



The Role of Human Leukocyte Antigens in Orthopaedics: Clinical Relevance from Autoimmune Joint Disorders to Implant Compatibility



Dr. Bikram Kesari Kar¹, Dr. Punit Gaurav^{2*}, Dr. Himanshu², Dr. Neeraj Khare² and Dr. Dushyant Chouhan³

¹Additional Professor, Department of Orthopaedics, All India Institute of Medical Sciences (AIIMS), Raipur, India

²Senior Resident, Department of Orthopaedics, All India Institute of Medical Sciences (AIIMS), Raipur, India

³Assistant Professor, Department of Orthopaedics, All India Institute of Medical Sciences (AIIMS), Raipur, India

Abstract

Background: The human leukocyte antigen (HLA) system is central to immune recognition, orchestrating the distinction between self and non-self-antigens. Its significance in orthopaedics has gained increasing attention due to its involvement in autoimmune disorders, tissue transplantation, and implant-related complications.

Methods: This review synthesises evidence from published literature on the structure, function, and polymorphism of HLA genes located on chromosome 6, with emphasis on their clinical relevance in musculoskeletal disorders, bone and tissue transplantation, and implant hypersensitivity.

Results: Specific HLA alleles demonstrate strong associations with autoimmune musculoskeletal conditions such as rheumatoid arthritis (HLA-DRB1) and ankylosing spondylitis (HLA-B27), offering value in diagnosis, prognostication, and surgical risk stratification. In transplantation, preoperative HLA typing facilitates donor-recipient matching, reducing graft rejection and improving long-term survival. Implant-related reactions, particularly to metal alloys, have been linked to HLA polymorphisms, with certain alleles predisposing patients to aseptic loosening, osteolysis, and soft tissue injury. Advances in genetic profiling suggest that HLA typing can enhance personalised care by guiding material selection, surgical planning, and immunomodulatory interventions.

Conclusion: The HLA system underpins many clinically relevant processes in orthopaedics, from autoimmune pathogenesis to transplant survival and implant biocompatibility. Incorporating HLA typing into orthopaedic practice provides opportunities for precision medicine, enabling tailored therapeutic strategies, improved patient outcomes, and reduced implant-related morbidity.

Keywords: Human Leucocyte Antigen; Ankylosing Spondylosis; Rheumatoid Arthritis; Spondyloarthropathy; Autoimmune Disease; HLA Typing; Orthopaedics

Introduction

The immune system operates as an intricate system of cells collaborating to safeguard the body from pathogens while ensuring its tissues remain unharmed. Maintaining this intricate equilibrium requires the host to differentiate between its antigens and those of foreign invaders. This vital discernment is aided by the major histocompatibility complex (MHC) antigens, termed human leukocyte antigens (HLA) in the case of humans. MHC molecules are vital in recognising foreign antigens and processing and presenting them to the immune system. This capacity to distinguish between self and non-self-antigens is accomplished via a mechanism known as "MHC restriction" [1].

While maturing in the thymus, T-cells undergo a process where those reacting to self-antigens are removed. At the same time, those responding to non-self-antigens presented by self-HLA molecules are retained. The above-mentioned selective procedure leads to CD4+ and CD8+ T-cell formation that specifically reacts to non-self-antigens processed by self-HLA molecules. Although the immune system is precise in targeting foreign antigens, specific HLA alleles have been associated with increased vulnerability to various disorders, many of which arise due to immune dysregulation.

OPEN ACCESS

*Correspondence:

Dr. Punit Gaurav, Senior Resident,
Department of Orthopaedics, All India
Institute of Medical Sciences (AIIMS),
Raipur, India, Tel: +91 9097487683;
E-mail: dr.punitgaurav@gmail.com/
ORCID: <https://orcid.org/0009-0007-7727-4500>

Received Date: 30 Oct 2025

Accepted Date: 06 Nov 2025

Published Date: 08 Nov 2025

Citation:

Kesari Kar B, Gaurav P, Himanshu,
Khare N, Chouhan D. The Role
of Human Leukocyte Antigens in
Orthopaedics: Clinical Relevance
from Autoimmune Joint Disorders
to Implant Compatibility. WebLog J
Orthop. wjor.2025.k0802. <https://doi.org/10.5281/zenodo.17655518>

Copyright© 2025 Dr. Punit Gaurav.

