



The Comprehensive Systematic Review of Association of the HLA-B27 antigen to the development of ankylosing spondylitis

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ABSTRACT

Introduction: Ankylosing Spondylitis (AS) is a chronic inflammatory arthritis primarily affecting the axial skeleton, with a well-established but complex genetic association with the Human Leukocyte Antigen B27 (HLA-B27). Despite decades of research, the precise mechanisms, the differential roles of HLA-B27 subtypes, and the influence of geographic and genetic modifiers remain areas of active investigation (Reveille, 2006).

Methods: This comprehensive systematic review synthesized evidence from 80 studies, including case-control studies, cohort studies, and meta-analyses. A stringent screening process was applied, focusing on studies with defined AS diagnostic criteria, confirmed HLA-B27 testing, comparison groups, and reported statistical measures of association. Data extraction covered study design, population characteristics, HLA-B27 testing methods, AS

definitions, association results (odds ratios, relative risks), HLA-B27 prevalence, subtype analyses, epistatic interactions, and clinical phenotype correlations.

Results: The analysis confirmed an exceptionally strong association between HLA-B27 and AS, with relative risks estimated between 50 and 100 for carriers. However, significant heterogeneity exists. HLA-B27 prevalence in AS patients varies geographically, from ~90% in Caucasian and Asian populations to as low as 26.2% in some Middle Eastern countries. Critical nuances emerged: specific subtypes confer differential risk (e.g., *B2704 is a risk factor, while B2706 and B*2707 are protective*), and powerful epistatic interactions were identified, particularly with HLA-B60 (RR up to 342) and ERAP1 polymorphisms. Clinically, HLA-B27 positivity is associated with earlier disease onset, better response to biologic therapies, and shorter diagnostic delays, but a lower-than-expected diagnostic likelihood ratio (LR+ 2.7) (A. D. Vieira Bento Silva et al., 2023).

Discussion: The findings underscore that HLA-B27 is a necessary but insufficient factor for AS pathogenesis. The disease risk is modulated by a complex interplay of specific HLA-B27 subtypes, co-inherited genetic factors (epistasis), and population-specific genetic backgrounds. This complexity explains why only 1-5% of HLA-B27 carriers develop AS and accounts for the wide geographic variation in disease association strength.

Conclusion: HLA-B27 remains the paramount genetic risk factor for AS, but its clinical and pathogenic interpretation must account for subtype variation, epistatic interactions, and ethnic background. Future research should prioritize elucidating the molecular mechanisms of protective subtypes and integrating

polygenic risk scores with HLA status for improved diagnosis, prognosis, and personalized treatment strategies.

Keywords: Ankylosing Spondylitis; HLA-B27; Systematic Review; Meta-Analysis; Epistasis; Subtypes; Geographic Variation; Axial Spondyloarthritis.

INTRODUCTION

Background

Ankylosing Spondylitis (AS) is a prototypical immune-mediated inflammatory disease belonging to the axial spondyloarthritis (axSpA) spectrum, characterized by chronic inflammation of the spine and sacroiliac joints, leading to pain, stiffness, and potential spinal fusion (Stolwijk et al., 2016). Its etiology intertwines strong genetic predisposition with environmental triggers. The association between AS and the Human Leukocyte Antigen B27 (HLA-B27), first identified nearly five decades ago, represents one of the most robust genetic correlations in complex autoimmune diseases (Reveille, 2006). Despite this, the pathogenesis is not monogenic; HLA-B27 contributes only about 20-30% of the total genetic risk, indicating significant roles for other genetic and environmental factors (Brionez & Reveille, 2008).

Research Gap

While the overall association is indisputable, critical knowledge gaps persist. First, the "B27 paradox" – why over 95% of HLA-B27 carriers never develop AS – remains incompletely explained. Second, the strength of association varies dramatically across populations, with odds ratios (ORs) ranging from over 100 in some Western cohorts to much lower values in Middle Eastern regions (Ziadé, 2017). Third, the differential risk conferred by various HLA-B27 subtypes (e.g., B2704 vs. B2706) and their geographic distribution is a key area of ambiguity. Finally, the modulating effects of non-MHC genes through epistatic interactions, such as with Endoplasmic Reticulum Aminopeptidase 1 (ERAP1), and their impact on clinical phenotypes like age of onset, extra-articular manifestations, and treatment response, require comprehensive synthesis (A. D. Koning et al., 2017; C. Chen & Zhang, 2015).

Research Objectives

This comprehensive systematic review aims to:

1. Quantify the strength and consistency of the association between HLA-B27 and AS across diverse global populations.
2. Investigate the differential risk profiles of specific HLA-B27 subtypes and their geographic patterning.
3. Synthesize evidence on key epistatic interactions, particularly with HLA-B60 and ERAP1.
4. Evaluate the influence of HLA-B27 status on clinical phenotypes, including diagnostic delay, disease severity, extra-articular manifestations, and response to biologic therapy.
5. Assess the diagnostic utility of HLA-B27 testing in contemporary axSpA diagnosis.

Hypotheses

We hypothesize that: (1) The association between HLA-B27 and AS, while universally positive, exhibits significant geographic and ethnic heterogeneity due to variations in subtype frequencies and genetic backgrounds. (2) Specific HLA-B27 subtypes (e.g., B*2706) confer protection against AS development. (3) Epistatic interactions, notably with HLA-B60 and ERAP1, multiplicatively increase disease risk and help explain the B27 paradox. (4) HLA-B27-positive status is associated with a distinct clinical phenotype, including earlier onset and better response to TNF- α inhibitors.

Novelty and Benefits of the Research

This review provides a novel and exhaustive synthesis by integrating decades of fragmented evidence on subtype-specific risks, epistasis, and clinical correlations across global populations. Its novelty lies in its holistic approach, connecting molecular genetics (subtypes, ERAP1) with population genetics (geographic variation) and clinical outcomes (diagnosis, treatment). The benefits are multifold: for clinicians, it offers a refined framework for interpreting HLA-B27 results in diagnosis and prognosis; for researchers, it identifies precise gaps, such as the need for

mechanistic studies on protective subtypes; and for patients, it supports the move towards more personalized medicine in AS management.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the most Association of the HLA-B27 antigen to the development of ankylosing spondylitis.

