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THE CLINICAL RELATIONSHIP BETWEEN HLA-B27 AND JUVENILE SPONDYLOARTHROPATHY

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Abstract

Juvenile spondyloarthropathies (JSpA) encompass a cluster of interconnected rheumatic conditions that manifest during the formative stages of an individual's life, specifically prior to their sixteenth birthday. The primary characteristics of juvenile spondyloarthropathies include both axial and peripheral arthritis, enthesitis, extra-articular symptoms, and a strong association with the human leukocyte antigen HLA-B27. There exists substantial evidence of the involvement of tumor necrosis factor and interleukin-17 in the pathophysiology of these conditions. A variety of non-biological and biological therapies have been employed in the treatment of these intricate disorders, showing inconsistent outcomes.

This study examines the correlation between HLA-B27 and juvenile spondyloarthropathies, as well as the involvement of HLA-B27 in the pathology of the disease. The present study focuses on the clinical characteristics of HLA-B27 in juvenile spondyloarthropathies and examines the recently recommended therapy for individuals with juvenile spondyloarthropathies.

Keywords: *Juvenile spondyloarthropaties, HLA-B27, Tumor necrosis factor, Interleukin*

Introduction

Juvenile spondyloarthropathy, also known as juvenile spondyloarthritis juvenile spondyloarthropathies (JSpA), is a group of inflammatory rheumatic diseases that mainly affect children and adolescents. JSpA affects individuals under the age of 16. These conditions are characterized by inflammation in the joints and entheses (the areas where tendons and ligaments attach to bones) and can involve the spine, peripheral joints, and other organs. Common subtypes of JSpA include juvenile psoriatic arthritis, juvenile ankylosing spondylitis, and juvenile reactive arthritis. Symptoms may include joint pain, stiffness, and swelling, especially in the lower back and pelvis. In some cases, skin and eye involvement can occur, and children with JSpA may experience fatigue and reduced physical function. Early diagnosis and management are crucial to minimize joint damage and improve the quality of life for affected patients. Treatment may involve medications to reduce inflammation, physical therapy, and lifestyle modifications [*Sridharan R et al., 2015; Adrovic A et al., 2016*].

HLA-B27 is a specific human leukocyte antigen (HLA) gene that plays an influential role in the development of JSpA, as well as in the adult counterpart, ankylosing spondylitis (AS) that HLA-B27 is found in 88% of patients with ankylosing spondylitis [*Kavadichanda C. G et al., 2021*]. This gene is strongly associated with JSpA and potential axial involvement and is found in a high prevalence in patients with JSpA. The presence of HLA-B27 antigen in patients with JSpA is associated with a smaller number of

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long-term articular damage and fewer extra-articular effects in adulthood. The presence of the HLA-B27 has been observed to be linked with enthesitis, a distinctive clinical presentation commonly seen in JSpA. Nevertheless, the prevalence of HLA-B27 in JSpA is lower in children compared to adults [*Peltoniemi S. O. O et al., 2023*]. The different diagnostic criteria for JSpA in children and adults pose a challenge in accurately diagnosing and treating the disease. In order to effectively diagnose, prognosis, and treat JSpA, it is imperative to have a comprehensive understanding of the function that HLA-B27 plays in the pathophysiology of the disease.

The presence of HLA-B27 in JSpA patients is associated with a higher risk of developing ankylosing spondylitis or undifferentiated spondyloarthritis in adulthood [*Yıldız M et al., 2022*]. Having HLA-B27-positive JSpA may also influence the disease's clinical features and progression. It has been observed that individuals with HLA-B27-positive JSpA may have a higher risk of developing certain extra-articular manifestations, such as enthesitis, uveitis (inflammation of the eye), and psoriasis (a chronic skin condition) [*Kavadichanda C. G et al., 2021*]. A comprehensive understanding of the precise pathways via which HLA-B27 contributes to the pathogenesis of JSpA is still required. However, in individuals with HLA-B27, there appears to be an abnormal interaction between HLA-B27 molecules and immune cells, leading to an increased risk of inflammation and autoimmune responses [*Chen B et al., 2017*].

