# HBB gene

hemoglobin subunit beta

## Normal Function

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 typically 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; the iron in the center of each heme can bind to one oxygen molecule. The hemoglobin within red blood cells binds to oxygen molecules in the lungs. The red blood cells then travel through the bloodstream and deliver oxygen to tissues throughout the body.

## Health Conditions Related to Genetic Changes

Beta thalassemia

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

*HBB* gene variants that decrease beta-globin production cause a condition called beta-plus ($\beta^{+}$) thalassemia. Variants that prevent cells from producing any beta-globin cause beta-zero ($\beta^{0}$) thalassemia.

Low levels of beta-globin can impact the production of hemoglobin. A lack of hemoglobin disrupts the normal development of red blood cells. A shortage of mature red blood cells can greatly reduce the amount of oxygen that is delivered to tissues. A lack of oxygen in the body's tissues can lead to poor growth, organ damage, and other health problems associated with beta thalassemia.

Methemoglobinemia, beta-globin type

Variants 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 variants 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 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 people with methemoglobinemia, beta-globin type, variants in the *HBB* gene alter the beta-globin protein and cause the heme iron to change from ferrous to ferric. This altered hemoglobin gives the blood a brown color and causes the skin, lips, and nails to appear bluish in color (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.

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 variant in the *HBB* gene that results in the production of an abnormal version of beta-globin called hemoglobin S (HbS). In people with this condition, hemoglobin S replaces both beta-globin subunits in hemoglobin.

The variant 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 (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 or crescent shape. The sickle-shaped cells die too early, which can lead to a shortage of red blood cells ( anemia). The rigid sickle-shaped cells can block small blood vessels, causing severe pain and organ damage.

Variants in the *HBB* gene can also cause other abnormalities in beta-globin, leading to other types of sickle cell disease. 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 version of beta-globin, such as hemoglobin C (HbC) or hemoglobin E (HbE).

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

Another condition, known as hemoglobin S-beta thalassemias (HbSBetaThal), is caused when the variants that result in hemoglobin S and beta thalassemia (described

above) occur together. Variants that combine sickle cell disease with beta-zero ($\beta^0$) thalassemia lead plus ($\beta^+$) thalassemia is generally milder.

Other disorders

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

Hemoglobin C, caused by the Glu6Lys change 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, caused by the Glu26Lys change in beta-globin, is 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 variants that produce hemoglobin E and beta thalassemia (described above) are found together. People with this hemoglobin combination can have signs and symptoms ranging from mild anemia to severe thalassemia major.

## Other Names for This Gene

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

## Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of HBB (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=3043[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28HBB+gene%5BTI%5D%29+OR+%28beta+hemoglobin%5BTI%5D%29+OR+%28beta+globin%5BTI%5D%2

9%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- HEMOGLOBIN--BETA LOCUS; HBB (https://omim.org/entry/141900)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/3043)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=HBB[gene])

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## Genomic Location

The *HBB* gene is found on chromosome 11 (https://medlineplus.gov/genetics/chromosome/11/).

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