3-Methylcrotonyl-CoA Carboxylase (3-MCC) Deficiency: MCCC1/MCCC2 Gene Deletion/Duplication

Test Code: JZ
Turnaround time: 2 weeks
CPT Codes: 81228 x1

**Condition Description**

3-Methylcrotonyl-CoA Carboxylase (3-MCC) deficiency is an autosomal recessive inborn error of leucine metabolism [1]. 3-MCC is a biotin-dependent enzyme in the L-leucine degradation pathway. Newborn screening which includes testing for 3-MCC by tandem mass spectrometry, may reveal increased levels of 3-hydroxyisovalerylcarnitine (C5-OH).

The clinical course has been shown to vary considerably, ranging from entirely asymptomatic to death in infancy [3]. Severe and mild phenotypes are not clearly defined, but the vast majority of individuals have mild phenotypes which may be asymptomatic, while a subgroup shows mild unspecific symptoms like fatigue and weakness during catabolic episodes or mild developmental delay.

Isolated 3-MCC deficiency, which is not responsive to treatment with biotin, can be distinguished from the biotin-responsive multiple-carboxylase deficiencies, which are due to disorders of biotin metabolism (biotinidase deficiency and holocarboxylase synthetase deficiency) and affect all four of the biotin-dependent carboxylases. Infants with elevated C5-OH may also be due to maternal 3-MCC deficiency[2].

The 3-MCC enzyme consists of two subunits encoded by the MCCC1 gene (or MCCA) on 3q26 and the MCCC2 gene (or MCCB) on 5q13. Sequencing analysis is available to test for mutations in the MCCC1 and MCCC2 genes, associated with 3-MCC deficiency.

References:

**Genes**

MCCC1, MCCC2

**Indications**

This test is indicated for:
- Individuals with clinical and biochemical findings consistent with 3-MCC deficiency.
- Carrier testing in individuals with a family history of 3-MCC deficiency.

**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. The CGH array will not detect point or intronic mutations. 3-MCC deficiency is rare with incidence estimates of 1:84,700 live births [2].

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:** 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.

**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 72 hours of collection. Do not freeze.

**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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**
- Organic Acids (OA) - Urine and Acylcarnitine Profile (AR) - Plasma are used in the diagnosis of a patient with 3-MCC deficiency.
- Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.

**Prenatal Custom Diagnostics** 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.