

HLA-DQB1 Gene

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1. Introduction

The *HLA-DQB1* gene provides instructions for making a protein that plays a critical role in the immune system. The *HLA-DQB1* 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-DQB1* 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-DQB1* gene attaches (binds) to the protein produced from another MHC class II gene, *HLA-DQA1*. Together, they form a functional protein complex called an antigen-binding DQαβ 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-DQB1* gene, each of which is given a particular number (such as *HLA-DQB1*06:02*).

2. Health Conditions Related to Genetic Changes

2.1. Celiac Disease

At least two specific combinations of HLA gene variants (HLA haplotypes) have been found to increase the risk of developing celiac disease, a disorder in which inflammation damages the intestinal tract and other organs and tissues. One of these haplotypes, known as DQ2, is composed of the protein produced from *HLA-DQB1* gene variants known as *HLA-DQB1*02:01* or *HLA-DQB1*02:02* bound to the protein produced from *HLA-DQA1* gene variants known as *HLA-DQA1*05:01* or *HLA-DQA1*05:05*. The other haplotype, known as DQ8, is composed of the protein produced from the *HLA-DQB1* gene variant known as *HLA-DQB1*03:02* bound to the protein produced from *HLA-DQA1* gene variants known as *HLA-DQA1*03:01* or *HLA-DQA1*03:02*.

The DQ2 and DQ8 haplotypes, which may occur separately or together, seem to increase the risk of an inappropriate immune response to the protein gluten, which is found in wheat, rye, and barley. This immune system malfunction results in the damage to the body's organs and tissues that occurs in celiac disease. However, the DQ2 and DQ8 haplotypes are also found in 30 percent of the general population, and only 3 percent of individuals with the gene variants develop celiac disease.

2.2. Narcolepsy

A version of the *HLA-DQB1* gene called *HLA-DQB1*06:02* increases the risk of developing the sleep disorder narcolepsy, particularly in people who also have cataplexy. (Cataplexy is a sudden loss of muscle tone in response to strong emotion, such as laughing, surprise, or anger.) It is unclear how *HLA-DQB1*06:02* causes this elevated risk. However, there is increasing evidence that narcolepsy is related to a malfunction of the immune system.

The sleep abnormalities associated with narcolepsy likely result from a loss of particular brain cells (neurons) in a part of the brain called the hypothalamus. These cells normally produce chemicals called hypocretins (also known as orexins), which have many important functions in the body. In particular, hypocretins regulate the daily sleep-wake cycle. Researchers speculate that an abnormality of the immune system may trigger the loss of hypocretin-producing neurons in people with narcolepsy. However, there is no direct evidence to show that immune system factors are responsible for this loss.

Most people who have narcolepsy with cataplexy have the *HLA-DQB1*06:02* variation, and many also have specific versions of other, closely related HLA genes (including *HLA-DQA1*). However, these variations are very common in the general population, and only a small percentage of people with particular variations in HLA genes develop narcolepsy. Other genetic and environmental factors, for example certain bacterial and viral infections, also affect the chances of developing this disorder.

2.3. Type 1 Diabetes

Combinations of variations in the *HLA-DQB1* 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-DQB1* and *HLA-DQA1* genes and another HLA gene called *HLA-DRB1*. 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.

2.4. Autoimmune Disorders

Normal variations of the *HLA-DQB1* gene have been associated with several additional disorders. Most of these disorders have an autoimmune basis, which means they occur when the immune system malfunctions and attacks the body's own tissues and organs. Autoimmune disorders that have been associated with *HLA-DQB1* include multiple sclerosis, pemphigus, and type 1 diabetes (described below).

Multiple sclerosis is a chronic disorder of the brain and spinal cord (central nervous system) that causes muscle weakness, poor coordination, numbness, and a variety of other health problems. Several variations of *HLA-DQB1* appear to increase the risk of developing this disorder. One of these variations, *HLA-DQB1*06:02*, is the same version of the gene that increases the risk of narcolepsy.

Some evidence suggests that the *HLA-DQB1* gene may also play a role in several forms of pemphigus, a condition that causes severe blistering of the skin and mucous membranes (such as the moist lining of the mouth).

It is unclear how different versions of the *HLA-DQB1* 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

- CELIAC1
- DQB1_HUMAN
- HLA class II histocompatibility antigen, DQ beta 1 chain
- HLA-DQB
- IDDM1
- major histocompatibility complex class II beta
- MHC class II antigen DQB1
- MHC class II antigen HLA-DQ-beta-1

- MHC class II DQ beta chain
- MHC class II HLA-DQ beta glycoprotein
- MHC class2 antigen
- MHC DQ beta

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