Hereditary Hemolytic Anemia Cascade

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Hereditary hemolytic anemia (HHA) is characterized by premature red blood cell (RBC) destruction and anemia due to intrinsic RBC defects, and encompasses a diverse group of heterogeneous disorders. Genetic testing is indicated when initial test results do not explain clinical presentation or mode of inheritance.

Disease Overview

Clinical presentation is highly variable and may include anemia, fatigue, gallstones, hyperbilirubinemia/jaundice, pallor, scleral icterus, and splenomegaly. Laboratory findings include decreased hemoglobin concentration, hematocrit, and RBC count. Blood smear abnormalities such as spherocytes, acanthocytes, schistocytes, bite cells, stomatocytes, polychromasia, and target cells may be present.

Associated Disorders

RBC Membrane Disorders

RBC membrane disorders, characterized by weakened RBC membranes that result in irregular shape, increased fragility, and hemolysis:

- Hereditary spherocytosis (HS)
  - Associated with *ANK1*, *EPB42*, *SLC4A1*, *SPTA1*, and *SPTB* genes
  - The most common RBC membrane disorder and is characterized by spherically shaped RBCs with decreased deformability.
  - Approximately 75% of HS cases are autosomal dominant and 25% are autosomal recessive or de novo.
- Hereditary elliptocytosis (HE) and hereditary pyropoikilocytosis (HPP) are related disorders with a wide spectrum of clinical phenotypes:
  - HE is characterized by elliptically shaped RBCs.
  - Marked anisopoikilocytosis with elliptocytes, microspherocytes, and bizarrely shaped RBCs is characteristically seen in HPP.
  - HE is autosomal dominant and HPP is autosomal recessive; variants in *SPTA1*, *SPTB*, and, less commonly, *EPB41* are causative.
  - Individuals with HE are generally asymptomatic but can have mild compensated hemolytic anemia.
  - Patients with HPP usually present with moderate to severe anemia.
- Dehydrated hereditary stomatocytosis (xerocytosis) is characterized by decreased intracellular potassium content, loss of cell water, increased cytoplasmic viscosity, and increased mean cell hemoglobin concentration.
  - Inheritance is autosomal dominant, and the most commonly involved gene is *PIEZO1*.
  - Splenectomy should be avoided in patients with some forms of hereditary stomatocytosis as it may predispose the patient to life-threatening thrombotic events.

RBC Enzymopathies

RBC enzymopathies include more than 20 recognized disorders caused by deficiencies of enzymes involved with glycolysis, hexose monophosphate shunt, glutathione metabolism, and nucleotide metabolism.

- Common forms:
  - G6PD deficiency (*G6PD*)
  - Pyruvate kinase deficiency (*PKLR*)
  - Pyrimidine 5′-nucleotidase (*NT5C3A*)

Featured ARUP Testing

Hereditary Hemolytic Anemia Cascade 3000894

Method: High Performance Liquid Chromatography (HPLC)/Electrophoresis/RBC Solubility/Polymerase Chain Reaction/Fluorescence Resonance Energy Transfer/Sequencing/Spectrophotometry/Visual Identification/Quantitative Enzymatic Assay/Quantitative Flow Cytometry/Cytochemical Stain/Multiplex Ligation-Dependent Probe Amplification/Massively Parallel Sequencing

- Optimal test to evaluate individuals with hereditary hemolytic anemia or unexplained long-standing hemolytic anemia
- A University of Utah School of Medicine hematopathologist personally directs and interprets each stage of testing through to completion.
- A comprehensive report is provided.
- Submit a recent CBC along with transfusion history to inform reflex cascade testing and aid in result interpretation.
- See Test Description for more information on the components included in this panel.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

For more information on the recommended testing strategy for hereditary hemolytic anemia, refer to the Hemolytic Anemias topic or Hemolytic Anemias Testing Algorithm.

- Associated findings:
  - Usually normocytic normochromic hemolytic anemia with no specific abnormalities of RBC morphology
  - Severity of hemolysis is variable and may be a result of an external stressor (eg, infection, administration of drugs, or ingestion of some foods).
  - Nonhematological manifestations may include:
    - Myopathy
    - Neurological dysfunction
    - Intellectual disability

Hemoglobinopathies

Hemoglobinopathies involve a quantitative defect in biosynthesis of one type of hemoglobin (Hb) chain or a structurally abnormal Hb.

- Alpha or beta thalassemia results from a quantitative defect in the synthesis of either the alpha- or beta-globin chain.
  - The unpaired subunits precipitate, bind to the RBC membrane, and lead to hemolysis.
- Structural Hb variants result from a structurally abnormal Hb that may polymerize, precipitate, or crystalize within the RBC, leading to membrane changes and hemolysis.

Prevalence

HHA disorders: 1/500-1,100

- HS: 1/2,000 northern Europeans
- HE/HPP: 1/2,000-4,000 worldwide
- G6PD deficiency: 400 million worldwide
  - Varies by ethnicity: 7/10 Kurdish Jewish males, 1/6-10 African American males, 1/7-9 Arabic males, 1/6-16 Southeast Asian males
- PKD: 1/20,000 Europeans

Inheritance

Dependent on gene: autosomal recessive, autosomal dominant, or X-linked

Test Description

Initial testing includes the following components (always performed):

- Peripheral blood smear evaluation
- Osmotic fragility testing
- Unstable hemoglobin evaluation
- Hemoglobinopathy testing using high-performance liquid chromatography (HPLC), capillary electrophoresis, and red blood cell solubility
- Qualitative flow cytometry (RBC band 3 protein reduction in hereditary spherocytosis)
- Quantitative enzymatic testing (pyruvate kinase and glucose-6-phosphate dehydrogenase)

Additional reflex testing is performed as needed:

- Alpha globin (HBA1 and HBA2) testing
- Beta globin (HBB) sequencing
- G6PD sequencing
- Hereditary hemolytic anemia sequencing panel
  - Refer to the Genes Tested table for genes included.

Clinical Sensitivity

Variable and dependent on phenotype/condition

Limitations

- A negative result does not exclude a heritable form of hemolytic anemia.
- This testing is not suitable for acquired causes of hemolytic anemia.
- See individual components for limitations, analytic sensitivity/specificity, interpretation considerations, and reference intervals.

Related Information

Hemolytic Anemias
Hemolytic Anemias Testing Algorithm
Hereditary Hemolytic Anemia Panel, Sequencing

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