

Methylmalonic Acidemia via *MUT* Gene Sequencing (Test #311)

Brief Description of Clinical Features: Methylmalonic acidemia (OMIM 251000) is caused by a deficiency in the activity of the enzyme methylmalonyl-CoA mutase. Methylmalonyl-CoA mutase catalyzes the last step the breakdown of certain amino acids (met, ile, thr, val), odd-numbered chain length fatty acids, and propionic acid from gut flora. Methylmalonic acidemia is typically a severe disease with onset in infancy. Patients may present with lethargy, vomiting, hepatomegaly, acidosis, hypoglycemia and neutropenia. Many patients die in childhood; those that survive often have neurological and renal complications. Milder forms of the disease are also known. Today, many cases are detected through routine neonatal screening with tandem mass spectrometry. For more information, see Venditti GeneReviews 2007 (www.genetests.org), Tanpaiboon (Mol Genet Metab 85:2-6, 2005), and the Organic Acidemia Association (www.oaanews.org).

Genetics: Methylmalonic acidemia is an autosomal recessive disease. The *MUT* gene on chromosome 6 encodes the methylmalonyl-CoA mutase enzyme. About 200 causative *MUT* mutations have been reported to date (see for example Acquaviva et al. Hum Mut 25:167-176, 2005; Worgan et al. Hum Mut 27:31-43, 2006). Of these, approximately 55% are missense, 20% frameshift, 15% nonsense, and 10% splicing. Although founder mutations are known in specific populations, no mutations are common in the mixed American population.

Methylmalonyl-CoA mutase requires adenosylcobalamin (a vitamin B₁₂ derivative) as a cofactor. Methylmalonic acidemia can be caused by *MUT* mutations, by vitamin B₁₂ deficiency, or by defects in vitamin B₁₂ metabolism (at least four genes involved - two of which have been identified).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 12 coding exons of the *MUT* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. We will sequence the gene in relatives of affected children in cases where DNA from the children is unavailable. We will also perform sequencing of any single or pair of exons for family members of patients with known mutations and to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000006.10 mRNA and protein: CCDS 4924.1

Indications for Test: All methylmalonic acidemia patients and their family members are candidates for this test. Ideally, patients should have deficiency in mutase activity that is not strongly responsive in cell culture to cobalamin and/or should be unresponsive to vitamin B₁₂ therapy. PreventionGenetics offers testing for many other neonatal screening disorders.

Sensitivity of Test: Lempp et al. (Mol Genet Metab 90:284-290, 2007) detected by genomic DNA sequencing 97% of possible *MUT* mutations in 32 mutase apoenzyme-deficient patients. Similarly, Worgan et al. 2006 detected 96% of causative mutations in 160 patients. One large deletion that would not be detected by genomic sequencing was reported (Acquaviva et al. 2005). The fraction of patients with abnormally high methylmalonic acid levels that have two *MUT* causative mutations is unknown.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *MUT* Exons 2-13 \$ 790

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x12	83898	\$ 240	Sequencing x12	83904	\$ 350
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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