in 27.2% of the patients, with the highest prevalence in enthesitis-related arthritis (71%), psoriatic arthritis (50%), and unclassified cases (86.7%). The study also highlighted that HLA-B27 positive patients were slightly older at disease onset (11 years compared to 10 years for HLA-B27 negative patients, $p < 0.001$) and exhibited higher resistance to disease-modifying antirheumatic drugs (DMARDs) and corticosteroids (23.1% vs. 15.2%, $p = 0.09$). This suggests that HLA-B27 may contribute to a more challenging clinical course in JIA”[1]. “In Belgium, Dequeker et al. (1978) performed a retrospective analysis of 246 patients diagnosed

with various forms of arthritis. They discovered that HLA-B27 was prevalent in 40% of seronegative rheumatoid arthritis (RA) cases, compared to just 5.6% in seropositive RA cases. The study found a significant association between HLA-B27 and seronegative arthropathies, with HLA-B27-associated diseases manifesting earlier than seropositive RA. This highlights the potential role of HLA-B27 in the pathogenesis of seronegative forms of arthritis"[2]. In **Colombia**, Villota et al. (2015) conducted a cross-sectional study involving 465 transplant recipients, finding a relatively low HLA-B27 prevalence of 4.5%. However, the prevalence was higher among males (6.5% vs. 2% in females). Notably, O N 21 patients positive for HLA B 27 19% of HLA-B27 positive patients reported joint pain, although no autoimmune diseases were detected, suggesting that while HLA-B27 may be present in these populations, its clinical manifestations may be less pronounced.[3] In Lebanon, Nasrallah et al. (1977) performed a prospective cohort study involving 109 patients with seronegative peripheral arthritis. They found that 23% of these patients were HLA-B27 positive, with a higher prevalence (71%) among those diagnosed with rheumatoid arthritis compared to normal subjects (7%). The study also noted that the onset of B27-associated arthritis was concentrated in the 12-24 years age group, indicating that HLA-B27 may influence the age of onset and disease course in this population[4]. In Sweden, Bjelle et al. (1982) conducted a population-based study Northern Sweden, finding a 16.6% prevalence of HLA-B27. The study suggested that the higher frequency of HLA-B27 was associated with a higher incidence of rheumatic diseases in the region and pointed to a genetic link between the populations of Northern Sweden. This underscores the potential role of HLA-B27 as a genetic marker for susceptibility to rheumatic diseases in specific populations[5]. In France, Saraux et al. (1997) performed a multicenter study involving 311 patients with rheumatoid arthritis across the country. They found a 9.6% prevalence of HLA-B27 in RA patients but noted no significant association between HLA-B27 and the clinical, biological, or radiological characteristics of RA. The study concluded that HLA-B27 typing was not useful for RA diagnosis, suggesting that its role may be limited in this form of arthritis in the French population[6]. In Japan, Tada et al. (2022) conducted a multicenter study involving 111 patients with ankylosing spondylitis, discovering a high HLA-B27 prevalence of 78%. The study found that HLA-B27-positive patients were younger and diagnosed earlier, with a possible relationship between HLA-B27 and HLA-B48. This finding indicates a strong genetic predisposition for ankylosing spondylitis in Japanese patients associated with HLA-B27, highlighting its importance in the early diagnosis and management of the disease.[7]. Overall, these studies demonstrate the varying prevalence and impact of HLA-B27 across different populations and types of arthritis, emphasizing the importance of considering geographic and ethnic factors in the study of HLA-B27 and its associated diseases. The findings also suggest that while HLA-B27 is a significant marker for certain forms of arthritis, its clinical relevance may differ depending on the population and specific arthritis type under study.

## 4. Discussion

This meta-analysis reveals significant geographic and ethnic variations in the prevalence of HLA-B27 and its association with different forms of arthritis. The findings highlight that HLA-B27 prevalence varies considerably across regions, from as low as 4.5% in Colombia to as high as 78% in Japan among ankylosing spondylitis patients. This variation may be due to genetic differences and evolutionary patterns in different populations. For instance, Sweden shows a 16.6% prevalence, which is linked to a higher incidence of rheumatic diseases, suggesting a regional genetic predisposition.

In addition, the prevalence and clinical impact of HLA-B27 also show differences within specific populations. For example, in Poland, HLA-B27 was found in 27.2% of patients with Juvenile Idiopathic Arthritis (JIA), and was associated with a more challenging clinical course, including resistance to disease-modifying antirheumatic drugs (DMARDs) and corticosteroids. Conversely, in Belgium, a 40% prevalence of HLA-B27 in seronegative rheumatoid arthritis cases suggests a strong association with seronegative forms of arthritis, while its presence in seropositive rheumatoid arthritis cases was much lower (5.6%). The findings from Lebanon indicate that HLA-B27 is present in 23% of patients with seronegative peripheral arthritis and tends to influence the age of onset, with a higher prevalence among younger patients. In France, however, a 9.6% prevalence of HLA-B27 in rheumatoid arthritis patients did not show a significant clinical association, suggesting limited utility for HLA-B27 typing in this context.

### 4.1. Clinical Implications

The diverse prevalence, variation and impact of HLA-B27 across different regions and types of arthritis underscore the importance of considering geographic and ethnic factors in clinical practice. In populations with a high prevalence of HLA-B27, such as Japan and Northern Sweden, clinicians should be aware of the potential for HLA-B27-associated conditions, such as ankylosing spondylitis and other seronegative spondyloarthropathies, and consider early screening and diagnosis. For regions with lower prevalence, such as Colombia, the utility of HLA-B27 testing may be less pronounced, and other diagnostic criteria may need to be emphasized. The variations in clinical manifestations and treatment responses also suggest that personalized approaches to diagnosis and management should be adopted. For instance, in areas where HLA-B27 is commonly associated with resistance to DMARDs and corticosteroids, alternative treatment strategies may be required. Additionally, understanding the age of onset and disease severity in relation to

HLA-B27 status can help tailor more effective management plans. Overall, while HLA-B27 remains a significant marker for certain forms of arthritis, its clinical relevance is influenced by population-specific factors. Thus, healthcare providers should incorporate regional prevalence data and ethnic considerations into their diagnostic and treatment strategies to optimize patient care.

## 5. Conclusion

The findings underscore the necessity for region-specific diagnostic and management strategies for arthritis, considering the prevalence and role of HLA-B27. In areas with high HLA-B27 prevalence, such as Japan the marker may be integral to diagnosing and managing conditions like ankylosing spondylitis and reactive arthritis. However, in regions with lower prevalence, the utility of HLA-B27 in diagnosis might be limited. Future research should aim to further explore the mechanisms linking HLA-B27 with specific arthritis types and consider interactions with other genetic and environmental factors. This approach will enhance the understanding of HLA-B27's role in arthritis and inform more precise diagnostic and treatment strategies tailored to different populations.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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