

## Maple Syrup Urine Disease Type III via *DLD* Gene Sequencing (Test #529)

**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 *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 *DLD* gene results in MSUD type III (E3-deficient), a rare variant of MSUD with primary lactic acidosis (Liu et al. Proc Natl Acad Sci USA 90:5186-5190, 1993). MSUD type III is characterized with severe lactic acidosis, neurologic deterioration, hypotonia, developmental delay, dystonia/chorea, and a Leigh-type encephalopathy. Biochemically, MSUD type III is characterized by lactic acidemia, lactic aciduria, elevation of plasma concentrations of branched-chain amino acids and excretion of 2-oxoglutarate (Liu et al. 1993; Hong et al. Hum Mol Genet 5:1925-1930, 1996; Grafakou et al. Eur J Pediatr 162:714-718, 2003).

**Genetics:** MSUD type III is an autosomal recessive disorder caused by mutations in the *DLD* gene. The *DLD* gene encodes the dihydrolipoamide dehydrogenase (E3 subunit). The DLD protein is a component of three different mitochondrial multi-enzyme complexes, including the pyruvate dehydrogenase complex, the alpha-ketoglutarate dehydrogenase complex, and the BCKD complex (Liu et al. 1993; Hong et al. 1996). A mix of missense, splicing, regulatory, small insertion and small deletions mutations in the *DLD* gene has been reported (Liu et al. 1993; Hong et al. 1996; Grafakou et al. 2003; Buckland et al. Hum Mutat 26:214-223, 2005).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of the 14 coding exons (exons 1-14) of the *DLD* 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\_000007.13 mRNA: NM\_000108.3 Protein: NP\_000099.2 (CCDS 5749.1)

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

**Sensitivity of Test:** Sensitivity of this test is currently unknown.

**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 *DLD* gene \$ 860

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x14	83898 \$ 250	Sequencing x14	83904 \$ 380
Separation x1	83894 \$ 50	Interpretation/Report x1	83912 \$ 110

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

**Contact:** Margaret Chen, PhD, FACMG, CGC, [margaret.chen@preventiongenetics.com](mailto:margaret.chen@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)