**Condition Description**

3-Hydroxy-3-methylglutaryl-CoA lyase (HMG) 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 elevation of 3-methylglutaryl carnitine and 3-hydroxyisovaleryl carnitine[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) in 93 patients 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.

Please click here for the OMIM summary on this condition.

**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**

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**

**Disclaimer:** This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Prevalence of HMG deficiency is rare with incidence estimates of 1:100,000 live births.

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) 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**

- Acylcarnitine Profile (AP)
- Organic Acids Analysis (OA) - Urine
- 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.