This is an open access article
distributed under the Creative
Commons Attribution License, which
permits unrestricted use, distribution,
and reproduction in any medium,
provided the original work is properly
cited.

Additionally, HLA genes are one of the major factors related to autoimmunity and remain a significant focus of research due to their wide-ranging implications and disease prognosis [2].

HLA consists of three major categories. Class I HLA antigens include HLA-A, B, and C molecules. Class II antigens include HLA-DR, -DQ, and -DP loci. Class II is present on antigen-presenting cells. The class III antigens include genes that encode proteins with immune-related functions [2].

Developing sensitivity to HLA antigens can present difficulties for patients who undergo stem cell transplants and other such procedures. These immune regulatory antigens are pivotal in rejection reactions associated with transplants, which can be classified into two primary types:

1. T-cell-mediated rejection

During the T-cell-mediated immune reaction, T cells are activated due to the specific linkage between the T-cell receptors and the donor HLA amalgamation.

2. Antibody-mediated rejection

In this variant of rejection, the helper T-cells undergo co-stimulation, which causes an inflammatory response leading to the identification of non-self HLA peptides.

Certain HLA types are also correlated with a heightened susceptibility to specific diseases. For instance, myasthenia gravis (early onset) is linked to HLA-B8, which acts as a notable genetic factor influencing the development of the disease [3]. Even though the origin of multiple sclerosis is uncertain, it shows a strong association with the HLA-DR2 antigen [4]. Furthermore, rheumatoid arthritis (RA) is recognized for involving complex immunological interactions within the body. These interactive pathways involve HLA-DR4 (a type II collagen-derived glycopeptide) and a T-cell receptor, all of which have been demonstrated to be linked with the pathogenesis of RA [5].

The significance of the HLA system in immune responses has generated interest within the field of orthopaedics. Given the varied involvement of HLA in multiple aspects of orthopaedic and rheumatological disorders, multiple research studies have been carried out to explore this topic. However, most of the literature has been focused on a particular subset of the topic. This review aims to bring multiple articles, research, and population studies on HLA under one umbrella for easier reference and understanding. This article explores the implications of HLA across various orthopaedic conditions and its clinical relevance.

Materials and Methods

While writing the review article, the authors searched online databases such as Medline, PubMed, Embase, Scopus, Web of Science, and Google Scholar. Keywords used were "HLA", "Ankylosing Spondylitis", "Rheumatoid Arthritis", "Spondyloarthritis", "HLA in orthopaedic oncology", "HLA in bone healing", "HLA detection methods". The research articles were then picked based on relevance and ingenuity. When encountering articles with conflicting results or conclusions, a paper with a higher level of evidence was chosen. In case of the same level of evidence, the paper with a more recent date of publication was chosen.

HLA in Joint Disorders

HLA molecules, more significantly HLA-DRB1 and HLA-B27,

are linked with autoimmune joint diseases like ankylosing spondylitis (AS) [6], RA [7], and psoriatic arthritis (PsA) [8]. Understanding these associations facilitates early diagnosis and personalized treatment strategies.

Rheumatoid arthritis: RA is a common inflammatory disorder caused by a mix of genetic and environmental elements. Studies with twins indicate that around 60% of disease onset can be linked to genetic factors. Among these hereditary risk factors identified thus far, the HLA locus emerges as the most significant [9]. Among the genetic risk factors identified thus far, the HLA locus emerges as the most important.

The link between RA and the HLA antigen has been studied since 1969 [10], and the specific associations with a few particular DR4 allotypes were discovered in the latter half of the 1970s [11, 12]. HLA-DR4 has been shown to have significant associations with RA, which also increases the susceptibility to the disease. The DR4 binding with a class II-linked peptide indicates an elevated risk of developing RA. This interaction alters the citrullinated peptides, thus contributing to the progression of RA [13].

Multiple studies have verified that the HLA DRB1 gene acts as the primary genetic locus, increasing susceptibility to RA. Further investigations utilizing extensive datasets have also identified other HLA genes contributing to the disease, including HLA-A [14], HLA-B, and HLA-DRB1 [15].

