Glucose-6-Phosphate Dehydrogenase (*G6PD*) Deficiency

Indications for Ordering

- Individuals (particularly those of African, Mediterranean, or Asian descent) with an acute hemolytic reaction triggered by exposure to a known oxidative drug, infection, or ingestion of fava beans
- Members (especially males) of families where jaundice, splenomegaly, or cholelithiasis are recurrent
- Newborns (particularly those of Mediterranean or African descent) with severe prolonged neonatal jaundice
- Asymptomatic individuals taking primaquine or other drugs that have adverse reactions in patients with G6PD deficiency

Test Description

Methodology

Glucose-6-Phosphate Dehydrogenase
- Quantitative enzymatic

Glucose-6-Phosphate Dehydrogenase Deficiency *(G6PD)* Sequencing
- Polymerase chain reaction (PCR) amplification of *G6PD* exons 2-13 (entire coding region) followed by bidirectional sequencing

Glucose-6-Phosphate Dehydrogenase *(G6PD)* 2 Mutations
- PCR amplification of *G6PD* exons 4 and 5 with specific detection of the A+ (A376G) and A- (G202A and A376G on the same chromosome) alleles using TaqMan probes and fluorescent monitoring

Tests to Consider

Glucose-6-Phosphate Dehydrogenase 0080135
- Preferred initial screening test for G6PD deficiency

Glucose-6-Phosphate Dehydrogenase Deficiency (*G6PD*) Sequencing 2007163
- Preferred test for individuals of high-risk ethnic backgrounds other than those of African descent
- Appropriate test for symptomatic individuals of African descent who do not carry the A- allele
- Detects most *G6PD* deficiency-causing gene variants

Glucose-6-Phosphate Dehydrogenase (*G6PD*) 2 Mutations 0051684
- Preferred test for individuals of African descent
- Detects the single most common pathogenic *G6PD* variant (the A- allele) in individuals of African descent

Disease Overview

Prevalence – 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

Symptoms
- Most symptomatic individuals have ~10% residual enzyme activity
- Presentation varies by gender
  - Males
    - Hemizygotes – variably affected
  - Females
    - Heterozygotes – may experience symptoms even in the presence of normal enzyme levels
    - Homozygotes – may be seen in populations where the *G6PD*-deficient allele is common
- May present variably
  - Acute hemolytic anemia in response to oxidative stress
  - Neonatal jaundice
  - Chronic nonspherocytic hemolytic anemia in the absence of oxidative stressors

Physiology
- G6PD protects red blood cell proteins from oxidative damage
- Decreased activity is associated with acute hemolytic anemia when individual is exposed to oxidative stress
  - Certain medications induce oxidative stress (eg, primaquine)
  - Other etiologies of stress
    - Diabetic ketoacidosis
    - Infections
    - Consumption of fava beans
- Severe decreases in enzyme activity (<10%)
  - Associated with chronic nonspherocytic hemolytic anemia in the absence of oxidative stressors

Genetics

Gene – *G6PD*

Inheritance – X-linked recessive

Penetrance – depends on variant; generally low

De novo variants – rare

Variants

- 400 allelic variants known
- >170 point variants in exons 2-13 are known to cause G6PD deficiency

Test Interpretation

Glucose-6-Phosphate Dehydrogenase

Clinical sensitivity – 99%

Results

- Positive
  - Class I – severe enzyme deficiency
    - Associated with chronic nonspherocytic hemolytic anemia
  - Class II – severe enzyme deficiency with <10% of normal activity
    - Associated with acute hemolytic anemia
  - Class III – mild to moderate enzyme deficiency (10-60% of normal activity)
    - Most common class
  - Class IV – very mild to almost normal enzyme activity (>60% of normal activity)
    - No clinical consequences

Limitations

- Reduced sensitivity for detection of G6PD deficiency in
  - Presence of hemolytic crises
  - Neonates
  - Presence of high reticulocyte count
  - After blood transfusion
  - Heterozygous females
- Diagnostic errors can occur due to rare sequence variations

Glucose-6-Phosphate Dehydrogenase Deficiency (*G6PD*) **Sequencing**

Sensitivity/specificity

Clinical sensitivity – >98%
Analytical sensitivity/specificity – 99%

Results

- Positive
  - Pathogenic variant(s) detected
- Negative
  - No pathogenic variant detected

Limitations

- Sequencing may detect variants of unknown clinical significance
- Diagnostic errors can occur due to rare sequence variations
- Not detected by sequencing
  - Deep intronic or regulatory region variants
  - Large deletions or duplications

Glucose-6-Phosphate Dehydrogenase (*G6PD*) 2 Mutations

Sensitivity/specificity

- Clinical sensitivity – 99% in individuals of African descent
- Analytical sensitivity/specificity – 99%

Results

Positive

- A- allele
  - Male hemizygotes and female homozygotes are predicted to be affected by G6PD deficiency
  - Female heterozygotes may be at risk for enzyme deficiency
- A+ allele
  - Not associated with G6PD deficiency phenotype

Limitations

- Variants other than A- and A+ will not be detected
- Diagnostic errors can occur due to rare sequence variations