Beta Globin (*HBB*) HbS, HbC, and HbE Mutations

TO DETECT THREE COMMON BETA GLOBIN ALLELES: HBS, HBC, AND HBE

Disease Overview

- Hemoglobin (Hb) is a tetrameric molecule that reversibly binds oxygen in red blood cells. The major adult Hb (HbA) is composed of two beta-globin chains and two alpha-globin chains.
- Defects in the formation of the hemoglobin complex can lead to hemoglobinopathies (structurally abnormal hemoglobin) and alpha- and beta-thalassemia (imbalance in the quantity of alpha and beta chains).
- Sickle cell anemia, the most common significant hemoglobinopathy, is characterized by hemolysis and episodes of vascular occlusion affecting numerous organs. Pain and swelling of hands and feet is often the first indication of the disease, and infection is a frequent complication.
- Milder forms of hemoglobinopathies may result in mild to moderate hemolytic anemia.

Epidemiology

- Hemoglobinopathies are the most common monogenic diseases, with approximately 7 percent of the world's population carrying a hemoglobin mutation.
- HbS is most common in sub-Saharan Africa, India, and the Middle East; 10 percent of African-Americans carry an HbS allele. Homozygosity for HbS is the most common form of sickle cell disease.
- Sickle cell affects one in 250–600 African-Americans. HbS causes 60–70 percent of sickle cell disease in the United States (one in 2,000 individuals).
- HbC and HbE occur frequently in individuals of West African and Southeast Asian ancestry, respectively.

Genetics

- Beta-globinopathies and beta-thalassemia occur due to mutations in the beta-globin (*HBB*) gene.
- More than 500 beta-chain variants have been described, including three common structural mutations: HbS (c.20A>T, p.E6V), HbC (c.19G>A, p.E6K), and HbE (c.79G>A, p.E26K).
- All three Hb variants, HbS, HbC, and HbE, are caused by an amino acid change in the beta-globin chain. While HbS and HbC result in abnormal beta-chain structure, the HbE mutation affects splicing efficiency, resulting in decreased amounts of beta chain.
- Inheritance for HbS, HbC, and HbE is autosomal recessive.

Indications for Ordering

- Confirmation of abnormal Hb variants detected by hemoglobin electrophoresis or HPLC.
- Prenatal diagnosis when both parents are known carriers of HbS, HbC, or HbE.

Interpretation

- Homozygous, heterozygous, compound heterozygous, and negative genotypes are reported.
- Negative: None of the beta-globin gene mutations, c.19G>A (HbC), c.20A>T (HbS), or c.79G>A (HbE), were identified.
- Heterozygous: One mutation was identified. Heterozygosity for HbS or HbC signifies carrier status for sickle cell disease, while heterozygosity for HbE may be associated with mild microcytosis.
- Homozygosity: Two copies of the same mutation were identified. HbS homozygosity is consistent with sickle cell anemia. Homozygosity for HbE or HbC may result in mild hemolytic anemia and microcytosis.
- Compound heterozygosity: Two different mutations were identified. HbS/C compound heterozygotes may exhibit significant hemolytic anemia and a sickle cell-like disease. Compound heterozygosity for HbC/E or HbS/E is often clinically benign, but may result in anemia.

Limitations

- Detects only the three most common missense variants in the beta-globin gene.
- Other beta- and alpha globin variants are not identified.

Methodology

- PCR and fluorescence resonance energy transfer for detection of c.19G>A (HbC), c.20A>T (HbS), and c.79G>A (HbE).
- Multiplex loci-spanning-probe interrogates the three loci simultaneously.
- Clinical sensitivity is greater than 70 percent for sickle cell disease; other hemoglobinopathies vary depending upon patient's ethnicity.
- Analytic sensitivity and specificity are greater than 99 percent.

Related Tests

- Beta globin (*HBB*) Sequencing (0050578)
- Beta globin (*HBB*) Familial Mutation, Targeted Sequencing (2001961)
- Beta globin (*HBB*) Familial Mutation, Targeted Sequencing, Fetal (2001980)

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ARUP is an enterprise of the University of Utah and its Department of Pathology.

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3. Giardine B, et al. HbVar database of human hemoglobin variants and thalassemia mutations: 2007 Update. *Hum Mutat* 2007:2(28)206–15.
4. Pont-Kingdon G, et al. Multiplex genotyping by melting analysis of loci-spanning probes: Beta-globin as an example. *BioTechniques* 2007;42:193–7.

Test Information

0051421	**Beta Globin (*HBB*) HbS, HbC and HbE Mutations**
0051422	**Beta Globin (*HBB*) HbS, HbC and HbE Mutations, Fetal**

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

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