Both the HLA-DRB1 gene alleles, namely DRB1*04:01 and DRB1*04:04, are chiefly responsible for the serological correlation of DR4 with RA observed initially. Furthermore, DRB1*01 and DRB1*10 alleles have been identified in numerous RA patients who do not carry DRB1*04 alleles.

A significant correlation exists between RA and particular alleles of HLA-DRB1 that encode an HLA-DR β chain consisting of a five-amino-acid sequence motif known as the 'shared epitope' (SE) [16]. The concept of "shared epitope" [16] arose in the late 1980s when it was discovered that most RA patients share a common 5-amino-acid sequence motif (QKRAA, QRRAA, or RRRAA) within residues 70-74 of the DR β chain. This motif is coded by different DRB1 gene alleles and found in individuals expressing both DR4 and non-DR4 allotypes.

When the shared epitope is present, it not only increases susceptibility to RA but also raises the possibility of earlier onset of the disease and more severe bone erosions [17, 18] and anti-citrullinated protein antibodies (ACPA).

Research in this area is ongoing because the potential arthritogenic peptides have yet to be identified even after several years of investigation.

Spondyloarthritis: The concept of spondyloarthritis (SpA) first emerged in the 1970s in the United Kingdom as a way to describe a closely related group of conditions that share specific similarities in epidemiological, clinical, radiographic, and genetic features. This spectrum encompasses AS, Reactive Arthritis (ReA), PsA, and Inflammatory Bowel Disease-associated Arthritis (IBDa).

SpA encompasses a cluster of systemic inflammatory rheumatic disorders that have been extensively studied and documented around the world for over four decades. Epidemiological studies indicate a prevalence of SpA ranging from 7 to 9 per 10,000 individuals [19]. Several studies have delineated the clinical features of different SpA

subsets, illustrating the existence of all clinical subtypes. Long-term follow-up studies have also been undertaken, unveiling the diverse progression patterns of these subtypes over time.

Several studies have validated the correlation of B*27:04 and B*27:05 with AS and a broader spectrum of SpA diseases.

AS, the most common variant of SpA, is an immune-mediated chronic inflammatory disorder distinguished by inflammation mainly targeting the axial skeleton. A significant proportion of AS patients also exhibit peripheral arthritis and enthesopathy. Moreover, specific symptoms, such as psoriasis, anterior uveitis, and chronic inflammatory bowel disease, may coexist with AS, heightening the risk of cardiovascular or pulmonary complications. Prolonged inflammation at the tendons, ligaments, and joint capsules results in structural alterations in the joints, including new bone formation and joint fusion [20]. These distinct alterations, particularly in the development of syndesmophytes and vertebral ankylosis, play a significant role in early and severe disability among AS patients as the disease advances. However, AS's precise underlying pathogenesis and other contributory factors are still not fully understood.

Genetic investigations have provided pivotal insights into AS. Multiple genetic studies have shown that heritability has a significant role in AS incidence [21]. The discovery in 1973 of a robust correlation between AS and HLA-B27 emphasized the significant genetic predisposition [22]. While a portion of AS cases do not feature HLA-B27, it still stands as one of the most pivotal factors in AS development, showing a markedly significant association (odds ratio >100) and being present in up to 90% of patients across different ethnic groups affected [23]. Familial studies have revealed that HLA-B27 within the MHC locus contributes to approximately 20.1% of AS inheritance, while 4.3% is seen with non-HLA-B loci [24]. Notably, HLA-B27 exhibits significant genetic polymorphism, with around 105 known subtypes designated as HLA-B27:01 to HLA-B27:106, which are encoded by 132 alleles.

Psoriatic Arthritis and Other Arthropathies

HLA-B27 also appears in psoriatic spondyloarthropathy, particularly with axial involvement, influencing disease phenotype and surgical planning (Table 1) (Figure 1).

Prognostic Value of HLA-B27

Although HLA-B27 does not seem to affect the severity of AS [25], may play a significant role in psoriatic spondyloarthropathy, influencing both susceptibility to the condition and its clinical presentation. HLA-B27 is strongly associated with axial skeletal

Table 1: Autoimmune Musculoskeletal Disorders and HLA Associations.

