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# The link between HLA genes and autoimmune disease: A comprehensive review

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## Abstract

Autoimmune diseases (ADs) are a heterogeneous group of chronic inflammatory diseases, where immunological self-antigen tolerance is lost. These diseases are multifactorial and are a complex combination of environmental influences and genetic susceptibility. The human leukocyte antigen (HLA) complex, found in the major histocompatibility complex (MHC) on chromosome 6, is the most important genetic determinant of autoimmune susceptibility. The review gives a detailed discussion of the association between HLA genes and autoimmune diseases and discusses the molecular pathways of such associations. We discuss particular HLA-disease associations, such as the association between HLA-DRB1 and rheumatoid arthritis, HLA-DQ2/DQ8 and celiac disease, HLA-DR4 and HLA-DR3, and type1 diabetes HLA-B27 with ankylosing spondylitis. In addition, we comment on emerging patterns, such as allele-specific polarization of macrophages, and HLA, the gut microbiome, and autoimmune comorbidity. Such complicated processes are necessary to comprehend to develop effective immunotherapies and personalized medicine approaches in the treatment of patients with autoimmune disorders.

**Keywords:** HLA; Autoimmune disease; Celiac disease; SLE

## 1. Introduction

Autoimmune diseases are chronic and multifaceted inflammatory, which is an abnormal immune reaction towards the body itself (Cruz-Tapias et al., 2013). They are said to be organ specific or systemic and caused by dysregulated humoral (B cell) and cellular (T cell) immune responses. The clinical features of autoimmunity are very varied, including organ-specific diseases such as type 1 diabetes mellitus (T1D), as well as systemic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Though their exact etiology has always been elusive, it is well known that ADs are caused by a set of environmental factors, as well as polygenic factors that determine how susceptible or protective an individual is (Thorsby & Lie, 2005).

The genetic structure of autoimmune diseases is not straightforwardly Mendelian; that is, it is multifactorial. In monozygotic and dizygotic twins, studies have always reported a significant genetic role in these disorders. As an example, twin studies have shown a much higher rate of concordance among monozygotic twins (63%) than among dizygotic twins (23%). In the case of ankylosing spondylitis (AS), the concordance rate is significantly higher among monozygotic twins (63% vs. 23%). Of the numerous genetic loci that have been associated with autoimmunity, the most appropriate and most widely studied are the genes found in the Major histocompatibility complex (MHC), namely the Human Leukocyte Antigen (HLA) class I and the class II genes (Caillat-Zucman, 2009). HLA genes have been linked to a higher number of diseases compared to any other part of the human genome. A comprehensive list of ADs has been linked with the variants of the HLA genes, especially class II genes (Cruz-Tapias et al., 2013).

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The correlation between HLA and disease is not linear. The alleles that come with different ADs could differ greatly between populations and even within a population, other alleles may be linked to different ADs. This incredible polymorphism is a characteristic of the HLA system, which is evolutionary in nature, to provide a wide population level protection against a wide range of pathogens. But the same diversity is simultaneously a predetermining factor of some people developing autoimmunity (Ruiz-Pablos et al., 2025). The purpose of this review is to provide a synthesis of the existing knowledge on the association between HLA genes and autoimmune diseases. We explore the molecular processes underlying the conversion of genetic predilection to pathogenic reality, examine the unique HLA relationships in different autoimmune diseases, and address the new role of the microbiome in regulating such genetic risks.

## 2. Molecular Pathogenesis of HLA-Disease Association

The basic mechanism by which HLA molecules works is attaching peptide fragments of the intracellular or extracellular proteins and displaying them on the cell surface to be recognized by T lymphocytes. This is the basis of the adaptive immune response because of this antigen presentation. But once this process becomes maladjusted, it may result in autoimmunity. Some theories have been put forward to support how certain HLA alleles result in vulnerability or immunity to autoimmune disease.

### 2.1. The Antigen Presentation and Molecular Mimicry Hypotheses

The antigen presentation hypothesis is the most classic explanation of the association of HLA-disease. According to this model, disease-related HLA molecules have a distinctive peptide-binding groove which enables them to selectively bind and display specific autoantigens (self-peptides) to autoreactive T cells (Moustakas et al., 2023). When these autoreactive T cells have not been eliminated by thymic negative selection (central tolerance) or peripheral tolerance, their activation may trigger an autoimmune cascade and closely related to this is the molecular mimicry concept. It is assumed that certain peptide sequences with infectious origin (viral or bacterial) may have a high structural similarity to those of self-proteins (Cruz-Tapias et al., 2013). Cross-reactivity can occur when the immune system develops a response to the invading pathogen and the structural similarity of the microbial antigen and the host tissue is too great. The response of microorganisms to the first antimicrobial initiates an autoimmune response that results in the display of self-proteins in the setting of HLA molecules although their sources are different (Sollid et al., 2014).