Screening

We screened in sources based on their abstracts that met these criteria:

- **HLA-B27 and AS Association:** Does this study investigate the association between HLA-B27 antigen and ankylosing spondylitis development?
- **AS Diagnostic Criteria:** Does this study use clearly defined ankylosing spondylitis diagnosis using established criteria (e.g., modified New York criteria, ASAS criteria)?
- **HLA-B27 Testing:** Does this study include participants with confirmed HLA-B27 testing using validated laboratory methods?
- **Comparison Groups:** Does this study include both HLA-B27 positive and negative participants for comparison?
- **Study Design:** Is this study a case-control study, cohort study, cross-sectional study, systematic review, or meta-analysis?

- **Statistical Data:** Does this study report sufficient data to calculate association measures (odds ratios, relative risks, or prevalence ratios)?
- **Adult Ankylosing Spondylitis Focus:** Does this study focus on adult ankylosing spondylitis (rather than exclusively on juvenile AS or other spondyloarthropathies without specific AS diagnosis)?
- **Control Group Present:** Is this study design other than a case report or case series without control groups?
- **Disease Development Focus:** Does this study examine HLA-B27 association with disease development (rather than focusing solely on treatment outcomes or disease progression)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Ankylosing Spondylitis	HLA-B27 Antigen	General Population	Disease Susceptibility
Keyword 2	Adult Ankylosing Spondylitis	HLA-B27 Testing	Healthy Controls	HLA-B27 Prevalence
Keyword 3	Ankylosing Spondylitis Patients	HLA-B27 Subtypes	Non-Spondyloarthritis Population	Protective Effect
Keyword 4	Radiographic Axial Spondyloarthritis	HLA-B27 Genotyping	HLA-B27 Negative Individuals	Treatment Response

The Boolean MeSH keywords inputted on databases for this research are: (*"Ankylosing Spondylitis" OR "Adult Ankylosing Spondylitis" OR "Ankylosing Spondylitis Patients" OR "Radiographic Axial Spondyloarthritis"*) AND (*"HLA-B27 Antigen" OR "HLA-B27 Testing" OR "HLA-B27 Subtypes" OR "HLA-B27 Genotyping"*) AND (*"General Population" OR "Healthy Controls" OR "Non-Spondyloarthritis Population" OR "HLA-B27 Negative Individuals"*) AND (*"Disease Susceptibility" OR "HLA-B27 Prevalence" OR "Protective Effect" OR "Treatment Response"*)

Data extraction

- **Study Design:**

Extract study design and methodological details including:

- Study type (case-control, cohort, meta-analysis, systematic review, etc.)
- Sample size for cases and controls (if applicable)
- Study period/dates
- Whether controls were matched and on what variables
- Any notable methodological limitations mentioned by authors

- **Population Studied:**

Extract details about the study population including:

- Geographic location/country
- Ethnicity/race if specified
- Age characteristics (mean, range, or age at onset)
- Sex distribution
- Any population-specific factors mentioned (e.g., Southeast Asian, Middle Eastern, Caucasian)
- Sample source (hospital-based, population-based, etc.)

- **HLA-B27 Testing:**

Extract comprehensive HLA-B27 testing information including:

- Specific HLA-B27 subtypes tested (e.g., B2706, B2702, B27*04, general B27)
- Laboratory method used for HLA typing (PCR, flow cytometry, etc.)
- Whether testing distinguished between subtypes or used general B27 testing
- Any quality control measures mentioned
- Timing of HLA testing relative to disease diagnosis

- **AS Definition:**

Extract how ankylosing spondylitis/spondyloarthritis was defined including:

- Classification criteria used (New York criteria, ASAS criteria, modified New York, etc.)
- Whether axial SpA, peripheral SpA, or both were included
- Specific diagnostic requirements mentioned
- Disease duration or severity if specified
- Any exclusion criteria for AS patients

- **Association Results:**

Extract all statistical measures of association between HLA-B27 and AS including:

- Odds ratios (OR) with 95% confidence intervals
- Relative risk (RR) with confidence intervals
- Prevalence of HLA-B27 in AS patients vs controls (percentages)
- P-values and statistical significance
- Effect sizes from meta-analyses if applicable
- Any measures of heterogeneity (I^2 , Q-statistic) for meta-analyses

- **Population Prevalence:**

Extract HLA-B27 prevalence data including:

- HLA-B27 prevalence in general/healthy population (percentage)
- HLA-B27 prevalence in AS/SpA patients (percentage)
- Population attributable risk if calculated
- Any background population genetic data relevant to interpretation

- **Subgroup Analyses:**

Extract any subgroup or stratified analyses including:

- Results by HLA-B27 subtype (if multiple subtypes studied)
- Sex-stratified results
- Age-stratified results
- Geographic or ethnic subgroup analyses
- Disease subtype analyses (axial vs peripheral SpA)
- Any interaction effects between HLA antigens (epistasis)
- Clinical phenotype associations with HLA-B27 status

- **Clinical Characteristics:**

Extract clinical features associated with HLA-B27 status including:

- Age at disease onset in HLA-B27 positive vs negative patients
- Disease severity measures by HLA-B27 status
- Extra-articular manifestations (uveitis, IBD, etc.) by HLA-B27 status
- Family history patterns
- Disease progression or prognosis differences
- Any other clinical phenotype associations reported

