3-Hydroxy-3-Methylglutaryl CoA Lyase (HMG) Deficiency: HMGCL Gene Sequencing

**Condition Description**

HMGCL deficiency is an autosomal recessive disorder that affects ketogenesis and L-leucine catabolism [1]. Patients with HMG deficiency have a reduced capacity to synthesize ketone bodies (acetoacetate and 3-hydroxybutyrate) which are primary energy sources for the brain when metabolic needs are not met by glucose [2].

Affected individuals usually present in the first year of life with severe vomiting and diarrhea, hypoketotic hypoglycemia, metabolic acidosis, hyperammonemia, and hepatomegaly. Acute pancreatitis and dilated cardiomyopathy can be some of the clinical complications. Patients may also have macrocephaly, hypotonia, and developmental delay. Untreated, this may progress rapidly to coma and death or may result in permanent neurological damage.

With dietary and pharmacologic treatment, the disease can be controlled, although recurrent metabolic decompensation can occur, especially with prolonged fasting and inter-current infections. Rapid biochemical diagnosis by plasma acylcarnitine analysis using tandem mass spectrometry reveals elevated 3-methylglutarylacarnitine and 3-hydroxyisovalerylacarnitine [3]. Urine analysis by gas chromatography mass spectrometry reveals the presence of 3-hydroxy-3-methylglutaric, 3-methylglutaconic and 3-hydroxyisovaleric acids. HMG can also be measured in various tissues including lymphocytes and fibroblasts [4]. HMG-CoA human mitochondrial lyase is encoded by the HMGCL gene located at the 1p36.1-p35 chromosomal locus. To date, 31 variant alleles in the HMGCL gene (29 mutations and 2 SNPs) have been reported [5]. In the coding region, missensed mutations are the most frequent (14), followed by nonsense mutations (4), frameshift deletions (4) or insertions (1), and 3 large deletions. Three mutations have been found in intron sequences that cause abnormal splicing. The mutational spectrum is population specific with higher frequency in Saudi Arabia and Portugal and lower frequency in Europe and Japan [6-10]. Genotype-phenotype correlations have been difficult to establish [5]. Sequencing of the HMGCL gene is recommended after a biochemical analysis consistent with HMG deficiency, and provides a complementary method to confirm the presence of mutations in a proband, identify carriers among the proband's relatives, and provide prenatal diagnosis in families with known mutations. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array.

**References:**


**Genes**

HMGCL

**Indications**

This test is indicated for:

- Individuals with a clinical and biochemical diagnosis consistent with HMG deficiency.
- Carrier testing in individuals with a family history of HMG deficiency.

**Methodology**

PCR amplification of 9 exons contained in the HMGCL 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:
• 68/72 mutations identified in 13 patients from Saudi Arabia [6].
• 10/10 mutations identified in 5 Japanese patients [7].
• 21/22 mutations identified in 11 Portuguese patients [9].
• 6/6 mutations identified in 3 Czech patients [10].

Analytical Sensitivity: ~99%.

Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

**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™ 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**

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**

- Acylcarnitine Profile (AR)
- Organic Acids Analysis (OA) - Urine
- Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- HMGCL Gene Deletion/Duplication (HD) is available separately for individuals where mutations are not identified by sequence analysis. Please refer to the test requisition form 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.