### 2.2. The Shared Epitope (SE) Hypothesis

One of the most prominent theories that explain the relationship between HLA and rheumatoid arthritis (RA) is the Shared Epitope (SE) hypothesis. This hypothesis, originally suggested by Gregersen *et al*., assumes that alleles of HLA-DRB1 that are linked to disease have a conserved motif in amino acid sequence in the third hypervariable region of the DRB1 chain (Holoshitz, 2010). In particular, through a comparison of amino acid sequences encoded by disease-related alleles of the HLA-DRB1, researchers revealed a conserved motif (L-LE-[Q/R]-[R/K]-R-A-A) at the residues 70-74 (Balsa et al., 2010).

It has been postulated that alleles with SE cause the activation of T cells that have autoreactive properties. This is validated by crystallographic studies showing that certain amino acid residues on the SE form a direct contact with the T cell receptor (TCR), and could be used to select a particular subset of "SE recognizing" T lymphocytes (Holoshitz, 2010). Moreover, alteration of 70-74 amino acid of the 70-74 amino-acid sequence of the 70-74 amino acid of the SE alleles can radically modify the repertoire of peptides that are initially presented by these molecules. On the other hand, protective alleles are also found in the HLA-DRB1 locus. Carriers with the same allele containing the sequence of deraa (i.e. aspartic acid at positions 70-74) are less susceptible to RA and typically do not develop the disease as severely (Balandraud et al., 2013).

### 2.3. Beyond Antigen Presentation: Macrophage Polarization

Allele-specific antigen presentation has been hypothesized to be the main culprit, but it has been unclear whether HLA molecules could also have non-antigen-presenting, disease-modulating effects. Cutting-edge studies have shed light on a new, antigen presentation-independent mode of action, through which HLA molecules control immune responses: the macrophage polarization modulation (van Drongelen et al., 2021). An influential experiment by van Drongelen *et al.* revealed differences in macrophage activation in response to HLA-DRB1 alleles that have been found to be either risk or protective of autoimmune diseases (van Drongelen et al., 2021). Macrophages are very plastic immune cells capable of taking different functional phenotypes based on their microenvironment. They can be broadly described as pro-inflammatory (M1) macrophages, which mediate tissue damage and inflammation, and anti-inflammatory (M2) macrophages, which mediate tissue repair and resolution of inflammation (Liu et al., 2011). Molecular processes that control the polarization of macrophage M1-M2 entail complicated signal transduction, transcriptional, and post-

transcriptional regulation .The molecular aspects involved in the maintenance of this polarization balance have been thoroughly investigated by Zen and colleagues who have identified some of the critical signaling molecules such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and suppressors of cytokine signaling (SOCS) proteins , Alteration of these pathways, possibly with HLA allelic variants, may switch the balance to the pro-inflammatory M1 polarization, which leads to the development of autoimmune diseases (Zen et al., 2014).

### 2.4. HLA Misfolding and Unfolded Protein Response.

The misfolding hypothesis, as an alternative to the peptide presentation models, is a plausible one in the context of HLA class I associations, especially the HLA-B27 and ankylosing spondylitis. In contrast to the majority of HLA class I molecules, HLA-B27 possesses an exclusive tendency to progress slowly and ineffectively during the endoplasmic reticulum (ER) (Colbert, 2014). The build-up of these misfolded heavy chains initiates the unfolded protein response (UPR), a cell stress program that is meant to restore ER homeostasis. But the chronic stimulation of the UPR in antigen-presenting cells such as macrophages and dendritic cells may cause the increase of pro-inflammatory cytokines such as Interleukin-23 (IL-23) (DeLay et al., 2009). Th17 cells (producing IL-17) are crucial to the survival and proliferation of Th17 cells, which are important mediators of inflammation and pathological bone formation in spondyloarthritis (Smith et al., 2014).

## 3. HLA-Autoimmune Disease Associations

The HLA-disease association landscape is immense, yet a few major associations have been thoroughly described, which offers important insights into disease pathogenesis.

