Propionic acidemia (PA) is an autosomal recessive disorder of organic acid metabolism caused by a defect of propionyl-CoA carboxylase (PCC) [1]. PCC catalyses the carboxylation of propionyl-CoA to D-methylmalonyl-CoA in the catabolic pathway of odd-numbered carbon fatty acids and amino acids, i.e. 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)[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 [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 PCCA (13q32) and PCCB (3q13) genes, respectively [4]. Mutations in either the PCCA or PCCB genes can cause reduced or deficient enzyme activity. In both genes, missense mutations are the most frequent defects (39 and 46%, for PCCA and 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 PCCA and PCCB genes (KK). For patients with mutations not identified by gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (KI).

References:

Genes

PCCA, PCCB

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of PA
- Carrier testing in adults with a family history of PA

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

The vast majority of patients with clinical and biochemical diagnosis of propionic acidemia will have an abnormal DNA test.

Clinical Sensitivity: 74/74 mutations identified in 37 patients [5].

Analytical Sensitivity: ~99%

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) 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. 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**

- 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.