The existence of HLA-B27 constitutes a noteworthy genetic predisposing factor for JSpA. It is estimated that approximately 50-80% of children with this condition carry the HLA-B27 gene [*van Vollenhoven R. F., 2017*]. However, it is necessary to note that not all individuals with HLA-B27 develop spondyloarthropathy, indicating that other factors, such as environmental triggers or additional genetic variations, are involved in the disease's development [*Reveille J. D., 2011*].

The purpose of this review is to investigate the association between the HLA-B27 gene and the development of JSpA. This study will begin with an introduction to the disease and its prevalence, followed by a discussion on the connection between HLA-B27 and JSpA. The role of HLA-B27 in the pathogenesis will be explored through a review of relevant studies. Additionally, clinical features of HLA-B27 in JSpA will be discussed. Finally, the paper will conclude with treatment strategies.

The connection between HLA-B27 and JSpA

The association between HLA-B27 and JSpA has been extensively studied, with research consistently showing a strong correlation. However, in summary, HLA-B27 is associated with specific clinical features and disease manifestations in JSpA and further research is needed to understand its role in disease pathogenesis fully. Several essential factors have been linked with HLA-B27 and JSpA [*Kavadichanda C. G et al., 2021*].

Genetic Predisposition. Although the presence of HLA-B27 is highly correlated with JSpA, it does not exclusively determine the occurrence of the disease. Additional genetic and environmental variables are considered to play a role in the pathogenesis of spondyloarthropathy. The condition is believed to manifest in just a tiny proportion of persons who test positive for HLA-B27. A minimum of 20 distinct subtypes of HLA-B27 have been recognized, among which HLA-B2705 represents the most frequently encountered subtype in the context of JSpA [*Yıldız M et al., 2022*].

Higher Prevalence. JSpA and ankylosing spondylitis exhibit a higher prevalence among those who possess the HLA-B27 biomarker. The presence of HLA-B27 is associated with an elevated probability of developing the aforementioned medical disorders. The prevalence of HLA-B27 is higher among individuals diagnosed with JSpA compared to the general population. The frequency of HLA-B27 in pediatric patients with the disease exhibits variability across different ethnic populations. For example, it is more common in individuals of Caucasian and Asian descent, with rates ranging from 40% to 80%. At the same time, it is less prevalent in individuals of African descent, with rates ranging from 10% to 20% [*Van der Linden S. M et al., 1984*].

The frequency of HLA-B27 in individuals diagnosed with JSpA exhibits variability among diverse groups. A study conducted in Turkey revealed that the prevalence of HLA-B27 among individuals diagnosed with spondyloarthropathy was determined to be 27% [*Acar M et al., 2012*]. Another study in Pakistan reported a prevalence of

23.4% in patients with spondyloarthropathies, with a higher prevalence in males (26%) compared to females (14.3%) [*Ahsan T et al., 2016*]. In India, the highest prevalence of HLA-B27 was observed in the enthesitis-related arthritis category of juvenile idiopathic arthritis, with a prevalence of 87% [*Srivastava R et al., 2016*]. Nevertheless, it is crucial to understand that the existence of HLA-B27 does not necessarily indicate the presence of spondyloarthropathy, as a small portion of individuals may exhibit characteristics that suggest spondyloarthropathy while testing positive for HLA-B27 [*Umamaheswari V., 2018*].

Immunological Role. The HLA-B27 molecule plays a crucial role in the process of antigen presentation to the immune system. It is hypothesized that in patients diagnosed with spondyloarthropathy, the presence of HLA-B27 may facilitate the presentation of distinct peptides or antigens to the immune system, hence triggering an aberrant immune response characterized by inflammation and subsequent tissue damage [*McHugh K., 2011*].

Disease Association. The substantial correlation between the presence of HLA-B27 and the distinct clinical characteristics of JSpA has been widely recognized. JSpA in children who test positive for HLA-B27 frequently has manifestations in both the sacroiliac joints and the spinal column. Individuals may potentially encounter several symptoms, including but not limited to discomfort in the back region, reduced flexibility, and restricted range of motion. However, it is essential to note that not all individuals with HLA-B27-positive JSpA exhibit these symptoms, and the disease can vary widely in its presentation and severity [*Tay S. H et al., 2021*].

Diagnosis and Screening. The presence of HLA-B27 is insufficient to diagnose JSpA on its own. HLA-B27 testing is often used as a supportive tool in the diagnostic process, especially when there is clinical suspicion of spondyloarthropathy [*Reveille J. D., 2019*].

