

# APOB Gene

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## 1. Normal Function

The *APOB* gene provides instructions for making two versions of the apolipoprotein B protein, a short version called apolipoprotein B-48 and a longer version known as apolipoprotein B-100. Both of these proteins are components of lipoproteins, which are particles that carry fats and fat-like substances (such as cholesterol) in the blood.

Apolipoprotein B-48 is produced in the intestine, where it is a building block of a type of lipoprotein called a chylomicron. As food is digested after a meal, chylomicrons are formed to carry fat and cholesterol from the intestine into the bloodstream. Chylomicrons are also necessary for the absorption of certain fat-soluble vitamins such as vitamin E and vitamin A.

Apolipoprotein B-100, which is produced in the liver, is a component of several other types of lipoproteins. Specifically, this protein is a building block of very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), and low-density lipoproteins (LDLs). These related molecules all transport fats and cholesterol in the bloodstream.

LDLs are the primary carriers of cholesterol in the blood. Apolipoprotein B-100 allows LDLs to attach to specific receptors on the surface of cells, particularly in the liver. Once attached, the receptors transport LDLs into the cell, where they are broken down to release cholesterol. The cholesterol is then used by the cell, stored, or removed from the body.

## 2. Health Conditions Related to Genetic Changes

### 2.1. Familial Hypercholesterolemia

More than 100 mutations in the *APOB* gene are known to cause familial hypercholesterolemia. This condition is characterized by very high levels of cholesterol in the blood and an increased risk of developing heart disease. Each mutation that causes this condition changes a single protein building block (amino acid) in a critical region of apolipoprotein B-100. (Apolipoprotein B-48 is normal.) The altered protein prevents LDLs from effectively attaching to their receptors on the surface of cells. As a result, fewer LDLs are removed from the blood, and blood cholesterol levels are much higher than normal. As the excess cholesterol circulates through the bloodstream, it is deposited abnormally in tissues such as the skin, tendons, and arteries that supply blood to the heart (coronary arteries). A buildup of cholesterol in the walls of coronary arteries greatly increases a person's risk of having a heart attack.

Most people with familial hypercholesterolemia inherit one altered copy of the *APOB* gene from an affected parent and one normal copy of the gene from the other parent. These cases are associated with an increased risk of early heart disease, typically beginning in a person's forties or fifties. Rarely, a person with familial hypercholesterolemia is born with two mutated copies of the *APOB* gene. This situation occurs when the person has two affected parents, each of whom passes on one altered copy of the gene. The presence of two *APOB* gene mutations results in a more severe form of hypercholesterolemia that usually appears in childhood.

### 2.2. Familial Hypobetalipoproteinemia

More than 120 mutations in the *APOB* gene have been found to cause familial hypobetalipoproteinemia (FHBL), a disorder that impairs the body's ability to absorb and transport fat. Most *APOB* gene mutations that cause FHBL lead to the production of apolipoprotein B that is abnormally short.

The severity of the condition largely depends on the length of the abnormal apolipoprotein B. Some mutations in the *APOB* gene lead to the production of a protein that is shorter than apolipoprotein B-100, but longer than apolipoprotein B-48. In these cases, normal apolipoprotein B-48 is still made in the intestine. The normal-length apolipoprotein B-48 can form chylomicrons normally, but the abnormally short apolipoprotein B-100 produced in the liver is less able to produce lipoproteins. Other mutations result in a protein that is shorter than both apolipoprotein B-48 and apolipoprotein B-100. In these cases, no normal-length apolipoprotein B protein is produced. The severely shortened protein is not able to form lipoproteins in the liver or the intestine. Generally, if both versions of the protein are shorter than apolipoprotein B-48, the signs and symptoms are more severe than if some normal length apolipoprotein B-48 is produced. All of these protein changes lead to a reduction of functional apolipoprotein B. As a result, the transportation of dietary fats and cholesterol is decreased or absent. A decrease in fat transport reduces the body's ability to absorb fats and fat-soluble vitamins from the diet, leading to the signs and symptoms of FHBL.

## 2.3. Other Disorders

Researchers are studying other variations (polymorphisms) in the *APOB* gene that may influence heart disease risk in people without inherited cholesterol disorders. Some studies have found that certain polymorphisms are associated with higher levels of LDLs in the blood and an increased chance of developing or dying of heart disease. Other studies, however, have not shown such an association. It is clear that a large number of genetic and lifestyle factors, many of which remain unknown, determine the risk of developing this complex condition.

## 3. Other Names for This Gene

- apoB-100
- apoB-48
- APOB\_HUMAN
- apolipoprotein B (including Ag(x) antigen)

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