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Patient Report

Patient Age/Sex: 1 day Male

Specimen Collected: 13-Dec-21 14:22

G6PD by NGS | **Received: 13-Dec-21 14:22** **Report/Verified: 13-Dec-21 14:25**

Procedure	Result	Units	Reference Interval
G6PD Specimen	Whole Blood		
G6PD Interp	Positive [f1 i1]		

Result Footnote

f1: G6PD Interp

RESULT
One pathogenic variant was detected in the G6PD gene.

PATHOGENIC VARIANT
Gene: G6PD (NM_001042351.3)
Nucleic Acid Change: c.1388G>A; Hemizygous
Amino Acid Alteration: p.Arg463His
Inheritance: X-linked

INTERPRETATION
One pathogenic variant, c.1388G>A; p.Arg463His, was detected in the G6PD gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic G6PD variants are inherited in an X-linked manner and are associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency (MIM: 300908). This is a class II pathogenic variant associated with a severe decrease in enzyme activity; therefore, this individual is predicted to be affected with G6PD deficiency. All female offspring will inherit the variant and be at risk for G6PD deficiency, while male offspring will not inherit the variant.

No additional pathogenic variants were identified in the G6PD gene by massively parallel sequencing. Please refer to the background information included in this report for limitations of this test.

Evidence for variant classification: The G6PD c.1388G>A; p.Arg463His variant (rs72554664), also known as G6PD Kaiping, is reported in the literature as a common G6PD deficiency variant in Asian populations (Chiu, 1991; Fu, 2018; Li, 1998; Nuchprayoon, 2002). This variant is reported in ClinVar (Variation ID: 100059) and is found in the East Asian population with an allele frequency of 0.70% (104/14,782 alleles, including 32 hemizygotes and a single homozygote) in the Genome Aggregation Database. The arginine at codon 463 is moderately conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.869). Additionally, other variants at this codon (c.1387C>T; p.Arg463Cys, c.1387C>A; p.Arg463Ser) have been reported in individuals with G6PD deficiency (Hirono, 1997; Rodrigues, 2002). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Hematologic and genetic consultations are recommended. Family members should be offered testing for the identified variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
Chiu DT, et al. Two commonly occurring nucleotide base substitutions in Chinese G6PD variants. Biochem Biophys Res Commun. 1991;180(2):988-93.

Fu C, et al. Newborn screening of glucose-6-phosphate dehydrogenase deficiency in Guangxi, China: determination of optimal cutoff value to identify heterozygous female neonates. Sci Rep. 2018;8(1):833.

Hirono A, et al. Molecular analysis of eight biochemically unique glucose-6-phosphate dehydrogenase variants found in Japan. Blood. 1997;89(12):4624-7.

Result Footnote

f1: G6PD Interp

Li P, et al. Analysis of common mutations and associated haplotypes in Chinese patients with glucose-6-phosphate dehydrogenase deficiency. Biochem Mol Biol Int. 1998;46(6):1135-43.

Nuchprayoon I, et al. Glucose-6-phosphate dehydrogenase (G6PD) mutations in Thailand: G6PD Viangchan (871G>A) is the most common deficiency variant in the Thai population. Human mutation. 2002;19(2):185.

Rodrigues MO, et al. Glucose-6-phosphate dehydrogenase deficiency in Portugal: biochemical and mutational profiles, heterogeneity, and haplotype association. Blood Cells Mol Dis. 2002;28(2):249-59.

This result has been reviewed and approved by [redacted]

Test Information

i1: G6PD Interp

BACKGROUND INFORMATION: Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) Sequencing

CHARACTERISTICS: Although G6PD deficiency is usually asymptomatic, it can result in episodic hemolytic anemia triggered by infections, specific foods, and drugs. In newborns, it may be causal for life-threatening acute hemolytic anemia with jaundice. Variants are classified as follows: Class I - severe enzyme deficiency associated with chronic nonspherocytic hemolytic anemia; Class II - severe enzyme deficiency (<10 percent of normal activity); Class III - mild to moderate enzyme deficiency (10-60 percent of normal activity); and Class IV - normal range (>60 percent of normal enzyme activity). G6PD deficiency is best managed by avoiding known environmental triggers. For a list of drugs that may cause adverse reactions in individuals with G6PD deficiency refer to: https://cpicpgx.org/genes-drugs/. EPIDEMIOLOGY: Highly variable but ranges between 5-30 percent in males of African, Asian, Mediterranean, and Middle Eastern descent.

CAUSE: Hemizygosity for a pathogenic G6PD germline variant in men, and homozygosity or compound heterozygosity in women. Some heterozygous women may be affected due to skewed X-chromosome inactivation.

INHERITANCE: X-linked.

PENETRANCE: Low.

CLINICAL SENSITIVITY: 98 percent.

GENE TESTED: G6PD (NM_001042351)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the G6PD gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. Human genome build 19 (Hg 19) was used for data analysis.

Test Information

i1: G6PD Interp

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of G6PD deficiency. This test only detects variants within the coding regions and intron-exon boundaries of the G6PD gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants, deep intronic variants, and large deletions/duplications will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.