HBB Gene

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Contributor: Dean Liu

Hemoglobin subunit beta

genes

1. Introduction

The *HBB* gene provides instructions for making a protein called beta-globin. Beta-globin is a component (subunit) of a larger protein called hemoglobin, which is located inside red blood cells. In adults, hemoglobin normally consists of four protein subunits: two subunits of beta-globin and two subunits of a protein called alpha-globin, which is produced from another gene called *HBA*. Each of these protein subunits is attached (bound) to an iron-containing molecule called heme; each heme contains an iron molecule in its center that can bind to one oxygen molecule. Hemoglobin within red blood cells binds to oxygen molecules in the lungs. These cells then travel through the bloodstream and deliver oxygen to tissues throughout the body.

2. Health Conditions Related to Genetic Changes

2.1. Beta Thalassemia

Nearly 400 mutations in the *HBB* gene have been found to cause beta thalassemia. Most of the mutations involve a change in a single DNA building block (nucleotide) within or near the *HBB* gene. Other mutations insert or delete a small number of nucleotides in the *HBB* gene.

HBB gene mutations that decrease beta-globin production result in a condition called beta-plus (β^+) thalassemia. Mutations that prevent cells from producing any beta-globin result in beta-zero (β^0) thalassemia.

Problems with the subunits that make up hemoglobin, including low levels of beta-globin, reduce or eliminate the production of this molecule. A lack of hemoglobin disrupts the normal development of red blood cells. A shortage of mature red blood cells can reduce the amount of oxygen that is delivered to tissues to below what is needed to satisfy the body's energy needs. A lack of oxygen in the body's tissues can lead to poor growth, organ damage, and other health problems associated with beta thalassemia.

2.2. Methemoglobinemia, Beta-globin Type

More than 10 mutations in the *HBB* gene have been found to cause methemoglobinemia, beta-globin type, which is a condition that alters the hemoglobin within red blood cells. These mutations often affect the region of the protein that binds to heme. For hemoglobin to bind to oxygen, the iron within the heme molecule needs to be in a form called ferrous iron (Fe^{2+}). The iron within the heme can change to another form of iron called ferric iron (Fe^{3+}), which cannot bind to oxygen. Hemoglobin that contains ferric iron is known as methemoglobin and is unable to efficiently deliver oxygen to the body's tissues.

In methemoglobinemia, beta-globin type, mutations in the *HBB* gene alter the beta-globin protein and promote the heme iron to change from ferrous to ferric. This altered hemoglobin gives the blood a brown color and causes a bluish appearance of the skin, lips, and nails (cyanosis). The signs and symptoms of methemoglobinemia, beta-globin type are generally limited to cyanosis, which does not cause any health problems. However, in rare cases, severe methemoglobinemia, beta-globin type can cause headaches, weakness, and fatigue.

2.3. Sickle Cell Disease

Sickle cell anemia (also called homozygous sickle cell disease or HbSS disease) is the most common form of sickle cell disease. This form is caused by a particular mutation in the *HBB* gene that results in the production of an abnormal version of beta-globin called hemoglobin S or HbS. In this condition, hemoglobin S replaces both beta-globin subunits in hemoglobin. The mutation that causes hemoglobin S changes a single protein building block (amino acid) in beta-globin. Specifically, the amino acid glutamic acid is replaced with the amino acid valine at position 6 in beta-globin, written as Glu6Val or E6V. Replacing glutamic acid with valine causes the abnormal hemoglobin S subunits to stick together and form long, rigid molecules that bend red blood cells into a sickle (crescent) shape. The sickle-shaped cells die prematurely, which can lead to a shortage of red blood cells (anemia). The sickle-shaped cells are rigid and can block small blood vessels, causing severe pain and organ damage.

Mutations in the *HBB* gene can also cause other abnormalities in beta-globin, leading to other types of sickle cell disease. These abnormal forms of beta-globin are often designated by letters of the alphabet or sometimes by a name. In these other types of sickle cell disease, just one beta-globin subunit is replaced with hemoglobin S. The other beta-globin subunit is replaced with a different abnormal variant, such as hemoglobin C or hemoglobin E.

In hemoglobin SC (HbSC) disease, the beta-globin subunits are replaced by hemoglobin S and hemoglobin C. Hemoglobin C results when the amino acid lysine replaces the amino acid glutamic acid at position 6 in beta-globin (written Glu6Lys or E6K). The severity of hemoglobin SC disease is variable, but it can be as severe as sickle cell anemia. Hemoglobin E (HbE) is caused when the amino acid glutamic acid is replaced with the amino acid lysine at position 26 in beta-globin (written Glu26Lys or E26K). In some cases, the hemoglobin E mutation is present with hemoglobin S. In these cases, a person may have more severe signs and symptoms associated with sickle cell anemia, such as episodes of pain, anemia, and abnormal spleen function.

Other conditions, known as hemoglobin sickle-beta thalassemias (HbSBetaThal), are caused when mutations that produce hemoglobin S and beta thalassemia occur together. Mutations that combine sickle cell disease with beta-zero (β^0) thalassemia lead to severe disease, while sickle cell disease combined with beta-plus (β^+) thalassemia is generally milder.

2.4. Other disorders

Hundreds of variations have been identified in the *HBB* gene. These changes result in the production of different versions of beta-globin. Some of these variations cause no noticeable signs or symptoms and are found when blood work is done for other reasons, while other *HBB* gene variations may affect a person's health. Two of the most common variants are hemoglobin C and hemoglobin E.

Hemoglobin C (HbC), caused by the Glu6Lys mutation in beta-globin, is more common in people of West African descent than in other populations. People who have two hemoglobin C subunits in their hemoglobin, instead of normal beta-globin, have a mild condition called hemoglobin C disease. This condition often causes chronic anemia, in which the red blood cells are broken down prematurely.

Hemoglobin E (HbE), caused by the Glu26Lys mutation in beta-globin, is a variant of hemoglobin most commonly found in the Southeast Asian population. When a person has two hemoglobin E subunits in their hemoglobin in place of beta-globin, a mild anemia called hemoglobin E disease can occur. In some cases, the mutations that produce hemoglobin E and beta thalassemia are found together. People with this hemoglobin combination can have signs and symptoms ranging from mild anemia to severe thalassemia major.

3. Other Names for This Gene

- beta globin
- beta-globin
- HBB_HUMAN
- hemoglobin beta gene
- hemoglobin, beta
- hemoglobin--beta locus

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