

# Beta Globin (*HBB*) Sequencing

## *TO DETERMINE AFFECTED OR CARRIER STATUS FOR A BETA GLOBINOPATHY OR BETA THALASSEMIA*

### Disease Overview

- Hemoglobin (Hb) is a tetrameric molecule that reversibly binds oxygen in red blood cells. The major adult Hb (Hb A) is composed of two beta globin chains and two alpha globin chains.
- Mutations in the *HBB* gene, which codes for the beta globin chain, can result in the formation of a structurally abnormal protein (hemoglobinopathy) or decrease the amount of protein produced (thalassemia).
- Carriers of one thalassemia mutation (beta thalassemia minor) are clinically asymptomatic but have minor hematologic anomalies that include reduced mean corpuscular volume (MCV) and elevated Hb A<sub>2</sub>.
- Patients who are homozygous or compound heterozygous for thalassemia mutations may be affected to varying extents. Beta thalassemia major, the most severe presentation, is associated with severe microcytic anemia and hepatosplenomegaly; affected individuals are transfusion-dependent. Beta thalassemia intermedia is associated with a milder presentation.
- Structural *HBB* mutations may have no clinical effect, or they may result in microcytic anemia, hemolytic anemia, cyanosis due to reduced oxygen affinity, or erythrocytosis due to increased oxygen affinity.
- Interactions between beta globin chains with different mutations may either alleviate or exacerbate the effects of the individual variants.
- Certain *HBB* deletions impair the developmental switch from fetal to adult Hb, resulting in hereditary persistence of fetal Hb, which compensates for the absent Hb A in mutation carriers.

### Epidemiology

- Approximately 5 percent of the world's population carries clinically important hemoglobin mutations.
- Annually, 300,000 individuals are born with a severe hemoglobinopathy.
- Beta thalassemias are most commonly observed in individuals from Southern Europe, Northern Africa, and India.

### Genetics

- Inheritance is usually autosomal recessive but may infrequently be autosomal dominant.
- Greater than 500 beta globin mutations have been described.

### Indications for Ordering

- To confirm the diagnosis of a beta thalassemia or beta globinopathy, especially when a definitive diagnosis cannot be made by HPLC or gel electrophoresis.
- Diagnostic testing in individuals with clinical findings of beta thalassemia or a hemoglobinopathy.
- Carrier testing for individuals with a family history of beta thalassemia or a hemoglobinopathy.
- To confirm a specific *HBB* mutation in parents prior to prenatal diagnosis.
- Prenatal diagnosis (requires documentation of both parental mutations).

### Interpretation

- For optimal test interpretation, please submit a Patient History for Hemoglobinopathy/Thalassemia Testing form detailing clinical findings, family history, and ethnicity.
- Lack of detection of a mutation in *HBB* does not exclude beta thalassemia, as the patient may have an undetectable mutation.
- Individuals with a single *HBB* mutation may be carriers of a structurally abnormal beta globin, beta thalassemia, or a benign mutation.
- Individuals with two *HBB* mutations are variably affected, depending on the specific mutations identified.

### Limitations

- Rare diagnostic errors can occur due to primer-site mutations.
- Large deletions (other than 619del), duplications, and some mutations in regulatory regions will not be detected.

### Methodology

- PCR amplification followed by bidirectional sequencing of the *HBB* coding region, intron/exon borders, proximal promoter, 5' and 3' untranslated regions, and IVS-II-654, IVS-II-705, and IVS-II-745 deep intronic mutations; PCR followed by gel electrophoresis for the 619del mutation.
- Clinical sensitivity is up to 97 percent depending upon ethnicity.
- Analytical sensitivity is 99 percent.

### Related Tests

- Beta Globin Gene Mutations for HbS, HbC, & HbE by PCR (0051421)
- Beta Globin Gene Mutations for HbS, HbC, & HbE by PCR, Fetal (0051422)
- Beta globin (*HBB*) Familial Mutation, Targeted Sequencing, Fetal (2001980)
- Beta globin (*HBB*) Familial Mutation, Targeted Sequencing (2001961)

### References

1. Bunn HF, Forget BG. 1986. *Hemoglobin: molecular, genetic, and clinical aspects*. Philadelphia: WB Saunders Co.
2. Hoffman R, et al, eds. 1991. *Hematology: basic principles and practice*. New York: Churchill Livingstone.
3. Thomas MW, McInnes RR, and Willard HF. The hemoglobinopathies: models of molecular disease. In *Genetics in medicine*, 5th edition. 1991; Philadelphia: WB Saunders Co., 247–70.

### Test Information

**0050388**      **Beta Globin (*HBB*) Full Gene Sequencing, Fetal**  
**0050578**      **Beta Globin (*HBB*) Sequencing**

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).