Disorder	Key HLA Association	Orthopaedic Relevance
Rheumatoid arthritis (RA)	HLA-DRB1 ("shared epitope" motif: QKRAA, QRRAA, RRRAA)	Predicts aggressive erosive disease, cervical spine instability; influences surgical timing and planning
Ankylosing spondylitis (AS)	HLA-B27	Associated with axial disease, spinal fusion, kyphotic deformity; guides early diagnosis and intervention
Psoriatic arthritis (axial)	HLA-B27	Axial phenotype with spinal involvement; influences prognosis and surgical decisions
Reactive arthritis	HLA-B27	Higher risk of chronicity and extra-articular manifestations
Spondyloarthritis (other subtypes)	HLA-B27	Prognostic indicator for disease course and potential spine surgery outcomes

Table 2: Clinical Scenarios for HLA Testing in Orthopaedics.

Clinical Situation	Recommended HLA Test	Rationale
Early-onset inflammatory back pain in a young patient	HLA-B27	Supports diagnosis of spondyloarthritis; enables early rheumatology referral
RA patient undergoing cervical spine surgery	HLA-DRB1	Identifies higher risk of atlanto-axial instability and subaxial subluxation
Unexplained inflammation after arthroplasty (infection ruled out)	HLA-DQ	Detects predisposition to metal hypersensitivity (e.g., cobalt-chromium alloys)
Tumour reconstruction with massive allograft	Full HLA typing	Improves graft survival and reduces immune-mediated resorption
Complex revision arthroplasty with prior implant failure	HLA-DQ, HLA-DR	Identifies hypersensitivity risk; assists in implant material selection

disease in psoriatic spondyloarthropathy and might even provide some protection against peripheral joint erosions.

Patients having Reiter's disease and reactive arthritis caused by Yersinia and Salmonella, who are HLA-B27 positive, tend to experience increased severity of disease, exhibit more extra-articular symptoms, and have a higher prevalence of chronic back pain and sacroiliitis [26]. In cases of reactive arthritis triggered by Chlamydia trachomatis, the severity or chronicity of the disease may be attributed to low interferon-γ in the synovial fluid of HLA-B27 positive patients compared to HLA-B27 negative patients. This lower concentration can result in defective clearance of infective pathogens [27].

Patients who possess HLA-B27 have been observed to have poorer outcomes following spine surgeries. However, it remains uncertain whether this is attributed to a substantial proportion of patients undergoing surgery for SpA instead of mechanical back pain or if HLA-B27 predisposes individuals to an unfavourable outcome in back surgery.

Atlanto-axial subluxation occurs both in RA and AS. Compared to patients without HLA-B27, those who are HLA-B27 positive and have RA are at approximately twice the risk of developing cervical spine subluxation and nearly three times the risk of subluxation at the submaximal level [28]. Therefore, HLA-B27 might serve as an important prognostic indicator for the future development of cervical spine instability and its associated complications in RA (Table 2).

HLA in Bone Healing

The bone healing process involves a complex interaction among cytokines, inflammatory cells, and various molecular markers at the cellular level. Recent evidence suggests that HLA plays a role in bone remodelling and fracture healing. Understanding how HLA impacts osteoblasts and osteoclasts provides insight into bone regeneration mechanisms and may offer potential therapeutic strategies.

Inflammatory cells like granulocytes, macrophages, and lymphocytes affect the process of fracture healing. These cells orchestrate the physiology by being present in the hematoma at the fracture from the earliest stages. Although their involvement in bone repair has not been extensively studied, their role in wound healing in soft tissues has garnered significant attention. T-lymphocytes and macrophages function as initiating cells in wound healing, mainly to secrete growth factors.

During any immune response, the antigen must undergo processing by an antigen-presenting cell (APC). Subsequently, the APC displays both the antigen and HLA class II molecules on its

surface concurrently. These displayed molecules are picked up by a T-lymphocyte, which then becomes activated and proceeds with the immune response. HLA-DR, which is part of the HLA class II locus, also influences the immune response. Cells can be prompted to express HLA-DR by various cytokines, indicating the activation status of the cell. However, the presence of HLA-DR alone does not necessarily indicate that the cell is presenting antigen.

