

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB: 5/21/2024
Gender: Male
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 00/00/0000 00:00

Galactosemia (GALT) Sequencing and Deletion/Duplication

ARUP test code 3004716

GALT Specimen whole Blood

GALT Interp

Positive

RESULT

Two copies of pathogenic variant were detected in the GALT gene.

PATHOGENIC VARIANT

Gene: GALT (NM_000155.4)
Nucleic Acid Change: c.563A>G; Homozygous
Amino Acid Alteration: p.Gln188Arg
Inheritance: Autosomal recessive

INTERPRETATION

Two copies of pathogenic variant, c.563A>G; p.Gln188Arg, were detected in the GALT gene by massively parallel sequencing. Pathogenic GALT variants are inherited in an autosomal recessive manner, and are associated with galactosemia 1 (MIM: 230400). This result is consistent with a diagnosis of galactosemia. Life-long dietary restriction of lactose and galactose is necessary.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:

The GALT c.563A>G, p.Gln188Arg variant (rs75391579) is the most common pathogenic GALT variant in Caucasians, and has been reported in multiple patients with galactosemia (Reichardt 1991, Viggiano 2015). Functional characterization of the variant protein indicates a significantly reduced enzymatic activity compared to wildtype (Reichardt 1991, Elsas 1994, Elsevier 1996, Lai 1999, Riehman 2001, Coelho 2014), and increased thermal instability (Elsevier 1996, Coelho 2014). This variant is reported in Clinvar (Variation ID: 3614), and is found in the general population with an overall allele frequency of 0.15% (412/282,840 alleles, including a single homozygote) in the Genome Aggregation Database. The glutamine at codon 188 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.975). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS

Genetic and metabolic consultations are indicated, including a discussion of medical screening and management. Correlation with galactose-1-phosphate uridylyltransferase (GALT) enzymatic activity is recommended. At-risk family members should be offered testing for the identified variants (Familial Targeted Sequencing, ARUP test code 3005867). This individual's future

H=High, L=Low, *=Abnormal, C=Critical

reproductive partner should be offered carrier testing for galactosemia.

COMMENTS

Likely benign and benign variants are not reported. Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES

Coelho A et al. Functional and structural impact of the most prevalent missense mutations in classic galactosemia. *Mol Genet Genomic Med.* 2014 2(6):484-96. PMID: 25614870.
 Elsas LJ et al. A common mutation associated with the Duarte galactosemia allele. *Am J Hum Genet.* 1994 54(6):1030-6. PMID: 8198125.
 Elsevier J et al. The Q188R mutation in human galactose-1-phosphate uridylyltransferase acts as a partial dominant negative. *J Biol Chem.* 1996 271(50):32002-7. PMID: 8943248.
 Lai K et al. The biochemical role of glutamine 188 in human galactose-1-phosphate uridylyltransferase. *J Biol Chem.* 1999 274(10):6559-66. PMID: 10037750.
 Reichardt J et al. Molecular characterization of two galactosemia mutations: correlation of mutations with highly conserved domains in galactose-1-phosphate uridylyl transferase. *Am J Hum Genet.* 1991 49(4):860-7. PMID: 1897530.
 Riehman K et al. Relationship between genotype, activity, and galactose sensitivity in yeast expressing patient alleles of human galactose-1-phosphate uridylyltransferase. *J Biol Chem.* 2001 276(14):10634-40. PMID: 11152465.
 Viggiano E et al. Clinical and molecular spectra in galactosemic patients from neonatal screening in northeastern Italy: structural and functional characterization of new variations in the galactose-1-phosphate uridylyltransferase (GALT) gene. *Gene.* 2015 559(2):112-8. PMID: 25592817.

This result has been reviewed and approved by [REDACTED]

BACKGROUND INFORMATION: Galactosemia (GALT) Sequencing and Deletion/Duplication

CHARACTERISTICS: Galactosemia type 1 is a disorder of galactose metabolism resulting from galactose-1-phosphate uridylyltransferase (GALT) deficiency and includes phenotypes of classic galactosemia, clinical variant galactosemia, and benign variant galactosemia. Classic galactosemia and clinical variant galactosemia may be life-threatening and clinical findings can include diarrhea, feeding problems, failure to thrive, hepatocellular damage, bleeding, sepsis, or neonatal death. A lactose-restricted diet is required and typically prevents neonatal complications when initiated in first days of life. Even with adequate early treatment, individuals with classic galactosemia are at increased risk for developmental delays, speech disorders, motor function issues, and females commonly have premature ovarian insufficiency. Individuals with clinical variant galactosemia who have received adequate early treatment may not be at risk for long-term complications. Benign variant galactosemia, the most common form being Duarte variant galactosemia (also known as D/G galactosemia) is associated with partial deficiency in erythrocyte GALT enzyme, but is typically not associated with clinical disease; thus, dietary therapy is often not recommended.

EPIDEMIOLOGY: Prevalence of classic galactosemia is 1 in 48,000 in the U.S.

CAUSE: Pathogenic biallelic germline variants in the GALT gene.

INHERITANCE: Autosomal recessive.

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PENETRANCE: 100 percent for classic or clinical variant galactosemia.

CLINICAL SENSITIVITY: Approximately 95 percent.

GENE TESTED: GALT (NM_000155).

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the GALT 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. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the GALT gene. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

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. Deletions of two exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of three exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of galactosemia. This test only detects variants within the coding regions and intron-exon boundaries of the GALT gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants 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.

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| VERIFIED/REPORTED DATES | | | | |
|-------------------------|---------------|------------------|------------------|-------------------|
| Procedure | Accession | Collected | Received | Verified/Reported |
| GALT Specimen | 24-150-402562 | 00/00/0000 00:00 | 00/00/0000 00:00 | 00/00/0000 00:00 |
| GALT Interp | 24-150-402562 | 00/00/0000 00:00 | 00/00/0000 00:00 | 00/00/0000 00:00 |

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical

Unless otherwise indicated, testing performed at:

ARUP LABORATORIES | 800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Laboratory Director

Patient: Patient, Example
ARUP Accession: 24-150-402562
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
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