

Hemoglobin Lepore (*HBD-HBB* Fusion) 3 Mutations

DETECTS HEMOGLOBIN LEPORE RESULTING FROM REARRANGEMENTS OF THE DELTA AND BETA GLOBIN GENES

Disease Overview

- Hemoglobin (Hb) is a tetrameric molecule that reversibly binds oxygen in red blood cells. Adult Hb is composed predominantly of two alpha globin chains and two beta globin chains.
- Hb Lepore is a hemoglobin variant resulting from a fusion between the delta globin gene (*HBD*) and the beta globin gene (*HBB*).
- Hb Lepore causes beta thalassemia. Thalassemias result from an imbalance in the quantity of alpha and beta globin chains.
- In its heterozygous form, Hb Lepore causes a beta thalassemia minor phenotype and is associated with mild anemia, hypochromic microcytosis, and moderately increased fetal hemoglobin.
- Homozygosity for Hb Lepore is rare. The associated phenotypes for homozygosity or compound heterozygosity for Hb Lepore/beta thalassemia are variable and often include beta thalassemia intermedia and major.
- The combination of Hb Lepore with structural hemoglobinopathies also leads to variable clinical presentations.
- Co-inheritance of alpha globin mutations or additional genetic modifiers may influence clinical presentation.
- The presence of Hb Lepore is often suggested by hemoglobin electrophoresis or HPLC. Molecular confirmation may be useful for optimal management, genetic counseling, and prenatal diagnosis.

Epidemiology

- There are three major forms of Hb Lepore:
 - Hb Lepore-Washington-Boston is the most common; it is reported in many populations but most common in Italians.
 - Hb Lepore-Baltimore is observed in Yugoslavian, Brazilian, American, Northern Sardinian, Spanish, and Portuguese individuals.
 - Hb Lepore-Hollandia is rare; it is observed in New Guinea and Bangladesh.

Genetics

- Autosomal recessive inheritance.
- Hb Lepore is classified as a β^+ thalassemia mutation, as it results in reduced beta globin chain synthesis.
- Due to the high homology of the DNA sequences of delta globin and beta globin genes, unequal crossovers can occur during recombination. This results in a delta/beta fusion gene that produces the abnormal delta/beta hybrid chain.

- The fusion gene involves the 5' portion of the delta globin gene and the 3' portion of the beta globin gene, and results in a deletion of approximately 7.4 kb. The fusion gene retains the promoter of the delta globin gene, decreasing transcription efficiency and production of the delta/beta hybrid chain.
- The three common Hb Lepore mutations described above are distinguished by their characteristic breakpoints within the delta and beta globin genes.
- Other rare delta/beta globin gene rearrangements have been described.

Indications for Ordering

- Molecular confirmation of a suspected Hb Lepore variant identified by hemoglobin evaluation.
- Carrier screening for individuals with a family history of Hb Lepore.

Interpretation

- For optimal test interpretation, please submit a Patient History for Hemoglobinopathy/Thalassemia Testing Form detailing clinical findings, family history, and ethnicity.
- Negative: None of the three common Hb Lepore mutations were identified. This result does not exclude beta thalassemia, as other beta globin gene mutation(s) are not identified by this assay.
- Heterozygous: One copy of an Hb Lepore mutation was identified. Carriers of Hb Lepore typically present with beta thalassemia minor, while individuals who are compound heterozygous for Hb Lepore and a second beta globin mutation may be variably affected.
- Homozygous or compound heterozygous: Two Hb Lepore mutations were identified, consistent with a diagnosis of beta thalassemia; associated phenotypes for homozygosity or compound heterozygosity are variable and often include beta thalassemia intermedia and major.

Methodology

- Multiplex PCR and gel electrophoresis to detect the three common Hb Lepore mutations: Hb Lepore-Washington-Boston (g.63632_71046del), Hb Lepore-Baltimore (g.63564_70978del), and Hb Lepore-Hollandia (g.63290_70702del).
- Clinical sensitivity and specificity are unknown.
- Analytical sensitivity and specificity for the mutations tested are 99 percent.

Limitations

- Only the three common Hb Lepore mutations will be detected. Rare delta/beta rearrangements and other mutations in the alpha, delta, or beta globin genes will not be identified.
- This assay may not be able to distinguish between homozygosity for a common Hb Lepore mutation and compound heterozygosity for a common Hb Lepore mutation and a rare delta/beta globin gene deletion.
- Rare diagnostic errors can occur due to primer-site mutations.

Related Test

Hemoglobin Evaluation with Reflex to Electrophoresis and/or RBC Solubility (0050610)

References

1. Chaibunruang A, et al. Interactions of hemoglobin Lepore ($\delta\beta$ hybrid hemoglobin) with various hemoglobinopathies: a molecular and hematological characteristics and differential diagnosis. *Blood Cells Mol Dis* 2010;44(3):140–5.
2. McKeown SM, et al. Rare occurrence of Hb Lepore-Baltimore in African Americans: molecular characteristics and variations of Hb Lepores. *Ann Hematol* 2009;88(6):545–48.
3. Goncalves I, et al. Fetal hemoglobin elevation in Hb Lepore heterozygotes and its correlation with β globin cluster linked determinants. *Am J Hematol* 2002;69:95–102.
4. Hartevelde CL, et al. Hb Lepore-Leiden: a new δ/β rearrangement associated with a β -thalassemia minor phenotype. *Hemoglobin* 2008,32(5):446–53.

Test Information

2004686 Hemoglobin Lepore (HDB-HBB Fusion) 3 Mutations

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.