Gamma Globin (HBG1 and HBG2) Sequencing

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.

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
- Analytical 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' and 3' untranslated regions 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
References