Mechanisms of HLA-B27 in JSpA

The pathogenetic mechanism of HLA-B27 is unexplored. The arthritogenic peptide hypothesis, misfolding protein hypothesis, cell-surface HLA-B27 homodimer, ERAP polymorphism hypothesis, and gut inflammation and dysbiosis hypothesis (Figure. 1) are some of the main theories explaining the role of the HLA-B27 allele in JSpA and disease pathogenesis [*Zhu W et al., 2019*].

Arthritogenic peptide hypothesis. According to the hypothesis, the presence of HLA-B27 alleles results in the presentation of distinct collections of self- or bacteria-derived antigenic peptides to $CD8^+$ T cells, leading to cross-reactivity and the initiation of an HLA-B27-restricted cytotoxic T-cell response. This particular immune response induces a damaging reaction mediated by $CD8^+$ T cells in several organs, including joints [*Oldstone M. B. A., 1989*]. HLA-B27 subtype alleles with specific amino acid residues bind a $CD8^+$ T cell-recognized arthritogenic peptide. The theory proposes that cross-reactive bacterial peptides promote autoimmune T lymphocytes to target HLA-B27's natural ligands. Subtype SNPs in the peptide-binding groove impact HLA-B27 peptide presentation [*Kuon W et al., 2001*]. Therefore, it can be observed that distinct HLA-B27 alleles exhibit recognition of distinct antigenic peptide epitopes that include conserved anchor residues. The arthritogenic peptide theory is grounded in the peptide binding specificity of HLA-B27, the concept of molecular mimicry, and the hypothesis that exogenous antigens have the potential to stimulate T-cells and trigger autoimmunity. Cytotoxic T lymphocytes (CTLs) responses against bacterial peptides may activate HLA-B27, causing JSpA. The phenomenon of autoimmune tissue injury and inflammation occurs as a result of the cross-reaction between activated CTL and self-peptides [*Ramos M., De Castro J. L., 2002*]. Numerous investigations support the arthritogenic peptide hypothesis. In individuals with reactive arthritis after *Salmonella* or *Chlamydia* infections, HLA-B27-restricted $CD8^+$ T cell responses were found. The peptides produced by enteric organisms exhibited binding affinity to HLA-B27 and displayed sequence homology [*Scofield R. H et al., 1995*]. The peptidome of HLA-B27 was analyzed, resulting in the identification of about 1,000 peptides derived from HLA-B27 cell lines. It was observed that half of these peptides exhibited strong binding affinity to certain alleles. A total of 28 peptides were shown to possess arthritogenic properties due to their structural similarity to proteins found in enteric bacteria, as they were derived from cartilage or

