

## Methylmalonic Acidemia (cblB type) via *MMAB* Gene Sequencing (Test #313)

**Brief Description of Clinical Features:** Methylmalonic acidemia (MMA) 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 experience 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](http://www.genetests.org)), and the Organic Acidemia Association ([www.oaanews.org](http://www.oaanews.org)). Vitamin B<sub>12</sub> responsive (or cbl type) MMA is caused by defective metabolism of adenosylcobalamin (AdoCbl; vitamin B<sub>12</sub>). Adenosylcobalamin is the cofactor for methylmalonyl-CoA mutase. Three distinct genetic causes of cbl type MMA have been identified; cblA, cblB and cblH. CblB type MMA (OMIM 251110) results from deficiency of cob(I)alamin adenosyltransferase, the enzyme that catalyzes the final step in synthesis of adenosylcobalamin.

**Genetics:** Methylmalonic acidemia is an autosomal recessive disease. *MMAB* encodes cob(I)alamin adenosyltransferase. Most reported *MMAB* mutations are missense, but small deletions, small insertions and splice site mutations have been described.

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of all 9 coding exons of the *MMAB* 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\_000012.10 mRNA: NM\_052845.4 Protein: NP\_443077.1

**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 responsive in cell culture to cobalamin and/or should be responsive to vitamin B<sub>12</sub> therapy.

**Sensitivity of Test:** Martinez et al. (*Mol Gen and Metab* 84:317-325, 2005) evaluated 25 MMA patients and found *MUT* mutations in 13 patients, *MMAA* mutations in 7 patients, and *MMAB* mutations in 2 patients. Dobson et al. (*Hum Mol Genetics*, 11:3361-3369, 2002) found two *MMAB* mutations in all six cblB patients studied, and one-half of all mutations were an Arg186Trp missense change.

**Turn Around Time:** Maximum of 40 days.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price:** Sequencing of *MMAB* Gene Exons 1-9 \$ 540

**CPT Codes:**

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x8	83898	\$ 120	Sequencing x8	83904	\$ 220
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)

**Contact:** Thomas L. Winder, PhD, FACMG, [tom.winder@preventiongenetics.com](mailto:tom.winder@preventiongenetics.com) ; [www.preventiongenetics.com](http://www.preventiongenetics.com)