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Patient Report

Patient Age/Gender: Male

Specimen Collected: 13-Aug-21 13:14

Glycogen Storage Disorders Panel by NGS | **Received: 17-Aug-21 17:09** **Report/Verified: 17-Aug-21 18:02**

Procedure	Result	Units	Reference Interval
Glycogen Storage Disease Specimen	DNA		
GSD NGS Interp	Positive [f1 i1]		

Result Footnote

f1: GSD NGS Interp

Section 79-1 of New York State Civil Rights Law requires informed consent be obtained from patients (or their legal guardians) prior to pursuing genetic testing. These forms must be kept on file by the ordering physician. Consent forms for genetic testing are available at www.aruplab.com. Incidental findings are not reported unless clinically significant but are available upon request.

RESULT
Two apparent copies of a pathogenic variant were detected in the GAA gene.

PATHOGENIC VARIANT
Gene: GAA NM_000152.5
Nucleic Acid Change: c.118C>T; Homozygous
Amino Acid Alteration: p.Arg40*
Inheritance: Autosomal Recessive

INTERPRETATION
Two apparent copies of a pathogenic variant, c.118C>T; p.Arg40*, were detected in the GAA gene by massively parallel sequencing. Pathogenic GAA variants are inherited in an autosomal recessive manner and are associated with glycogen storage disease II (MIM: 232300). This individual is predicted to be affected with glycogen storage disease II; clinical manifestations are variable.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The GAA c.118C>T; p.Arg40* variant (rs767409395) is reported in the literature in several individuals affected with type 2 glycogen storage disease (Fukuhara 2018, Reuser 1995). This variant is also listed in ClinVar as pathogenic (Variation ID: 426593). This variant is found in the general population with an overall allele frequency of 0.001% (4/280,068 alleles) in the Genome Aggregation Database. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic and dietary consultations are recommended, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individual's reproductive partner should be offered genetic testing to determine carrier status.

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

REFERENCES
Fukuhara Y et al. A molecular analysis of the GAA gene and clinical spectrum in 38 patients with Pompe disease in Japan. Mol Genet Metab Rep. 2018 Mar. PMID: 29124014

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Result Footnote

f1: GSD NGS Interp

Reuser AJ et al. Glycogenosis type II (acid maltase deficiency). Muscle Nerve Suppl. 1995 PMID: 7603530

Test Information

i1: GSD NGS Interp

BACKGROUND INFORMATION: Glycogen Storage Disorders Panel by NGS

CHARACTERISTICS: Glycogen storage diseases (GSD) are a group of inborn errors of metabolism, typically caused by enzyme defects, resulting in a buildup of glycogen in the liver, muscles, and other organs. Common clinical features of these disorders include hepatomegaly, hypoglycemia, slow growth, cardiomyopathy, and muscle weakness. Other disorders with a similar clinical presentation to GSD are included on this panel.

EPIDEMIOLOGY: Incidence of GSD ranges from 1 in 10,000 to 1 in one million, depending on specific types and ethnic backgrounds.

CAUSE: Pathogenic germline variants in the GYS1, G6PC, SLC37A4, GAA, AGL, GBE1, PYGM, PYGL, PFKM, PHKA2, PHKB, PHKG2, PHKA1, PGAM2, SLC2A2, ALDOA, ENO3, and GYG1 genes are associated with glycogen storage diseases.
Pathogenic germline variants in the ACAT1, ALDOB, CPT2, FBP1, GYS2, LAMP2, LDHA, NHLRC1, OXCT1, PGK1, PGM1, PRKAG2, RBCK1, and SLC16A1 genes are associated with disorders that have phenotypes similar to GSD.

INHERITANCE: Autosomal recessive; X-linked recessive for PHKA1 and PHKA2 genes.

PENETRANCE: Variable

CLINICAL SENSITIVITY: Variable, depending on GSD type and subtype.

GENES TESTED: ACAT1, AGL, ALDOA, ALDOB, CPT2, ENO3*, FBP1, G6PC, GAA, GBE1, GYG1, GYS1, GYS2, LAMP2, LDHA, NHLRC1, OXCT1*, PFKM*, PGAM2, PGK1, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PRKAG2, PYGL, PYGM, RBCK1, SLC16A1, SLC2A2, SLC37A4

*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93

Test Information

i1: GSD NGS Interp

percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of glycogen storage disorder. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified, including GBE1 (NM_000158.4) intron 15. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
ENO3(NM_001374524) exon(s) 1
OXCT1(NM_001364299) exon(s) 5
OXCT1(NM_001364300) exon(s) 1
OXCT1(NM_001364303) exon(s) 1
PFKM(NM_001354735) exon(s) 4
PFKM(NM_001354736) exon(s) 4
PFKM(NM_001354740) exon(s) 1
PFKM(NM_001354741) exon(s) 2
The following may not be detected:
An Ashkenazi Jewish founder mutation in GBE1 (HGMD ID: CX153579)

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.