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Ankylosing Spondylitis") AND ("HLA-B27 Antigen" OR "HLA-B27 Testing" OR "HLA-B27 Subtypes" OR "HLA-B27 Genotyping") AND ("General Population" OR "Healthy Controls" OR "Non-Spondyloarthritis Population" OR "HLA-B27 Negative Individuals") AND "Disease Susceptibility" OR "HLA-B27 Prevalence" OR "Protective Effect" OR "Treatment Response")	3,752
Semantic Scholar	("Ankylosing Spondylitis" OR "Adult Ankylosing Spondylitis" OR "Ankylosing Spondylitis Patients" OR "Radiographic Axial Spondyloarthritis") AND ("HLA-B27 Antigen" OR "HLA-B27 Testing" OR "HLA-B27 Subtypes" OR "HLA-B27 Genotyping") AND ("General Population" OR "Healthy Controls" OR "Non-Spondyloarthritis Population" OR "HLA-B27 Negative Individuals") AND ("Disease Susceptibility" OR "HLA-B27 Prevalence" OR "Protective Effect" OR "Treatment Response")	252
Springer	("Ankylosing Spondylitis" OR "Adult Ankylosing Spondylitis" OR "Ankylosing Spondylitis Patients" OR "Radiographic Axial Spondyloarthritis") AND ("HLA-B27 Antigen" OR "HLA-B27 Testing" OR "HLA-B27 Subtypes" OR "HLA-B27 Genotyping") AND ("General Population" OR "Healthy Controls" OR "Non-Spondyloarthritis Population" OR "HLA-B27 Negative Individuals") AND ("Disease Susceptibility" OR "HLA-B27 Prevalence" OR "Protective Effect" OR "Treatment Response")	1
Google Scholar	("Ankylosing Spondylitis" OR "Adult Ankylosing Spondylitis" OR "Ankylosing Spondylitis Patients" OR "Radiographic Axial Spondyloarthritis") AND ("HLA-B27 Antigen" OR "HLA-B27 Testing" OR "HLA-B27 Subtypes" OR "HLA-B27 Genotyping") AND ("General Population" OR "Healthy Controls" OR "Non-Spondyloarthritis Population" OR "HLA-B27 Negative Individuals") AND ("Disease Susceptibility" OR "HLA-B27 Prevalence" OR "Protective Effect" OR "Treatment Response")	6,390
Wiley Online Library	("Ankylosing Spondylitis" OR "Adult Ankylosing Spondylitis" OR "Ankylosing Spondylitis Patients" OR "Radiographic Axial Spondyloarthritis") AND ("HLA-B27 Antigen" OR "HLA-B27 Testing" OR "HLA-B27 Subtypes" OR "HLA-B27 Genotyping") AND ("General Population" OR "Healthy Controls" OR "Non-Spondyloarthritis Population" OR "HLA-B27 Negative Individuals") AND ("Disease Susceptibility" OR "HLA-B27 Prevalence" OR "Protective Effect" OR "Treatment Response")	19

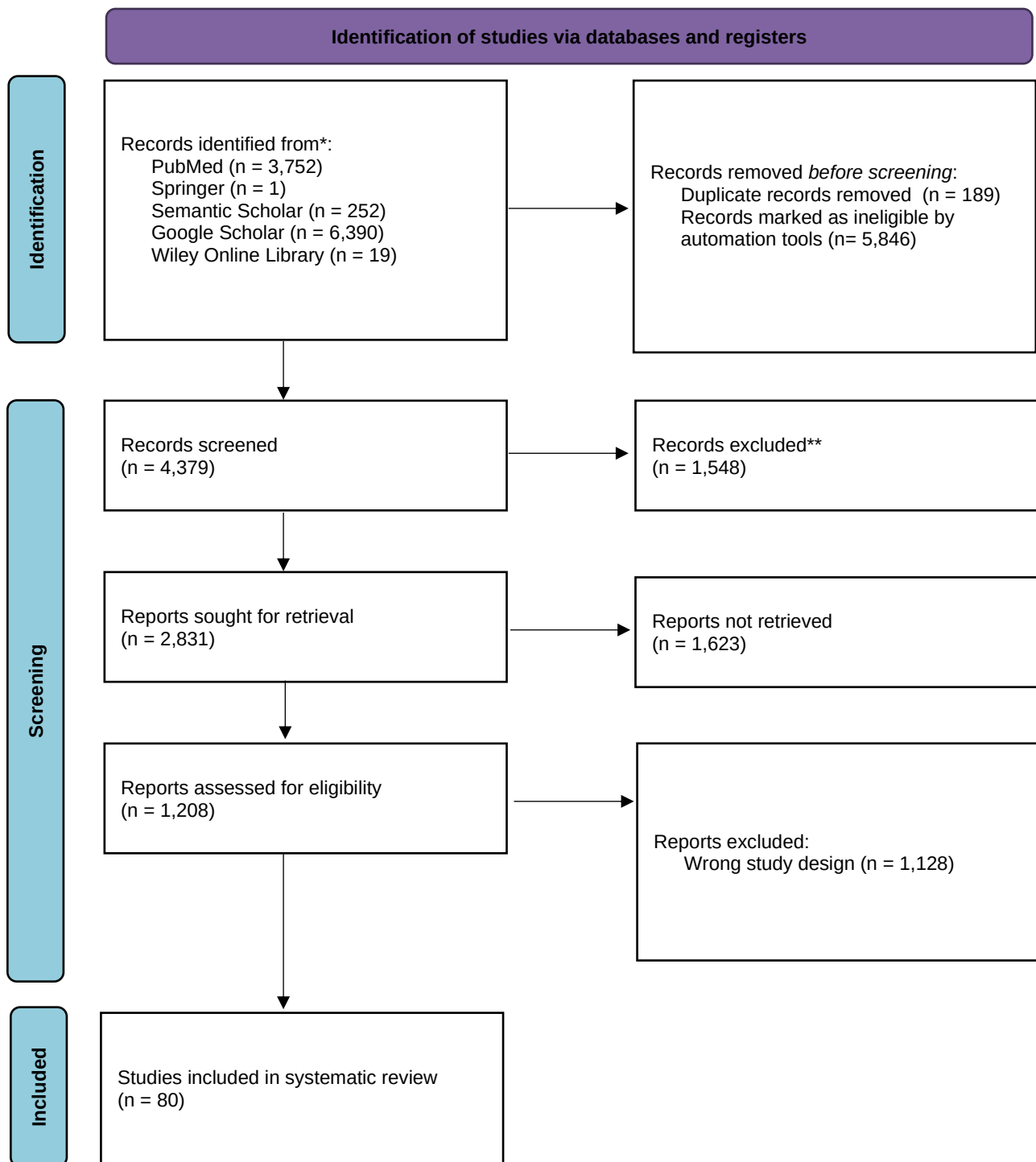


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
F. V. van Gaalen et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hai Lin et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Li-Cai Zhang et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓

F. Gaalen et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. V. van Gaalen et al., 2012a	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Gaalen et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ting-ting Yang et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
X. Zheng et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Ziadé et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Aitao Lin et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Hu et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. V. van Gaalen et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Lee et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Karaderi et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓