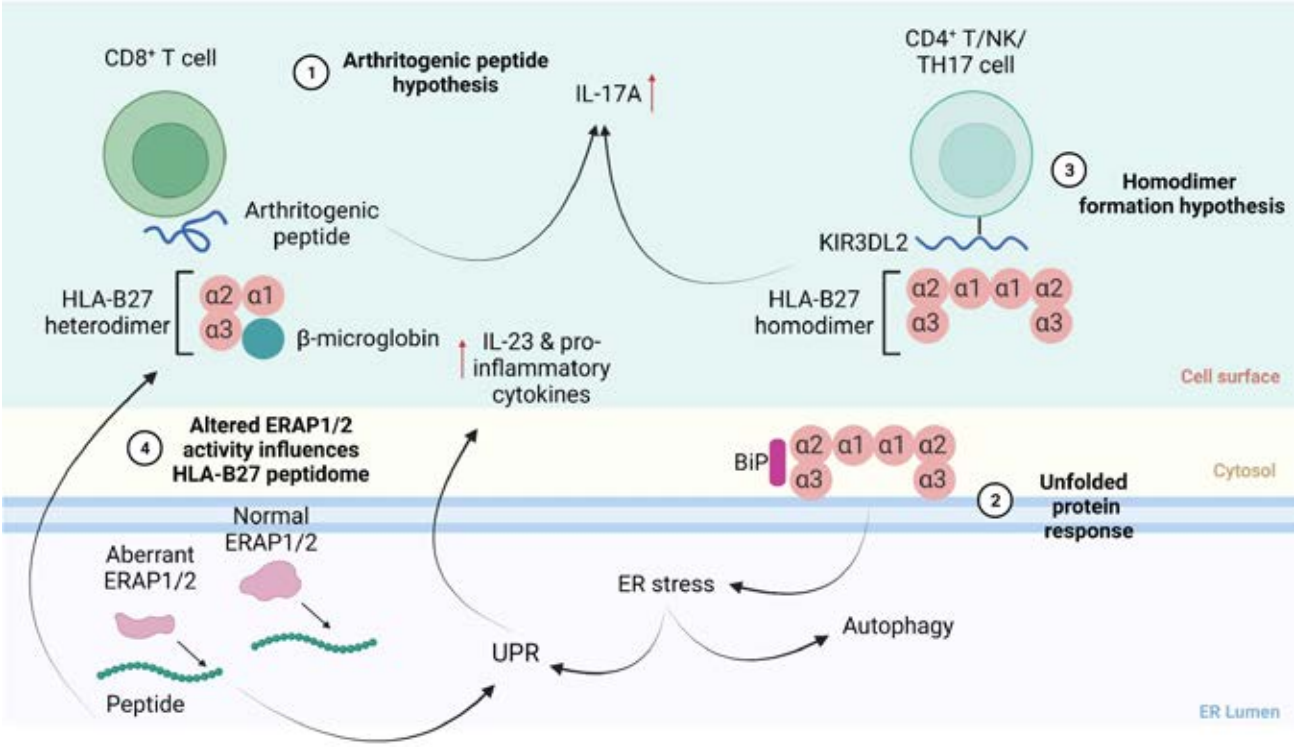

Figure 1. *Illustration of the hypothesis of the pathogenetic role of HLA-B27 molecules in JSpA. (1) Inflammation happens when autoreactive CD8⁺ T lymphocytes detect arthritogenic peptides that are presented by appropriately folded HLA-B27 molecules. (2) The presence of misfolded HLA-B27 chains and subsequent interaction with BiP induces ER stress, triggering the activation of the UPR. This activation subsequently results in an upregulation of interleukin-23 production, along with other proinflammatory cytokines. (3) Cell surface homodimers of HLA molecules interact with CD4⁺ T cells via innate immune receptors, including KIR3DL2, hence promoting the activation of cell-mediated autoimmune reactions. (4) Modulation of ERAP1 activity can lead to alterations in peptide processing, resulting in the possibility of pathogenic consequences. ER: endoplasmic reticulum; KIR3DL2: killer immunoglobulin-like receptor; ERAP1: ER aminopeptidases; UPR: unfolded protein response.*

bone proteins. These data imply that these antigenic peptides can cause JSpA pathology via T-cell-mediated immunity [*Ben Dror L et al., 2010*].

In addition to bacterial peptides, viral peptides have the potential to induce JSpA. Some individuals with JSpA were reported to have cross-reactive CD8⁺ T cell responses to both Epstein-Barr virus epitopes and VIPR self-peptides [*Fiorillo M. T et al., 2000*]. However, it should be noted that Epstein-Barr virus infection is not considered a cause for JSpA. Hence, further investigation is required to examine these findings. Studies of HLA-B27 alleles and JSpA cause support the arthritogenic peptide theory. Some alleles, such as HLA-B2705, B2702, and B2704, are highly associated with disease pathogenesis, while others, like HLA-B2706 and B2709, barely associate [*Syrbe U., Sieper J., 2020*].

The unfolded protein response hypothesis. An additional idea about the role of HLA-B27 in the development of JSpA is the unfolded protein response (UPR) theory. HLA-B27 exhibits an extended residence time within the endoplasmic reticulum (ER) relative to other MHC molecules, resulting in a delayed folding process or a propensity for misfolding. ER stress caused by misfolded HLA-B27 promotes the UPR, a homeostatic process that restores cell function [*Kenna T. J et al., 2015*]. UPR hinders the process of protein translation while simultaneously increasing the expression of ER chaperones, including BiP and ERdj4. The activation of the CCAAT-enhancer-binding protein homologous protein transcription factor leads to an increase in the production of pro-inflammatory cytokines, including interleukin-23, Interferon-β, and interleukin-1 [*Ambarus C. A et al., 2018*]. The UPR induces the activation of surface receptors and subsequently triggers inflammatory signaling pathways, such as the interleukin-23/ interleukin-17 pathway, which in turn modulates the production of cytokines. ER stress

