Isobutyryl Co-A Dehydrogenase Deficiency: \textit{ACAD8} Gene Deletion/Duplication

**Test Code:** OQ  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

### Condition Description

The first patient with isobutyryl Co-A dehydrogenase deficiency (IBD deficiency) was a 12-month old infant whose clinical symptoms were described in a 1998 publication \cite{1}. This patient presented with dilated cardiomyopathy, anemia, and carnitine deficiency. An elevated C4-acylcarnitine was noted in a plasma acylcarnitine profile, but a subsequent urine organic acid analysis was normal. Treatment with oral L-carnitine supplementation led to catch-up growth and normalization of the cardiac status. It was reported that the patient remained carnitine-dependent at almost 11 years of age \cite{2}. Twenty-one subsequent patients were all identified through newborn screening because of an isolated elevation of C4-acylcarnitine \cite{2-5}. Twelve patients were asymptomatic at the time of reporting. One patient was noted to have muscle hypotonia and mild developmental delay at 8 months of age. Two patients were treated for speech delay at 5 years and 2 years of age, respectively, but had normal growth and development. One patient was incidentally noted at 1 year of age to have mild branch peripheral pulmonary stenosis. One patient required frequent hospitalizations due to emesis and dehydration during the first 2 years of life but was developing normally at 5 years of age. Others were lost to follow up.

The \textit{ACAD8} gene (11q25) encodes isobutyryl Co-A dehydrogenase, which catalyzes the third step of the degradation of the branched chain amino acid valine \cite{6,7}. \textit{ACAD8} is a member of the Acyl-coenzyme A (CoA) dehydrogenases (ACADs) family of mitochondrial enzymes that catalyze the first dehydrogenation step in the beta-oxidation of fatty acyl-CoA derivatives \cite{7}. Fatty acids provide important respiratory fuel for many tissues, including heart, skeletal muscle, brown adipose tissue, kidney, and liver, as is evident in individuals with defects in any of the ACAD family members. The mitochondrial beta-oxidation pathway is a cycle of 4 sequential reactions in which the fatty acid substrate is shortened by 2 carbon atoms with each cycle, releasing an acetyl-CoA molecule that can then be used in the tricarboxylic acid cycle or for ketogenesis.

### References:


### Genes

\textbf{ACAD8}

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of IBD deficiency in individuals who have tested negative for sequence analysis  
- Carrier testing in adults with a family history of IBD deficiency who have tested negative for sequence analysis

### 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. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### 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, 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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the ACAD8 gene is available and is required before deletion/duplication 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.