Fatty Acid Oxidation Disorders Panel, Sequencing

Fatty acid oxidation disorders are a heterogeneous group of disorders, and clinical presentation varies in both severity and age of onset. Specific symptoms may differ depending on whether an individual experiences neonatal onset or a later onset but may include hypoketotic hypoglycemia, lethargy, episodic emesis, seizures, hepatomegaly, cardiomyopathy, Reye-like symptoms, skeletal myopathy, myalgia, exercise intolerance, coma, or sudden death.

Featured ARUP Testing

Fatty Acid Oxidation Disorders Panel, Sequencing 3001851

Method: Massively Parallel Sequencing

Preferred molecular test to confirm or rule out a diagnosis of a fatty acid oxidation disorder following clinical and/or biochemical presentation

For biochemical test options, refer to the Laboratory Test Directory.

Disease Overview

Symptoms

Common Symptoms Based on Age of Onset	
Neonatal Onset	**Later Onset**
• Hypoketotic hypoglycemia • Lethargy • Episodic emesis • Seizures • Arrhythmia • Reye-like symptoms • Hypertrophic cardiomyopathy • Hepatomegaly, hepatic failure • Encephalopathy • Coma • Sudden death	• Myopathy • Myalgia • Muscle weakness • Exercise intolerance or exercise-induced rhabdomyolysis • Acute metabolic episodes triggered by fasting, infection, surgery

Testing Strategy

When a disorder of fatty acid oxidation is suspected, the following tests should be ordered:

- Plasma acylcarnitines
- Carnitine panel
- Urine organic acids

In addition, acylglycines may be helpful for some disorders.

Because biochemical studies may be completely normal if obtained while patient is metabolically stable, molecular testing or functional studies are often needed for definitive diagnosis. For biochemical test options, refer to the Laboratory Test Directory.

Incidence

Approximately 1 in 5,000 to 1 in 10,000 births

Genetics

Etiology

Pathogenic germline variants in genes associated with fatty acid oxidation disorders (refer to the Genes Tested table)

Inheritance

Mostly autosomal recessive (AR); rarely autosomal dominant (AD) or X-linked (XL)

Test Interpretation

Clinical Sensitivity

Dependent on clinical phenotype

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One or more pathogenic or likely pathogenic variants detected	Diagnosis of heritable fatty acid oxidation defect is confirmed Specific diagnosis depends on the variant(s) detected
Inconclusive	One or more variants of uncertain significance detected	Diagnosis of fatty acid oxidation defect remains uncertain
Negative	No pathogenic variants detected	Diagnosis of heritable fatty acid oxidation defect is less likely, but not excluded

Limitations

- A negative result does not exclude a diagnosis of a fatty acid oxidation disorder.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants, including the common SLC22A5 c.-149G>A variant
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - LPIN1(NM_001349200) exon 13
    - LPIN1(NM_001349201) exon 12
  - Large deletions/duplications in any of the tested genes
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Low-level somatic variants

Genes Tested

Gene	MIM No.	Disorders	Inheritance
ACAD9	611103	Mitochondrial complex I nuclear type 20 deficiency (ACAD9 deficiency)	AR
ACADM	607008	Medium chain acyl-CoA dehydrogenase deficiency (MCAD deficiency)	AR
ACADS	606885	Short chain acyl-CoA dehydrogenase deficiency (SCAD deficiency)	AR
ACADVL	609575	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD deficiency)	AR
ACAT1	607809	Beta-ketothiolase deficiency (B-ketothiolase deficiency, alpha-methylacetoacetic aciduria, 2-methyl-3-hydroxybutyric acidemia, 2-methylacetoacetyl-coenzyme A thiolase deficiency, 3-alpha-oxothiolase deficiency, 3-ketothiolase deficiency, 3-oxothiolase deficiency, MAT deficiency, methylacetoacetyl-coenzyme A thiolase deficiency, mitochondrial 2-methylacetoacetyl-CoA thiolase deficiency, mitochondrial acetoacetyl-CoA thiolase deficiency, or T2 deficiency)	AR
CPT1A	600528	Carnitine palmitoyltransferase 1A deficiency (CPT1A deficiency)	AR
CPT2	600650	Carnitine palmitoyltransferase II (CPT II deficiency), lethal neonatal, and severe infantile onset	AR
		CPT II deficiency, myopathic form	AR, AD
ECHS1	602292	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1 Deficiency)	AR
ETFA	608053	Multiple acyl-CoA dehydrogenase deficiency (MADD types I and II, Glutaric acidemia II, Glutaric aciduria II)	AR
ETFB	130410	Multiple acyl-CoA dehydrogenase deficiency (MADD types I and II, glutaric acidemia II, glutaric aciduria II)	AR
ETFDH	231675	Multiple acyl-CoA dehydrogenase deficiency (MADD type III, glutaric acidemia II, glutaric aciduria II)	AR
FLAD1	610595	Lipid storage myopathy due to flavin adenine dinucleotide synthetase deficiency (MADD-like illness)	AR
HADH	601609	Familial hyperinsulinism (3-hydroxyacyl-CoA dehydrogenase deficiency, familial hyperinsulinemic hypoglycemia, congenital hyperinsulinism [CHI], persistent hyperinsulinemic hypoglycemia of infancy [PHHI])	AR
HADHA	600890	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD deficiency, acute fatty liver pregnancy [AFLP] and hypertension, elevated liver enzymes, and low platelet [HELLP] syndromes, mitochondrial trifunctional protein deficiency)	AR
HADHB	143450	Trifunctional protein deficiency	AR
HMGCL	613898	3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG-CoA lyase deficiency)	AR
HMGCS2	600234	3-hydroxy-3-methylglutaryl-CoA synthase 2 deficiency (HMG-CoA synthase-2 deficiency)	AR
HSD17B10	300256	Hydroxysteroid 17-Beta Dehydrogenase Type 10 deficiency (HSD10 mitochondrial disease, HSD17B10 deficiency)	XL
LPIN1	605518	Acute recurrent myoglobinuria (LPIN1 deficiency)	AR
MLYCD	606761	Malonyl-CoA decarboxylase deficiency	AR
SLC22A5	603377	Systemic primary carnitine deficiency (carnitine transport defect, carnitine uptake defect, CDSP)	AR
SLC25A20	613698	Carnitine-acylcarnitine translocase deficiency (CACT deficiency)	AR
SLC52A1	607883	Riboflavin transporter deficiency 1 (riboflavin deficiency)	AD

Gene	MIM No.	Disorders	Inheritance
SLC52A2	607882	Riboflavin transporter deficiency 2 (Brown-Vialetto-Van Laere syndrome 2)	AR
SLC52A3	613350	Riboflavin transporter deficiency 3 (Brown-Vialetto-Van Laere syndrome 1, Fazio-Londe syndrome)	AR

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