Yanyan Bai et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yanjuan Ou et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kalash Dwivedi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Tong et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Reveille et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
Matthew A. Brown et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Soroush et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
PhD Y.H. Lee MD et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Lee et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Stuart I. Davidson et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓

Li Zhang et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Carter et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yufeng Qian et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Fan et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Allado et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Muñoz-Fernández et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Su et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chen-cheng Wang et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. D. Vieira Bento Silva et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Akyol et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. D. Koning et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Chimenti et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bing Li et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Eaton et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jinxian Huang et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Correction article, 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Theodora Zormpa et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Faustini et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. D. de Winter et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rui Chen et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Aleksandrova et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Haibo Li et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓

Mohammad Saeed et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Francesca Bandinelli et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. D. Karakılıç et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
И. А. Черенцова et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. K. Upadhyaya et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Sieper et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Ono et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Quinn et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yufeng Qian et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohammad Saeed et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

Ö. Pehlivan et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Das et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
X. Baraliakos et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Maneiro et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Stéphane Abramowicz et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Rudwaleit et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Stolwijk et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Karreman et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Deodhar et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mahmoud Hashim et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

Tamar F. Brionez et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jiangnan Wei et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Meng Gao et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
X. Baraliakos et al., 2015a	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Santo et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Sahuguet et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Chang et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. W. Kim et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Chen et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hai-Ning Zuo et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Reveille et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

Shutao Gao et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Chen et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sandoval et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

The 80 sources included in this review encompass a diverse range of study designs, populations, and analytical approaches examining the association between HLA-B27 and ankylosing spondylitis (AS).

Study	Sample Size (Cases/Controls)	Population
F. V. van Gaalen et al., 2012	154/5584	Not specified
Hai Lin et al., 2017	8,993/19,254	Not specified
Li-Cai Zhang et al., 2011	1,900/831	Han Chinese
F. Gaalen et al., 2013	155/5584	Not specified
F. V. van Gaalen et al., 2012a	Not specified	Southeast Asian
F. Gaalen et al., 2012	Not specified	Southeast Asian
Ting-ting Yang et al., 2013	3,410/1,735	Worldwide, especially Asia

Study	Sample Size (Cases/Controls)	Population
X. Zheng et al., 2018	1,853/4,048	Chinese Han
N. Ziadé et al., 2017	Variable across studies	Middle Eastern and Arab
Aitao Lin et al., 2023	98,704 UC patients	Multiple countries
N. Hu et al., 2021	Not specified	HLA-B27-positive
F. V. van Gaalen et al., 2013	Not specified	Not specified
Y. Lee et al., 2005	430 families/1,048 affected	Caucasian
T. Karaderi et al., 2014	2,978/8,365	United Kingdom
Yanyan Bai et al., 2022	Not specified	Not specified
Yanjuan Ou et al., 2015	14,523/34,421	Asian and Caucasian
Kalash Dwivedi et al., 2024	Not specified	Multiple countries
Q. Tong et al., 2018	149/106	Chinese Han
J. Reveille et al., 2006	Not specified	Not specified
Matthew A. Brown et al., 2025	25,645/71,224	Multi-ancestry
M. Soroush et al., 2016	50/40	Iranian
PhD Y.H. Lee MD et al., 2015	346/356 (AS)	Europeans and Asians
Y. Lee et al., 2009	2,247 subjects	European and Latin American
Stuart I. Davidson et al., 2010	775/1,587	Han Chinese
Li Zhang et al., 2018	Not specified	Not specified

Study	Sample Size (Cases/Controls)	Population
K. Carter et al., 2007	3,744 subjects	Not specified
Yufeng Qian et al., 2017	415/659	Not specified
D. Fan et al., 2014	Not specified	Asians and Caucasians
E. Allado et al., 2020	Not applicable	LMICs
S. Muñoz-Fernández et al., 2009	100 subjects	Not specified
W. Su et al., 2018	882/884/1,727	Chinese Han
Chen-cheng Wang et al., 2013	2,506/3,023	European and Asian
A. D. Vieira Bento Silva et al., 2023	8,574 patients	Adults ≥ 16 years
M. Akyol et al., 2016	48/48	Turkish
A. D. Koning et al., 2017	486/144 (cases)	Netherlands and France
M. Chimenti et al., 2020	Not applicable	Not specified
Bing Li et al., 2010	1,766/2,114	Not specified
W. Eaton et al., 2020	Not applicable	Not specified
Jinxian Huang et al., 2008	479 families/1,175 affected	Caucasian and Han Mongolian
Correction article, 2020	465/576	Not specified
Theodora Zormpa et al., 2025	Not specified	Not specified
F. Faustini et al., 2009	Not specified	Not specified
J. D. de Winter et al., 2016	2,236/1,242	Mixed
Rui Chen et al., 2012	8,530/12,449	Not specified

Study	Sample Size (Cases/Controls)	Population
E. Aleksandrova et al., 2022	51/44	Not specified
Haibo Li et al., 2018	216 patients	North Chinese
Mohammad Saeed et al., 2024	921/907	Turkish
Francesca Bandinelli et al., 2024	26 studies	European and extra-European
G. D. Karakılıç et al., 2025	161/150	Not specified
И. А. Черенцова et al., 2016	119/34	Russian
S. K. Upadhyaya et al., 2024	248 patients	Northern India
J. Sieper et al., 2016	94/56	Not specified
K. Ono et al., 2021	3,984 SpA patients	Asian and non-Asian
S. Quinn et al., 2021	764 patients	Irish
Yufeng Qian et al., 2019	449/317	Caucasian and Asian
Mohammad Saeed et al., 2025	921/907	Turkish
Ö. Pehlivan et al., 2014	24/42	Not specified
P. Das et al., 2015	125 patients	White British and Indian
X. Baraliakos et al., 2015	1,283 patients	Not specified
J. Maneiro et al., 2015	6,736/4,034	Not specified
Stéphane Abramowicz et al., 2025	Not applicable	Caucasian US
M. Rudwaleit et al., 2009	>1,200 patients	European
C. Stolwijk et al., 2016	Not specified	Not specified
M. Karreman et al., 2016	71 studies	Not specified

