Beta Globin (HBB) Sequencing

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Variants in the beta (β)-globin gene (*HBB*) can result in anemia, β thalassemia, or sickling disorders of varying severity. Initial testing includes biochemical assessment for abnormal hemoglobin (Hb) variants using high-performance liquid chromatography (HPLC) and electrophoresis. A diagnosis is confirmed using molecular analysis of the *HBB* gene.

Disease Overview

Associated Phenotypes

Phenotypes Caused by *HBB* Variants	
Phenotype	**Characteristics**
Thalassemia: decrease in protein produced	β thalassemia major • Associated with severe microcytic anemia and hepatosplenomegaly • Affected individuals are transfusion dependent β thalassemia intermedia • Milder clinical presentation than β thalassemia major β thalassemia minor (trait) • Usually clinically asymptomatic, mild anemia may be present • Minor hematologic anomalies, including reduced MCV and elevated HbA2
Hemoglobinopathy: structurally abnormal protein	Sickling disorders: • Sickle cell anemia (HbSS) • Hb S-C disease Microcytic or hemolytic anemia Cyanosis (reduced oxygen-affinity HbS) Erythrocytosis (increased oxygen-affinity HbS) No clinical effect
Hereditary persistence of fetal Hb (HPFH)[a]	Persistent HbF production resulting from variants of the β-globin gene cluster that alter normal Hb switching Clinically benign condition

[a] *HBB* sequencing not recommended for detection of HPFH variants; refer to the Laboratory Test Directory for additional test options.

HbA2, hemoglobin, alpha 2; MCV, mean corpuscular volume

Featured ARUP Testing

Beta Globin (HBB) Sequencing 3004547

Method: Massively Parallel Sequencing

- Use to confirm carrier status or diagnosis of β thalassemia or β globinopathy in an individual with clinical findings or family history of β thalassemia or hemoglobinopathy
- Use to identify or confirm abnormal hemoglobin variant(s) detected by HPLC or Hb electrophoresis

Beta Globin (HBB) Sequencing, Fetal 3004550

Method: Massively Parallel Sequencing

Use for molecular confirmation of β thalassemia or β globinopathy on fetal samples

Test Description

Massively parallel sequencing of all coding exons, exon-intron junctions, 5' proximal promoter and untranslated region, 3' polyadenylation signal, and intronic variants c.93-21G>A (IVS-I-110), c.316-197C>T (IVS-II-654), c.316-146T>G (IVS-II-705), and c.316-106C>G (IVS-II-745) of the *HBB* gene

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Etiology

β thalassemia and certain hemoglobinopathies are caused by pathogenic germline variants within the *HBB* gene or variants involving the beta globin gene cluster and its regulatory elements.

Epidemiology

- Approximately 5% of the world's population carries clinically important Hb variants.
- 300,000 individuals with a severe hemoglobinopathy are born annually.
- β thalassemias are most commonly observed in individuals from southern Europe, northern Africa, and India.

Genetics

Gene

HBB (NM_000518)

Inheritance

Autosomal recessive (typically)

Structure/Function

- Major adult Hb (HbA) is composed of two β-globin chains and two alpha (α)-globin chains.
- Typically, adults have two functional β-globin genes (*HBB*) and four functional α-globin genes (two copies each of *HBA1* and *HBA2*).
- β-globin chains with different variants may interact to alleviate or exacerbate the effects of the individual variants.
  - Variants in the *HBB* gene can result in formation of a structurally abnormal protein or decrease the amount of protein produced.
  - Certain *HBB* deletions impair the developmental switch from fetal to adult Hb, resulting in hereditary persistence of fetal Hb.

Test Interpretation

Clinical Sensitivity

99% for β thalassemia and hemoglobinopathies associated with the *HBB* gene

Analytical Sensitivity

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytical Specificity (NPA)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Interpretation
Heterozygous	One pathogenic variant detected	Carrier of a structurally abnormal Hb or β thalassemia, depending on the specific variant identified
Homozygous or compound heterozygous	Two pathogenic variants detected (either the same variant or two different variants)	Variably affected, depending on the specific variant(s) identified

Result	Variant(s) Detected	Clinical Interpretation
Negative	No pathogenic variants detected	Significantly decreases possibility of β thalassemia or β globinopathy Clinically benign structural variants predicted to produce an abnormal electrophoresis/HPLC result will be reported

Limitations

- A negative result does not exclude a diagnosis of β thalassemia.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- Certain gene therapies may impact the performance of this test and interpretation of results; the presence or absence of variants, zygosity, and *HBB* gene copy number may not be determined in such cases.
- The following will not be evaluated:
  - Variants outside the *HBB* coding regions and intron-exon boundaries
  - Regulatory region variants upstream of c.-250, and deep intronic variants other than: c.93-21G>A (IVS-I-110), c.316-197C>T (IVS-II-654), c.316-146T>G (IVS-II-705), and c.316-106C>G (IVS-II-745)
  - Noncoding transcripts
  - Large exonic deletions/duplications/inversions
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Low-level somatic variants
  - Certain other variants, due to technical limitations in the presence of pseudogenes or repetitive/homologous regions

Related Information

Hemoglobin Evaluation Reflexive Cascade
Hemoglobinopathies
Hemoglobinopathies Testing Algorithm
Thalassemias