

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD): Gene Sequencing Panel

Test Code: GQ

Turnaround time: 4 weeks

CPT Codes: 81479 x1

Condition Description

Multiple acyl-CoA dehydrogenase deficiency (MADD), which is also called glutaric aciduria type II (GAll), is an autosomal recessive disorder of mitochondrial fatty acid oxidation, amino acid, and choline metabolism [1]. In most cases, this disorder is due to enzymatic defects of either electron transfer flavoprotein (ETF) or electron transfer flavoprotein dehydrogenase, both of which are required for electron transfer in the mitochondrial respiratory chain.

Three clinical phenotypes have been described [2]. The neonatal onset with the congenital anomalies such as renal cystic dysplasia, facial dysmorphism, rocker bottom feet, and abnormalities of the external genitalia is categorized as type I. Patients with neonatal onset but without congenital abnormalities, are categorized as type II. Newborns (Type I and II) may present with hypotonia, hepatomegaly, hypoketotic hypoglycemia, metabolic acidosis, and hyperammonemia. Severe cardiomyopathy or symptoms of Reye syndrome-like decompensations have been reported [3]. The remaining patients present with the late-onset form of the disease (Type III). They develop with heterogeneous symptoms such as intermittent episodes of vomiting, hypoglycemia, and metabolic acidosis, muscle weakness and progressive lipid storage myopathy [4]. During acute decompensations, the late-onset patients have organic aciduria and increase of all chain length acylcarnitines. Some patients respond to the treatment with riboflavin.

Three genes have been shown to be involved in patients with MADD. *ETFA* (15q23-25) and *ETFB* (19q13.3) genes encode the two ETF subunits while the *ETFDH* (4q32) gene encodes the electron transfer flavoprotein dehydrogenase [5]. Gene sequence analysis is available to test for mutations in the *ETFA*, *ETFB*, and *ETFDH* genes (GQ). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (GV).

References:

1. Schiff et al. Electron transfer Flavoprotein deficiency: Functional and molecular aspects. *Mol Genet Metab* (2006) 88:153-158.
2. Rhead et al. Clinical and biochemical variation and family studies in the multiple acyl-CoA dehydrogenation disorders. *Pediatr Res* 21 (1987) 371-376.
3. Loehr et al. Glutaric acidemia type II: heterogeneity of clinical and biochemical phenotypes. *Pediatr Res* 27 (1990) 311-315.
4. Beresford et al. So doctor, what exactly is wrong with my muscles Glutaric aciduria type II presenting in a teenager. *Neuromuscul Disord* 16(4):269-73 (2006).
5. Olsen et al. Clear relationship between ETF/ETFDH genotype and phenotype in patients with multiple acyl-CoA dehydrogenation deficiency. *Hum Mutat* 2003; 22: 12-23.
6. Olsen et al. ETFDH mutations as a major cause of riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency. *Brain* (2007) 130:2045-2054.
7. Schulze et al. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. *Pediatrics* 2003, 111(6 Pt 1):1399-406.

Genes

[ETFA](#), [ETFB](#), [ETFDH](#)

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of MADD
- Carrier testing in adults with a family history of MADD

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

The majority of patients with clinical and biochemical diagnosis of MADD will have an abnormal DNA test.

Clinical Sensitivity: 30/32 mutations (26 in the *ETFA* and 4 in the *ETFB* genes) were identified in 16 patients [5]; 30/30 mutations in the *ETFDH* gene were identified in 15 patients [6]. Analytical Sensitivity: ~99%

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Prevalence: MADD is rare with incidence estimates of 1:250,000 live births [7].

Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated**Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml)

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

Related Tests

- Biochemical tests for diagnosis of MADD include Urine Organic Acids (OA) and Plasma Acylcarnitine Profile (AR)
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing
- For comprehensive testing, a Deletion/Duplication Assay is available separately. This test is indicated for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.