Maple Syrup Urine Disease (MSUD): *BCKD* Complex Gene Sequencing

**Condition Description**

Maple Syrup Urine Disease (MSUD) is an organic aciduria that is caused by the inability to break down branch-chain amino acids, leucine, isoleucine, and valine. The resulting build-up of these amino acids results in:

- vomiting
- dehydration
- severe metabolic acidosis
- characteristic maple syrup odor of the sweat and urine

MSUD is among the disorders tested for by newborn screening and is treatable by dietary modification. MSUD affects between 1 in 125,000-300,000 people in the general population. MSUD is common in the Old Order Mennonite population of southeastern Pennsylvania, occurring in 1 in 760 live births. MSUD is inherited in an autosomal recessive manner, therefore the recurrence risk for carrier parents of an affected child is 1 in 4.

MSUD is diagnosed by biochemical analysis of urine organic acids by gas chromatography/mass spectrometry (GC/MS) and by assay of the BCKD enzyme activity. Patients with MSUD may have mutations in either the *BCKDHA* (19q13), *BCKDHB* (6p21), or *DBT* gene (1p31), which encode the E1 alpha, E1 beta, and DBT subunits of BCKD complex, respectively. Sequencing of BCKD complex genes is recommended after a biochemical diagnosis of BCKD deficiency 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. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array.

Please click here for the GeneReviews summary on this condition.

**Genes**

*BCKDHA, BCKDHB, DBT*

**Indications**

This test is indicated for:

- Individuals with biochemical diagnosis of MSUD.
- Family members of an individual with MSUD who are at risk to be carriers.

Sequencing is not appropriate for prenatal samples in which familial mutations have not been identified.

**Methodology**

**Next Generation Sequencing**: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

It is estimated that sequencing will detect 85-90% of mutations in *BCKHA, BCKHB*, and *DBT* genes. Mutations in the promoter region, some mutations in the introns or other regulatory element mutations, and large deletions cannot be detected by this analysis.

Results of molecular analysis should be interpreted in the context of the patient's 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) or ACD (yellow 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.

**Special Instructions**

Please submit copies of diagnostic biochemical test results along with the sample. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Organic Acid Analysis (OA) and Amino Acid Analysis - Plasma (AA) are used in the diagnoses of a patient with MSUD.
- BCKD Enzyme Activity Analysis (BC) is used to confirm the diagnosis of MSUD in a patient with elevations of branched chain amino acids.
- Known 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.