BETA HEMOGLOBINOPATHIES

GENETIC TESTING

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What are beta hemoglobinopathies?

Beta hemoglobinopathies are inherited disorders caused by the abnormal production of hemoglobin in the blood. Hemoglobin is a protein found in red blood cells that carries oxygen from the lungs to all parts of your body. If the molecular structure of hemoglobin is abnormal, or if there is not enough hemoglobin in your blood, your organs and tissues may not receive enough oxygen. This can result in symptoms of anemia, which include tiredness (fatigue), weakness, shortness of breath, and pale skin. Anemia may lead to more severe complications, such as organ damage, that may be life threatening.

Beta hemoglobinopathies are most common in people of African, Asian, Hispanic, Italian, Middle Eastern, West Indian, and Mediterranean descent.[1,2] Examples of these disorders include sickle cell disease and beta-thalassemia. When diagnosed and treated early, some of the health problems caused by beta hemoglobinopathies may be prevented.[2]

What is sickle cell disease?

Sickle cell disease is caused by the presence of abnormal hemoglobin molecules in red blood cells. Sickle cell anemia, a common type of sickle cell disease, is caused by the presence of an abnormal hemoglobin molecule called hemoglobin S.

Red blood cells that contain normal hemoglobin molecules are disc-shaped and flexible. Those containing hemoglobin S have an abnormal, sickle shape (like a crescent moon or the letter C) and are stiff and sticky.

- Sickle-shaped red blood cells break apart easily, which leads to a shortage of red blood cells to carry oxygen to organs and tissues. This is the cause of anemia.
- The stiff, sickle-shaped cells can get stuck inside small blood vessels, which can prevent blood from flowing into or out of organs and tissues. This can lead to health problems ranging from episodes of pain to recurring infections to serious organ damage.

Complications of sickle cell disease usually develop in early childhood and may include the following[3,4]:

- Anemia
- Painful swelling of the hands and feet
- Yellowing of the skin (jaundice)
- Recurring infections
- Blockage of blood vessels in the spleen causing enlargement and restriction of blood flow (splenic sequestration)
- Recurrent pain crises (severe pain in the arms, legs, head, chest, abdomen, or back)
- High blood pressure in the lungs (pulmonary hypertension) causing shortness of breath, chest pain, and a rapid heart rate
- Blockage of blood vessels in the brain, which can lead to stroke
- Blockage of blood vessels in the lungs (acute chest syndrome) causing shortness of breath, cough, chest pain, and fever

What is beta thalassemia?

Beta-thalassemia leads to reduced production of hemoglobin, and affected people also have a shortage of mature red blood cells that are able to deliver oxygen to organs and tissues. Beta thalassemia is classified into 2 types: thalassemia major (also known as Cooley's anemia) is a severe form, and thalassemia intermedia is a less severe form.[5,6]

Children with thalassemia major typically develop signs and symptoms during the first 2 years of life.[5,6] They have severe anemia, which can become life threatening if not treated. Other complications may include[5,6]:

- Jaundice
- Poor weight gain and growth (failure to thrive)
- Feeding problems

- Irritability
- Recurrent fevers
- Enlarged abdomen due to enlargement of the spleen (hepatomegaly)
- Misshapen bones resulting from expansion of bone marrow

People who have thalassemia intermedia may develop signs and symptoms during childhood or later in life. Their anemia may be mild to moderately severe, and they may also have growth delays and bone abnormalities.[6]

What causes beta hemoglobinopathies?

Beta hemoglobinopathies are caused by abnormal changes in certain genes. Genes are found in every cell in your body. They carry the instructions for making proteins that control how each of your cells work. Genes can undergo abnormal changes (called mutations) that may cause cells to stop working the way they should. Gene mutations may result in health problems, and they may be passed from parent to child (inherited).

Beta hemoglobinopathies are caused by mutations in the beta-globin (*HBB*) gene, which instructs cells to make a protein called beta-globin. Normal hemoglobin consists of 2 beta-globin subunits and 2 alpha-globin subunits.

- Certain *HBB* mutations lead to the production of hemoglobin S, which causes sickle cell disease.
- Some *HBB* mutations lead to decreased production of beta-globin. Others prevent cells from making any beta-globin at all. These are the mutations that cause beta thalassemia.

