

Multiple Carboxylase Deficiency (Juvenile Onset) via *BTD* Gene Sequencing (Test #520)

Brief Description of Clinical Features: Multiple carboxylase deficiency (MCD) is an inborn error of metabolism resulting from defective biotin metabolism. Juvenile (also called late) onset MCD (OMIM #253260) results from profound or partial deficiency of biotinidase (*BTD*), whereas early onset MCD (OMIM #253270) is caused by holocarboxylase synthetase (*HLCS*) 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. Eczema, alopecia, dermatitis, and skin infections are also common findings, and cutaneous presentations in conjunction with neurological symptoms greatly limit the differential diagnosis. Clinical variability is documented. Untreated patients with partial biotinidase deficiency may experience fewer and milder symptoms than patients with complete deficiency (Suormala et al., *J of Inherited metabolic Disease* 13:76-92, 1990). Asymptomatic adults with profound biotinidase deficiency have also been reported (Wolf et al., *Amer J Med Genet* 73:5-9, 1997).

Genetics: Multiple carboxylase deficiency is an autosomal recessive disorder. Mutations in the *BTD* gene are the genetic cause of juvenile or late onset MCD. Over 100 *BTD* mutations have been reported in children affected with profound biotinidase deficiency. Most mutations are missense changes but nonsense, small insertions and deletions, splice site mutations and indels have also been found. Three mutations (p.Cys33PhefsStop36, p.[Ala171Thr;Asp444His], and p.Gln456His) are commonly found in biotinidase-deficient newborns ascertained by newborn screening in the USA. Only the first mutation is found commonly in symptomatic patients (Norrgard et al., *Pediatr Res* 46:20-27, 1999). One other mutation (p.Arg538Cys; Pomponio et al., *Hum Genet* 99:506-512, 1997) is common among symptomatic children, but not among newborns with a positive biotinidase screen. The worldwide carrier frequency for *BTD* mutations is thought to be 1 in 120 (Wolf et al., *J Inherit Metab Dis* 14:923-927, 1991).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 4 coding exons of the *BTD* gene. 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_000003.10 mRNA: NM_000060.2 protein: NP_000051.1

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

Sensitivity of Test: Pomponio et al., (*Pediatr. Res.* 42:840-848, 1997) identified mutations on each *BTD* allele in all 30 biotinidase-deficient probands analyzed. The p.Arg538Cys and p.Cys33PhefsStop36 mutations accounted for over 50% of the mutant alleles in this study.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See bottom of Page 2 of Requisition Form.

Price: Sequencing of complete coding regions of *BTD* Gene \$ 540

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x6	83898	\$ 135	Sequencing x6	83904	\$ 205
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 80

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