

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells (RBCs) mainly affecting males. G6PD generates NADPH and protects RBCs from oxidative injury. G6PD deficiency can result in RBC hemolysis.

The most common condition associated with G6PD deficiency is hemolytic anemia, which can be triggered by bacterial or viral infections, by certain antibiotics and malaria medications, and by consumption of fava beans or inhaling fava pollen (called favism).

G6PD deficiency can also be a significant cause of mild to severe jaundice in newborns.

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 sex:

- 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 antibiotics and malaria medications (eg, primaquine)
 - Nondrug etiologies:
 - Diabetic ketoacidosis
 - Infections
 - Fava bean consumption
- Severe decreases in enzyme activity (<10%) associated with chronic nonspherocytic hemolytic anemia in the absence of oxidative stressors

Tests to Consider

Glucose-6-Phosphate Dehydrogenase 0080135

Method: Quantitative Enzymatic

Preferred initial screening test for G6PD deficiency.

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) Sequencing 2007163

Method: Polymerase Chain Reaction/Sequencing

- Preferred test to detect pathogenic *G6PD* variants in 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.

Glucose-6-Phosphate Dehydrogenase (G6PD) 2 Mutations 0051684

Method: Polymerase Chain Reaction/TaqMAN

- Preferred genetic test for individuals of African descent.
- Use to detect the single most common pathogenic *G6PD* variant (the A-allele) in individuals of African descent.

Genetics

Gene

G6PD

Inheritance

X-linked recessive

Penetrance

Depends on variant; generally low

De novo Variants

Rare

Variants

- 400 allelic variants are known.
- >170 sequence 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%¹
- 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 descent²
- 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 is not associated with G6PD deficiency phenotype.

Limitations

- Variants other than c.376A>G and c.202G>A will not be detected.
- Diagnostic errors can occur due to rare sequence variations.

References

1. Gómez-Manzo S, Marcial-Quino J, Vanoye-Carlo A, et al. [Glucose-6-phosphate dehydrogenase: update and analysis of new mutations around the world](#). Int J Mol Sci. 2016;17(12):2069. PubMed
2. Beutler E, Duparc S, G6PD Deficiency Working Group. [Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development](#). Am J Trop Med Hyg. 2007;77(4):779-789. PubMed

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