

3-Hydroxy-3-MethylGlutaryl-CoA Lyase Deficiency via *HMGCL* Gene Sequencing (Test #240)

Brief Description of Clinical Features: 3-Hydroxy-3-MethylGlutaryl (HMG)-CoA Lyase Deficiency (OMIM 246450) is a rare defect in the last step in leucine catabolism. The defect also affects breakdown of fatty acids and reduces production of ketone bodies. Typically, the disorder is diagnosed in infants with symptoms of vomiting, lethargy, hepatomegaly, and seizures. The disorder can be lethal. During disease episodes, children develop hypoketotic hypoglycemia, hyperammonemia and acidosis. HMG-CoA Lyase Deficiency has also been diagnosed in adults with leukoencephalopathy (Bischof et al. Ann Neurol 56:727-730, 2004). The disease may lead to lifelong learning problems and mental retardation. These days, many cases are detected through routine neonatal screening with tandem mass spectrometry. For more information, see Seashore GeneReviews 2006 (www.genetests.org) and the Organic Acidemia Association (www.oaanews.org).

Genetics: HMG-CoA Lyase Deficiency is an autosomal recessive disease. The enzyme is encoded by the *HMGCL* gene on chromosome 1p36. About 30 causative *HMGCL* mutations have been reported. They are missense, nonsense, splicing, and frameshift. A few larger deletions that would not be detectable by DNA sequencing have been reported (see for example Muroi et al. 107:320-326, 2000). The disorder appears to be particularly common in Saudi Arabia (Al-Sayed et al. BMC Med Genet 7:86, 2006) and Portugal.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 9 exons of the *HMGCL* 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_000001.9 mRNA: NM_000191.2 protein: NP_000182.2

Indications for Test: All HMG-CoA Lyase Deficiency patients and their family members are candidates for this test. PreventionGenetics offers testing for many other neonatal screening disorders.

Sensitivity of Test: Sensitivity of this test for patients diagnosed by biochemistry should be high. Because, as noted above, larger deletions exist, only one causative mutation may be detected in some patients.

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *HMGCL* Exons 1-9 \$ 590

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x9	83898	\$ 160	Sequencing x9	83904	\$ 230
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 for info: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com ; www.preventiongenetics.com