Maple Syrup Urine Disease, Type III (E3 Deficiency): *DLD* Gene Deletion/Duplication

**Condition Description**

The *DLD* gene (7q31-q32) encodes the protein dihydrolipoamide dehydrogenase, sometimes called E3. The DLD protein is a component of the pyruvate dehydrogenase complex, the alpha-ketoglutarate dehydrogenase complex, and the branched-chain alpha-keto acid dehydrogenase complex (BCKD), all of which are mitochondrial multienzyme complexes.

Mutations in *DLD* are responsible for a very rare variant form of the recessive condition maple syrup urine disease (MSUD). MSUD type III (or E3 deficient MSUD) initially presents in newborns with symptoms common to intermediate MSUD, but also includes severe lactic acidosis, which is potentially life-threatening. Persistent lactic acidosis occurs between eight weeks and six months of life. In addition to lactic acidosis, patients with E3-deficient MSUD can display neurologic deterioration, hypotonia, developmental delay, and movement disorders. Laboratory findings include elevated blood pyruvate, lactate, alpha-ketoglutarate, branched-chain amino acids, alpha-hydroxyisovalerate, and alpha-hydroxyglutarate. Dietary therapy, vitamin therapy with thiamine and biotin, and lipoic acid therapy have all been attempted without success.

Sequencing of the *DLD* gene is recommended after a biochemical diagnosis of E3-deficient MSUD, and provides a complementary method to confirm the presence of mutations in a proband, identify carriers among the proband's relatives, and provide prenatal diagnosis in families with known mutations.

**Genes**

*DLD*

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of E3-deficient MSUD
- Carrier testing in adults with a family history of E3-deficient MSUD

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

**Detection**

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

*Submit only 1 of the following specimen types*

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
- EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
  - 3µg
  - Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample. Contact the laboratory if further information is needed.
Related Tests

Plasma Amino Acid Analysis (AA)
Urine Organic Acid Analysis (OA)
Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.