Beta Globin (HBB) Sequencing and Deletion/Duplication

Last Literature Review: December 2021 Last Update: April 2026

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 disease) • Hb S-C disease Microcytic or hemolytic anemia Cyanosis (reduced oxygen-affinity HbS) Erythrocytosis (increased oxygen-affinity HbS) No clinical effect
HPFH	Persistent HbF production resulting from variants of the β-globin gene cluster that alter normal Hb switching Clinically benign condition

HbA2, hemoglobin, alpha 2; HbF, fetal hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; 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.

Beta Globin (HBB) Deletion/Duplication by MLPA 3019876

Method: Multiplex Ligation-Dependent Probe Amplification (MLPA) / Capillary Electrophoresis

Use to identify *HBB* gene deletions associated with β thalassemia, elevated hemoglobin F (such as in hereditary persistence of fetal hemoglobin [HPFH] or δβ thalassemia), or to confirm gene fusion hemoglobin variants (e.g., hemoglobin Lepore).

Etiology

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

Prevalence and/or Incidence

- 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 HbF to HbA, resulting in HPFH.

Test Interpretation

Clinical Sensitivity

This test is 99% sensitive for β thalassemia and hemoglobinopathies associated with the *HBB* gene (≥90% for large deletions using multiplex ligation probe amplification [MLPA]).

Analytic Sensitivity for Next Generation Sequencing

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic 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 analytic 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

Result	Variant(s) Detected	Clinical Interpretation
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
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 by massively parallel sequencing (MPS)
  - 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 by MPS
  - Sequence variants by MLPA
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Single exon deletions/duplications based on the breakpoints of the rearrangement by MLPA
  - Intragenic deletions other than HBB in the β globin cluster genes by MLPA
  - Low-level mosaic or 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

© 2026 ARUP Laboratories. All Rights Reserved.