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

Indications for Ordering

- Confirmation of 3 common hemoglobin (Hb) variants (HbS, HbC, and HbE) detected by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC)
- Prenatal diagnosis when both parents are known carriers of HbS, HbC, or HbE

Test Description

PCR and fluorescence resonance energy transfer

Tests to Consider

Primary tests

Beta Globin (*HBB*) HbS, HbC and HbE Mutations 0051421
- Confirm suspected HbS, HbC, or HbE variants

Beta Globin (*HBB*) HbS, HbC, and HbE Mutations, Fetal 0051422
- Genetic test on fetal specimens for prenatal detection of HbS, HbC, or HbE variants

Related tests

Beta Globin (*HBB*) Sequencing and Deletion/Duplication 2010117
- Preferred test for molecular confirmation of β thalassemia or a hemoglobinopathy involving the β-globin gene

Beta Globin (*HBB*) Gene Sequencing 0050578
- Molecular confirmation of a suspected structural hemoglobinopathy or β thalassemia

Beta Globin (*HBB*) Deletion/Duplication 2010113
- Detects large deletions of the β-globin gene cluster associated with β thalassemia or HPFH

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Familial Mutation, Targeted Sequencing, Fetal 2001980
- Fetal test to detect a previously characterized variant in a family member

Hemoglobin Evaluation with Reflex to Electrophoresis and/or RBC Solubility 0050610
- Effective test for screening and follow up of individuals with known hemoglobinopathies
- Optimal test for the initial diagnosis of a suspected hemoglobinopathy is the Hemoglobin Evaluation Reflexive Cascade

Hemoglobin Evaluation Reflexive Cascade 2005792
- Optimal test for the initial and confirmatory diagnosis of any suspected hemoglobinopathy
- Cascade reflex testing may include electrophoresis, solubility testing, and/or molecular analyses of the globin genes
- Do not use for the follow-up of an individual with a known diagnosis

Disease Overview

Prevalence

- ~5% of the world's population carries clinically important Hb variants
- Annually, 300,000 individuals are born with a severe hemoglobinopathy
- HbS – most common in sub-Saharan Africa, India, and Middle East
- Sickle cell anemia (HbSS) accounts for 60-70% of sickle cell disease in the U.S.
  - Sickle cell disease affects 1/250-600 African Americans
  - 10% of African Americans carry an HbS allele
- Other forms of sickle cell disease result from HbS with other abnormal β-chain variants (eg, HbSC disease, sickle β^0 thalassemia, and sickle β^+ thalassemia)
- HbC – common in west Africa
- HbE – common in southeast Asia

Symptoms

- Clinical symptoms are related to defects in the formation of the Hb complex
  - Hemoglobinopathies – structurally abnormal Hb
  - Thalassemia – decrease in the amount of protein produced
- Sickle cell anemia (HbSS)
  - Most common significant hemoglobinopathy
  - Characterized by hemolysis and episodes of vascular occlusion affecting numerous organs
  - Pain and swelling of hands and feet – often the first indication of the disease
  - Infection is a frequent complication
- Sickling disorders of varying severity may result from HbS with a second β-globin variant
- HbE may result in thalassemia of varying severity when co-inherited with a β^+ or β^0 variant

Pathophysiology

- Hb is a tetrameric molecule
  - Reversibly binds oxygen in red blood cells
- Major adult Hb (HbA) – composed of 2 β-globin chains and 2 α-globin chains
- Defects in the formation of the Hb complex
  - Hemoglobinopathies – synthesis of structurally abnormal Hb
    - Many structural Hb variants – no clinical effect, unless paired with a second variant
    - Reduced oxygen affinity – microcytic anemia, hemolytic anemia, cyanosis
    - Increased oxygen affinity – erythrocytosis
  - α and β thalassemia – reduced synthesis of structurally normal globin subunits
    - Imbalance in the quantity of α and β chains

Genetics

Gene – *HBB* (β globin)

Inheritance – autosomal recessive

Structure/function

- HbS, HbC, and HbE caused by an amino acid change in the β-globin chain
  - HbS and HbC result in abnormal β-chain structure
  - HbE affects splicing efficiency, resulting in decreased amounts of β chain

Variants

- >500 β-chain variants
- 3 common structural variants
  - HbS (c.20A>T, E6V)
  - HbC (c.19G>A, E6K)
  - HbE (c.79G>A, E26K)

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - Sickle cell disease – >70%
  - Other hemoglobinopathies – varies by ethnicity
- Analytical sensitivity – 99%

Results

- Heterozygous – 1 variant identified
  - HbS or HbC – signifies carrier status for sickle cell disease
  - HbE – may be associated with mild microcytosis
- Homozygous – 2 copies of the same variant identified
  - HbSS – consistent with sickle cell anemia
  - HbEE or HbCC – may result in mild hemolytic anemia and microcytosis
- Compound heterozygosity – 2 different variants identified
  - HbS/C – may exhibit significant hemolytic anemia and a sickle cell-like disease
  - HbC/E or HbS/E – often clinically benign, but may result in anemia
- Negative – none of the targeted β-globin gene variants HbS, HbC, or HbE were identified

Limitations

- Detects only the 3 most common missense variants in the β-globin gene
- Other β- and α-globin variants are not identified
- Diagnostic errors can occur due to rare sequence variations