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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	3/28/2020
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (ACADVL) Sequencing

ARUP test code 2002001

VLCAD FGS Specimen	Whole Blood

VLCAD (ACADVL) Sequencing	Positive

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TEST PERFORMED - 2002001
TEST DESCRIPTION - Very Long-Chain Acyl-CoA Dehydrogenase
Deficiency (ACADVL) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
Two pathogenic variants were detected in the ACADVL gene.

DNA VARIANTS
Classification: Pathogenic
Gene: ACADVL
Nucleic Acid Change: c.1405C>T; Heterozygous
Amino Acid Alteration: p.Arg469Trp

Classification: Pathogenic
Gene: ACADVL
Nucleic Acid Change: c.956C>A; Heterozygous
Amino Acid Alteration: p.Ser319Ter

INTERPRETATION
Two pathogenic variants, c.1405C>T; p.Arg469Trp, and c.956C>A;
p.Ser319Ter, were detected in the ACADVL gene by sequencing. The
presence of two pathogenic variants, one in each copy of the
ACADVL gene, is causative for VLCAD deficiency. Therefore, if
these variants are on opposite chromosomes this molecular result
is consistent with a diagnosis of very long-chain acyl-CoA
dehydrogenase (VLCAD) deficiency; clinical manifestations are
highly variable. Although the identified variants have not
previously been reported to occur on the same chromosome,
parental testing could confirm their orientation.

Evidence for variant classifications:
The ACADVL c.1405C>T; p.Arg469Trp variant (rs113994170), also
known as Arg429Trp, has been reported in multiple individuals
with VLCAD deficiency, including three severely affected
individuals that were homozygous for the variant (Andresen
1999). Additionally, functional studies have shown that the
variant protein has significantly reduced enzymatic activity
(Goetzman 2007, Hoffmann 2012). This variant is reported in
ClinVar (Variation ID: 21017), and observed in the general
population with low overall allele frequencies of 0.008 percent
(1/13006 alleles, Exome Variant Server), and 0.003 percent
(7/246250 alleles, Genome Aggregation Database). The arginine at
codon 469 is well conserved across species, and computational
algorithms (SIFT, PolyPhen2, MutationTaster) predict this
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H=High, L=Low, *=Abnormal, C=Critical

variant to be damaging to the protein. Taken together, this variant is considered pathogenic.

The ACADVL c.956C>A p.Ser319Ter variant (rs149467828) is reported in the literature in at least one individual affected with very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency (Pena 2016). This variant is reported in ClinVar (Variation ID: 557676), and is only observed on one allele in the 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. Additionally, several downstream truncating variants have been described in individuals with VLCAD deficiency and are considered pathogenic (Pena 2016). Based on available information, this variant is considered pathogenic.

RECOMMENDATIONS
Genetic and dietary consultations are strongly recommended. Parental testing is recommended to determine the chromosomal origin of the identified variants. Family members should be offered testing for the pathogenic variant(s) in their lineage (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individual's future reproductive partner should be offered ACADVL genetic testing to determine carrier status.

COMMENTS
Reference Sequence: GenBank # NM_000018.2 (ACADVL)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Andresen BS et al. Clear correlation of genotype with disease phenotype in very-long-chain acyl-CoA dehydrogenase deficiency. Am J Hum Genet. 1999 Feb;64(2):479-94.

Goetzman ES et al. Expression and characterization of mutations in human very long-chain acyl-CoA dehydrogenase using a prokaryotic system. Mol Genet Metab. 2007 Jun;91(2):138-47.

Hoffmann L et al. VLCAD enzyme activity determinations in newborns identified by screening: a valuable tool for risk assessment. J Inherit Metab Dis. 2012 Mar;35(2):269-77.

Pena LD et al. Outcomes and genotype-phenotype correlations in 52 individuals with VLCAD deficiency diagnosed by NBS and enrolled in the IBEM-IS database. Mol Genet Metab. 2016 Aug;118(4):272-81.

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

BACKGROUND INFORMATION: Very Long-Chain Acyl-CoA Dehydrogenas Deficiency (ACADVL) Sequencing

CHARACTERISTICS: Fatty acid beta-oxidation disorder leading to hypoketotic hypoglycemia, hepatic failure, Reye-likesymptoms, cardiomyopathy, skeletal myopathy and sudden death. Clinical presentation varies in severity and age of onset.
INCIDENCE: Approximately 1 in 40,000.
INHERITANCE: Autosomal recessive.
CAUSE: Deleterious ACADVL gene mutations.
CLINICAL SENSITIVITY: 80-90 percent.
METHODOLOGY: Bidirectional sequencing of the entire ACADVL coding region and intron-exon boundaries.
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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
VLCAD FGS Specimen	20-095-400303	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
VLCAD (ACADVL) Sequencing	20-095-400303	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