

Methylmalonic Aciduria and Homocystinuria, *cbfF* type, via *LMBRD1* Gene Sequencing, Test #326

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 *cblA* through *cblG*. In *CblF* deficiency, cobalamin accumulates in lysosomes and cannot be used to synthesize the cofactors adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl). As a result, methylmalonyl CoA mutase cannot convert L-methylmalonyl-CoA to succinyl CoA, and methionine synthase cannot convert homocysteine to methionine. Patients have elevated homocysteine and methylmalonic acid concentrations in blood and urine, and some patients with increased propionylcarnitine concentrations are identified through newborn screening (Rutsch et al. *Nat Genet* 41:234-239, 2009). Clinical presentation is variable, but includes being small for gestational age, poor feeding, failure to thrive, developmental delay, and persistent stomatitis (Gailus et al. *J Inherit Metab Dis* 33:17-24, 2010; Rutsch et al. 2009). Hematological abnormalities are common and include macrocytic anemia, neutropenia, thrombocytopenia, and pancytopenia. Two patients have been reported to have minor craniofacial abnormalities (including pegged teeth and bifid incisors), and four patients have been described with congenital heart defects (Rutsch et al. 2009).

Genetics: Genetic mutations in *LMBRD1* on chromosome 6q13 are responsible for autosomal recessive methylmalonic aciduria and homocystinuria, *cbfF* type (OMIM 277380). The *LMBRD1* gene consists of 16 coding exons and encodes the 540 amino acid LMBD1 protein that localizes to lysosomal membranes. This protein shares some homology with the lipocalin-1 interacting membrane receptor (LIMR), and while the exact function of LMBD1 protein remains unknown, it has been hypothesized to act as a lysosomal exporter for cobalamin (Rutsch et al. 2009). The vast majority of *LMBRD1* mutations identified to date include small deletions detectable by sequencing. Furthermore, there appears to be a common European founder mutation, c.1056delG (p.L352fsX18) in exon 11. In one recent study of 12 unrelated patients with *cbfF* defect, 18 of 24 alleles carried this particular mutation (Rutsch et al. 2009).

Description of This Particular Test: Bidirectional sequencing of all 16 *LMBRD1* 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. Exon 11 sequencing may be ordered prior to sequencing the remainder of the gene.

Reference Sequences: Genomic: NC_000006.11 mRNA: NM_018368.3 Protein: NP_060838.3 (CCDS 4969.1)

Indications for Test: Candidates for this test are patients with biochemical findings and/or clinical symptoms consistent with *cbfF* deficiency, including infants with a positive newborn screen. Testing is also indicated for family members of patients with known *LMBRD1* mutations.

Sensitivity of Test: In the largest published study of patients with *cbfF* deficiency, all 12 affected patients were found to have *LMBRD1* mutations in either a compound heterozygous or homozygous state (Rutsch 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 *LMBRD1* \$ 920

CPT Codes							
Test	83890 x1	83891 x1	83898 x16	83904 x16	83894 x1	83912 x1	Total
<i>LMBRD1</i>	\$30	\$40	\$270	\$400	\$70	\$110	\$920

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

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