

Propionic Acidemia Sequential Testing via *PCCB* and *PCCA* Gene Sequencing (Test #390)

Brief Description of Clinical Features: Propionic Acidemia (PA) (OMIM 606054) is a severe and often lethal defect in the catabolism of certain amino acids (met, ile, thr, val), odd-numbered chain length fatty acids and cholesterol. PA patients lack substantial activity in the mitochondrial enzyme propionyl-CoA carboxylase. Clinical onset is usually in infancy or early childhood. Clinical features include food intolerance, vomiting, lethargy, failure to thrive, ketoacidosis, hyperammonemia, and neutropenia. For more information, see Seashore GeneReviews 2006 (www.genetests.org), Desviat et al. J Hum Genet 51:992-997, 2006 and the Propionic Acidemia Foundation (www.pafoundation.com).

Genetics: PA is an autosomal recessive condition. Propionyl-CoA carboxylase is comprised of two subunits, alpha and beta, encoded by the *PCCA* and *PCCB* genes, respectively. Defects in either gene can cause PA. Roughly 60 different causative mutations in *PCCA* and 70 in *PCCB* have been reported to date (Desviat et al. Mol Genet Metab 83:28-37, 2004; www.hgmd.cf.ac.uk; www.uchsc.edu/sm/cbs/pcc/pccmain.htm). See also the individual Test Descriptions for these two genes.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 15 coding exons of *PCCB* and all 24 exons of *PCCA*. The two gene tests may be requested in either order, but the default order is *PCCB* then *PCCA*, because the *PCCB* gene is shorter and therefore less expensive to sequence. Test sensitivity for *PCCB* also appears to be higher than for *PCCA*. If one or two likely causative mutations are found in the first gene, we will not proceed with sequencing of the second. There do not appear to be any phenotypic differences between patients with *PCCA* mutations and those with *PCCB* mutations.

Indications for Test: All PA patients are candidates for this test. Many patients will already have had propionyl-CoA carboxylase enzyme assays performed on lymphocyte or fibroblast specimens. While it is possible to biochemically distinguish the two complementation groups in PA patients (see for example Rodriguez-Pombo et al Am J Hum Genet 63:360-369, 1998), it may be easier to simply perform the DNA tests.

In cases where DNA from an affected child is unavailable, we will sequence the DNA of parents or other family members. We will also sequence any single exon or pair of exons in either gene in family members of patients with known mutations, and to confirm research results (\$190-340 charge).

Sensitivity of Test: Based on results from the literature, we estimate that at least one causative mutation will be detected in nearly all PA patients and two causative mutations in the great majority (Rodriguez-Pombo et al Am J Hum Genet 63:360-369, 1998; Ugarte et al. Hum Mut 14:275-282, 1999).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See bottom of page two of the Requisition Form.

Price: Sequencing of <i>PCCB</i> Exons 1-15	\$ 740
Sequencing of <i>PCCA</i> Exons 1-24	\$ 1150
Total	\$ 1890

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x38	83898	\$640	Sequencing x38	83904	\$ 980
Separation	83894	\$ 70	Interpretation/Report	83912	\$ 130

Contact for info: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com ; www.preventiongenetics.com