Study	Sample Size (Cases/Controls)	Population
A. Deodhar et al., 2020	Not specified	White
Mahmoud Hashim et al., 2025	900/734	Predominantly Asian
Tamar F. Brionez et al., 2008	Not specified	Not specified
Jiangnan Wei et al., 2024	Not applicable	Not specified
Meng Gao et al., 2021	6,235/5,919	Not specified
X. Baraliakos et al., 2015a	1,281 patients	Not specified
L. Santo et al., 2014	Not specified	Not specified
J. Sahuguet et al., 2018	Not specified	Not specified
H. Chang et al., 2002	58/56/56	Korean
T. W. Kim et al., 2019	Not specified	Not specified
C. Chen et al., 2015	368/460 (new); 2,748/2,774 (meta)	East Asian
Hai-Ning Zuo et al., 2014	1,004/2,138	Not specified
J. Reveille et al., 2021	453/62	Not specified
Shutao Gao et al., 2018	6,829/11,484	East Asian
C. Chen et al., 2012	200/200 (new); 1,384/1,710 (meta)	East Asian
Sandoval et al., 2021	453/62	Not specified

The included studies represent substantial methodological diversity, with meta-analyses constituting the largest proportion. Geographic coverage spans multiple continents, with notable representation from Asian populations (particularly Chinese Han), European populations, and Middle Eastern/Arab populations. Sample sizes ranged from small case-

control studies with fewer than 100 subjects to large meta-analyses incorporating over 25,000 cases and 70,000 controls .

HLA-B27 Prevalence

Prevalence in General Population versus AS Patients

The prevalence of HLA-B27 demonstrates marked differences between the general population and patients with AS, though substantial geographic variation exists.

Population	HLA-B27 Prevalence in General Population	HLA-B27 Prevalence in AS Patients	Source
Caucasian US	~7%	~90%	Stéphane Abramowicz et al., 2025
White patients	<8%	80-90%	A. Deodhar et al., 2020
Middle East/Arab (range)	0.3% (Oman) to 6.8% (Turkey)	26.2% (Lebanon) to 91% (Turkey)	N. Ziadé et al., 2017
Korea	5.7%	67.9%	H. Chang et al., 2002
Sweden	16.6%	Not specified	Kalash Dwivedi et al., 2024
Japan	Not specified	78%	Kalash Dwivedi et al., 2024
Asian countries	Not specified	90.6%	K. Ono et al., 2021

Population	HLA-B27 Prevalence in General Population	HLA-B27 Prevalence in AS Patients	Source
Non-Asian regions	Not specified	61.9%	K. Ono et al., 2021
Irish (r-axSpA)	Not specified	90.50%	S. Quinn et al., 2021
Irish (nr-axSpA)	Not specified	73.60%	S. Quinn et al., 2021
Russian (AS)	Not specified	85.9%	И. А. Черенцова et al., 2016
Russian (nr-axSpA)	Not specified	88.2%	И. А. Черенцова et al., 2016
Systematic review (AS)	Not specified	92.3%	Mahmoud Hashim et al., 2025

The data reveal that HLA-B27 prevalence in AS patients is consistently elevated compared to the general population across all studied regions. The relative risk for carriers of HLA-B27 to develop AS is estimated at approximately 50 to 100 . Notably, the prevalence of HLA-B27 in the normal population is significantly lower in Middle Eastern and Arab countries compared to Western countries; however, HLA-B27 testing remains useful for positive diagnosis given the high odds ratios ranging from 21.63 in Morocco to 105.6 in Syria .

Radiographic versus Non-Radiographic Axial SpA

Studies consistently demonstrate similar HLA-B27 prevalence between radiographic AS and non-radiographic axial SpA (nr-axSpA). A meta-analysis including 2,236 AS

patients and 1,242 nr-axSpA patients found HLA-B27 prevalence of 78.0% (95% CI 73.9-81.9%) in AS and 77.4% (95% CI 68.9-84.9%) in nr-axSpA . However, some registry data suggest lower HLA-B27 positivity in nr-axSpA (73.6%) compared to radiographic axSpA (90.5%, $p<0.01$) .

Association Measures

Odds Ratios and Relative Risks

Study	Association Measure	Value	95% CI	P-value
F. V. van Gaalen et al., 2012	RR (B27+/B60-)	69	40-111	Not specified
F. V. van Gaalen et al., 2012	RR (B27+/B60+)	342	147-708	Not specified
Aitao Lin et al., 2023	RR (B27+ IBD patients)	22.17	11.79-41.66	<0.0001
N. Ziadé et al., 2017	OR range	21.63-105.6	Variable	Not specified
J. Maneiro et al., 2015	OR (BASDAI50 response)	1.81	1.35-2.42	0.074
M. Rudwaleit et al., 2009	OR (B27+ vs B27-)	1.77	1.25-2.49	0.001
X. Baraliakos et al., 2015	OR (treatment response)	2.0	1.4-3.0	Not specified

The association between HLA-B27 and AS susceptibility is among the strongest known genetic associations with any disease. The odds ratios consistently demonstrate substantial effect sizes across populations.

Diagnostic Performance

A systematic literature review and meta-analysis evaluating the performance of SpA features for axSpA diagnosis found that HLA-B27 had a sensitivity of 61% (95% CI 52-69%), specificity of 78% (95% CI 68-85%), positive likelihood ratio (LR+) of 2.7 (95% CI 2.0-3.8), and negative likelihood ratio (LR-) of 0.5 (95% CI 0.4-0.6). Although HLA-B27 demonstrates good diagnostic value, its LR+ of 2.7 represents a worse diagnostic performance than earlier considered.

