Isovaleric Acidemia: IVD Gene Deletion/Duplication

Test Code: HH
Turnaround time: 2 weeks
CPT Codes: 81228 x1

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 manifest symptoms of the chronic intermittent. Neutropenia, thrombocytopenia, or, rarely, pancytopenia often occurs with acidic 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 to 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 to the IVD gene (HF).

References:

Genes

IVD

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. 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. Prevalence: IVA has an estimated incidence of 1:62,500 live births [7].

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

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.