Condition Description

Multiple acyl-CoA dehydrogenase deficiency (MADD), which is also called glutaric aciduria type II (GAI1), 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. ETFα (15q23-25) and ETFβ (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 ETFα, ETFβ, and ETFDH genes (GQ).

References:

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

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

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

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood
Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

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)
- Sequence analysis of the $ETFA$, $ETFB$, $ETF DH$ genes is available and is required before deletion/duplication analysis.
- 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.