MetaboSeq®

Fatty Acid Oxidation Disorders Panel by Next-Generation Sequencing

Genes Tested

ACAD9	*CPT2*	*HADH*	*PPARG*
ACADM	*ETFA*	*HADHA*	*SLC22A5*
ACADS	*ETFB*	*HADHB*	*SLC25A20*
ACADVL	*ETFDH*	*HMGCL*	*TAZ*
CPT1A	*GLUD1*	*HSD17B10*	

Disorder: Fatty acid oxidation defects (FAOD) are disorders of energy metabolism which affect about 1 in 9,000 newborns worldwide (with a lower incidence in Asians). Patients typically present before the age of three years with nonspecific symptoms including hypoketotic hypoglycemia, hypotonia, rhabdomyolysis, liver failure, and/or hepatic encephalopathy, typically induced by metabolic stress. These symptoms and their age at onset may be quite variable between affected individuals. Mutation(s) in any one of a number of specific genes result in FAOD. FOAD may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner.

Rationale for Testing: Identification of the specific cause of a patient's metabolic symptoms or abnormal newborn screening result is crucial for medical management and prognosis. It also provides very specific information on which to base genetic counseling for parents and other at-risk family members.

MetaboSeq® is our next-generation sequencing panel of 19 clinically relevant genes (see above) associated with FAOD. MetaboSeq® is indicated for patients with symptoms of FAOD which have not been clearly defined by biochemical testing and/or who previously had negative genetic testing for the most likely diagnosis. MetaboSeq® was designed to detect mutation(s) in the most common genes causing nonspecific FAOD symptoms.

Indications:

- Abnormal newborn screen
- Unexplained neonatal hypoglycemia
- Recurrent maternal fatty liver of pregnancy
- Reye syndrome
- Rhabdomyolysis/skeletal myopathy
- Cardiomyopathy and/or arrhythmias
- Other nonspecific symptoms of FAOD including:
  - liver failure
  - seizures
  - lethargy
  - vomiting
  - coma

Note: Children with acylcarnitine results or other clinical findings indicating a specific metabolic syndrome may benefit from molecular testing for mutations in that particular gene prior to MetaboSeq® testing.

Additional information and test requisitions are available at: www.cchmc.org/molecular-genetics

Shipping Instructions

Please enclose **test requisition** with sample.
All information must be completed before sample can be processed.

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

Cincinnati Children's
Human Genetics

Molecular Genetics Laboratory
CLIA#: 36D0656333
Phone: (513) 636-4474
Fax: (513) 636-4373
Email: moleculargenetics@cchmc.org

MetaboSeq®

Specimen: 5 mLs of whole blood in purple/lavender top (EDTA) tube. Label tube with patient's name, birth date, and date of collection. Phlebotomist must initial tube to verify patient's identity.

Testing Methodology: This test is performed by enrichment of the exons, flanking intronic and untranslated regions (5' and 3') of *ACAD9, ACADM, ACADS, ACADVL, CPT1A, CPT2, ETFA, ETFB, ETFDH, GLUD1, HADH, HADHA, HADHB, HMGCL, HSD17B10, PPARG, SLC22A5, SLC25A20,* and *TAZ* using microdroplet PCR technology followed by next-generation sequencing with > 40 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined by bioinformatic analysis, are confirmed by Sanger sequencing.

Test Sensitivity:

Clinical Sensitivity: Sequencing of MetaboSeq® genes which have a specific clinical phenotype (eg *ACADM, ACADVL, CPT1A, CPT2*) detects 85-100% of disease-causing alleles in affected patients. Many of the panel genes, however, result in rare or overlapping phenotypes, and the clinical sensitivity of gene sequencing has not been determined.

Analytical Sensitivity: The sensitivity of next-generation sequencing is over 99% for the detection of nucleotide base changes and small deletions and insertions (<10 bases) in the regions analyzed. Larger deletions, insertions and genetic recombinational events are not identified using this test methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes in the panel.

Turn-Around Time:

- Three months for NGS of the panel
- 4-12 weeks for analysis of any gene by Sanger sequencing

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Cost: Please call 1-866-450-4198 for current pricing, insurance precertification, or with any billing questions.

CPT Codes:

- Fatty acid oxidation disorders panel by NGS: 81404, 81405x2, 81406x5, 81479x9
- Single gene sequencing of *CPT2* 81404
- Single gene sequencing of *ACADS* 81405
- Single gene sequencing of *ACADVL, HADHA, TAZ* 81406
- Single gene sequencing of any other panel gene 81479

Results: Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

References:

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Lindner, M., G. F. Hoffmann, et al. (2010). Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. J Inherit Metab Dis 33(5): 521-526.

Lund, A. M., F. Skovby, et al. (2010). Clinical and biochemical monitoring of patients with fatty acid oxidation disorders. J Inherit Metab Dis 33(5): 495-500.

Spiekerkoetter, U. (2010). Mitochondrial fatty acid oxidation disorders: clinical presentation of long-chain fatty acid oxidation defects before and after newborn screening. J Inherit Metab Dis 33(5): 527-532.

Tewhey, R., J. B. Warner, et al. (2009). Microdroplet-based PCR enrichment for large-scale targeted sequencing. Nat Biotechnol 27(11): 1025-1031.

Wanders, R. J., J. P. Ruiter, et al. (2010). The enzymology of mitochondrial fatty acid beta-oxidation and its application to follow-up analysis of positive neonatal screening results. J Inherit Metab Dis 33(5): 479-494.

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