PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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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, whereas early onset MCD (OMIM #253270) is caused by holocarboxylase synthetase deficiency. Both forms of MCD are responsive to biotin therapy. 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 MCD 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 (Suorrmala et al. *J Inher Metab Dis* 13:76-92, 1990). Asymptomatic adults with profound biotinidase deficiency have also been reported (Wolf et al. *Am J Med Genet* 73:5-9, 1997).

Genetics: Multiple carboxylase deficiency is an autosomal recessive disorder. Mutations in the *BTD* gene (OMIM #609019) 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 pathogenic variants are missense mutations although nonsense, small insertions and deletions, and splice site mutations 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 (Cowan et al. *Genetics in Medicine* 12:464-470, 2010). The p.Cys33PhefsStop36 mutation is found commonly in symptomatic patients (Norrgard et al. *Pediatr Res* 46:20-27, 1999). One other mutation (p.Arg538Cys) is common among symptomatic children, but not among newborns with a positive biotinidase screen (Pomponio et al. *Hum Genet* 99:506-512, 1997). The p.Asp444His mutation reduces enzyme activity ~50% and results in a partial biotinidase deficiency when present in trans with a severe mutation. 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: Biotinidase is encoded by exons 1-4 of the *BTD* gene on chr 3p25. Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. As indicated, we will also sequence any single exon (Test #100) or pair of exons (Test #200) for family members of patients with known mutations and to confirm previous research results ($190-340 charge).

Reference Sequences: **Genomic: NC_000003.10** **mRNA: NM_000060.2**
Protein: NP_000051.1 **Protein and mRNA: CCDS 2628.1**

Indications for Test: Patients suspected of having multiple carboxylase deficiency based on biochemical testing and/or clinical features.

Sensitivity of Test: Pomponio et al. (*Pediat 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.

Turnaround 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 *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

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