Isovaleric Acidemia: IVD Gene Deletion/Duplication

**Condition Description**

Isovaleric acidemia (IVA) is an autosomal recessive inborn error of leucine metabolism caused by a deficiency of the mitochondrial enzyme isovaleryl-CoA dehydrogenase (IVD) resulting in the accumulation of derivatives of isovaleryl-CoA [1]. IVD is a flavoenzyme that catalyzes the conversion of isovaleryl-CoA to 3-methylcrotonyl-CoA and transfers electrons to the electron transfer flavoprotein. Biochemical metabolites characteristic of IVA include C5 acylcarnitine and 2-methylbutyrylcarnitine [2]. Early diagnosis and treatment with a protein restricted diet and supplementation with carnitine and glycine are effective in promoting normal development in affected individuals. IVA can cause significant morbidity and mortality with both intra- and interfamilial variability. IVA is characterized by three phenotypes with either acute neonatal, chronic intermittent or asymptomatic presentations. Neonatal symptoms are non-specific and include poor feeding, vomiting, lethargy and seizures. Acute episodes of metabolic acidosis and moderate ketosis are observed. The chronic intermittent form is characterized by periodic episodes of metabolic acidosis. Infants with the neonatal form may later exhibit symptoms of the chronic intermittent. Neutropenia, thrombocytopenia, or, rarely, pancytopenia often occurs with acidoic episodes. A characteristic smell of "sweaty feet" may be present when the patient is acutely sick. Acidosis with an unexplained anion gap, hyperammonemia, hyper- or hypoglycemia and hypocalcemia may be present. IVA is caused by mutations in the IVD gene at 15q14) [3]. One missense mutation, 932C>T (A282V), is particularly common in patients identified through newborn screening with mild metabolite elevations and who are asymptomatic. This mutation leads to a partially active enzyme with altered catalytic properties; however, its effects on clinical outcome and the necessity of therapy are still unknown. Gene sequence analysis is available to test for mutations in the IVD gene (HF).

References:

**Indications**

This test is indicated for:

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

**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.

**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
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™ 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. 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 Profile (AR) are used in the diagnoses of a patient with IVA
- 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.