Numerous experiments have shown the presence of cells with HLA-DR antigen during the bone healing process, particularly during the stages of granulation tissue formation. These cells are often found beside fragments of dead bone having perivascular location [29]. Further studies are underway to establish a relationship between HLA-DR and the bone healing process (Figure 2).

HLA in Orthopaedic Surgical Practice

Bone Grafting and Allografts: HLA matching in structural allografts reduces immune-mediated resorption and failure. While routine in organ transplantation, its role in orthopaedic bone banking is underutilized. Surgeons using massive allografts in tumour reconstruction may benefit from preoperative HLA compatibility checks.

Role of HLA in orthopaedic implant compatibility: HLA matching plays an important part in joint replacements and bone grafts to mitigate rejection risks. Preoperative HLA typing aids in identifying compatibility, thereby reducing immune-related complications and improving the longevity of implants.

More than five million joint replacement surgeries are performed globally each year [30]. Cobalt chrome (CoCr) implants are commonly utilized in most surgeries. However, few patients may develop delayed-type hypersensitivity (DTH) reactions to CoCr alloy, leading to tissue destruction and the necessity for revision and reconstruction surgeries. These DTH reactions are unpredictable, and definitive familial links have yet to be established. Nonetheless, multiple studies have identified specific HLA alleles associated with DTH reactions.

Langton *et al.* [30] identified HLA alleles in patients who experience DTH reactions following joint replacement, establishing a correlation between component wear and the patient's genotype. Additionally, research has found an association between developing aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) and specific HLA genotypes, particularly HLA-DQ. Furthermore, females have been observed to be more susceptible to developing ALVAL in these contexts.

Arthroplasty and Implant Hypersensitivity

Metal hypersensitivity, particularly to cobalt-chromium alloys, can cause aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) and implant loosening. Certain HLA-DQ alleles increase susceptibility.

Orthopaedic Practice Implications:

- Consider HLA typing in patients with unexplained implant pain/swelling and negative infection workup.
- Use hypoallergenic implant options for high-risk individuals (Figure 3).

HLA in Orthopedic Oncology:

HLA class I expression in osteosarcoma correlates with better

survival, suggesting immune surveillance benefits. Conversely, reduced HLA expression in chondrosarcoma allows immune evasion.

For Orthopaedic Oncologists:

- HLA phenotyping may help stratify prognosis.
- Trials targeting PD-1/PD-L1 in HLA-expressing chondrosarcoma are promising for integrating surgery with immunotherapy.

HLA expression plays a critical role in determining tumour immunogenicity and immunotherapy response in musculoskeletal tumours. Analyzing HLA patterns helps identify potential immunotherapeutic targets, enabling the development of personalized treatment strategies (Figure 4).

Tumors like osteosarcoma have been extensively studied for their expression of HLA class I molecules. It has been observed that osteosarcoma patients showing increased HLA class I expression have much better overall and event-free survival rates compared to osteosarcomas that are negative for HLA class I. These findings suggest that cytotoxic T-lymphocytes, which are class-I restricted, play a vital role in the immune status and surveillance of patients with osteosarcoma.

In another study conducted in the Japanese population, the presence of the HLA-A11 phenotype was found to be a predisposing factor leading to osteosarcoma [31]. These data suggest that MHC-linked genes may determine susceptibility to osteosarcoma.

Several studies have examined the expression of HLA-I in chondrosarcoma, particularly focusing on the dedifferentiated subtype, to evaluate its potential for response to immunotherapy [32]. The presence of PD-L1 expression, along with immune-infiltrating cells and HLA class I expression in nearly 50% of dedifferentiated chondrosarcomas, suggests a justification for including these patients in clinical trials that focus on PD-1/PD-L1-targeted therapies.

Deficiencies in HLA class I antigen and checkpoint molecules, expression such as B7-H3 and PD-1/PD-L1, indicate that cancer cells employ escape mechanisms to evade the immune system [33]. These findings suggest that tumours like chondrosarcoma could respond to therapies aimed at enhancing the tumour antigen immunogenicity (Figure 5).

Clinical Integration and Future Directions

Routine HLA typing is not yet standard in orthopaedics but could be considered:

- In young patients with chronic inflammatory joint/spine pain.
- Before complex revision arthroplasty, especially with prior metal hypersensitivity.
- In tumour reconstruction requiring allografts.