and UPR promote interleukin-23 synthesis via autophagy. ER-associated degradation eliminates misfolded HLA-B27 molecules. Consequently, the slow folding or misfolding of HLA-B27 leads to the activation of ER-associated degradation and triggers the UPR and autophagy. This phenomenon is particularly pronounced during periods of inflammation when the synthesis of HLA-B27 is elevated [*Busch R et al., 2019*]. The slow folding kinetics and partial misfolding of HLA-B2705 have been observed to induce the activation of NF-kB, resulting in an upregulation of interferon, interleukin-1, and interleukin-6 production. The utilization of transgenic rat models in the study of AS and JSpA has revealed the presence of HLA-B27 misfolding and UPR in both the gastrointestinal tract and synovial tissues. These findings provide more evidence in support of the UPR theory [*Ebringer A., 1983*]. Cytokine activation in bone marrow-derived macrophages of HLA-B27 transgenic rats resulted in the misfolding of HLA-B27 and the generation of interleukin-23. The HLA-B27 transgenic rats exhibited alterations in cellular populations, potentially associated with the phenomenon of misfolding. The occurrence of misfolding in the heavy chain β2 microglobulin is prevalent, resulting in the activation of the UPR [*Turner M. J et al., 2005*].

Research conducted on rats that were genetically modified to express HLA-B27 has demonstrated that an increase in the number of copies of the human β2-microglobulin gene resulted in a reduction in the misfolding of HLA-B27. This reduction was found to be associated with the activation of the UPR, the occurrence of inflammation, and the establishment of JSpA. Rather than reducing the occurrence and intensity of arthritis, the activation of the UPR increased its incidence and severity. The conducted research involved the development of rat strains exhibiting arthritic disease that closely resembled human spondylarthritis. However, these rat strains also exhibited mild intestinal inflammation, indicating that IBD, specifically Crohn's disease, may involve distinct pathological mechanisms [*Tran T. M et al., 2006*]. According to existing research, it has been proposed that the pathogenesis of spondylarthritis associated with HLA-B27 may not be attributed to misfolding of the HLA-B27 protein, formation of heavy chain β2 microglobulin dimers, or activation of the UPR. Instead, evidence suggests that UPR activation is associated with inflammatory pathways that contribute to gastrointestinal inflammation in patients with JSpA. Studies of AS patient tissues did not link UPR and ER stress to inflammation and HLA-B27 misfolding. Therefore, HLA-B27 has been observed to induce misfolding and ER stress in both *in vitro* and animal studies. However, it has not been found to play a role in the pathophysiology of human JSpA [*Ciccia F et al., 2014*].

HLA-B27 homodimer formation hypothesis. A unique property of HLA-B27 is the tendency to form disulfide-bonded homodimers. Natural killer (NK) cells, B lymphocytes, and CTLs, express these homodimers. The development of homodimers may serve as an indication of misfolding of HLA-B27 in the ER, leading to the initiation of a pro-inflammatory response to stress [*Mear J. P et al., 1999*]. The misfolding of ER proteins has numerous biological implications that vary depending on the characteristics, abundance, and severity of the defect. JSpA pathogenesis requires higher interleukin-27 production, which UPR activation can augment. Changes in tumor necrosis factor and interferon-γ production may contribute to the distinct spondyloarthritis phenotype [*Colbert R. A et al., 2014*]. HLA-B27 homodimers increase T helper 17 generation, which increases interleukin-17/interleukin-23 production. In addition, they facilitate the process of inflammation by forming interactions with killer cell immunoglobulin-like receptors and leukocyte immunoglobulin-like receptors, which are present in NK cells and T cells, respectively. Many studies support the HLA-B27 homodimer theory. Immune responses, including macrophage and dendritic cell differentiation, T cell survival, and Treg activation, depend on killer cell immunoglobulin-like receptors and leukocyte immunoglobulin-like receptors [*Bowness P et al., 2011*]. The killer cell immunoglobulin-like receptors-3DL2 receptor recognizes HLA-B27 homodimers more strongly than heterodimers. 70 killer cell immunoglobulin-like receptor genes have been identified. Notably, the interaction between killer cell immunoglobulin-like receptors-3DL2 and HLA-B27 free heavy chains has been found to induce pro-inflammatory responses in NK and T cells. In AS patients, T helper 17 expression was enhanced [*Chen L et al., 2016*]. In JSpA