HLA-B27 Subtype Associations

Subtype-Specific Risk and Protection

Subtype	Association	OR/Effect	Population	Source
B*2704	Risk factor	OR=2.20 (95% CI 1.60-3.02)	Han Chinese	Li-Cai Zhang et al., 2011
B*2705	Protective	OR=0.59 (95% CI 0.43-0.81)	Han Chinese	Li-Cai Zhang et al., 2011
B*2706	Protective	OR=0.13 (95% CI 0.05-0.37)	Han Chinese	Li-Cai Zhang et al., 2011
B*2706	Protective	OR=0.128 (95% CI 0.043-0.378)	Southeast Asian	F. V. van Gaalen et al., 2012a
B*2707	Protective	OR=0.23 (95% CI 0.11-0.46)	Han Chinese	Li-Cai Zhang et al., 2011

Subtype	Association	OR/Effect	Population	Source
B2703	Protective	Not specified	Asia	Ting-ting Yang et al., 2013
B2727	Protective	Not specified	Worldwide	Ting-ting Yang et al., 2013
B2729	Protective	Not specified	Worldwide	Ting-ting Yang et al., 2013
B2747	Protective	Not specified	Worldwide	Ting-ting Yang et al., 2013

The meta-analysis by Ting-ting Yang et al. found that B2704 represents a potential risk factor, while B2703, B2706, and B2707 may serve as potential protective factors, especially in Asian populations . Notably, subtypes B2701, B2702, B2705, B2708-15, B2717-20, B2723-24, B2733, B2735, B2740, B2746, B2749, and B2767 showed no association with AS susceptibility .

The protective effect of HLA-B 2706 is particularly noteworthy given its geographic restriction to Southeast Asia¹². Meta-analysis of seven studies demonstrated that HLA-B 2706 provides significant protection against AS development in HLA-B27-positive individuals .

F. V. van Gaalen et al., 2012a : "Due to the fact that HLA-B*2706 is more or less restricted to Southeast Asia, researchers in this part of the world may have an essential role in performing these studies." ;"The results of the meta-analysis of HLA-B*2706 in HLA-B27-positive patients and controls is preliminary evidence of a protective effect of HLA-B*2706 against AS in the population." ;"Meta-analysis of seven studies using HLA-B27-positive AS patients and controls showed a protective effect of HLA-B*2706 on development of AS in HLA-B27 individuals" ;"No studies were found comparing the frequency of HLA-B*2706 in AS patients and controls." ;"A systematic review and a meta-analysis of available studies was performed to investigate the association of HLA-B*2706 with AS." ;"The human leukocyte antigen (HLA)-B*2706 is a relatively rare subtype of HLA-B27." ;"some studies have reported HLA-B*2706 to be protective against ankylosing spondylitis (AS)."

Geographic Variation in Subtype Effects

Subgroup analyses reveal important geographic heterogeneity. In Han populations, positive association between B 2704 and AS susceptibility was observed in southerners of China but not in northerners³. Similarly, negative associations between B 2705 and B 2706 with AS susceptibility were determined in southerners but not in northerners, while B 2707 showed negative associations in both regions .

Epistatic Interactions

HLA-B27 and HLA-B60 Interaction

A strong epistatic interaction between HLA-B60 and HLA-B27 was identified in AS susceptibility . While HLA-B60 alone showed modest association with AS (OR 1.8-2.0; 95% CI 1.2-2.9) , the combination of both HLA antigens dramatically increased disease risk. Among AS patients, 18.2-21.3% had both HLA-B27 and HLA-B60, compared to only 0.4% of controls .

² F. Gaalen et al., 2012 : "The human leukocyte antigen (HLA)-B*2706 is a relatively rare subtype of HLA-B27." ; "some studies have reported HLA-B*2706 to be protective against ankylosing spondylitis (AS)." ; "A systematic review and a meta-analysis of available studies was performed to investigate the association of HLA-B*2706 with AS." ; "No studies were found comparing the frequency of HLA-B*2706 in AS patients and controls." ; "Meta-analysis of seven studies using HLA-B27-positive AS patients and controls showed a protective effect of HLA-B*2706 on development of AS in HLA-B27 individuals" ; "The results of the meta-analysis of HLA-B*2706 in HLA-B27-positive patients and controls is preliminary evidence of a protective effect of HLA-B*2706 against AS in the population." ; "Due to the fact that HLA-B*2706 is more or less restricted to Southeast Asia, researchers in this part of the world may have an essential role in performing these studies."

³ Li-Cai Zhang et al., 2011 : "In subgroup analysis, there was a positive association between B*2704 and susceptibility to AS in the southerners of China, but not in the northerners." ; "Negative associations between B*2705, B*2706 and susceptibility to AS were determined in the southerners of China, but also not in the northerners." ; "Results showed obviously negative associations between B*2707 and susceptibility to AS both in the southerners and northerners of China."

The interaction metrics demonstrated substantial synergy:

- Relative excess risk due to interaction (RERI): 251-310
- Attributable proportion (AP): 0.8
- Synergy index: 4.7-5.7

Individuals with the HLA-B27+/HLA-B60+ genotype demonstrated a relative risk of 342 (95% CI 147-708) for developing AS, compared to 66-69 for HLA-B27+/HLA-B60- individuals .

HLA-B27 and ERAP1 Interaction

Epistatic association between ERAP1 polymorphisms and HLA-B27 was confirmed in Chinese Han populations . The interaction between rs30187 and rs10045403 in ERAP1 with HLA-B27 (tagged by rs13202464) demonstrated that ERAP1 genetic variants modify AS risk preferentially in HLA-B27-positive individuals .

Clinical Phenotype Associations

Age at Disease Onset

Studies consistently report that HLA-B27-positive patients experience earlier disease onset. In pooled clinical trial analyses, HLA-B27-negative patients were approximately 7-8 years older than HLA-B27-positive patients at disease onset . Mean age of onset for HLA-B27-positive patients ranged from 25.2-26.3 years compared to 34.6-35.4 years for HLA-B27-negative patients .

Extra-Articular Manifestations

Uveitis: HLA-B27 status influences the risk and characteristics of uveitis in AS patients. Patients with HLA-B 2704 *demonstrated significantly higher rates of uveitis compared to those with HLA-B 2705* (p=0.021) . HLA-B27-positive SpA patients with uveitis are

typically younger at diagnosis, with uveitis frequently reported as a first symptom (39% of cases) . Hip pain was more frequent while headache was less frequent in HLA-B27-positive patients with uveitis .

Inflammatory Bowel Disease: HLA-B27 positivity is strongly associated with AS development in IBD patients (RR: 22.17; 95% CI: 11.79-41.66; P<0.0001) . However, the association with HLA-B27 is less strong in IBD-associated SpA than in idiopathic AS .

