

# Hemoglobin Lepore (*HBD/HBB* Fusion) 3 Mutations

## Indications for Ordering

- Molecular confirmation of a suspected Hemoglobin (Hb) Lepore variant identified by Hb evaluation
- Carrier screening for individuals with a family history of Hb Lepore

## Test Description

Qualitative polymerase chain reaction/qualitative electrophoresis

## Tests to Consider

### Primary test

[Hemoglobin Lepore \(\*HBD/HBB\* Fusion\) 3 Mutations 2004686](#)

- Confirmation of Hb Lepore
- Carrier screening for Hb Lepore

### Related tests

[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

[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

[Beta Globin \(\*HBB\*\) Sequencing and Deletion/Duplication 2010117](#)

- Preferred test for molecular confirmation of  $\beta$  thalassemia or a hemoglobinopathy involving the  $\beta$ -globin gene

[Beta Globin \(\*HBB\*\) Gene Sequencing 0050578](#)

- Molecular confirmation of a suspected structural hemoglobinopathy or  $\beta$  thalassemia

[Beta Globin \(\*HBB\*\) Deletion/Duplication 2010113](#)

- Detect large deletions of the  $\beta$ -globin gene cluster associated with  $\beta$  thalassemia or hereditary persistence of fetal hemoglobin

## Disease Overview

### Prevalence

- Hb Lepore-Washington-Boston
  - Most common Lepore variant observed in many populations, most common in Italian individuals
- Hb Lepore-Baltimore
  - Observed in Yugoslavian, Brazilian, American, Northern Sardinian, Spanish, and Portuguese individuals
- Hb Lepore-Hollandia
  - Rare, has been observed in New Guinea and Bangladeshi individuals

### Symptoms

- Heterozygosity for Hb Lepore
  - $\beta$  thalassemia minor – clinically asymptomatic, mild anemia (hypochromic and microcytic), moderately increased fetal hemoglobin
- Homozygosity for Hb Lepore is rare
  - Associated phenotypes
    - $\beta$  thalassemia intermedia – pallor, jaundice, cholelithiasis, hepatosplenomegaly, skeletal disease
    - $\beta$  thalassemia major – severe anemia, hepatosplenomegaly, growth retardation, jaundice
- Coinheritance with other globin variants may influence clinical presentation
  - Examples of expected phenotypes
    - Hb Lepore with sickle cell trait (HbS) – mild sickling disorder
    - Hb Lepore with HbE trait –  $\beta$  thalassemia intermedia
    - Hb Lepore and  $\beta$  thalassemia trait –  $\beta$  thalassemia intermedia to  $\beta$  thalassemia major
    - Presence of  $\alpha$  globin variant(s) or other genetic modifiers may impact clinical presentation

### Physiology

- Hb is a tetrameric molecule that reversibly binds oxygen in red blood cells
- Adult Hb is composed predominantly of 2  $\alpha$ -globin chains and 2  $\beta$ -globin chains
- Hb Lepore results from a fusion between the  $\Delta$ -globin gene (*HBD*) and the  $\beta$ -globin gene (*HBB*)

## Genetics

**Genes** – *HBD/HBB*

**Inheritance** – Autosomal recessive

### Structure/function

- Fusion involving the 5' portion of the  $\Delta$ -globin gene and the 3' portion of the  $\beta$ -globin gene
  - Results in a deletion of approximately 7.4 kb
  - Fusion gene retains the promoter of the  $\Delta$ -globin gene, decreasing transcription efficiency and production of the  $\Delta/\beta$ -hybrid chain
  - Hb Lepore is classified as a  $\beta$  thalassemia variant as it results in reduced  $\beta$ -chain synthesis

### Variants

- 3 common variants
  - Hb Lepore-Washington-Boston (g.63632\_71046del)
  - Hb Lepore-Baltimore (g.63564\_70978del)
  - Hb Lepore-Hollandia (g.63290\_70702del)
- Other rare  $\Delta/\beta$ -globin gene rearrangements have been described

### Test Interpretation

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#### Sensitivity/specificity

- Clinical sensitivity/specificity – unknown
- Analytical sensitivity/specificity – 99%

#### Results

- Positive
  - Heterozygous – one copy of a Hb Lepore variant was identified
    - Carriers of Hb Lepore typically present with  $\beta$  thalassemia minor
  - Homozygous or compound heterozygous – two Hb Lepore variants were identified
    - Consistent with a diagnosis of  $\beta$  thalassemia
    - Associated phenotypes are variable and often include  $\beta$  thalassemia intermedia and major
- Negative
  - The 3 common Hb Lepore variants were not identified

#### Limitations

- Negative result does not exclude  $\beta$  thalassemia, as other  $\beta$ -globin gene variants are not identified by this test
- Diagnostic errors may occur due to rare sequence variation