Propionic Acidemia (PA): *PCCA* and *PCCB* Gene Deletion/Duplication

**Condition Description**

Propionic acidemia (PA) is an autosomal recessive disorder of organic acid metabolism caused by a defect of propionyl-CoA carboxylase (PCC) [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. isoleucine, valine, threonine, and methionine. The major biochemical features of PA include:

- mild to severe ketoacidosis
- hyperammonemia
- hyperglycinemia
- diagnostic urine organic acid profile (3-hydroxypropionate, methylcitrate, propionylglycine, and tiglylglycine)[2]

The common clinical presentation includes:

- frequent vomiting
- lethargy
- refusal to feed
- hypotonia

In most 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. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array.

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**

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**

Please submit copies of diagnostic biochemical test results along 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**

- Amino Acid Analysis - Plasma (AA), Urine Organic Acids (OA), and Acylcarnitine Profile - Plasma (AR) are used in the diagnoses of a patient with PA.
- 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.