MAYO CLINIC LABORATORIES

Test Definition: HFAOP

Fatty Acid Oxidation Gene Panel

Overview

Useful For

Follow up for abnormal biochemical results suggestive of a fatty acid oxidation disorder

Establishing a molecular diagnosis for patients with a fatty acid oxidation disorder

Identifying variants within genes known to be associated with a fatty acid oxidation disorder, allowing for predictive testing of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 44 genes associated with fatty acid oxidation disorders: *ACAA2, ACACA, ACAD8, ACAD9, ACADL, ACADM, ACADS, ACADSB, ACADVL, ACAT1, ACAT2, ACOT9, ALDH5A1, CPT1A, CPT2, DECR1, ECHS1, ECI1, ETFA, ETFB, ETFDH, ETHE1, FLAD1, GLUD1, HADH, HADHA, HADHB, HMGCL, HMGCS2, HSD17B10, LPIN1, MLYCD, NADK2, OPA1, PPARG, SLC22A5, SLC25A20, SLC25A29, SLC25A32, SLC52A1, SLC52A2, SLC52A3, TANGO2, TAZ*. See Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for fatty acid oxidation disorders.

Additional first-tier testing may be considered/recommended. For more information see Advisory Information.

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions
- Targeted Genes and Methodology Details for Fatty Acid Oxidation Gene Panel

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
FIBR	Fibroblast Culture	Yes	No
CRYOB	Cryopreserve for Biochem Studies	No	No

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

The recommended first-tier tests to screen for fatty acid oxidation disorders include acylcarnitine profile in plasma (ACRN / Acylcarnitines, Quantitative, Plasma) and urine organic acids (OAU / Organic Acids Screen, Urine)

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.
Specimen Stability Information: Ambient (preferred)/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Molecular Genetics: Biochemical Disorders Patient Information (T527) in Special Instructions

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Minimum Volume

See Specimen Required

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

Clinical & Interpretive

Clinical Information

Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation. Disorders of fatty acid oxidation (FAO) are characterized by hypoglycemia, hepatic dysfunction, encephalopathy, skeletal myopathy, and cardiomyopathy. Most FAO disorders have

a similar presentation and their biochemical diagnosis can, at times, be difficult. Commonly used metabolite screens such as urine organic acids, plasma acylcarnitines, and fatty acids are influenced by dietary factors and the clinical status of the patient. This often leads to incomplete diagnostic information or even false-negative results. Enzyme assays are limited to one enzyme per assay, which doesn't allow for comprehensive testing for all FAO disorders.
A comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features, given the broad clinical spectrum and genetic heterogeneity of FAO disorders.
Acylcarnitine profile in plasma (ACRN / Acylcarnitines, Quantitative, Plasma) and urine organic acids (OAU / Organic Acids Screen, Random, Urine) are the recommended first-tier tests to assess individuals for a FAO disorder. Additional testing includes an assay in fibroblasts (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture), which is useful following molecular testing to determine whether variants of uncertain significance are pathogenic. The purpose of the in vitro probe assay is to offer screening for several defects of FAO and organic acid metabolism under controlled laboratory conditions using fibroblast cultures.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in context of clinical findings, family history, and other laboratory data.
Misinterpretation of results may occur if the information provided is inaccurate or incomplete.
If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at risk individuals.
To discuss the availability of further testing options, for assistance in general test selection, or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 800-533-1710.
Technical Limitations:
Next-generation sequencing (NGS) may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If specific clinical disorders are suspected, evaluation by alternative methods can be considered.
If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, these results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.
There may be regions of genes that cannot be effectively amplified for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.
This assay will not reliably detect insertions/deletions (indels) of 40 or more base pairs (bp), including Alu insertions, long interspersed nuclear elements (LINES), and short interspersed nuclear elements (SINES). The bioinformatics software pipeline is verified to detect 95% of deletions up to 75 bp and insertions up to 47 bp. Additionally, low level

mosaic variants may not be detected.
This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.
Reclassification of Variants-Policy:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.
Variant Evaluation:
Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) recommendations as a guideline.(1) Other gene specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.
Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment. Intronic and synonymous sequence variants not predicted to impact splicing or otherwise contribute to disease are not reported.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424
2. Vockley J, Bennett MJ, Gillingham MB: Mitochondrial fatty acid oxidation disorders. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed October 28, 2020. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=247995158&bookid=2709&Resultclick=2

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.
There may be regions of genes that cannot be effectively amplified for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria. PCR-based methods and/or Sanger sequencing is used to confirm variants detected by NGS when appropriate.(Unpublished Mayo method)
Genes analyzed: *ACAA2, ACACA, ACAD8, ACAD9, ACADL, ACADM, ACADS, ACADSB, ACADVL, ACAT1, ACAT2, ACOT9, ALDH5A1, CPT1A, CPT2, DECR1, ECHS1, ECI1, ETFA, ETFB, ETFDH, ETHE1, FLAD1, GLUD1, HADH, HADHA, HADHB, HMGCL, HMGCS2, HSD17B10, LPIN1, MLYCD, NADK2, OPA1, PPARG, SLC22A5, SLC25A20, SLC25A29, SLC25A32, SLC52A1, SLC52A2, SLC52A3, TANGO2, TAZ*

PDF Report
No

Specimen Retention Time
Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees & Codes

Test Classification
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81443

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HFAOP	Fatty Acid Oxidation Gene Panel	In Process

Result ID	Test Result Name	Result LOINC Value
608740	Test Description	62364-5
608741	Specimen	31208-2
608742	Source	31208-2
608743	Result Summary	50397-9
608744	Result	82939-0
608745	Interpretation	69047-9
608746	Resources	In Process
608747	Additional Information	48767-8
608748	Method	85069-3
608749	Genes Analyzed	48018-6
608750	Disclaimer	62364-5
608751	Released By	18771-6