

MUT, MMAA, and MMAB Gene Analysis in Methylmalonic Acidemia

DISORDER ALSO KNOWN AS

Methylmalonic acidemia, cblB Type; Methylmalonic acidemia, cblA; 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 mut⁰, 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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the MUT, MMAA, and/or MMAB genes are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

REFERENCES:

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