ARUP LABORATORIES | www.aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: (801) 583-2787, toll free: (800) 522-2787
Julio C. Delgado, MD, MS, Director of Laboratories

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	[redacted]
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Primary Carnitine Deficiency (SLC22A5) Sequencing

ARUP test code 0051682

PCD FGS Specimen: Whole Blood

PCD Sequencing Interpretation: See Note *

TEST PERFORMED - 0051682
TEST DESCRIPTION - Primary Carnitine Deficiency (SLC22A5) Sequencing
INDICATION FOR TEST - Not Provided

RESULT
One pathogenic variant and one variant of uncertain significance were detected in the SLC22A5 gene.

DNA VARIANTS
Classification: Pathogenic
Gene: SLC22A5
Nucleic Acid Change: c.41G>A; Heterozygous
Amino Acid Alteration: p.Trp14Ter

Classification: Uncertain
Gene: SLC22A5
Nucleic Acid Change: c.34G>A; Heterozygous
Amino Acid Alteration: p.Gly12Ser

INTERPRETATION
One copy of the pathogenic variant, c.41G>A; p.Trp14Ter, and one copy of the variant of uncertain clinical significance, c.34G>A; p.Gly12Ser, were detected in the SLC22A5 gene by sequencing. Therefore, this individual is at least a carrier of primary carnitine deficiency (PCD). This individual may be affected with PCD if the uncertain variant is later determined to be pathogenic and on the opposite chromosome from the identified pathogenic variant, or if an additional pathogenic variant, not detected by this assay (e.g. deep intronic or regulatory region variants), is present.

Evidence for variant classifications:
The SLC22A5 c.41G>A; p.Trp14Ter variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant is also absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Premature truncating variants occurring in the downstream part of the protein have been associated with carnitine deficiency (Frigeni 2017, Li 2010, Roussel 2016). Based on available information, this variant is considered to be pathogenic.

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

The SLC22A5 c.34G>A; p.Gly12Ser variant (rs139203363) is reported in the literature in an individual with plasma carnitine deficiency affected with sudden infant death syndrome-like episode (Li 2010) and in two individuals who exhibited sudden unexpected death in infancy (Hertz 2016, Neubauer 2017). This variant is reported as a variant of uncertain significance in ClinVar (Variation ID: 25349). This variant is found in the general population with an overall allele frequency of 0.07% (195/280474 alleles, including one homozygote) in the Genome Aggregation Database. The glycine at codon 12 is highly conserved and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. However, this variant exhibited 51.7% of normal carnitine transport activity in functional assays, and it is unclear if this decrease is sufficient to cause disease (Frigeni 2017). Due to limited information, the clinical significance of the p.Gly12Ser variant is uncertain at this time.

RECOMMENDATIONS
Medical screening and management of this individual, including initiation of dietary carnitine supplementation, should rely on clinical and biochemical findings. Because this test may not detect all pathogenic SLC22A5 variants (e.g., large deletions/duplications, deep intronic or regulatory region variants), SLC22A5 deletion/duplication analysis (ARUP test code 2004199) or measurement of carnitine transport activity in fibroblasts should be considered if symptoms are present. Parental testing for the identified pathogenic variant and uncertain variant to determine if they are on the same or opposite chromosomes may help clarify clinical significance. At-risk relatives should be offered targeted testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individual's reproductive partner should be offered carrier testing for pathogenic SLC22A5 variants. Genetic consultation is recommended. Surveillance of the literature for new information concerning the uncertain variant is recommended.

COMMENTS
Reference Sequence: GenBank # NM_003060.3 (SLC22A5)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Frigeni M et al. Functional and molecular studies in primary carnitine deficiency. Hum Mutat. 2017 38:1684-1699.
Hertz CL et al. Genetic investigations of sudden unexpected deaths in infancy using next-generation sequencing of 100 genes associated with cardiac diseases. Eur J Hum Genet. 2016 24:817-822.
Li FY et al. Molecular spectrum of SLC22A5 (OCTN2) gene mutations detected in 143 subjects evaluated for systemic carnitine deficiency. Hum Mutat. 2010 31:E1632-1651.
Neubauer J et al. Post-mortem whole-exome analysis in a large sudden infant death syndrome cohort with a focus on cardiovascular and metabolic genetic diseases. Eur J Hum Genet. 2017 25:404-409.
Roussel J et al. Carnitine deficiency induces a short QT syndrome. Heart Rhythm. 2016 13:165-174.

This result has been reviewed and approved by Steven Steinberg, Ph.D.

BACKGROUND INFORMATION: Primary Carnitine Deficiency (SLC22A5) Sequencing

CHARACTERISTICS: Hypoketotic hypoglycemia during periods of fasting, hepatomegaly, Reye syndrome, sudden infant death, developmental delay, cardiac and/or skeletal myopathy, hypotonia and enlarged heart.
INCIDENCE: 1 in 40,000 for European Caucasian and Japanese, lower in other populations.
INHERITANCE: Autosomal recessive.
CAUSE: Deleterious SLC22A5 gene mutations causing a non-functional protein (OCTN2)
CLINICAL SENSITIVITY: Approximately 82 percent
METHODOLOGY: Bidirectional sequencing of the entire coding region and intron/exon boundaries of SLC22A5 gene.
ANALYTICAL SENSITIVITY: Greater than 99 percent
LIMITATIONS: Mutations in genes other than SLC22A5 will not be detected; large deletions, deep intronic mutations and promoter mutations in the SLC22A5 gene are not detected by this assay; analytical sensitivity may be compromised by rare primer site mutations. Diagnostic errors can occur due to rare sequence variations.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
PCD FGS Specimen	19-294-401737	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
PCD Sequencing Interpretation	19-294-401737	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