# HBB Gene: - Beta-Thalassemia & Sickle Cell Disease

## Description

Hemoglobin is a protein found in red blood cells that helps carry oxygen throughout the body. If hemoglobin is not formed correctly, or at all, it affects the amount of red cells that are available for the body to use and how oxygen is distributed to the body. Beta-globin is a primary subunit of hemoglobin. 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. **There are two major genetic disorders that are associated with beta-globin: - 1) sickle cell disease and 2) beta-thalassemia.** Life expectancy for sickle cell disease and beta-thalassemia is variable, but can be prolonged with proper treatment and management.

### Sickle Cell Disease

**Sickle cell disease affects the formation of hemoglobin and changes the shape of red blood cells from their normal circular shape to a half-moon/crescent shape. It is an inherited disorder characterized by anemia, joint pain, and a shortage of red blood cells.** Sickle cell disease can damage the lungs, liver and kidneys. The amount of the pain, organ damage, and swelling varies among individuals with sickle cell disease.

**Sickle cell anemia,** a common form of sickle cell disease, is caused by a particular mutation in the HBB gene. This mutation 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 changes a single 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 or crescent shape. **Sickle-shaped cells die prematurely, which can lead to a shortage of red blood cells (anemia). 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.

### Beta-Thalassemia

**Beta-thalassemia (BT) occurs when the production of beta-globin is decreased, thus affecting the function of hemoglobin. This causes a lack of oxygen and iron buildup inside the body.** Effects of the more severe form of BT, thalassemia major or Cooley's anemia can be seen within the first six months to 2 years of age. Children affected with BT fail to gain weight or to grow at normal rates, may have diarrhea, enlarged organs, or irritability. Thalassemia intermedia is a less severe form of BT. Symptoms typically appear anytime from childhood into adulthood and tend to be similar to those of beta thalassemia, but milder. Chelation therapy and blood transfusions are necessary for those more severely affected for normal growth and development, but may only be needed on occasion for those mildly affected individuals.

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 type of the condition called beta-plus (B+) thalassemia. Mutations that prevent cells from producing any beta-globin result in beta-zero (B0) thalassemia.

## Frequency - How Often Does Beta Thalassemia & Sickle Cell Disease Occur?

Sickle cell disease is common in the African American population as well as individuals from sub-Saharan Africa, India, Saudi Arabia and the Mediterranean, for example: Greece and Italy. It is estimated 1 in 12 African Americans have sickle cell trait. It is estimated that over 100,000 people have sickle cell disease in the Unites States. Beta-thalassemia occurs in about 1 in 100,000 newborns worldwide, but it is more common in the Mediterranean, Middle Eastern, Central Asian, Southeast Asian, and Indian populations.

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## Normal Function of the HBB Gene And Genetic Changes

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 another protein called alpha-globin, which is produced from another gene called HBA. Each of these protein subunits is 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.

## Pattern of Inheritance - How Is Beta Thalassemia & Sickle Cell Disease Inherited?

**Both sickle cell disease and beta thalassemia are inherited in an autosomal recessive manner.** This type of inheritance requires the presence of two copies of a pathogenic variant in the gene for a person to have the genetic disease. **Therefore both parents must be carriers of a pathogenic variant in the gene in order to be at risk to have an affected child.** The child must inherit a pathogenic variant from each carrier parent in order to be affected. When both parents are carriers there is a 1 in 4 chance that a baby will inherit two mutated copies of the gene and be affected.

## What Does It Mean To Be A Carrier?

People who have sickle cell trait or people who are carriers of sickle cell disease usually do not have signs of the disease although they can acquire problems from extreme exercise, dehydration, or high altitude. Carriers of BT are not at risk for any symptoms other than having a slightly lower red cell count. They are often referred to as having thalassemia minor. In both cases carriers have a higher risk of having children affected with each condition. Testing of reproductive partners with consideration to their ethnicity is recommended for carriers of sickle cell trait or beta thalassemia.

**Carrier Rates**

| Ethnicity | Detection Rate | Carrier Frequency |
|---|---|---|
| African/African American | >99% | 1 in 10 |
| East Asian | >99% | 1 in 78 |
| General Population | >99% | 1 in 129 |
| Hispanic | >99% | 1 in 83 |
| Middle Eastern | >99% | 1 in 5 |
| South Asian | >99% | 1 in 32 |
| Southeast Asian | >99% | 1 in 30 |
| Southern European Caucasian | >99% | 1 in 59 |

## Clinician References

OMIM [Sickle Cell Disease:603903] (http://www.ncbi.nlm.nih.gov/omim)

Gene Reviews: Sickle Cell Disease (http://www.ncbi.nlm.nih.gov/books/NBK1377/)

OMIM [BETA-THALASSEMIA :613985] (http://www.ncbi.nlm.nih.gov/omim)

Gene Reviews: Beta-Thalassemia (http://www.ncbi.nlm.nih.gov/books/NBK1426/)

## Patient and Family Resources

Genetics Home Reference: Sickle cell disease (http://ghr.nlm.nih.gov/)

NIH Health Information: Sickle Cell Anemia (http://www.nhlbi.nih.gov/health/)

Sickle Cell Disease Association: About Sickle Cell Disease (http://www.sicklecelldisease.org/)

Genetics Home Reference: beta thalassemia (http://ghr.nlm.nih.gov/)

Kids Health: Beta Thalassemia (http://kidshealth.org/parent/medical/)

Cooley's Anemia Foundation (http://www.thalassemia.org/)