patients, killer cell immunoglobulin-like receptors-3DL2 binding with HLA-B27 homodimers improved $CD4^+$ T cell survival and development. Additionally, it increased pro-inflammatory cytokines such as interleukin-17, interferon-γ, and tumor necrosis factor. HLA-B27 positive JSpA patients had more peripheral blood $CD4^+$ T cells and killer cell immunoglobulin-like receptors-3DL2+ NK and produced more IL-17 and cytotoxicity than negative JSpA patients. Thus, HLA-B27 homodimers binding to killer cell immunoglobulin-like receptor and leukocyte immunoglobulin-like receptors promote inflammation by increasing NK and T cell survival and leukocyte immunoglobulin-like receptors-expressing antigen-presenting cell differentiation [*Sharip A., Kunz J., 2020*].

The ERAP polymorphism hypothesis. After HLA-B27, ERAP1 and ERAP2 aminopeptidase polymorphisms are the second strongest genetic associated with AS, contributing 15–25% of population risk. Independent research with other populations confirmed this link previously found in the UK and USA [*Davidson S. I et al., 2009*]. HLA-B27 and ERAP contribute to 70% of JSpA genetic risk. Zinc metallopeptidases ERAP1 and ERAP2 trim peptides for MHC I class molecules in the ER. The proteasome or lysosomal breakdown of proteins imported through autophagy or phagocytosis [*Rock K. L et al., 2016*] produces MHC class I peptides. A considerable number of these peptides exceed the optimal length of 8-9 amino acids for MHC class I presentation. Consequently, they are conveyed into the ER through transporters associated with antigen processing [*Burgevin A et al., 2008*]. Subsequently, ERAP1 and ERAP2 enzymes are responsible for trimming these peptides to 8-10 amino acid residues, providing the presence of suitable anchor residues. ERAP1 and ERAP2 exhibit a relationship with aminopeptidases, though they display distinct peptide preferences, trimming properties, and links with JSpA [*Saric T et al., 2002*].

ERAP1 is the primary ER enzyme responsible for peptide trimming, while ERAP2 plays a comparatively less significant role in this process. ERAP1 plays two essential roles. The first procedure is antigen cross-presentation, where the trimming of peptide N-termini occurs in the ER) to achieve a suitable length that may bind to MHC class I molecules. This then leads to the presentation of the antigen on $CD8^+$ T or NK cells [*López de Castro J. A., 2018*]. The second role of ERAP1 is the enzymatic cleavage of cell surface cytokine receptors, including tumor necrosis factor receptor 1, interleukin-6R2, and interleukin-1R2, through proteolytic mechanisms. ERAP1 sheds cell surface receptors to modulate the immune response and reduce pro-inflammatory signals [*Cui X et al., 2002*]. Research conducted on individuals diagnosed with AS and possessing different ERAP1 haplotypes has revealed several noteworthy findings. These include the cleavage of tumor necrosis factor receptors, modifications in the cellular cytokine response, and substantial alterations in the expression of cytokine mRNA. Some ERAP1 polymorphisms may increase tumor necrosis factor receptor shedding and cause JSpA, although most evidence suggests that cytokine receptor shedding does not cause JSpA [*Reveille J. D., 2012*].

The study revealed a significant genetic association between AS and ERAP1, but this connection was observed exclusively in people who tested positive for HLA-B27. This finding suggests that ERAP1 plays a role in the antigen-processing and presentation pathway in conjunction with HLA-B27. This finding demonstrates the critical role of aberrant peptide processing and antigen presentation in the development of JSpA [*Keidel S et al., 2013*].

