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

\textbf{Test Code:} JY  
\textbf{Turnaround time:} 6 weeks  
\textbf{CPT Codes:} 81406 x1

\section*{Condition Description}

3-Methylcrotonyl-CoA Carboxylase (3-MCC) deficiency is an autosomal recessive inborn error of leucine metabolism \cite{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 \cite{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\cite{2}.

The 3-MCC enzyme consists of two subunits encoded by the \textit{MCCC1} (MCCA) gene on 3q26 and the \textit{MCCC2} (MCCB) gene on 5q13. Sequencing analysis is available to test for mutations in the \textit{MCCC1} and \textit{MCCC2} genes, associated with 3-MCC deficiency. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array.

\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}

\textbf{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.

\section*{Detection}

\textbf{Clinical Sensitivity:}

- 52/56 mutations identified in 28 patients \cite{5}.
- 7/8 mutations identified in 4 patients \cite{6}.
- 4/4 mutations identified in 2 patients \cite{7}.

Analytical Sensitivity: \approx 99\%. The majority of patients with clinical and biochemical diagnosis of 3-MCC deficiency will have gene mutations detected by sequence analysis.

\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) 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) - 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.
- For comprehensive testing, **3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC): MCCC1/MCCC2 Gene Deletion/Duplication (JZ)** is available separately. This test is indicated for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.

**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.