

Glucose-6-Phosphate Dehydrogenase (G6PD) Two Mutations

TO DIAGNOSE AND DETERMINE CARRIER STATUS FOR G6PD DEFICIENCY RESULTING FROM THE AFRICAN A- AND A+ ALLELES

Disease Overview

- G6PD deficiency is the most common enzyme deficiency worldwide, with the greatest frequency in individuals of African, Sephardi Jewish, Arab/Mediterranean, Southeast Asian, and Asian-Indo/Pakistani descent.
- G6PD protects red blood cell proteins from oxidative damage by generating NADPH, which maintains high levels of reduced glutathione.
- The majority of affected individuals have moderate G6PD deficiency (approximately 10 percent normal activity), which can cause neonatal jaundice and acute hemolytic anemia in response to oxidative stress. Oxidative stress may be caused by certain medications, diabetic ketoacidosis, some infections, and consumption of fava beans in susceptible individuals.
- Rarely, individuals have severe G6PD deficiency (less than 10 percent normal activity) resulting in neonatal jaundice and chronic nonspherocytic hemolytic anemia in the absence of oxidative stressors.
- Treatment for severe hemolytic anemia may necessitate blood transfusions.
- Affected individuals should avoid foods and medications that trigger hemolytic episodes.

Epidemiology

Prevalence of G6PD deficiency: one in 10 males and ~20 percent in females of African descent.

Genetics

- X-linked recessive inheritance.
- Affects hemizygous males, as well as both heterozygous and homozygous females.
- Several hundred *G6PD* mutations have been described. Some are benign, while others result in intermittent or chronic hemolytic anemia.
- Greater than 99 percent of G6PD deficiency among individuals of African descent is caused by the G6PD A- allele harboring both the G202A and A376G mutations on the same chromosome (in cis).

- Approximately 10 percent of African-American males and 20 percent of females carry a copy of the G6PD A- allele. Expected enzyme level in hemizygous males is approximately 10 percent of normal, except during or just after hemolysis, when levels may be normal.
- Expected level in heterozygous females ranges from approximately 10 percent to normal levels; however, as this gene is a subject to X-chromosome inactivation, heterozygous females have a variable proportion of red blood cells with G6PD deficiency. Thus, female carriers may have hemolytic episodes even if G6PD enzyme studies are normal because deficient as well as non-deficient red cells coexist at various proportions.
- Hemizygous males and heterozygous or homozygous females with the G6PD A- allele are at risk for intermittent hemolytic anemia upon exposure to oxidative stress, although most individuals never become symptomatic.
- The A376G variant, seen alone in 11 percent of African-Americans males, is benign and known as the G6PD A+ allele. It is associated with a mild, non-significant decrease of enzyme activity.

Indications for Ordering

- Diagnostic or carrier screening for individuals of African descent (even with normal G6PD enzyme activity).
- For identification of affected individuals of African descent that are asymptomatic to prevent hemolysis prior to administering certain medications.

Contraindications

Prenatal testing.

Additional Ordering Notes

If there is a positive family history of G6PD deficiency, provide information regarding the relationship of the affected individual to the patient and the specific *G6PD* mutation(s), if known.

Interpretation

- Lack of detection of a *G6PD* mutation does not rule out G6PD deficiency since this assay only identifies two common *G6PD* mutations in the African population.
- One or two copies (in females) of the A376G mutation alone are not associated with significantly decreased G6PD enzyme levels or hemolysis.
- Males with one copy of the *G6PD* double mutant (A376G and G202A) A- allele and females with two copies are predicted to be affected with G6PD deficiency and are at risk for intermittent hemolytic anemia.
- Females heterozygous for the *G6PD* double mutant (A376G and G202A) A- allele are at risk for hemolysis.

Methodology

- Two common *G6PD* gene mutations, c. (p.A376G) and c. (p.G202A), are detected by allele-specific hydrolysis probes (TaqMan®) and fluorescent monitoring.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is 99 percent in individuals of African descent.

Limitations

- *G6PD* mutations, other than A376G and G202A, are not evaluated by this assay.
- Rare diagnostic errors can occur due to probe-site mutations.

Related Test

Glucose-6-Phosphate Dehydrogenase (0080135)—measures G6PD enzymatic activity

References

1. Mason PJ, Bautista JM, Gilsanz F. G6PD deficiency: the genotype-phenotype association. *Blood Reviews* 2007;21:267–83.
2. Luzzatto L, Vulliamy TJ, Mehta A. Glucose 6-phosphate dehydrogenase deficiency. Scriver CR, Beaudet AL, Sly D, Valle D, editors. In *The Metabolic and Molecular Bases of Inherited Disease*. CR Scriver, et al., eds. 2001; New York: McGraw-Hill, 451–3.
3. Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician* 2005;72:1277–82.
4. Prchal JT, Gregg XT. Red Cell Enzymes. *Hematology Am Soc Hematol Educ Program* 2005;19–23.

Test Information

0051684

Glucose-6-Phosphate Dehydrogenase, *G6PD* Mutations, African Alleles

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.