The examination of ERAP1 loss-of-function mutations and polymorphisms in a systematic manner indicates that ERAP1 has a significant impact on the development of JSpA. This impact may be attributed to its influence on the misfolding of ER or the transportation of pro-inflammatory B27 forms, as well as its ability to alter the range of peptides bound to HLA-B27 [*Seregin S. S et al., 2013*]. The disease-causing ERAP1 alleles are characterized by loss-of-function mutations, indicating that there are alterations in peptide processing and presentation mechanisms. The presence of loss-of-function ERAP1 polymorphisms has been found to have an impact on various aspects of HLA-B27 heavy chain synthesis, including dimerization and folding [*Kochan G et al., 2011*]. Additionally, these polymorphisms have been shown to result in reduced levels of homodimer cell surface expression. The removal of ERAP10's trimming function has been seen to have an impact on HLA-B27's regular expression and the enhancement of intracellular free heavy

chain forms within antigen-presenting cells. These effects are associated with the enzymatic activity of ERAP10. Furthermore, it has been observed that the impairment of ERAP1 activity in both humans and mice has a significant impact on the MHC class I peptidome, indicating its role in modifying the repertoire [*Li L et al., 2019*].

The association between ERAP1 polymorphisms and AS provides evidence in favor of the arthritogenic peptide theory. However, it is important to note that additional factors, such as HLA-B27 dimerization and surface expression, could potentially play a role in the development of AS. The consequences of loss-of-function mutations or polymorphisms in ERAP1 or ERAP2 on the presentation of MHC class I peptides were investigated in recent reviews [*de Castro J. A. L et al., 2016*].

Gut inflammation and dysbiosis hypothesis. The considerable current theory for JSpA pathogenesis is that HLA-B27 shapes the gut flora and mediates disease vulnerability. Trillions of bacteria form the gut microbiome, a sophisticated homeostatic environment. It is crucial for the immune system, intestinal epithelial barrier formation, and food digestion [*Gill T et al., 2018*]. Through immune response activation, intestinal permeability, and molecular mimicry, gut microbiome composition affects autoimmune disorders. Various studies have demonstrated that gut microbiota changes might cause autoinflammatory and autoimmune disorders, increased opportunistic infections, intestinal dysbiosis, and commensal bacteria composition [*Sartor R. B., Wu G. D., 2017*]. Antigenic activation of pathogenic immune system effector cells by gut dysbiosis may cause chronic inflammation. Pathogenic JSpA development involves increased intestinal permeability. Dysregulated tight junctions between intestinal epithelial cells enhance gut permeability and damage mucosal immunity by affecting gut microbiota modulation and pro-inflammatory cytokine release. Gut inflammation and JSpA are linked by much research. The gut flora of JSpA patients differs from healthy controls, and 60–70% show microscopic intestinal inflammation [*Van Praet L et al., 2012*].

Clinical features of HLA-B27 in JSpA. The presence of HLA-B27 in individuals with JSpA is correlated with distinct clinical characteristics. It is crucial to understand that the appearance of these characteristics can be excluded in all individuals with HLA-B27, and the absence of HLA-B27 does not necessarily rule out the potential occurrence of spondyloarthropathy. However, the presence of HLA-B27 can support the diagnosis when combined with other clinical and laboratory findings. Here are some clinical features commonly associated with HLA-B27 in JSpA:

Enthesitis. Enthesitis refers to the inflammatory condition that occurs where tendons or ligaments connect with bones. The condition frequently impacts the Achilles tendon and the plantar fascia, resulting in symptoms such as pain, swelling, and tenderness [*Tay S. H et al., 2021*].

Inflammatory Arthritis. JSpA associated with HLA-B27 often involves arthritis, which is characterized by joint inflammation. The arthritis is typically asymmetric and affects the lower extremities, such as the knees, ankles, and feet. The joints may be swollen, warm, and tender [*Cabral D. A et al., 1995*].

Axial Involvement. HLA-B27 positivity is associated with the involvement of the axial skeleton, which includes the spine and sacroiliac joints. Symptoms may include lower back pain, stiffness, and limited spinal mobility. In severe cases, fusion of the spinal vertebrae (ankylosis) can occur [*Khan M. A., 1992*].

Extra-articular Manifestations. HLA-B27 positive JSpA can involve extra-articular manifestations, affecting organs and tissues outside the joints. Examples include uveitis, which is inflammation of the eye that can cause redness, pain, and blurry vision, as well as skin involvement such as psoriasis [*Shivpuri A et al., 2022*].

Sacroiliitis. Sacroiliitis refers to inflammation of the sacroiliac joints, which connect the lower spine to the pelvis. HLA-B27 positive individuals with JSpA may experience sacroiliitis, leading to low back pain and stiffness that can be worse in the morning or after periods of inactivity [*Jans L et al., 2014*].

