

Maple Syrup Urine Disease Type II via *DBT* Gene Sequencing (Test #528)

Brief Description of Clinical Features: Maple syrup urine disease (MSUD; OMIM 248600) is a heterogeneous organic aciduria disorder caused by the impairment of the branched-chain α -keto acid dehydrogenase complex (BCKD). BCKD is a mitochondrial complex, encoded by four nuclear genes (*BCKDHA*, *BCKDHB*, *DBT* and *DLD*), which is involved in the metabolism of branched-chain amino acids (leucine, isoleucine, and valine) (Morton et al. Pediatrics 109:999-1008, 2002; Nellis et al. Molec Genet Metab 80:189-195, 2003; Chuang et al. J Biol Chem 279:17792-17800, 2004). Defective BCKD complex activity leads to the accumulation of the branch-chain amino acids to toxic levels (Chuang et al. 2004). MSUD, in untreated neonates, is characterized by mental and physical retardation, maple syrup odor in cerumen and urine, poor feeding, ketonuria, irritability, lethargy, intermittent apnea, opisthotonus, stereotyped movements such as “fencing” and “bicycling”, coma and respiratory failure. Biochemically, MSUD is characterized by elevated plasma concentrations of branched-chain amino acids (leucine, isoleucine, and valine) and allo-isoleucine, as well as a generalized disturbance of plasma amino acid concentration ratios (Schadewaldt et al. Clin Chem 45:1734-1740, 1999; Morton et al. 2002; Nellis et al. 2003; Chuang et al. 2004).

Genetics: MSUD is an autosomal recessive genetically heterogeneous disorder caused by mutations in one of the four BCKD complex encoded genes (*BCKDHA*, *BCKDHB*, *DBT* and *DLD*). MSUD Type II is caused by mutations in *DBT* gene, which encodes the dihydrolipoyl transacylase; the E2 component of the BCKD complex (Hummel et al. J Biol Chem 263:6165-6168, 1988; Danner et al. J. Biol. Chem. 264: 7742-7746, 1989). A mix of missense, nonsense, splicing, regulatory, small deletions mutations as well as gross deletion mutations within the *DBT* gene have been reported (Herring et al. Am J Hum Genet 48:342-350, 1991; Fisher et al. Am J Hum Genet 52:414-424, 1993; Tsuruta et al. J Hum Genet 43:91-100, 1998; Henneke et al. Hum Mutat 22:417-422, 2003; Chuang et al. 2004; Rodriguez et al. Hum Mutat 27:715-727, 2006; Brodtkorb et al. Mol Genet Metab 100:324-332, 2010).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 11 coding exons (exons 1-11) of the *DBT* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. 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.

Reference Sequences: Genomic: NC_000001.10 mRNA: NM_001918.2 Protein: NP_001909.2 (CCDS 767.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with MSUD and family members of patients who have known *DBT* mutations.

Sensitivity of Test: It has been reported that mutations in the *DBT* gene are responsible of approximately 19% of the MSUD cases, while mutations in the *BCKDHA* and the *BCKDHB* genes are responsible for approximately 33% and 38% of MSUD cases, respectively (Nellis and Danner Am J Hum Genet 68:232-237, 2001).

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

Specimen Requirements: See page four of the Requisition Form.

Prices: Sequencing of *DBT* gene \$ 820

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x13	83898 \$ 240	Sequencing x13	83904 \$ 360
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 110

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

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