

## Maple Syrup Urine Disease Type IB via *BCKDHB* Gene Sequencing (Test #527)

**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  $\alpha$ -keto acid dehydrogenase complex (BCKD). BCKD is a mitochondrial complex, encoded by four nuclear genes (*BCKDHA*, *BCKDHB*, *DBT* and *DLSD*), 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 *DLSD*). MSUD Type IB is caused by mutations in *BCKDHB* gene, which encodes the 2-oxoisovalerate dehydrogenase subunit beta of the of the BCKD complex (Nobukuni et al. J Clin Invest 87:1862-1866, 1991; Mitsubuchi et al. J Biol Chem 266:14686-14691, 1991; Chuang et al. Am J Hum Genet 58: 1373-1377, 1996). A mix of missense, nonsense, splicing, small insertion and deletions mutations as well as gross deletion mutations within the *BCKDHB* gene have been reported (Nobukuni et al. 1991; Henneke et al. Hum Mutat 22:417-422, 2003; Chuang et al. 2004; Rodriguez et al. Hum Mutat 27:715-727, 2006).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of the 10 coding exons (exons 1-10) of the *BCKDHB* 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\_000006.11 mRNA: NM\_183050.2 Protein: NP\_898871.1 (CCDS 4994.1)

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

**Sensitivity of Test:** It has been reported that mutations in the *BCKDHB* gene are responsible of approximately 38% of the MSUD cases, while mutations in the *BCKDHA* and the *DBT* genes are responsible for approximately 33% and 19% 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 *BCKDHB* gene \$ 730

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x11	83898 \$ 210	Sequencing x11	83904 \$ 300
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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