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 β thalassemia or a hemoglobinopathy involving the β-globin gene

Beta Globin (*HBB*) Gene Sequencing 0050578

- Molecular confirmation of a suspected structural hemoglobinopathy or β thalassemia

Beta Globin (*HBB*) Deletion/Duplication 2010113

- Detect large deletions of the β-globin gene cluster associated with β 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
  - β thalassemia minor – clinically asymptomatic, mild anemia (hypochromic and microcytic), moderately increased fetal hemoglobin
- Homozygosity for Hb Lepore is rare
  - Associated phenotypes
    - β thalassemia intermedia – pallor, jaundice, cholelithiasis, hepatosplenomegaly, skeletal disease
    - β thalassemia major – severe anemia, hepatosplenomegaly, growth retardation, jaundice
- Co-inheritance with other globin mutations may influence clinical presentation
  - Examples of expected phenotypes
    - Hb Lepore with sickle cell trait (HbS) – mild sickling disorder
    - Hb Lepore with HbE trait – β thalassemia intermedia
    - Hb Lepore and β thalassemia trait – β thalassemia intermedia to β thalassemia major
    - Presence of α globin mutation(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 α-globin chains and 2 β-globin chains
- Hb Lepore results from a fusion between the Δ-globin gene (*HBD*) and the β-globin gene (*HBB*)

Genetics

Genes – *HBD*/*HBB*

Inheritance – Autosomal recessive

Structure/function

- Fusion involving the 5’ portion of the Δ-globin gene and the 3’ portion of the β-globin gene
  - Results in a deletion of approximately 7.4 kb
  - Fusion gene retains the promoter of the Δ-globin gene, decreasing transcription efficiency and production of the Δ/β-hybrid chain
  - Hb Lepore is classified as a β thalassemia mutation as it results in reduced β-chain synthesis

Mutations

- 3 common mutations
  - Hb Lepore-Washington-Boston (g.63632_71046del)
  - Hb Lepore-Baltimore (g.63564_70978del)
  - Hb Lepore-Hollandia (g.63290_70702del
- Other rare Δ/β-globin gene rearrangements have been described

Test Interpretation

Sensitivity/specificity

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

Results

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

Limitations

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