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

\textbf{Test Code: JZ}
\textbf{Turnaround time: 2 weeks}
\textbf{CPT Codes: 81228 x1}

\section*{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 \textit{MCCC1} gene (or MCCA) on 3q26 and the \textit{MCCC2} gene (or MCCB) on 5q13. Sequencing analysis is available to test for mutations in the \textit{MCCC1} and \textit{MCCC2} genes, associated with 3-MCC deficiency.

\section*{References}


\section*{Genes}

\textit{MCCC1, MCCC2}

\section*{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.

\section*{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.

\section*{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.

\section*{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.

**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.