Beta hemoglobinopathies are inherited in an autosomal recessive manner.[4-6] This mean a child needs to inherit 2 copies of an *HBB* mutation (1 from each parent) in order to be affected. The severity and age of onset of beta hemoglobinopathies vary from person to person. These differences may be related to the specific combination of *HBB* gene mutations present and whether any other globin genes are mutated.[2,6] To date, hundreds of *HBB* mutations have been identified, not all of which have been linked with health problems.[7]

A person who inherits 1 copy of an *HBB* mutation is a "carrier" and is not expected to have related health problems. Carriers of sickle cell disease may be described as having sickle cell trait.[3] Carriers of beta thalassemia may be described as having beta thalassemia minor (and may have mild anemia).[5] When both parents are carriers of *HBB* mutations, each of their children will have a 1 in 4 chance of being affected with a beta hemoglobinopathy.[2]

How are beta hemoglobinopathies diagnosed?

- Newborns are tested for beta hemoglobinopathies.[2,3]
- A complete blood count (CBC) is typically the first test done to identify people with anemia who may benefit from additional testing to find out if they have a beta hemoglobinopathy.
- A blood test called hemoglobin electrophoresis can identify the amount and types of hemoglobin (such as hemoglobin S) present in a person's blood and may help identify of people who need more testing to diagnose thalassemia disorders.

Genetic tests for *HBB* mutations are available and may be used to confirm a diagnosis of a beta hemoglobinopathy, identify carriers of *HBB* mutations, or determine whether a developing baby (fetus) is affected.

- *HBB* full gene sequencing is a procedure that reads the instructions (DNA) that make up the *HBB* gene. This is a way to identify the presence of an altered *HBB* gene in a person's cells, which may help a doctor confirm the diagnosis of a beta hemoglobinopathy.
- Duplication/deletion testing is a way to find out whether the *HBB* gene contains mutations resulting from the presence of extra (duplicated) or missing (deleted) parts of DNA code.

The above tests can be performed on:

- A sample of blood.
- Cells obtained by swabbing the inside of the mouth (buccal swab).
- Prenatal samples of amniotic fluid (the watery substance that surrounds a fetus) or the chorionic villi (a small piece of tissue taken from the placenta).

Who should be tested for HBB gene mutations?

The American College of Obstetricians and Gynecologists (ACOG) recommends offering beta hemoglobinopathy carrier testing for people planning a pregnancy if they are of African, Southeast Asian, or Mediterranean descent.[1] It is also important for you to inform your health care provider if anyone in your family has or is a carrier of any of these conditions. Additionally, ACOG recommends genetic counseling if both parents are found to be carriers of beta hemoglobinopathies.[1]

What possible results of full gene sequencing can be reported and what do they mean?

- **Negative:** After scanning the *HBB* gene, no detectable mutations were found. This test does not detect all possible mutations in the gene. For this reason, a negative result cannot completely rule out the presence of a gene mutation that is causing a person's symptoms.
- **Positive – Abnormal**: After scanning the *HBB* gene, 2 mutations were found. Along with a person's signs

and symptoms, a positive genetic test result may confirm a diagnosis of a beta hemoglobinopathy.

- **Positive – Carrier**: After scanning the *HBB* gene, 1 mutation was found. It is likely that this person is a carrier of a beta hemogoblinopathy. This person may benefit from genetic counseling to discuss how his/her carrier status may affect family planning, testing of his/her reproductive partner, and testing of at-risk family members.
- **Variant of unknown significance:** After scanning the *HBB* gene, a mutation was found that has not been reported before. It is unclear if the mutation is the cause of a person's signs and symptoms. Genetic testing of family members may provide more information. If all affected family members have the same mutation, then it is likely to be linked to the inherited disorder. If some affected family members do not have the mutation, it is less likely to be linked to the disorder.

Full gene sequencing test results should be combined with clinical findings and reviewed by a heath professional who specializes in medical genetics.

Where can I find more information?

If you have questions or want more information about genetic testing for beta hemoglobinopathies, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at **www.nsgc.org**.

Other information resources include:

- Centers for Disease Control and Prevention
  Home page: **www.cdc.gov**
- Genetics Home Reference
  Home page: **http://ghr.nlm.nih.gov**
- March of Dimes
  Telephone: (914) 997-4488
  Home page: **www.marchofdimes.com**

Note: This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

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