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

<table>
<thead>
<tr>
<th>Test Code: JZ</th>
<th>Turnaround time: 2 weeks</th>
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<td>CPT Codes: 81228 x1</td>
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**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-hydroxyisovaleryl carnitine (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.

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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.