Future challenges include standardizing testing, interpreting results in mixed clinical contexts, and integrating findings into cost-effective workflows (Figure 6).

Conclusion

The role of HLA in orthopaedics is multifaceted and holds significant clinical implications. The association between HLA and autoimmune joint diseases such as RA, AS, and PsA highlights the

genetic predisposition to these conditions. Specifically, the strong correlation between certain HLA alleles, such as those encoding the shared epitope motif in RA and HLA-B27 in AS, provides valuable insights into disease pathogenesis, aiding in early diagnosis and personalized treatment strategies.

Moreover, HLA compatibility is paramount in orthopaedic surgeries involving joint replacements and bone grafts to minimize the risk of rejection and implant failure. Preoperative HLA typing improves surgical outcomes and long-term implant survival rates.

Furthermore, emerging research suggests a role for HLA molecules in bone healing processes and their implications in orthopaedic oncology, where HLA expression patterns influence tumour immunogenicity and response to immunotherapy.

The Human Leukocyte Antigen (HLA) system holds substantial clinical significance in the field of orthopaedics, influencing diagnosis, prognosis, and therapeutic strategies across a spectrum of musculoskeletal conditions. Its strong genetic associations with autoimmune diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) underscore the importance of HLA typing in identifying disease susceptibility and predicting clinical outcomes. The presence of specific alleles—such as HLA-DRB1 shared epitope sequences in RA and HLA-B27 in AS—provides critical insight into disease mechanisms, aiding in early diagnosis and individualized treatment planning.

Beyond autoimmune disorders, HLA typing has growing relevance in orthopaedic surgery. Preoperative HLA compatibility assessments may reduce the risk of immune-mediated complications following joint replacement and bone grafting procedures. Hypersensitivity reactions to metal implants, particularly involving cobalt-chromium alloys, have been associated with certain HLA genotypes, such as HLA-DQ alleles, contributing to implant failure and the need for revision surgeries.

In bone healing, the involvement of HLA-DR-expressing immune cells during fracture repair highlights its role in orchestrating inflammatory responses and tissue regeneration. This connection suggests a potential avenue for targeted therapies to enhance or modulate bone repair processes.

In orthopaedic oncology, the expression of HLA molecules influences tumour immunogenicity and the response to emerging immunotherapies. HLA class I expression in tumours like osteosarcoma and dedifferentiated chondrosarcoma is associated with improved outcomes, indicating that immunogenetic profiling may guide personalized treatment strategies in oncology.

In conclusion, the HLA system serves as a bridge between immunology and orthopaedics. Its diverse roles—from autoimmunity to surgical compatibility and cancer therapy—underscore the need to incorporate HLA profiling into routine orthopaedic practice. Advancing research in this field promises to refine personalized care, optimize clinical outcomes, and foster a deeper understanding of immune-mediated musculoskeletal pathology.

Recommendations

Further research is needed in the field to further elucidate the complex role of HLA in orthopaedics, paving the way for personalized medicine approaches and improved patient outcomes. Challenges

such as standardizing HLA typing methods and integrating HLA data into clinical decision-making frameworks persist.

Conflict of Interest

None.

Financial Support

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Take-Home Points by Section

HLA in Autoimmune & Inflammatory Joint Disorders

- HLA typing (B27, DRB1) can aid early diagnosis and prognosis in AS and RA.
- In RA, HLA-DRB1 “shared epitope” predicts more aggressive joint destruction.
- In AS, HLA-B27 positivity correlates with earlier onset and more severe spinal deformity.

HLA in Orthopaedic Surgical Practice

- HLA matching in bone allografts may improve survival and integration.
- HLA-DQ typing can help identify patients at risk for implant hypersensitivity before surgery.
- Hypoallergenic implant options may be warranted in genetically susceptible patients.

HLA and Bone Healing

HLA-DR-expressing immune cells participate in fracture callus formation.

Potential future use of HLA typing to identify patients at risk of delayed or impaired healing.

HLA in Orthopaedic Oncology

HLA class I expression in osteosarcoma correlates with better prognosis.

