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Patient Report

Patient Age/Sex: Female

**Specimen Collected: 26-Jan-22 13:30**

**GALT by NGS, DelDup** | **Received: 26-Jan-22 13:30** | **Report/Verified: 26-Jan-22 13:42**

| Procedure | Result | Units | Reference Interval |
|---|---|---|---|
| GALT Interp | Positive [f1 i1] | | |
| Spcm GALT | See Note | | |

## Result Footnote

f1: GALT Interp

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

PATHOGENIC VARIANT
Gene: GALT (NM_000155.2)
Nucleic Acid Change: c.563A>G; Homozygous
Amino Acid Alteration: p.Gln188Arg
Inheritance: Autosomal recessive

INTERPRETATION
Two copies of a 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 type 1 (MIM: 230400). This result is consistent with a diagnosis of galactosemia. Lifelong dietary restriction of lactose and galactose is necessary.

No additional pathogenic variants were identified in the GALT gene by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for 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 Whites, 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 the wild type (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 uridyltransferase (GALT) enzymatic activity is recommended. At-risk family members should be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individual's future reproductive partner should be offered carrier testing for galactosemia.

COMMENTS
Likely benign and benign variants are not reported.

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):484-496.

Elsas LJ, et al. A common mutation associated with the Duarte galactosemia allele. Am J Hum Genet. 1994;54(6):1030-1036.

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

## Result Footnote

f1: GALT Interp

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):32002-32007.

Lai K, et al. The biochemical role of glutamine 188 in human galactose-1-phosphate uridyltransferase. J Biol Chem. 1999;274(10):6559-6566.

Reichardt J, et al. Molecular characterization of two galactosemia mutations: correlation of mutations with highly conserved domains in galactose-1-phosphate uridyl transferase. Am J Hum Genet. 1991;49(4):860-867.

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):10634-10640.

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 uridyltransferase (GALT) gene. Gene. 2015;559(2):112-118.

This result has been reviewed and approved by [redacted]

## Test Information

i1: GALT Interp

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

CHARACTERISTICS: Galactosemia type 1 is a disorder of galactose metabolism resulting from galactose-1-phosphate uridyltransferase (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.

## Test Information

i1: GALT Interp

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.

## Test Information

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

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