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

**Test Code:** HJ  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

### 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. Persistant 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. Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### 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

* Preferred specimen type: Whole Blood

#### Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

#### Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

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### 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.