Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: arup, arup

Patient: EXAMPLE, POSITIVE

DOB	
Gender:	Female
Patient Identifiers:	32595
Visit Number (FIN):	32904
Collection Date:	9/9/2021 09:21

Fatty Acid Oxidation Disorders Panel, Sequencing

ARUP test code 3001851

Fatty Acid Oxidation Disorders Specimen	Whole Blood

Fatty Acid Oxidation Disorders Interp

Positive

INDICATION FOR TESTING
Elevated C14:1, abnormal newborn screening (NBS).

RESULT
Two pathogenic variants on opposite chromosomes (in trans) were detected in the ACADVL gene.

PATHOGENIC VARIANT
Gene: ACADVL (NM_000018.4)
Nucleic Acid Change: c.848T>C; Heterozygous
Amino Acid Alteration: p.Val283Ala
Inheritance: Autosomal Recessive

PATHOGENIC VARIANT
Gene: ACADVL (NM_000018.4)
Nucleic Acid Change: c.869dup; Heterozygous
Amino Acid Alteration: p.Ile291Hisfs*7
Inheritance: Autosomal Recessive

INTERPRETATION
Two in trans pathogenic variants, c.848T>C; p.Val283Ala, and c.869dup; p.Ile291Hisfs*7 were detected in the ACADVL gene by massively parallel sequencing. Pathogenic ACADVL variants are inherited in an autosomal recessive manner and are associated with VLCAD deficiency (MIM:201475). This result is consistent with a diagnosis of VLCAD deficiency.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The ACADVL c.848T>C; p.Val283Ala variant (rs113994167) is a common variant-associated VLCAD deficiency reported in numerous families, including cohort studies (Andresen 1996, Coughlin 2010, Hesse 2018, Miller 2015, Tabor 2014). This variant is also reported in ClinVar as pathogenic (Variation ID: 21025). This variant is found in the general population with an overall allele frequency of 0.1% (346/282,744 alleles, including 2 homozygotes) in the Genome Aggregation Database. Functional studies of this variant demonstrate a significant reduction in enzyme activity (Hoffmann 2012). The valine at codon 283 is moderately conserved, and computational analyses predict that

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

this variant is deleterious (REVEL: 0.91). Based on available information, this variant is considered to be pathogenic.

The ACADVL c.869dup; p.Ile291Hisfs*7 variant (rs886044671) has been reported in two patients affected with VLCAD deficiency (Miller 2015). This variant is also reported in ClinVar as pathogenic (Variation ID: 291163). This variant is found in the general population with an overall allele frequency of 0.001% (3/ 251,288 alleles) in the Genome Aggregation Database. This variant causes a frameshift by inserting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic and dietary consultations are strongly recommended. Family members should be offered testing for the detected variants (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individual's future reproductive partner should be offered genetic testing to determine carrier status.

COMMENTS
Likely benign and benign variants are not included in this report, but are available upon request.

REFERENCES
Andresen BS et al. Cloning and characterization of human very-long-chain acyl-CoA dehydrogenase cDNA, chromosomal assignment of the gene and identification in four patients of nine different mutations within the VLCAD gene. Hum Mol Genet. 1996 Apr. PMID: 8845838

Coughlin CR, 2nd et al. Genotype-phenotype correlations: sudden death in an infant with very-long-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2010 Dec. PMID: 20107901

Hesse J et al. The diagnostic challenge in very-long chain acyl-CoA dehydrogenase deficiency (VLCADD). J Inherit Metab Dis. 2018 Nov. PMID: 30194637

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. PMID: 21932095

Miller MJ et al. Recurrent ACADVL molecular findings in individuals with a positive newborn screen for very long chain acyl-coA dehydrogenase (VLCAD) deficiency in the United States. Mol Genet Metab. 2015 Nov. PMID: 26385305

Tabor HK et al. Pathogenic variants for Mendelian and complex traits in exomes of 6,517 European and African Americans: implications for the return of incidental results. Am J Hum Genet. 2014 Aug 7. PMID: 25087612

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Fatty Acid Oxidation Disorders Panel, Sequencing

CHARACTERISTICS: Fatty acid oxidation disorders can present with hypoketotic hypoglycemia, lethargy, episodic emesis, seizures, dicarboxylic aciduria, hepatomegaly, hepatic failure, cardiomyopathy, Reye-like symptoms, skeletal myopathy, myalgia, exercise intolerance, coma, and sudden death. Clinical presentation varies in severity and age of onset.

INCIDENCE: Approximately 1 in 5,000 to 1 in 10,000 births.

CAUSE: Pathogenic germline variants in genes associated with fatty acid oxidation disorders.

INHERITANCE: Mostly autosomal recessive; rarely autosomal dominant or X-linked.

CLINICAL SENSITIVITY: May be as high as 96 percent.

GENES TESTED: ACAD9, ACADM, ACADS, ACADVL, ACAT1, CPT1A, CPT2, ECHS1, ETFA, ETFB, ETFDH, FLAD1, HADH, HADHA, HADHB, HMGCL, HMGCS2, HSD17B10, LPIN1*, MLYCD, SLC22A5, SLC25A20, SLC52A1, SLC52A2, SLC52A3
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed to fill in regions of low coverage and confirm reported variants as necessary. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of a fatty acid oxidation disorder. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified.
Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
LPIN1(NM_001349200) exon 13
LPIN1(NM_001349201) exon 12

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Fatty Acid Oxidation Disorders Specimen	21-252-103110	9/9/2021 9:21 00 AM	9/9/2021 9:21:34 AM	9/9/2021 9:25 00 AM
Fatty Acid Oxidation Disorders Interp	21-252-103110	9/9/2021 9:21 00 AM	9/9/2021 9:21:34 AM	9/9/2021 9:25 00 AM

END OF CHART

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