

Methylmalonic Aciduria: *MUT* Gene Sequencing

Test Code: DH

Turnaround time: 6 weeks

CPT Codes: 81479 x1

Condition Description

Methylmalonic aciduria (MMA) is an autosomal recessive inborn error of organic acid metabolism resulting from partial or complete deficiency of the enzyme L-methylmalonyl CoA mutase. The most common form of MMA is mutase deficient MMA, which may present lethargy, recurrent vomiting, hepatomegaly, metabolic acidosis, encephalopathy, and may lead to multiorgan failure. Other forms of MMA may be B12 responsive, and affected infants may show failure to thrive, chronic or episodic acidemia, benign persistent methylmalonic aciduria, or developmental delay. These symptoms may be associated with times of infection or stress. Patients with defects in the synthesis of adenosyl cobalamin (CblA and CblB) generally show a decrease in urine and blood concentration of methylmalonic acid in response to B12 supplementation. The prevalence of MMA is approximately 1 in 30,000 newborns.

Methylmalonyl CoA mutase catalyzes the isomerization of methylmalonyl CoA into succinyl-CoA. The coenzyme adenosylcobalamin (AdoCbl) is also required for this reaction. Mutations in the *MUT* gene cause mutase-deficient MMA. *MUT* is a nuclear gene (6q21) that codes for the mitochondrial enzyme, methylmalonyl CoA mutase. Based on enzymatic activity in cultured fibroblasts, two phenotypic variants of mutase deficient MMA have been defined. The *mut0* phenotype has no detectable enzymatic activity and is associated with severe symptoms in patients. The *mut-* phenotype has residual activity that is increased by supplementation of hydroxycobalamin and is associated with variable severity.

Apart from primary deficiency of mutase activity, insufficient metabolism of cobalamin can also result in deficient mutase activity. *MMAA* and *MMAB* genes are involved in the adenosylcobalamin metabolism (associated with the *cblA* and *cblB* complementation groups of MMA, respectively). (Refer to *MMAA* and *MMAB* gene sequencing for more information.)

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array NK.

Genes

[MMUT](#)

Indications

This test is indicated for:

- Clinical symptoms of possible non-B12 responsive MMA
- Follow up to abnormal newborn screening results suggestive of MMA
- Clinical symptoms of MMA, with negative *MMAA/MMAB* gene sequencing
- Family members who are at risk to be carriers of MMA, when the proband is unavailable for testing.

Sequencing is not appropriate for prenatal samples in which familial mutations have not been identified.

Methodology

The 13 exons and flanking regions of the *MUT* gene are amplified by PCR and sequenced in both the forward and reverse directions. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as previously described mutations, novel mutations, or variations of unknown significance. This analysis may detect novel variants of unclear effect, which may require further studies.

Detection

This assay will detect over 95% of sequence variants in the coding region and splice junctions. Mutations in the promoter region, some mutations in the introns, and other regulatory elements cannot be detected by this analysis. Large deletion and insertion mutations will not be detected by this assay. It is possible that some patients with a typical presentation may not carry a mutation detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

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: 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: 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 72 hours of collection. Do not 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 of EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

Related Tests

- Organic Acid Analysis (OA) is used in the diagnosis of patients with MMA
- Methylmalonic Acid Quantitation (MQ) is used in diagnosis and follow up of propionate and methylmalonic disorders, as well as defects of cobalamin synthesis; it can also detect acquired cobalamin, and/or folate deficiency
- *MMAA/MMAB* (MU) Gene Sequencing may be considered in patients with a biochemical diagnosis of MMA but with normal *MUT* gene sequencing
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Prenatal testing is available to couples who are confirmed carriers of gene mutations. Please contact the laboratory genetic counselor prior to sending a specimen.