

Multiple Carboxylase Deficiency (Early Onset) via *HLCS* Gene Sequencing (Test #521)

Brief Description of Clinical Features: Multiple carboxylase deficiency (MCD) is an inborn error of metabolism resulting from defective biotin metabolism. Early onset MCD (OMIM #253270) results from deficiency of holocarboxylase synthetase (*HLCS*), whereas juvenile (also called late) onset MCD (OMIM #253260) is caused by biotinidase (*BTD*) deficiency. *BTD* and *HLCS* forms of MCD are both responsive to biotin therapy. However, making a distinction between the two types is difficult and relies largely on age of onset rather than clinical features. Clinical signs of juvenile onset *BTD* typically appear after 3 months of age while early onset MCD is typically evident earlier than 3 months of age (Wolf et al., *Ann. Neurol.* 18:614-617, 1985). *In vitro* enzyme studies are capable of distinguishing between the two disorders. The earliest presenting sign is usually seizures, but other early non-specific symptoms include hypotonia, respiratory symptoms, developmental delay and ataxia. Eczma, alopecia, dermatitis, and skin infections are also common findings, and cutaneous presentations in conjunction with neurological symptoms greatly limit the differential diagnosis. Clinical variability for *HLCS*-related MCD is documented, and an asymptomatic homozygous adult has been reported (Suzuki et al., *Hum Mutation* 26:285-290, 2005).

Genetics: Multiple carboxylase deficiency is an autosomal recessive disorder. Mutations in the *HLCS* gene are the genetic cause of early onset MCD. Approximately 30 *HLCS* mutations have been reported. Most mutations are missense changes but nonsense mutations, small insertions and deletions, and splice site mutations have also been found. Among Northern Europeans a splice site mutation (c.1519+5G>A) is prevalent, and among Japanese two mutations (p.Leu237Pro and p.Gly261ValfsStop20) are predominant (Suzuki et al., *Hum Mutation* 26:285-290, 2005). The p.Arg508Trp mutation has been found in multiple patients from several ethnic groups from East Asia, the Middle East and the USA (Suzuki et al., *Hum Mutation* 26:285-290, 2005).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the *HLCS* coding region (exons 4-12). The entire coding region and ~50 bp of flanking non-coding DNA on either side of each splice site are sequenced.

Reference Sequences: Genomic: NC_000021.7 mRNA: NM_000411.4 protein: NP_000402.3

Indications for Test: Patients suspected of having multiple carboxylase deficiency based on biochemical testing and/or clinical features. All patients with reduced holocarboxylase synthetase activity are candidates for this test. We will also sequence the *HLCS* gene to determine carrier status.

Sensitivity of Test: Dupuis et al. (*Hum. Molec. Genet.* 5:1011-1016, 1996) found two causative *HLCS* mutations in each of 9 patients studied, and Aoki et al. (*Hum. Genet.* 104:143-148, 1999) found two causative mutations in each of their 7 holocarboxylase deficient patients.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of complete coding regions of *HLCS* Gene \$ 740

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x10	83898	\$ 210	Sequencing x10	83904	\$ 320
Separation	83894	\$ 60	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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