

MUT, *MMAA*, and *MMAB* Gene Analysis in Methylmalonic Acidemia

Disorder also known as: Methylmalonic acidemia, cbIB Type; Methylmalonic acidemia, cbIA; Methylmalonic acidemia due to methylmalonyl-CoA mutase deficiency

Clinical Features:

The methylmalonic acidemias are a family of disorders characterized by deficient activity of mitochondrial methylmalonyl-CoA mutase. This inborn error of organic acid metabolism leads to defects in organic acid, amino acid and lipid metabolism. Patients have a characteristic facies that includes a high forehead, broad nasal bridge and a long, smooth filtrum¹. Affected infants often have recurrence of acute illness with metabolic acidosis, vomiting, failure to thrive, lethargy, hypotonia, hepatomegaly, seizures and respiratory distress. The most severe clinical presentation is in the neonatal period and can result in death. The disorder may also have a later onset, in the first months or years or less commonly in early childhood. An adult form can have a benign course with a mild biochemical defect; however these individuals are at risk for acute metabolic decompensation. Complications of methylmalonic acidemia include mental retardation, nephritis, chronic renal tubular acidosis, metabolic stroke, pancreatitis, growth failure and functional immune impairment.

Genetics:

Pathogenic variants in *MMAA*, *MMAB* and *MUT* genes cause methylmalonic acidemia. Methylmalonic acidemia may also be caused by the nutritional deficiency of vitamin B₁₂, which can occur in children born to vegan mothers. The most common genetic cause of methylmalonic acidemia is due to variants in the *MUT* gene that prevent the production of any functional protein. These variants are designated *mut*⁰, which is the most severe form of methylmalonic acidemia. Variants that change the structure of methylmalonyl-CoA mutase but do not eliminate its activity cause a form called *mut*. The *mut* form is typically less severe. Less frequent causes of methylmalonic acidemia are due to variants in the *MMAA* or *MMAB* genes that are required for proper function of the *mut* protein. Although more rare, defects in other genes may also be responsible for methylmalonic acidemia. The incidence of methylmalonic acidemia has been estimated to be approximately 1/48,000 births in the U.S.²

Inheritance Pattern:

Autosomal Recessive

Test Methods:

Variant analysis of *MUT*, *MMAA* and/or *MMAB* genes is performed on genomic DNA from the submitted specimen by bi-directional sequence analysis of the entire coding region and splice junctions. For patients who have a single variant identified after full sequencing of all three genes at GeneDx, or if clinically indicated, reflex deletion/duplication testing with exon-level

resolution (ExonArrayDx) will be performed at no additional charge. Variants in *MUT*, *MMAA* or *MMAB* found in the first person of a family tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:

Bi-directional sequence analysis performed at GeneDx will detect more than 95% of variants due to point variants, small deletions or duplications. In patients with methylmalonic acidemia identified by biochemical analysis as having defects in the *MUT*, *MMAA* or *MMAB* genes, this method of analysis is predicted to detect two variants in approximately 95% of patients.^{3,4,5, 6} The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

References:

1. Nyhan, WL, Barshop, BA, Ozand, PT (2005) Atlas of Metabolic Diseases Oxford University Press. NY
2. Coulombe J.T et al., (1981) Pediatrics 67:26-31
3. Worgan, LC et al., (2006) Hum Mut 27:31-43
4. Lerner-Ellis, J.P. et al., (2004) Hum Mut 24:509-516
5. Lerner-Ellis, J.P. et al., (2006) Mol Genet Metab 87:219-225.
6. Merinero et al., (2008) J Inherit Metab Dis 31:55-66.