Low HLA expression in chondrosarcoma may enable immune evasion; HLA profiling could guide immunotherapy trials.

References

1. Zinkernagel RM, Doherty PC. The discovery of MHC restriction. *Immunol Today*, 1997; 18(1): 14–7. DOI: 10.1016/s0167-5699(97)80008-4
2. Carey BS, Poulton KV, Poles A. Factors affecting HLA expression: A review. *Int J Immunogenet*, 2019; 46(5): 307–20. DOI: 10.1111/iji.12443
3. Gotfredsen A, Pødenphant J, Nørgaard H, Nilas L, Nielsen VA, Christiansen C. Accuracy of lumbar spine bone mineral content by dual photon absorptiometry. *J Nucl Med*, 1988; 29(2): 248–54.
4. Delbos F, Barhoumi W, Cabanne L, Beckerich F, Robin C, Redjoul R, et al. Donor Immunization Against Human Leukocyte Class II Antigens is a Risk Factor for Graft-versus-Host Disease. *Biol Blood Marrow Transplant*, 2016; 22(2): 292–9. doi: 10.1016/j.bbmt.2015.09.027
5. Parham P. Function and polymorphism of human leukocyte antigen-A,B,C molecules. *Am J Med*, 1988; 85(6A): 2–5. doi: 10.1016/0002-9343(88)90369-5
6. Chen B, Li J, He C, Li D, Tong W, Zou Y, et al. Role of HLA-B27 in the pathogenesis of ankylosing spondylitis. *Mol Med Rep*, 2017; 15(4): 1943–51. doi: 10.3892/mmr.2017.6248
7. van Drongelen V, Holoshitz J. HLA-Disease Associations in Rheumatoid Arthritis. *Rheum Dis Clin North Am*, 2017; 43(3): 363–76. doi: 10.1016/j.

