Ketothiolase Deficiency: *ACAT1* Gene Deletion/Duplication

**Test Code:** JF  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

**Condition Description**

Beta-Ketothiolase deficiency (BKTD) is an autosomal recessive inborn error of ketone body and isoleucine metabolism [1]. Clinical manifestations of BKTD include intermittent episodes of severe ketoacidosis, usually with normoglycemia or hyperglycemia that can result in hyperventilation, dehydration, lethargy, coma, and death. Episodes are usually associated with severe vomiting and are triggered by infections or other illnesses. Therapy consists of mild protein restriction to limit the intake of isoleucine, avoidance of fasting, supplementation with carnitine, avoidance of prolonged fasting, and prompt treatment of illnesses that can precipitate acute attacks. The outcome of BKTD is favorable with early diagnosis, dietary therapy, and appropriate treatment of ketoacidosis.

BKTD is caused by deficiency of enzyme 3-ketothiolase (also called mitochondrial acetoacetyl-CoA thiolase or T2). Analysis of urine organic acids during acute episodes reveals high excretion of 2-methyl-3-hydroxybutyrate, 2-methylacetoacetate, and tiglylglycine with large amounts of 3-hydroxybutyrate and acetoacetate [2]. Analysis of plasma acylcarnitines shows increased concentrations of C5OH (2-methyl-3-hydroxybutyryl carnitine) and C5:1 (tiglyl carnitine).

3-ketothiolase is encoded by the *ACAT1* gene (11q22) which has been found to have heterogenous mutations in patients with BKTD [3-5]. Although no definitive correlation between phenotype and genotype has been identified, differences in the biochemical profiles under stable conditions between the groups with different mutations have been reported [6]. Newborn screening by tandem mass spectrometry can identify infants with BKTD caused by severe mutations, but may miss infants with the "milder" mutations. Gene sequence analysis is available to test for mutations in *ACAT1* gene (JE).

**References:**

**Genes**

*ACAT1*

**Indications**

This test is indicated for:
- Confirmation of a clinical/biochemical diagnosis of ketothiolase deficiency
- Carrier testing in adults with a family history of ketothiolase 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. Array CGH will not detect point mutations 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

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* 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**

Submit copies of diagnostic biochemical test results with the sample. 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**

- Plasma Amino Acid (AA) Analysis, Urine Organic Acids (OA), and Plasma Acylcarnitine Profiles (AR) are used in the diagnoses of a patient with BKTD. Urine Acylcarnitine and Acylglycine Profiles can also be helpful.
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor before collecting a fetal sample.