

Methylmalonic Aciduria and Homocystinuria, cblC Type: *MMACHC* Gene Sequencing

Test Code: SMACH

Turnaround time: 4 weeks

CPT Codes: 81479 x1

Condition Description

Vitamin B₁₂ (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:

- o Clinical syndromes involving defects in MUT function alone are called methylmalonic acidemia. Such defects can be caused by defective MUT enzyme or missing B₁₂ cofactor. Certain subtypes of methylmalonic acidemia may be further defined by complementation analysis. Complementation groups causing isolated methylmalonic acidemia include cblA and cblB.
- o 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.
- o 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 genetic testing in diagnosis is evolving; molecular genetic testing may be faster and less expensive than complementation class analysis in establishing a specific diagnosis in a family.

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

[Click here](#) for the GeneTests summary on this condition.

Genes

[MMACHC](#)

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of cblC
- Carrier testing in adults with a family history of cblC

Methodology

PCR amplification of 5 exons contained in the *MMACHC* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: Saliva**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

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

8µg

Isolation using the Perkin Elmer™ Chemagen™ 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.

Related Tests

- Deletion/duplication analysis of the *MMACHC* gene is also available.
- [Custom diagnostic mutation analysis \(KM\)](#) is available to family members if mutations are identified by targeted mutation testing or sequencing 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.