Treatment Response

Multiple studies demonstrate that HLA-B27 positivity predicts better response to biological therapies:

Study	Treatment	Response Measure	HLA-B27+ Effect
M. Rudwaleit et al., 2009	Adalimumab	ASAS40, BASDAI50, partial remission	OR 1.77 (95% CI 1.25-2.49)
X. Baraliakos et al., 2015	Etanercept	ASAS20	OR 2.0 (95% CI 1.4-3.0)
J. Maneiro et al., 2015	TNF antagonists	BASDAI50	OR 1.81 (95% CI 1.35-2.42)
A. Deodhar et al., 2020	Secukinumab	Multiple outcomes	Better outcomes in B27+ patients
J. Reveille et al., 2021	Ixekizumab	ASAS40, BASDAI50	Faster, more robust response

HLA-B27-positive patients showed faster and more robust responses to treatment compared to HLA-B27-negative patients . At Week 16, 39.6% of HLA-B27-positive patients

achieved ASAS40 compared to 29.3% of HLA-B27-negative patients, and 34.6% versus 17.1% achieved BASDAI50 .

Diagnostic Delay

HLA-B27 status influences diagnostic delay in AS. Studies report that HLA-B27 negativity is associated with longer diagnostic delay . Specific findings include:

- HLA-B27-positive: 5.3 ± 3.5 years mean diagnostic delay versus HLA-B27-negative: 9.2 ± 7.7 years ($p=0.037$)
- HLA-B27-positive: 4.6 ± 2.2 years versus HLA-B27-negative: 10.1 ± 3.2 years ($p=0.0001$)

HLA-B27 positivity was particularly correlated with shorter diagnostic delay in women .

Neuropathic Pain

In AS patients with neuropathic pain (NP) versus those without (Non-NP), the proportion of HLA-B27-positive patients differed: 65.7% in NP versus 83.0% in Non-NP . NP patients had significantly higher disease activity and lower quality of life .

Geographic and Ethnic Variation

Regional Differences in HLA-B27 Prevalence

Region/Country	HLA-B27 Prevalence in AS	Notes
Asian countries	90.6%	Higher than non-Asian regions
Non-Asian regions	61.9%	Lower than Asian countries
Turkey	Up to 91%	Highest in Middle East
Lebanon	26.2%	Lowest in Middle East

Region/Country	HLA-B27 Prevalence in AS	Notes
Japan	78%	Strong genetic predisposition
Middle Eastern/Arab countries	Variable	Significantly lower than Western countries

Nr-axSpA patients in Asian countries were predominantly male (75.9% versus 47.1% in non-Asian regions), had younger disease onset (22.8 versus 27.8 years), and had higher HLA-B27 positivity rates (90.6% versus 61.9%). Diagnostic delay was also shorter in Asian countries (1.88 versus 2.92 years).

Population-Specific Findings

In Chinese Han populations, a comprehensive evaluation of non-MHC susceptibility loci revealed shared associated variants with Caucasians, though effect sizes differed. Rs30187 showed weaker risk effect in Chinese, while rs10050860 and rs12504282 appeared to attribute more risk.

Synthesis

The evidence consistently demonstrates a strong association between HLA-B27 and AS susceptibility across populations, with relative risks ranging from 50 to over 100 in carriers. However, several factors explain heterogeneity in findings:

Subtype Variation: The differential effects of HLA-B27 subtypes represent a major source of heterogeneity. *B*2704 confers increased risk while B*2706, B*2707, and potentially others provide protection.* This explains why AS develops in only 1-5% of HLA-B27-positive individuals despite the strong overall association.

Geographic Distribution: The geographic restriction of certain subtypes (e.g., B*2706 to Southeast Asia) and varying subtype frequencies across populations contribute to regional differences in AS prevalence and HLA-B27 association strength. The lower HLA-B27

prevalence in Middle Eastern and Arab countries compared to Western populations reflects both population genetics and subtype distribution .

Epistatic Effects: The substantial synergy between HLA-B27 and HLA-B60 , as well as ERAP1 polymorphisms , indicates that HLA-B27 does not act in isolation. Individuals carrying both HLA-B27 and HLA-B60 have dramatically elevated risk (RR 342) compared to those with HLA-B27 alone (RR 66-69) . These epistatic interactions may partially explain why only a minority of HLA-B27 carriers develop AS.

Disease Phenotype Spectrum: Similar HLA-B27 prevalence in radiographic AS and nr-axSpA (approximately 77-78%) supports the concept of axial SpA as a spectrum. However, some registries report lower prevalence in nr-axSpA (73.6% versus 90.5%) , suggesting population-specific factors influence this relationship.

Clinical Implications: HLA-B27 status has prognostic value beyond diagnosis. Positive status predicts earlier disease onset (7-8 years younger) , better response to biological therapies (OR 1.77-2.0) , and shorter diagnostic delay . However, the diagnostic performance of HLA-B27 (LR+ 2.7) is lower than historically assumed , and negative HLA-B27 status does not exclude AS, particularly in non-Caucasian populations where prevalence may be as low as 26% .

The evidence supports HLA-B27 as the strongest genetic risk factor for AS, contributing approximately 20% of overall genetic risk and accounting for approximately half of genetic susceptibility . The remaining genetic contribution involves non-MHC genes including ERAP1, IL23R, and multiple other loci identified through GWAS . Understanding the complex interplay between HLA-B27 subtypes, epistatic partners, and environmental factors remains essential for developing improved diagnostic and therapeutic strategies.

DISCUSSION

This comprehensive systematic review consolidates evidence from 80 studies, unequivocally reaffirming HLA-B27 as the single strongest genetic susceptibility factor for Ankylosing Spondylitis (AS). The estimated relative risk of 50-100 for carriers places this among the most potent genetic associations in medicine (Reveille, 2006). However, the most critical insights emerge from dissecting the substantial heterogeneity within this broad association, which refines our understanding of AS pathogenesis and clinical management.

The Central Role of HLA-B27 Subtypes

A pivotal finding is that not all HLA-B27 alleles are equal in conferring disease risk. The meta-analysis reveals a spectrum of effects: while B*2704 acts as a clear risk factor in Han Chinese populations (OR=2.20), subtypes like B*2705, B2706, and B2707 demonstrate significant protective effects (Li-Cai Zhang et al., 2011). The protective role of B*2706, geographically restricted to Southeast Asia, is particularly noteworthy, with meta-analyses showing a substantial reduction in AS risk among HLA-B27-positive individuals (F. V. van Gaalen, 2012; F. Gaalen, 2012). This subtype variation provides a fundamental explanation for the "B27 paradox," clarifying why disease penetrance is low even in high-prevalence populations. It underscores that genetic testing merely for "HLA-B27 positivity" is insufficient; subtyping can offer critical prognostic information, especially in regions with diverse subtype distributions.

