

Isovaleric Acidemia: *IVD* Gene Sequencing

Test Code: HF

Turnaround time: 4 weeks

CPT Codes: 81406 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 exhibit symptoms of the chronic intermittent. Neutropenia, thrombocytopenia, or, rarely, pancytopenia often occurs with acidotic 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).

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (HH).

References:

1. Vockley and Ensenauer. Isovaleric Acidemia: New Aspects of Genetic and Phenotypic Heterogeneity. *Am J Med Genet Part C (Seminars in Medical Genetics)* 142C:95-103 (2006).
2. Sweetman and Williams. 2001. Branched chain organic acidurias. In: Scriver C, Beaudet AL, Sly W, Valle D, editors. *The metabolic and molecular basis of inherited disease*, 8th edition. New York: McGraw-Hill, p.2125-2164.
3. Vockley et al. Identification of the molecular defects responsible for the various genotypes of isovaleric acidemia. *Prog Clin Biol Res* 1992, 375:533-540.
4. Vockley et al. Exon skipping in *IVD* RNA processing in isovaleric acidemia caused by point mutations in the coding region of the *IVD* gene. *Am J Hum Genet* 2000, 66:356-367.
5. Ensenauer et al. A Common Mutation Is Associated with a Mild, Potentially Asymptomatic Phenotype in Patients with Isovaleric Acidemia Diagnosed by Newborn Screening. *Am J Hum Genet* 2004, 75:1136-1142.
6. Lin et al. Genetic mutation profile of isovaleric acidemia patients in Taiwan. *Mol Genet Metab* 2007, 90:134-139.
7. Schulze et al. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. *Pediatrics* 2003, 111(6 Pt 1):1399-406.

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

PCR amplification of 12 exons contained in the *IVD* gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then 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. Large deletions are not detected by this analysis.

Detection

The majority of patients with clinical and biochemical diagnosis of *IVD* deficiency will have an abnormal DNA test.

Clinical Sensitivity: 38/38 mutations identified in 19 patients [5]; 12/12 mutations identified in 6 patients [6].

Analytical Sensitivity: ~99%

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

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Orangene™ 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: DNA, Isolated**Specimen Requirements:**

Microtainer

8µg

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.

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.

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.
- A Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor before collecting a fetal sample.