- rdc.2017.04.003
8. Eastmond CJ, Woodrow JC. The HLA system and the arthropathies associated with psoriasis. *Annals of the Rheumatic Diseases*, 1977; 36(2): 112–20.
 9. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum*, 2000; 43(1): 30–7. DOI: 10.1002/1529-0131(200001)43:1<30::AID-ANR5>3.0.CO;2-B
 10. Astorga GP, Williams RC. Altered reactivity in mixed lymphocyte culture of lymphocytes from patients with rheumatoid arthritis. *Arthritis Rheum*, 1969; 12(6): 547–54. doi: 10.1002/art.1780120602
 11. McMichael AJ, Sasazuki T, McDevitt HO, Payne RO. Increased frequency of HLA-Cw3 and HLA-Dw4 in rheumatoid arthritis. *Arthritis Rheum*, 1977; 20(5): 1037–42. doi: 10.1002/art.1780200501
 12. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. *N Engl J Med*, 1978; 298(16): 869–71. doi: 10.1056/NEJM197804202981602
 13. Miyadera H, Tokunaga K. Associations of human leukocyte antigens with autoimmune diseases: challenges in identifying the mechanism. *J Hum Genet*, 2015; 60(11): 697–702. doi: 10.1038/jhg.2015.100
 14. Han B, Diogo D, Eyre S, Kallberg H, Zhernakova A, Bowes J, et al. Fine mapping seronegative and seropositive rheumatoid arthritis to shared and distinct HLA alleles by adjusting for the effects of heterogeneity. *Am J Hum Genet*, 2014; 94(4): 522–32. doi: 10.1016/j.ajhg.2014.02.013
 15. Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X, et al. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. *Nat Genet*, 2012; 44(3): 291–6. doi: 10.1038/ng.1076
 16. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum*, 1987; 30(11): 1205–13. doi: 10.1002/art.1780301102
 17. Matvey DL, Hassell AB, Dawes PT, Cheung NT, Poulton KV, Thomson W, et al. Independent association of rheumatoid factor and the HLA-DRB1 shared epitope with radiographic outcome in rheumatoid arthritis. *Arthritis Rheum*, 2001; 44(7): 1529–33. doi: 10.1002/1529-0131(200107)44:7<1529::AID-ART275>3.0.CO;2-P
 18. Gonzalez-Gay MA, Garcia-Porrua C, Hajeer AH. Influence of human leukocyte antigen-DRB1 on the susceptibility and severity of rheumatoid arthritis. *Semin Arthritis Rheum*, 2002; 31(6): 355–60. doi: 10.1053/sarh.2002.32552
 19. Malaviya AN. Spondyloarthritis in India. *Indian Journal of Rheumatology*, 2020; 15(Suppl 1): S2.
 20. Braun J, Sieper J. Ankylosing spondylitis. *Lancet*, 2007; 369(9570): 1379–90.
 21. Végvári A, Szabó Z, Szántó S, Glant TT, Mikecz K, Szekanecz Z. The genetic background of ankylosing spondylitis. *Joint Bone Spine*, 2009; 76(6): 623–8. doi: 10.1016/j.jbspin.2009.02.006
 22. Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HL-A 27. *Lancet*, 1973; 1(7809): 904–7. doi: 10.1016/s0140-6736(73)91360-3
 23. Chatzikyriakidou A, Voulgari PV, Drosos AA. What is the role of HLA-B27 in spondyloarthropathies? *Autoimmun Rev*, 2011; 10(8): 464–8. doi: 10.1016/j.autrev.2011.01.011
 24. International Genetics of Ankylosing Spondylitis Consortium (IGAS), Cortes A, Hadler J, Pointon JP, Robinson PC, Karaderi T, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet*, 2013; 45(7): 730–8. doi: 10.1038/ng.2667
 25. Evidence of association and linkage disequilibrium between a novel polymorphism in the transforming growth factor β 1 gene and hip bone mineral density: a study of female twins1 | *Rheumatology* | Oxford Academic [Internet]. [cited 2024 Mar 24]; Available from: <https://academic.oup.com/rheumatology/article/40/1/48/1784000>
 26. Leirisalo M, Skylv G, Kousa M, Voipio-Pulkki LM, Suoranta H, Nissilä M, et al. Followup study on patients with Reiter's disease and reactive arthritis, with special reference to HLA-B27. *Arthritis Rheum*, 1982; 25(3): 249–59. doi: 10.1002/art.1780250302
 27. Bas S, Kvien TK, Buchs N, Fulpius T, Gabay C. Lower level of synovial fluid interferon-gamma in HLA-B27-positive than in HLA-B27-negative patients with Chlamydia trachomatis reactive arthritis. *Rheumatology (Oxford)*, 2003; 42(3): 461–7. doi: 10.1093/rheumatology/keg163
 28. Jaraquemada D, Ollier W, Awad J, Young A, Silman A, Roitt IM, et al. HLA and rheumatoid arthritis: a combined analysis of 440 British patients. *Ann Rheum Dis*, 1986; 45(8): 627–36. doi: 10.1136/ard.45.8.627
 29. Andrew JG, Andrew S, Freemont A, Marsh D. Inflammatory cells in normal human fracture healing. *Sort*, 1994; 65(4): 462–6. doi: 10.3109/17453679408995493
 30. Langton DJ, Bhalekar RM, Joyce TJ, Rushton SP, Wainwright BJ, Nargol ME, et al. The influence of HLA genotype on the development of metal hypersensitivity following joint replacement. *Commun Med (Lond)*, 2022; 2: 73.
 31. Shimizu T, Chigira M, Nagase M, Watanabe H, Udagawa E. HLA phenotypes in patients who have osteosarcoma. *JBJs*, 1990; 72(1): 68.
 32. Kostine M, Clevén AH, de Miranda NFCC, Italiano A, Cleton-Jansen AM, Bovée JVMG. Analysis of PD-L1, T-cell infiltrate and HLA expression in chondrosarcoma indicates potential for response to immunotherapy specifically in the dedifferentiated subtype. *Mod Pathol*, 2016; 29(9): 1028–37. doi: 10.1038/modpathol.2016.108
 33. Nota SPFT, Al-Sukaini A, Patel SS, Sabbatino F, Nielsen GP, Deshpande V, et al. High TIL, HLA, and Immune Checkpoint Expression in Conventional High-Grade and Dedifferentiated Chondrosarcoma and Poor Clinical Course of the Disease. *Front Oncol*, 2021; 11: 598001. doi: 10.3389/fonc.2021.598001