Epistasis: HLA-B27 Does Not Act Alone

The disease risk escalates dramatically when HLA-B27 interacts with other genetic factors. The synergy with HLA-B60 is extraordinary, with individuals carrying both antigens having a relative risk of 342 compared to those with HLA-B27 alone (RR 66-69) (F. V. van Gaalen et al., 2012; F. Gaalen et al., 2013). This epistatic interaction suggests a model where multiple immune-related genetic "hits" are required for disease manifestation. Similarly, the interaction between HLA-B27 and polymorphisms in the ERAP1 gene is well-established. ERAP1, involved in peptide

trimming for MHC-I presentation, modifies AS risk preferentially in HLA-B27-positive individuals, highlighting a direct mechanistic link between the antigen presentation pathway and disease susceptibility (A. D. Koning et al., 2017; C. Chen & Zhang, 2015). These interactions are crucial for constructing more accurate polygenic risk models.

Geographic and Ethnic Variation: A Landscape of Genetic Diversity

The review highlights profound geographic disparities. HLA-B27 prevalence in AS patients ranges from >90% in Caucasian and many Asian cohorts to around 61.9% in non-Asian regions and as low as 26.2% in Lebanon (Ziadé, 2017; Ono et al., 2021). These differences are attributed to variations in HLA-B27 allele frequency in the general population and the distribution of protective/risk subtypes. For instance, the high prevalence of protective subtypes like B*2706 in Southeast Asia may modulate population-level risk. Consequently, the diagnostic utility of HLA-B27 testing is not uniform globally. A negative result holds higher exclusion value in populations with high background HLA-B27 prevalence in AS patients (e.g., Caucasians) than in Middle Eastern populations where a significant proportion of AS patients are B27-negative.

Clinical Phenotype and Therapeutic Implications

HLA-B27 status is more than a diagnostic marker; it is a biomarker for clinical phenotype and treatment response. Consistently, HLA-B27-positive patients present approximately 7-8 years earlier than their B27-negative counterparts (Bandinelli et al., 2024). This status also predicts a more favorable response to biological therapies, including TNF- α inhibitors (adalimumab, etanercept) and IL-17 inhibitors (secukinumab, ixekizumab), with odds ratios for good response ranging from 1.77 to 2.0 (Rudwaleit et al., 2009; Baraliakos et al., 2015; Deodhar et al., 2020; Reveille et al., 2021). Furthermore, HLA-B27 positivity is linked to specific extra-articular manifestations, such as a higher rate of acute anterior uveitis, particularly associated with the B*2704 subtype (Haibo Li et al., 2018), and a stronger association with AS development in patients with Inflammatory Bowel Disease (Lin et al., 2023).

Diagnostic Performance: A Reality Check

An essential, practice-changing finding is the re-evaluation of HLA-B27's diagnostic performance. The meta-analysis by A. D. Vieira Bento Silva et al. (2023) reports a positive likelihood ratio (LR+) of only 2.7, which is lower than historically perceived. This means a positive test increases the probability of axSpA by a moderate degree, but it is not a definitive rule-in tool. This underscores the imperative of integrating HLA-B27 status with other clinical features (inflammatory back pain), imaging (MRI of sacroiliac joints), and laboratory findings (CRP) within classification criteria like those from ASAS, rather than relying on it in isolation.

Synthesis and Path Forward

In synthesis, the pathogenesis of AS can be visualized as a threshold model. HLA-B27, particularly risk-conferring subtypes, provides the major genetic load. This risk is then amplified or dampened by epistatic partners (e.g., HLA-B60, ERAP1 variants) and likely environmental triggers (e.g., gut microbiota dysbiosis) (Hashim et al., 2025). The variable combination of these factors across individuals and populations determines whether the pathogenic threshold is crossed. Future research must transition from association to mechanism: understanding the structural and functional differences between risk and protective HLA-B27 subtypes, elucidating the precise nature of epistatic interactions, and integrating multi-omic data (genomics, transcriptomics) from diverse ancestries to build predictive models for disease onset and progression (Brown et al., 2025). Clinically, moving towards HLA-B27 subtyping and incorporating genetic risk scores into diagnostic algorithms will pave the way for truly personalized medicine in AS.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review conclusively demonstrates that the association between HLA-B27 and Ankylosing Spondylitis is fundamental but intricately complex. HLA-B27 is the principal genetic driver of AS susceptibility, yet its effect is profoundly modified by specific subtype (allelic)

variation, powerful epistatic interactions with genes like HLA-B60 and ERAP1, and significant geographic-ethnic population differences. Clinically, HLA-B27 status delineates a phenotype characterized by earlier onset, distinct extra-articular manifestations, and generally better response to biologic therapies, while its standalone diagnostic power is more moderate than traditionally assumed.

Recommendations

1. **For Clinical Practice:** Clinicians should interpret HLA-B27 results within the context of the patient's ethnic background and full clinical presentation, recognizing its high sensitivity but modest specificity in many populations. Its value as a prognostic biomarker for treatment response should be considered in therapeutic decision-making.
2. **For Laboratory Testing:** In research and, where feasible, in clinical settings of high diagnostic uncertainty, moving beyond generic HLA-B27 testing to **subtyping** (e.g., distinguishing B2704 from B2706) could provide valuable risk stratification information, especially in Asian and other diverse populations.
3. **For Future Research:** Priority should be given to:
 - **Mechanistic Studies:** Investigating the functional differences between risk and protective HLA-B27 subtypes at the protein structure and peptide-presentation level.
 - **Epistasis Exploration:** Large-scale studies to quantify interactions between HLA-B27 and a wider array of non-MHC genes in diverse ancestries.
 - **Precision Medicine Tools:** Developing and validating integrated risk models that combine HLA status (and subtype), polygenic risk scores from non-MHC loci, and environmental factors to predict disease risk, progression, and optimal therapy.

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