Methylmalonic Aciduria and Homocystinuria, cblC Type: MMACHC Gene Deletion/Duplication

**Condition Description**

Vitamin B\textsubscript{12} (cobalamin) is a cofactor required by two enzymes, methionine synthase (MTR) and methylmalonyl-CoA mutase (MUT). Disorders of intracellular cobalamin metabolism may impair the function of either or both enzymes:

- Clinical syndromes involving defects in MUT function alone are called methylmalonic acidemia. Such defects can be caused by defective MUT enzyme or missing B\textsubscript{12} cofactor. Certain subtypes of methylmalonic acidemia may be further defined by complementation analysis. Complementation groups causing isolated methylmalonic acidemia include cblA and cblB.

- Clinical syndromes involving defective MTR function can be caused by defective MTR enzyme, missing cofactor, or defects in an enzyme that regenerates MTR: methionine synthase reductase (MTRR). Defective MTR function is associated with variable hyperhomocysteinemia and/or homocystinuria.

- Disorders that cause isolated defects in MTR function, as well as disorders that cause combined defects in both MTR and MUT function, are named by complementation group. MTR-only and combined MUT/MTR cobalamin disorders include cblC, cblD, cblD variant 1, cblD variant 2, cblE, cblF, and cblG.

The clinical manifestations of disorders of intracellular cobalamin metabolism, identified by complementation class as cblC, cblD, cblD variant 1, cblD variant 2, cblF, cblE, and cblG, can be highly variable even within a single complementation class. cblC is the most common of these disorders. The age of initial presentation of cblC ranges from (1) newborns who can be small for gestational age (SGA) and have microcephaly; to (2) infants who can have poor feeding, failure to thrive, pallor, and neurologic signs, and occasionally hemolytic uremic syndrome (HUS) and/or seizures including infantile spasms; to (3) toddlers who can have failure to thrive, poor head growth, cytopenias (including megaloblastic anemia), global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures; and to (4) young adults/adults who can have confusion, other mental status changes, cognitive decline, and megaloblastic anemia.

Metabolic screening tests such as urine organic acid analysis and plasma amino acid analysis help categorize the clinical syndrome. Analysis in specialized laboratories can establish the specific complementation class. Mutations in the **MMACHC** (1p34.1) gene cause cblC. The role of molecular genetictesting in diagnosis is evolving; molecular genetictesting may be faster and less expensive than complementation class analysis in establishing a specific diagnosis in afamilial.

All disorders of intracellular cobalamin metabolism are inherited in an autosomal recessive manner. Heterozygotes (carriers) are asymptomatic.

For patients with suspected cblC, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**Genes**

**MMACHC**

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of cblC in an individual in whom sequence analysis is negative
- Carrier testing in adults with a family history of cblC in whom sequence analysis is negative

**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.

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: 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.

Type: DNA, Isolated

Specimen Requirements:
- Microtainer
- 3µg
- Isolation using the Perkin Elmer™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.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. 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

- Sequencing analysis of the MMACHC gene is available and is required before deletion/duplication analysis.
- Prenatal testing 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.