### 3.1. Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a systemic autoimmune disorder, which is accompanied by chronic inflammation of the synovial joints, and destruction of cartilage and bone. One of the strongest results in complex genetics is the genetic association between RA and HLA complex, namely, the HLA-DRB1 gene (Cruz-Tapias et al., 2013). The HLA-DRB104:05 gene in Spaniards and Japanese, and HLA-DRB101:02 and HLA-DRB101:01 in Israelis are also relevant HLA genes implicated in predisposition to RA (Cruz-Tapias et al., 2013). Importantly, the interdependence between HLA-DRB1 and RA is closely connected with the existence of a particular autoantibodies. It has been found that the relationship between DRB1 SE alleles and RA is specifically limited mostly in anti-cyclic citrullinated peptide antibody (ACPA)-positive RA (Too et al., 2012). Citrullination is a non-coded post-translational modification, in which the amino acid arginine is replaced with citrulline by peptidylarginine deiminase (PAD) proteins. The hypothesis is that the SE-containing HLA-DR molecules have a peptide-binding groove that especially favors accommodating and presenting the citrullinated peptides to T cells and thus breaking tolerance and triggering the ACPA-positive fraction of RA (Klareskog et al., 2011).

### 3.2. Type 1 Diabetes (T1D) and Celiac Disease (CD)

Two different autoimmune diseases, type 1 diabetes and celiac disease, have an impressive overlapping genetic composition in the HLA class II region. T1D is an autoimmune destruction of insulin-producing beta cells in the pancreas whereas CD is an enteropathy caused by the ingestion of dietary gluten in genetically susceptible people. HLA-DR3 and DR4 haplotypes are strongly associated with disease susceptibility (Atkinson et al., 2014). HLA-DQ locus is strongly related to both diseases. About 95 percent of people with celiac disease have the HLA class II genes DQ2 and DQ8 (Rogalidou et al., 2026). This common genetic composition often leads to clinical comorbidity; T1D patients are many times at a very high risk of developing CD than the general population, and vice versa. In celiac disease, the mechanism is exceptionally well-characterized. The HLA-DQ2 and HLA-DQ8 molecules have binding grooves that preferentially bind gluten peptides that have been deamidated by the enzyme tissue transglutaminase (tTG) in the gut mucosa (Kim et al., 2004). This binding presents the modified gluten to CD4+ T cells, triggering a robust inflammatory response. The shared HLA-DQ2/DQ8 background in T1D suggests that similar mechanisms of specific peptide presentation are at play, although the precise autoantigens (e.g., insulin, glutamic acid decarboxylase) differ (Tran et al., 2021). The mechanism is exceptionally well-characterized in the case of celiac disease. The HLA-DQ2 and HLA-DQ8 molecules have binding grooves that preferentially bind gluten peptides that have been deamidated by the enzyme tissue transglutaminase (tTG) in the gut mucosa (Kim et al., 2004). This binding introduces the modified gluten to the CD4+ T cells, causing a strong inflammatory response. The HLA-DQ2/DQ8 commonality in T1D indicates that the same mechanisms of specific peptide presentation are involved, but the actual autoantigens (e.g., insulin, glutamic acid decarboxylase) are different (Tran et al., 2021).

### 3.3. Ankylosing Spondylitis (AS)

Ankylosing spondylitis is a disease that is autoimmune, chronic inflammatory and is predominantly active in the joints of the spine resulting in severe pain and severe cases leading to the fusion of the spine (Zhu et al., 2019). One very strong HLA-disease association and one of the strongest known relationships is that between AS and HLA-B27 allele, 90 percent to 95 percent of the AS patients are HLA-B27 positive (Reveille et al., 1989). Nonetheless, the HLA-B27 alone cannot cause the disease and only 1%2% of HLA-B27-positive groups develop AS, meaning that other genetic or environmental factors are necessary (Wang et al., 2021). Moreover, HLA-B27 is very polymorphic with more than 100 subtypes. These subtypes occur more frequently in some ethnicities with HLA-B27:05 the most common in Caucasians, and HLA-B27:04 in Chinese populations (Zhu et al., 2019). The pathogenesis of AS is complicated. HLA-B27 can present a microbial peptide which can stimulate a cross-reactive CD8+ T cell response with a self-peptide, according to arthritogenic peptide hypothesis (Cruz-Tapias et al., 2013). At the same time, HLA-B27 misfolding and the IL-23/IL-17 axis activation contribute significantly to the development of the typical inflammation and osteoprolliferation observed in AS (DeLay et al., 2009).

