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.

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.

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
- 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 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.