Overview

Useful For
An adjunct in the interpretation of hemoglobin electrophoresis results

Evaluation for suspected gamma variants or nondeletional hereditary persistence of fetal hemoglobin (HPFH)

Assessment of unstable gamma chain variants when other tests for causes of hemolysis are unrevealing)

Genetics Test Information
The beta-like hemoglobins include the epsilon, gamma, beta, and delta globins, whose genes are present on chromosome 11 in a linked cluster (ie, the beta globin complex). The gamma genes, \textit{HBG1} (Ay) and \textit{HBG2} (Gy), contain 3 exonic coding regions and 2 intronic intervening sequences (IVS). The genes produce gamma globin chains that form tetramers with alpha globin chains to create fetal hemoglobin (Hb F). \textit{HBG1} and \textit{HBG2} differ only in which amino acid is located at position 136 (alanine or glycine). The resultant proteins are named A-gamma and G-gamma, respectively. Although G-gamma is predominant at birth, this gradually reverses during the first year of life to become the normal adult G-gamma/A-gamma ratio, which is 2:3. Some people maintain an increased G-gamma:A-gamma ratio throughout life, which has been linked to certain alterations in either gene. Additionally, some alterations in the promoter regions of the gamma globin genes are known to cause a form of hereditary persistence of fetal hemoglobin (HPFH), which is characterized by a significant but harmless elevation of Hb F into adulthood. If co-inherited with sickle cell disease, HPFH has a strong modulating effect on the condition and appears to protect against some, but not all, of its complications. Some gamma genetic variations result in gamma chain hemoglobin variants, most of which are clinically insignificant; however, an incompletely studied subset causes neonatal disorders, such as hemolytic anemia, cyanosis, and methemoglobinemia.

Highlights
This test should be used as an adjunct to abnormal results detected by hemoglobin electrophoresis testing. It will assist with:

-Diagnosis of nondeletional hereditary persistence of fetal hemoglobin (HPFH)

-Identification of abnormal gamma chain variants (eg, unstable, high- or low-oxygen affinity, or M hemoglobins)

-Predicting the severity of a co-inherited sickling disorder

-Evaluation of unexplained neonatal anemia, cyanosis, or hyperbilirubinemia

Special Instructions

- \textit{Thalassemia/Hemoglobinopathy Patient Information}
- \textit{Informed Consent for Genetic Testing}
- \textit{Informed Consent for Genetic Testing (Spanish)}

Method Name
Polymerase Chain Reaction (PCR) Amplification/Sanger Sequence Analysis

NY State Available
Yes
Specimen Type
Varies

Necessary Information
A complete patient history is strongly encouraged.

Specimen Required
Submit only 1 of the following specimens:

Specimen Type: Peripheral blood

Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD)

Specimen Volume: 4 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in the original tube.

Specimen Stability Information: Refrigerate 30 days(preferred)/Ambient 14 days

Specimen Type: Extracted DNA from whole blood

Container/Tube: 1.5-2 mL tube

Specimen Volume: Entire specimen

Collection Instructions: Label specimen as extracted DNA from blood and provide indication of volume and concentration of the DNA

Specimen Stability Information: Frozen (preferred)/Refrigerate/Ambient

Forms
1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)

2. Thalassemia/Hemoglobinopathy Patient Information (T358) in Special Instructions

Specimen Minimum Volume
Blood: 1 mL;
Test Definition: WGSEQ
Gamma Globin Full Gene Sequencing

Extracted DNA: 50 mcL at 50 ng/mcL concentration

Reject Due To

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<tr>
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Specimen Stability Information

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Clinical and Interpretive

Clinical Information

Hemoglobin F (Hb F) is the dominant hemoglobin at birth but is gradually replaced by adult hemoglobin (Hb A) during the year after birth (normal value < or =1% of total hemoglobin after age 2). Increased Hb F levels may continue after the neonatal period and into adulthood for various reasons. Genetic causes include deletional and nondeletional forms of hereditary persistence of fetal hemoglobin (HPFH) and delta-beta thalassemia mutations. Over 100 mutations have been described in the gamma genes and, if detectable, the protein expression will vary over time according to the overall Hb F expression. Gamma globin variants can manifest either as a quantitative (gamma thalassemia or nondeletional HPFH) or a qualitative (gamma variant) abnormality. Nondeletional HPFH alterations frequently modulate the expected severity of sickling disorders due to the inhibitory properties of Hb F on sickle formation. Many gamma chain variants are benign, although some, such as unstable, high- and low-oxygen affinity, or M hemoglobin variants, cause hemolytic anemia/hyperbilirubinemia, erythrocytosis, cyanosis, and methemoglobinemia, respectively. The percentages of gamma variants will vary according to if they are present on the HBG1 or HBG2 genes, as these genes are differentially expressed depending on the age of the patient. Symptoms due to gamma variants are expected to decrease along with the normal decrease in Hb F and therefore most resolve after the first 6 months of life.

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variants in the gene. If positive, the alteration will be correlated with clinical significance, if known.

Cautions

This test cannot be used in isolation to confirm or exclude hemoglobin conditions. Large deletions, crossover events, as well as other variants may not be detected. This test is used in conjunction with adequately studied protein analysis results.

If multiple alterations are identified, gamma globin gene sequencing is not able to distinguish between variants that are found in the same allele (in cis) and variants found on different alleles (in trans). This limitation of sequencing...
may complicate diagnosis or classification and has implications for inheritance and genetic counseling. To resolve these cases, molecular results must be correlated with electrophoretic and protein data and/or family studies.

**Clinical Reference**


**Performance**

**Method Description**

Total genomic DNA is extracted from the sample and the full gamma globin genes are amplified by PCR in separate reactions followed by Sanger sequencing. Review of the sequence data is performed using a combination of automated calls and manual inspection.(Unpublished Mayo method)

**PDF Report**

No

**Day(s) and Time(s) Test Performed**

Monday through Friday; Varies

**Analytic Time**

4 days

**Maximum Laboratory Time**

10 days

**Specimen Retention Time**

DNA 3 months

**Performing Laboratory Location**

Rochester
Test Definition: WGSEQ
Gamma Globin Full Gene Sequencing

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
81479-Unlisted molecular

LOINC® Information

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