

# HLA-DRB1 Gene

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## 1. Introduction

The *HLA-DRB1* gene provides instructions for making a protein that plays a critical role in the immune system. The *HLA-DRB1* gene is part of a family of genes called the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria.

The HLA complex is the human version of the major histocompatibility complex (MHC), a gene family that occurs in many species. The *HLA-DRB1* gene belongs to a group of MHC genes called MHC class II. MHC class II genes provide instructions for making proteins that are present on the surface of certain immune system cells. These proteins attach to protein fragments (peptides) outside the cell. MHC class II proteins display these peptides to the immune system. If the immune system recognizes the peptides as foreign (such as viral or bacterial peptides), it triggers a response to attack the invading viruses or bacteria.

The protein produced from the *HLA-DRB1* gene, called the beta chain, attaches (binds) to another protein called the alpha chain, which is produced from the *HLA-DRA* gene. Together, they form a functional protein complex called the HLA-DR antigen-binding heterodimer. This complex displays foreign peptides to the immune system to trigger the body's immune response.

Each MHC class II gene has many possible variations, allowing the immune system to react to a wide range of foreign invaders. Researchers have identified hundreds of different versions (alleles) of the *HLA-DRB1* gene, each of which is given a particular number (such as *HLA-DRB1\*04:01*).

## 2. Health Conditions Related to Genetic Changes

### 2.1. Autoimmune Addison Disease

Certain variations in the *HLA-DRB1* gene have been linked to an increased risk of developing an autoimmune disorder called autoimmune Addison disease. Autoimmune disorders occur when the immune system malfunctions and attacks the body's tissues and organs. In autoimmune Addison disease, the immune system attacks the adrenal glands, which are small hormone-producing glands located on top of each kidney. Loss of hormones produced by the adrenal glands leads to the features of the condition, which include extreme tiredness (fatigue), nausea, low blood pressure (hypotension), and abnormally dark areas of skin (hyperpigmentation), especially in regions that experience a lot of friction such as the armpits, elbows, and knuckles. A particular *HLA-DRB1* gene variant called *HLA-DRB1\*04:04* is the most well-known risk factor for autoimmune Addison disease.

Normally, the immune system responds only to proteins made by foreign invaders, not to the body's own proteins. In autoimmune Addison disease, however, an immune response is triggered by a normal adrenal gland protein; in about 85 percent of people with autoimmune Addison disease, the protein is 21-hydroxylase. 21-hydroxylase is found in the adrenal glands where it plays a key role in producing a variety of hormones that regulate many essential functions in the body. The prolonged immune attack triggered by 21-hydroxylase damages the adrenal glands (specifically the outer layers of the glands known, collectively, as the adrenal cortex), preventing hormone production. A shortage of adrenal hormones (adrenal insufficiency) disrupts several normal functions in the body, leading to the diverse features of autoimmune Addison disease. It is not clear how *HLA-DRB1\*04:04* and other *HLA-DRB1* variations are involved in the inappropriate immune response that causes autoimmune Addison disease.

## 2.2. Multiple Sclerosis

Variations in the *HLA-DRB1* gene have been associated with an increased risk of developing multiple sclerosis. This condition affects the brain and spinal cord (central nervous system), causing muscle weakness, poor coordination, numbness, and a variety of other health problems. One variant of this gene, called *HLA-DRB1\*15:01*, is the most strongly linked genetic factor for the risk of multiple sclerosis.

Because the *HLA-DRB1* gene is involved in the immune system, changes in it might be related to the autoimmune response and inflammation that damage nerves and the protective coating surrounding them (the myelin sheath), leading to the signs and symptoms of multiple sclerosis. However, it is unclear exactly what role *HLA-DRB1* gene variants play in development of multiple sclerosis. A combination of genetic and environmental factors is likely involved in this condition.

## 2.3. Rheumatoid Arthritis

Several common variations of the *HLA-DRB1* gene are associated with a person's risk of developing rheumatoid arthritis. This disease causes chronic abnormal inflammation that primarily affects the joints. *HLA-DRB1* is one of several genes in the HLA complex that have been associated with rheumatoid arthritis; variations of this gene are the most significant known genetic risk factor for the disease.

The *HLA-DRB1* gene variations associated with an increased risk of rheumatoid arthritis affect single protein building blocks (amino acids) in the beta chain. These changes occur near the antigen-recognizing binding groove, which is the part of the protein that attaches (binds) to viral or bacterial peptides. This binding triggers the immune response that attacks foreign invaders. Although the mechanism by which *HLA-DRB1* gene variations increase the risk of rheumatoid arthritis is unclear, researchers suspect it is related to changes in peptide binding that stimulate an abnormal immune response. However, many other genetic and environmental factors also contribute to a person's overall risk of developing rheumatoid arthritis.

A few variations of the *HLA-DRB1* gene appear to decrease the risk of developing rheumatoid arthritis. It is unclear why these particular changes may be protective.

## 2.4. Type 1 Diabetes

Combinations of variations in the *HLA-DRB1* gene and other HLA genes affect the risk of type 1 diabetes. Type 1 diabetes is characterized by high blood sugar levels resulting from a shortage of the hormone insulin and is caused by autoimmune damage to insulin-producing cells in the pancreas.

Type 1 diabetes risk is most increased by two specific combinations of variations of the *HLA-DRB1* gene and other HLA genes called *HLA-DQA1* and *HLA-DQB1*. Combinations of HLA gene variants are called HLA haplotypes. One haplotype, written as *DRB1\*03:01-DQA1\*05:01-DQB1\*02*, is called DR3. The other haplotype, written as *DRB1\*04:01/02/04/05/08-DQA1\*03:01-DQB1\*02*, is called DR4. People at highest risk of developing type 1 diabetes have one copy of the DR3 haplotype and one copy of the DR4 haplotype in each cell. Other HLA haplotypes only mildly increase the risk of type 1 diabetes, while some haplotypes seem to protect against developing this condition. Variations in other genes and environmental factors are also thought to affect the risk of this complex disorder.

## 2.5. Autoimmune Disorders

Normal variations of the *HLA-DRB1* gene have been associated with many other autoimmune disorders, including pemphigus, sarcoidosis, and others listed on this page. Pemphigus is a condition that causes severe blistering of the skin and mucous membranes (such as the moist lining of the mouth). Sarcoidosis is a disorder in which inflammation occurs in many organs and tissues of the body.

It is unclear how different versions of the *HLA-DRB1* gene influence the risk of developing autoimmune disorders. These disorders typically result from a combination of multiple environmental and genetic factors. Changes in other HLA and non-HLA genes, some of which remain unknown, also likely contribute to the risk of developing these complex conditions.

## 3. Other Names for This Gene

- 2B13\_HUMAN
- 2B1F\_HUMAN
- 2B1G\_HUMAN

- DRB1
- DRw10
- DW2.2/DR2.2
- HLA class II histocompatibility antigen, DR-1 beta chain
- HLA-DR1B
- HLA-DRB
- human leucocyte antigen DRB1
- lymphocyte antigen DRB1
- major histocompatibility complex, class II, DR beta 1 precursor
- MHC class II antigen
- MHC class II HLA-DR beta 1 chain
- MHC class II HLA-DR-beta cell surface glycoprotein
- MHC class II HLA-DRw10-beta
- SS1

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