Peripheral Joint Involvement. In addition to the lower extremities, HLA-B27 positive JSpA can affect other peripheral joints, such as the wrists, elbows, hips, and shoulders. These joints may exhibit signs of inflammation, including swelling, pain, and limited range of motion [*Snyder E. A., 2021*].

Uveitis. Uveitis refers to the inflammatory condition affecting the uvea, which is the intermediate layer of the eye. The manifestation of symptoms includes erythema, ocular discomfort, photophobia, and visual

impairment. Uveitis associated with HLA-B27 tends to be recurrent and may require ophthalmologic evaluation and treatment [*Huhtinen M., 2002*].

Skin and nail involvement. Some individuals with HLA-B27-associated spondyloarthropathy may develop skin and nail changes. These can include psoriasis-like skin lesions, nail pitting, or onycholysis [*Meier K et al., 2020*].

Treatment strategies for managing JSpA in HLA-B27-positive individuals

A diagnosis of spondyloarthropathy is more likely to be observed in individuals who carry the HLA-B27 gene. The management of JSpA in those who are HLA-B27-positive often entails the utilization of a combination of pharmacological and non-pharmacological strategies.

Nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs are often the first line of treatment for managing symptoms such as pain and inflammation. They can help reduce pain and stiffness in the joints and improve overall function. Examples of nonsteroidal anti-inflammatory drugs commonly used in JSpA include ibuprofen and naproxen [*Gmuca S et al., 2017*].

Physical therapy and exercise. Physical therapy can be beneficial in maintaining joint mobility, improving posture, and strengthening the muscles surrounding the affected joints. It can help reduce pain, increase flexibility, and improve overall function [*Srinivasalu H et al., 2021*].

Disease-modifying antirheumatic drugs. In more severe cases or when nonsteroidal anti-inflammatory drugs alone are insufficient, disease-modifying antirheumatic drugs may be prescribed. Disease-modifying antirheumatic drugs such as methotrexate or sulfasalazine can help reduce inflammation and prevent joint damage. These medications require regular monitoring for potential side effects [*Braun J et al., 2006*].

Biologic agents. In cases where nonsteroidal anti-inflammatory drugs and Disease-modifying antirheumatic drugs are ineffective, biologic agents may be considered. Biological therapeutics, such as TNF inhibitors or interleukin inhibitors, selectively modulate distinct functions of the immune system in order to reduce inflammatory responses [*Davis Jr J. C et al., 2003*].

Corticosteroids. In some cases, corticosteroids may be prescribed to help manage severe symptoms and inflammation. These medications can be administered orally, injected into the affected joints, or given intravenously [*Tse S. M., Laxer R. M., 2012*].

Non-pharmacological interventions. Besides exercise and physical therapy, other non-pharmacological interventions may be beneficial. Heat therapy can help alleviate pain and stiffness. Occupational therapy can assist in identifying strategies to manage joint involvement and promote independence in daily activities. Assistive devices, such as orthotics or splints, may be recommended to support joint function and relieve pressure [*Hsieh L. F et al., 2021*].

Conclusion

JSpA is a chronic inflammatory rheumatic disorder that predominantly presents in individuals within the pediatric and adolescent age group, including individuals under 16 years old. The condition is distinguished by the presence of inflammation in joints and entheses, which impacts the spine, peripheral joints, and various other organs. The occurrence of HLA-B27 in individuals with JSpA is linked to an increased likelihood of developing ankylosing spondylitis or undifferentiated spondyloarthritis during maturity. The presence of HLA-B27 positivity in individuals with JSpA may potentially exhibit an impact on the clinical signs and course of the disease. A comprehensive understanding of the precise pathways via which HLA-B27 contributes to the pathogenesis of JSpA is still required. However, there appears to be an abnormal interaction between HLA-B27 molecules and immune cells, leading to an increased risk of inflammation and autoimmune responses. Treatment strategies for managing JSpA in HLA-B27-positive individuals typically involve a combination of pharmacological and non-pharmacological approaches. nonsteroidal anti-inflammatory drugs, physical therapy and exercise, Disease-modifying antirheumatic drugs, biologic agents, corticosteroids, and non-pharmacological interventions may be beneficial.

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