

Isovaleric Acidemia via *IVD* Gene Sequencing (Test #250)

Brief Description of Clinical Features: Isovaleric acidemia (OMIM 243500) is a metabolic defect in the catabolism of the branched-chain amino acid leucine. Isovaleric acidemia patients have deficiency in the activity of the mitochondrial enzyme isovaleryl-CoA dehydrogenase (Rhead and Tanaka *Proc Nat Acad Sci USA* 77:580-583, 1980). This deficiency leads to abnormally high concentrations of isovaleric acid in cells, blood and urine. Isovaleric acid is toxic to the CNS. Clinically, isovaleric acidemia exhibits wide variation in severity. The acute, neonatal form presents with massive metabolic acidosis in the first days of life. Poor feeding, vomiting and seizures follow and coma and death are often the outcomes. At the other end of the spectrum, the chronic form of isovaleric acidemia exhibit periodic crisis of severe ketoacidosis, but otherwise asymptomatic intervening periods. Intermediate forms may have a childhood onset and are characterized by varying degrees of developmental delay and recurrent episodes of vomiting and lethargy. Patients often have the distinctive “sweaty feet” odor of isovaleric acid during acute illness. Patients can sometimes suffer stroke, and cerebellar hemorrhage has been described in some of the organic acidemias including isovaleric acidemia (Testai and Gorelick *Arch. Neurol* 67:148-153, 2010). Isovaleric acidemia can mimic propionic acidemia and methylmalonic acidemia by producing hyperglycinemia, leukopenia, and episodic ketoacidosis (Ando et al. *Pediat Res* 5:478-486, 1971). Early diagnosis appears to be highly beneficial for patients.

Genetics: Isovaleric acidemia is an autosomal recessive disorder. Nearly 40 different *IVD* causative mutations have been reported. The majority of these mutations result in amino acid substitutions. Ensenauer et al. (*Am J Hum Genet* 75:1136-1142, 2004) reported that one common mutation, c.932C>T (p.Ala311Val; also referred to in the literature as p.Ala282Val), comprises ~50% of mutations in patients detected through newborn screening. Importantly, these authors found the same abnormal genotype among siblings who had biochemical evidence of isovaleric acidemia but no clinical symptoms of the disease.

Description of This Particular Test: Isovaleryl-CoA dehydrogenase is encoded by exons 1 - 12 of the *IVD* (OMIM 607036) gene. Testing is accomplished by amplifying all coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. If requested, we will sequence exon 9 containing the common p.Ala311Val mutation prior to testing the other 11 exons. As indicated, we will also sequence one (Test #100, \$190) or two (Test #200, \$340) exons in family members of patients with known mutations or to confirm research results.

Reference Sequences: Genomic: **NC_000015.9** mRNA: **NM_002225.3**
 Protein: **NP_002216.2** mRNA and protein: **CCDS 10057.2**

Indications for Test: Individuals with elevated 3-OH isovaleric acid and conjugated isovaleryl glycine in urine. Evaluation of serum amino acids is not considered diagnostic.

Sensitivity of Test: Analytical sensitivity should be high because all reported mutations are of the types which are detectable by sequencing. Clinical sensitivity should also be high. For example, Ensenauer et al. (2004) reported the detection by DNA sequencing of two likely causative *IVD* mutations in 18 out of 19 patients identified through newborn screening. Only one causative mutation was found in the 19th child.

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of complete coding regions of *IVD* Gene **\$ 590**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x10	83898	\$ 160	Sequencing x10	83904	\$ 240
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 80

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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