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.)

Genes

MUT

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

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.

Detection

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow 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**

- 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.