Isobutyryl Co-A Dehydrogenase Deficiency: \textit{ACAD8} Gene Sequencing

\textbf{Test Code:} ON
\textbf{Turnaround time:} 6 weeks
\textbf{CPT Codes:} 81479 x1

\section*{Condition Description}

The first patient with isobutyryl Co-A dehydrogenous 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.

\section*{References:


\section*{Genes}

\textit{ACAD8}

\section*{Indications}

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of isobutyryl co-A dehydrogenase deficiency
- Carrier testing in females/adults with a family history of isobutyryl co-A dehydrogenase deficiency

\section*{Methodology}

PCR amplification of 11 protein-encoding exons contained in the \textit{ACAD8} 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.

\section*{Detection}

\textbf{Clinical Sensitivity:} 17/18 alleles were identified in 9 patients with IBD deficiency \cite{2}.  
\textbf{Analytical Sensitivity:} \textasciitilde99%

\section*{Specimen Requirements}

\textit{Submit only 1 of the following specimen types}

\textbf{Type: Saliva}

\textbf{Specimen Requirements:}
Oragene™ Saliva Collection Kit
Oragene™ 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: 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 24 hours of collection. Do not refrigerate or freeze.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™ 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.

Special Instructions
Submit copies of diagnostic biochemical test results with the sample. Contact the laboratory if further information is needed.

Related Tests
The Acylcarnitine Profile (AR) is used in the diagnosis of individuals with IBD deficiency.
Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.

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.