Propionic Acidemia (PA): \textit{PCCA} and \textit{PCCB} Gene Sequencing

\textbf{Test Code:} KK  
\textbf{Turnaround time:} 6 weeks  
\textbf{CPT Codes:} 81406 x1

\section*{Condition Description}
Propionic acidemia (PA) is an autosomal recessive disorder of organic acid metabolism caused by a defect of propionyl-CoA carboxylase (PCC) \cite{1}. PCC catalyzes the carboxylation of propionyl-CoA to D-methylmalonyl-CoA in the catabolic pathway of odd-numbered carbon fatty acids and amino acids, i.e.

\textit{isoleucine, valine, threonine, and methionine}. The major biochemical features of PA include mild to severe ketoacidosis, hyperammonemia, hyperglycinemia, and a diagnostic urine organic acid profile (3-hydroxypropionate, methylcitrate, propionylglycine, and tiglylglycine)\cite{2}. The common clinical presentation includes frequent vomiting, lethargy, refusal to feed, and hypotonia. In most of the patients there is a neonatal clinical onset associated with development delay and neurological impairment, but late-onset patients are also described with a milder course \cite{3}. Conventional treatment of PA consists of dietary restriction of protein, increase of caloric intake, avoidance of long-fasting periods and carnitine supplementation and may include oral antibiotic therapy.

PCC is a biotin-dependent mitochondrial enzyme which consists of two non-identical alpha and beta-subunits, encoded by the \textit{PCCA} (13q32) and \textit{PCCB} (3q13) genes, respectively \cite{4}. Mutations in either the \textit{PCCA} or \textit{PCCB} genes can cause reduced or deficient enzyme activity. In both genes, missense mutations are the most frequent defects (39 and 46\%, for \textit{PCCA} and \textit{PCCB}, respectively), followed by small insertions/deletions and splicing mutations (24-29\% each in either gene), with most resulting in a truncated protein. Gene sequencing is available to test for mutations in the \textit{PCCA} and \textit{PCCB} genes (KK). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (KI).

\section*{References:}

\section*{Genes}
\textit{PCCA, PCCB}

\section*{Indications}
This test is indicated for:
- Confirmation of a clinical/biochemical diagnosis of PA
- Carrier testing in adults with a family history of PA

\section*{Methodology}
\textbf{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.

\section*{Detection}
The vast majority of patients with clinical and biochemical diagnosis of propionic acidemia will have an abnormal DNA test.  
\textbf{Clinical Sensitivity:} 74/74 mutations identified in 37 patients \cite{5}.  
\textbf{Analytical Sensitivity:} ~99\%  
Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

\section*{Specimen Requirements}
\textit{Submit only 1 of the following specimen types}
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.

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.

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.

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 PA
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- 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.