

## Methylmalonic Aciduria and Homocystinuria, *cbID* type, via *MMADHC* Gene Sequencing, Test #212

**Brief Description of Clinical Features:** Cobalamin (Cbl or vitamin B12) is an important cofactor in homocysteine metabolism and in branched-chain amino acid and odd-chain fatty acid catabolism. A series of inherited inborn errors of cobalamin metabolism have been identified, designated *cbIA* through *cbIG*. The rare *cbID* disorder shows clinical and biochemical variability, as this disorder may be associated with either isolated or combined deficiency of methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl) synthesis (Suormala et al. *J Biol Chem* 279:42742-42749, 2004). In *classic cbID* disorder, patients have combined homocystinuria and methylmalonic aciduria. However, in *cbID variant 1*, patients have isolated homocystinuria, and in *cbID variant 2*, patients have isolated methylmalonic aciduria. Presenting features of *cbID* deficiency include developmental delay, focal neurologic signs, megaloblastic anemia, marfanoid appearance, venous thrombosis, cerebral atrophy, and hydrocephalus (Miousse et al. *J Pediatr* 154:551-556, 2009).

**Genetics:** Genetic mutations in *MMADHC* on chromosome 2q23.2 are responsible for autosomal recessive methylmalonic aciduria and homocystinuria, *cbID* type (OMIM 277410). The *MMADHC* gene consists of eight exons (seven of which encode protein). While the exact function of the gene product remains unknown, it appears to be a cobalamin-binding mitochondrial protein which shows homology to the putative ATPase component of a bacterial ABC transporter (Miousse et al. 2009). There does appear to be a genotype-phenotype correlation (see Coelho et al. *N Engl J Med* 358:1454-1464, 2008). While patients with *cbID variant 2* (isolated methylmalonic aciduria) have been found with severe mutations in the N-terminal region of the protein, patients with *cbID variant 1* (isolated homocystinuria) have been found to have more mild missense mutations in the C-terminal portion of the protein. Patients with *classic (combined) cbID* disorder have been found with severe mutations in the protein's C-terminus. It has been hypothesized that Met62 is capable of acting as a second start codon for reinitiation of translation in patients with a severe N-terminal mutation. These patients would produce a shorter functional protein lacking mitochondrial sequence but capable of normal methylcobalamin synthesis (Coelho et al. 2008).

**Description of This Particular Test:** Bidirectional sequencing of all seven *MMADHC* coding exons plus ~50 base pairs of flanking non-coding intronic DNA on either side of each exon is performed using genomic DNA. As indicated, we will also perform sequencing of any single exon (Test #100, \$190) or pair of exons (Test #200, \$340) for family members of patients with known mutations and to confirm previous research results.

**Reference Sequences:** Genomic: NC\_000002.11 mRNA: NM\_015702.2 Protein: NP\_056517.1 (CCDS 2189.1)

**Indications for Test:** Candidates for this test are patients with biochemical findings and/or clinical symptoms consistent with *cbID* deficiency, including infants with a positive newborn screen. Testing is also indicated for family members of patients with known *MMADHC* mutations.

**Sensitivity of Test:** In two studies which examined a total of 10 patients with *cbID* defect, all individuals were found to have *MMADHC* mutations in either a compound heterozygous or homozygous state (see Coelho et al. 2008; Miousse et al. 2009).

**Turnaround Time:** Maximum of 40 calendar days, although many tests are completed in 2 – 3 weeks.

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

**Price:** Sequencing of *MMADHC* \$ 570

| CPT Codes    |          |          |          |          |          |          |       |
|--------------|----------|----------|----------|----------|----------|----------|-------|
| Test         | 83890 x1 | 83891 x1 | 83898 x7 | 83904 x7 | 83894 x1 | 83912 x1 | Total |
| <i>MMADH</i> | \$30     | \$40     | \$160    | \$235    | \$30     | \$75     | \$570 |

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

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