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

Physician: Doctor, Example

Patient: Patient, Example

DOB	8/8/2019
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Galactosemia (GALT), Sequencing

ARUP test code 2006697

Galactosemia (GALT) Sequencing Specimen: Whole Blood

Galactosemia (GALT) Sequencing Interp: **Positive** *

TEST PERFORMED - 2006697
TEST DESCRIPTION - Galactosemia (GALT) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

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

DNA VARIANT(S)
Classification: Pathogenic
Gene: GALT
Nucleic Acid Change: c.563A>G; Homozygous
Amino Acid Alteration: p.Gln188Arg

INTERPRETATION
Two apparent copies of a pathogenic variant, c.563A>G; p.Gln188Arg, were detected in the GALT gene. Although sequence analysis cannot detect copy number, p.Gln188Arg is a common pathogenic variant associated with classic galactosemia (Elsas 1998), so most likely it is present in two copies. Therefore, this result is consistent with classic galactosemia. Life-long dietary restriction of lactose and galactose is necessary.

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 as pathogenic by multiple laboratories 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 (SIFT, PolyPhen-2) predict that this variant is deleterious. Based on available information, this variant is considered pathogenic.

RECOMMENDATIONS
Metabolic and genetic consultations are strongly recommended. Family members, ideally beginning with the parents, should be offered targeted sequencing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code

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

2001961). This individual's future reproductive partner should be offered carrier testing for galactosemia.

COMMENTS
Reference Sequence: GenBank Ref #NM_000155.2
Nucleotide numbering begins at the "A" of the ATG initiation codon.
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):484-96.

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

Elsas LJ 2nd, Lai K. The molecular biology of galactosemia. Genet Med. 1998 Nov-Dec;1(1):40-8. PMID: 11261429.

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.

Lai K et al. The biochemical role of glutamine 188 in human galactose-1-phosphate uridyltransferase. J Biol Chem. 1999 274(10):6559-66.

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):860-7.

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.

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):112-8.

This result has been reviewed and approved by [redacted], [redacted]

BACKGROUND INFORMATION: Galactosemia (GALT), Sequencing

CHARACTERISTICS: Vomiting, diarrhea, feeding problems, failure to thrive, hepatocellular damage, bleeding, sepsis, mental retardation, and neonatal death. If treated early, most symptoms resolve, although speech, motor problems, developmental delay and premature ovarian failure may persist.
INCIDENCE: Approximately 1 in 30,000.
INHERITANCE: Autosomal recessive.
PENETRANCE: 100 percent for severe mutations.
CAUSE: Pathogenic galactose-1-phosphate uridyl transferase (GALT) gene mutations.
CLINICAL SENSITIVITY: 98 percent.
METHODOLOGY: Bidirectional sequencing of the entire GALT coding region, intron/exon boundaries and partial 5'UTR.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations, deep intronic mutations, and large deletions/duplications will not be detected. Mutations in genes other than GALT are not evaluated.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Galactosemia (GALT) Sequencing Specimen	19-227-402850	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Galactosemia (GALT) Sequencing Interp	19-227-402850	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