Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency by DNA

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder in humans. It is most frequent in individuals of African, Mediterranean, and Asian descent due to its protective effect against mild malaria. The G6PD enzyme is present in all cells to prevent cellular damage from reactive oxygen species. Because red blood cells (RBCs) are especially at risk of damage due to their role in carrying oxygen to the tissues, G6PD deficiency can result in RBC hemolysis.

Since G6PD deficiency is an X-linked condition, it mainly affects males. Heterozygous females can be affected due to skewed X-chromosome inactivation. Complete absence of G6PD enzyme is an embryonic lethality; thus, pathogenic *G6PD* variants result in a partial, but not complete, reduction of G6PD enzyme levels or function.

Featured ARUP Testing

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) Sequencing 3004457

Method: Massively Parallel Sequencing

Preferred test for detection of *G6PD* variants in females or any individual with reduced G6PD enzyme activity

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

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

Secondary test to confirm pathogenic *G6PD* A- variant in individuals of sub-Saharan African descent with reduced G6PD enzyme activity

Disease Overview

Prevalence

400 million worldwide

- Most commonly affects males of African (7.5%), Southeast Asian (4.7%), Mediterranean (3.9%), and Middle Eastern (6.0%) descent[1]

Presentation

Symptoms include neonatal jaundice peaking at 2-3 days of life with lethargy, extreme sleepiness, and poor muscle tone. In newborns, G6PD deficiency increases the risk for hyperbilirubinemia by a factor of two. Untreated G6PD deficiency causes 20% of all cases of kernicterus. In adults, G6PD deficiency may trigger hemolytic anemia, resulting in pallor, jaundice, fatigue, splenomegaly, and dark urine. These episodes may be triggered by stress, infection, exposure to foods with high levels of oxidative substances (like fava beans), or from treatment with many common drugs such as antimalarial medications.

Although severe (class I) *G6PD* variants cause chronic nonspherocytic hemolytic anemia, most males with one pathogenic *G6PD* variant and females with two pathogenic *G6PD* variants remain asymptomatic throughout their lives. Heterozygous females may experience symptoms even in the presence of normal enzyme levels.

Genetics

Gene

G6PD (NM_001042351)

Inheritance

X-linked

Penetrance

Depends on variant; generally low

Variants

Over 500 *G6PD* variants are known[2]

- 85% are single nucleotide substitutions[3]
- 8% of variant alleles have multiple missense variants
- 5% of variants are small deletions
- 1% of variants are intronic

Classification of Enzyme Variants	Enzyme Activity	Disease Association
Class I	<5%	Chronic nonspherocytic anemia
Class II	<10%	Acute hemolytic anemia
Class III	10-60%	Most common variant type, mild to moderate deficiency
Class IV	>60%	None

Test Interpretation

Clinical Sensitivity

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

98%[4]

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

Variable; dependent on country of origin

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Results for *G6PD* Sequencing and *G6PD* 2 Mutations	
Test Result	**Interpretation**
No variants detected	Individual's risk to be affected with G6PD deficiency is reduced Specific risk reduction is dependent on clinical sensitivity of the DNA test
One class IV variant (c.376A>G, otherwise known as the A+ allele) detected	Individual's risk to be affected with G6PD deficiency is reduced Specific risk reduction is dependent on clinical sensitivity of the DNA test

Test Result	Interpretation
One pathogenic variant identified	Males are predicted to be affected and females are at increased risk to be affected
Two pathogenic variants detected on opposite chromosomes	Individual is predicted to be affected
One VUS detected	It is unknown if the individual is affected or not If the VUS is determined to be pathogenic in the future, males are predicted to be affected and females are at an increased risk to be affected
One pathogenic variant and one VUS detected	Males are predicted to be affected Females are at an increased risk to be affected and are predicted to be affected if the VUS is later determined to be pathogenic

VUS, variant of unknown significance

Limitations

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

- A negative result does not exclude a diagnosis G6PD deficiency.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the *G6PD* gene
  - Regulatory region and deep intronic variants
  - Large deletions/duplications in the *G6PD* gene
  - Noncoding transcripts
  - Phase of variants on complex alleles; concurrent detection of c.376A>G and c.202G>A is presumed to reflect the complex A- allele (both variants on the same chromosome)
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes or repetitive/homologous regions

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

- G6PD variants other than c.376A>G and c.202G>A are not detected.
- This assay is not able to determine phase; concurrent detection of c.376A>G and c.202G>A is presumed to reflect the complex A- allele (both variants present on the same chromosome).
- Diagnostic errors can occur due to rare sequence variations.

References

1. Nkhoma ET, Poole C, Vannappagari V, et al. The global prevalence of glucose-6 phosphate dehydrogenase deficiency: a systemic review and meta-analysis. *Blood Cells Mol Dis*. 2009;42(3):267-278.

2. Cooper DN, Ball EV, Stenson, AD, et al. The Human Gene Mutation Database (HGMD). Institute of Medical Genetics in Cardiff. Accessed Sep 2021.

3. Minucci A, Moradkhani K, Hwang MJ, et al. Glucose-6-phosphate dehydrogenase (G6PD) mutations database: review of the "old" and update of the new mutations. *Blood Cells Mol Dis*. 2012;48(3):154-165.

4. 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.