Gamma Globin (HBG1 and HBG2) Sequencing

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Fetal hemoglobin (Hb F) is the predominant hemoglobin in the fetus and is comprised of two alpha globin chains and two gamma chains. A-gamma is expressed from the *HBG1* gene and G-gamma is expressed from the *HBG2* gene. Promoter variants in either *HBG1* or *HBG2* can result in nondeletional hereditary persistence of fetal hemoglobin (HPFH), a clinically benign condition but can ameliorate disease severity in sickle cell disease and thalassemia. The majority of genetic variants in the gamma genes are clinically benign; however, rare variants that result in qualitative defects may produce a clinical phenotype in neonates. Unstable variants may result in hemolytic anemia/hyperbilirubinemia, high- or low-oxygen affinity variants may present as erythrocytosis or cyanosis, and M-hemoglobin variants may cause methemoglobinemia. Such clinical symptoms related to gamma chain variants typically resolve after 6 months of age due to the gamma- to beta-globin switch.

Featured ARUP Testing

Gamma Globin (HBG1 and HBG2) Sequencing 3001957

Method: Polymerase Chain Reaction/Sequencing

- Use to assess for gamma globin gene variants resulting in neonatal hemolytic anemia, cyanosis, or methemoglobinemia in symptomatic infants when other etiologies have been excluded
- Use to assess for nondeletional HPFH in individuals with elevated fetal hemoglobin
- Characterizes abnormal hemoglobins identified by electrophoresis suspected to represent gamma chain variants

Disease Overview

Expression of variant gamma proteins is related to the overall expression of Hb F and will vary over time.

Clinical symptoms related to gamma chain variants commonly resolve after the first 6 months of life, given the normal switch from fetal hemoglobin expression to adult hemoglobin expression that occurs at that time.

Clinical presentations in neonates include:

- Hemolytic anemia/hyperbilirubinemia
- Erythrocytosis
- Cyanosis
- Methemoglobinemia

HPFH may occur in adults:

- A clinically benign disorder characterized by elevated Hb F into adulthood
- When coinherited with sickle cell disease or beta thalassemia, HPFH may ameliorate disease severity

Genetics

Genes

HBG1 (A-gamma) and *HBG2* (G-gamma)

Inheritance

Autosomal dominant

Variants

Over 100 gamma globin variants have been described, many of which are clinically benign.

- Qualitative defects:
  - Unstable variants may result in hemolytic anemia/hyperbilirubinemia
  - High- or low-oxygen affinity variants may result in erythrocytosis or cyanosis, respectively
  - M hemoglobin variants may cause methemoglobinemia

- Quantitative defects
  - Promoter region variants may be associated with non-deletional HPFH, a clinically benign condition
  - Polymorphisms may influence expression of the gamma genes

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: Unknown
  - Gamma globin variants are a rare cause of neonatal hemolytic anemia, cyanosis, erythrocytosis, or methemoglobinemia
- Analytic sensitivity/specificity: >99%

Test Methodology

- Long-range polymerase chain reaction (PCR) followed by nested PCR and bidirectional sequencing of all coding regions, intron/exon boundaries, proximal promoter, and 5' proximal promoters of the *HBG1* and *HBG2* genes

Results

- No pathogenic variants detected
  - Reduces the likelihood of a gamma globinopathy or nondeletional gamma HPFH
- Pathogenic variant detected
  - Consistent with a diagnosis of a gamma globinopathy or nondeletional gamma HPFH
  - Clinical manifestations are variable and dependent on the effect of the identified variant on protein function/expression and on the age of the patient
  - Correlation with hematologic parameters and hemoglobin electrophoresis results is strongly recommended
- Gamma globin gene sequencing may identify variants of unknown clinical significance

Limitations

- Diagnostic errors can occur due to rare sequence variations or repeat element insertions
- Large deletions/duplications, distal regulatory region variants, deep intronic variants, and hybrid gene events will not be detected

Additional Resources

Manca L, Masala B. Disorders of the synthesis of human fetal hemoglobin. *IUBMB Life*. 2008;60(2):94-111.

Patrinos GP, Giardine B, Riemer C, et al. Improvements in the HbVar database of human hemoglobin variants and thalassemia mutations for population and sequence variation studies. *Nucleic Acids Res*. 2004;32(Database issue):D537-D541.

Related Information

Unstable Hemoglobinopathies

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