### 3.4. Multiple Sclerosis (MS)

Multiple sclerosis is a chronic, inflammatory and demyelinating central nervous system (CNS) disease that is autoreactive, mediated by autoreactive T cells against myelin antigens. The HLA class II region, HLA-DRB1*15:01, is also closely connected with genetic predisposition to MS, so that people with at least one allele are at a threefold risk of MS (Klotz et al., 2025). The dominant hypothesis is that the HLA-DRB1*15:01 molecules are unusually effective in presenting peptides of myelin origin to the CD4+ T cells (Fguirouche et al., 2025). Recent reports also indicate that Epstein-Barr virus (EBV) infection can re-program the transcriptome and immunopeptidome displayed on the MS-related HLA-DR15, to trigger the autoimmune response (Wang et al., 2025).

### 3.5. Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a very heterogeneous, systemic autoimmune disorder, which involves the production of autoantibodies that target a large range of nuclear antigens. SLE has a very complex genetic pathophysiology, although the HLA region has played a major role (Leffers et al., 2025). Strength in detail, alleles of HLA class II, especially, HLA-DRB103:01 (HLA-DR3) and HLA-DRB115:01 (HLA-DR15) are always linked with the higher risk factor of the development of SLE (Xue et al., 2018). Such molecules are believed to be very effective in presenting nuclear autoantigens to helper T cells, which offer the help required by the autoreactive B cells to generate pathogenic autoantibodies (Graham et al., 2007).

## 4. HLA-Environmental Trigger Interplay

The fact that HLA-associated diseases are incompletely penetrant is a strong indicator that environmental factors are needed to trigger them. environmental exposures are one of the main cause that have a role of autoimmune pathogenesis (Table 1).

**Table 1** HLA Alleles Associated with autoimmune disease

| Autoimmune Disease | Associated HLA Alleles | Proposed Mechanism | Environmental Trigger/ Antigen |
|---|---|---|---|
| Rheumatoid Arthritis | HLA-DRB1 (Shared Epitope) | Antigen presentation, M1 macrophage polarization | Smoking (induces citrullination) |
| Celiac Disease | HLA-DQ2,HLA-DQ8 | Presentation of tTG-deamidated peptides | Dietary Gluten |
| Ankylosing Spondylitis | HLA-B27 | UPR/ER stress, molecular mimicry | Microbial infections (e.g., Salmonella) |
| Type 1 Diabetes | HLA-DR3,HLA-DR4 | Autoantigen presentation | Viral infections (suspected) |
| Multiple Sclerosis | HLA-DRB1*15:01 | Myelin antigen presentation | Epstein-Barr Virus (EBV) |

### 4.1. Smoking and Citrullination in Rheumatoid Arthritis

The relationship between smoking and HLA-DRB1 Shared Epitope (SE) alleles in RA is an interesting instance of gene-environment interaction. Smoking causes Oxidative stress and lungs inflammation which triggers PAD enzymes to convert arginine residues into citrulline (Klareskog et al., 2011). A person with HLA-DRB1 SE alleles has genetically predisposed immune system that is better able to identify these citrullinated peptides. the SE-containing HLA-DR molecules effectively bind and present these neo-antigens causing the ACPAs to be produced (Too et al., 2012). Rheumatoid arthritis is a serious disease that can be managed through smoking and citrullination.

### 4.2. The HLA-Microbiome-Autoimmunity Triplex

The crossroads of host genetics, the gut microbiome, and autoimmunity is an emerging field of research. Autoimmunity is frequently associated with dysbiosis, resulting in loss of barrier function and permeability of tight junctions ("leaky gut") (Berryman et al., 2023). Importantly, the connection between HLA and the microbiome seems bi-directional. HLA haplotypes that are associated with autoimmune risks are related to gut dysbiosis even prior to the development of autoimmune disease According to this "HLA-microbiome-autoimmunity triplex," certain HLA molecules influence the shaping of the developing microbiome by selective tolerance, or response to specific microbial antigens (Russell et al., 2019). The high-risk HLA alleles can also result in a microbiome that is intrinsically more pro-inflammatory, thus reducing the autoimmune activation threshold (Berryman et al., 2023).

## 5. Conclusion

The association of HLA genes with autoimmune disease is the biggest genetic input to the breakdown of immunological self-tolerance. Since the classical models of antigen presentation and molecular mimicry, to the more subtle models of the shared epitope and HLA misfolding, our knowledge of these mechanisms has changed significantly. The finding that HLA-DRB1 allelic epitopes have the capability to directly stimulate reciprocal polarization of macrophages without the need to present antigens provides an intriguing twist of complexity . Moreover, the understanding that these genetic factors are intertwined with environmental stimuli, as well as the gut microbiome, demonstrates the need to consider autoimmunity in a holistic, systems-biology, framework. Eventually, this enhanced understanding will propel the development of precision medicine, which will provide specific therapies that interrupt the pathogenic pathways that are determined by an individual HLA profile.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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