ACAD9 Deficiency: ACAD9 Gene Sequencing

Condition Description

In 2007, He et al. reported three cases of acyl-CoA dehydrogenase 9 (ACAD9) deficiency. The three cases presented with episodic liver dysfunction during otherwise mild illness or cardiomyopathy, along with chronic neurologic dysfunction.

The first affected individual was a previously healthy 14-year-old boy who died of a Reye-like episode and cerebellar stroke triggered by ingestion of aspirin during a minor viral illness. He had markedly elevated plasma ammonia concentration and elevated results from liver function tests. Also elevated were serum salicylate levels, serum lactate levels, lactate dehydrogenase levels, and creatine kinase levels.

The second affected individual was a 10-year-old girl who initially presented with fulminant liver failure at age 4 months. Her blood glucose level at time of presentation was not detectable and AST was >100,000 U/liter. She responded well to intravenous glucose therapy, but continued to have recurrent episodes of hepatocellular dysfunction with hypoglycemia usually triggered by viral infections.

The third affected individual was a 4.5-year-old girl who died of cardiomyopathy and dilated left ventricle. Her sibling also died of cardiomyopathy at age 22 months. She presented during an episode of acute illness at age 18 months with severe left ventricular dysfunction, hepatomegaly, and a blood glucose level <20 mg/dl. She then developed a pattern of recurrent rhabdomyolysis with intercurrent illness. She died of congestive heart failure at age 4.5 years, and autopsy revealed dilated cardiomyopathy with prominent liver necrosis.

Mutations in the ACAD9 gene (3q26) cause ACAD9 deficiency.

For patients with suspected ACAD9 deficiency, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

References:

Genes

ACAD9

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of ACAD9 deficiency
- Carrier testing in adults with a family history of ACAD9 deficiency

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:
In EDTA (purple top) or ACD (yellow 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, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Deletion/duplication analysis of the ACAD9 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- **Custom diagnostic mutation analysis (KM)** is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.