

Propionic Acidemia Testing via *PCCA* Gene Sequencing (Test #391)

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* 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). Causative mutations are mostly frameshift, splicing, and nonsense, with a few missense mutations. Mutations are located throughout the length of the gene. Except for founder mutations in some isolated populations, no mutations are predominant.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 24 exons of the *PCCA* gene. Sequencing includes about 50 bp of flanking non-coding DNA of either side of the coding region of each exon. As indicated, we will also sequence one (Test #100, \$190) or two (Test #200, \$340) exons in family members of patients with known mutations or to confirm research results.

Reference Sequences: Genomic: NC_000013.10 mRNA: NM_000282.3 Protein: NP_000273.2 (CCDS 9496.2)

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 the complementation group is unknown, we recommend sequencing the *PCCB* gene first (see our Sequential PA Test).

Sensitivity of Test: PA patients are about equally split between those with mutations in *PCCA* and those with mutations in *PCCB*. Ugarte et al. (Hum Mut 14:275-282, 1999) reported that about 70% of causative mutations were detected in *PCCA* complementation group patients, but this may be an underestimate due to relatively early, inefficient detection methods. We estimate that at least one likely causative mutation will be detected in nearly all patients with low propionyl-CoA carboxylase activity in the *PCCA* complementation group. Some large deletions (~10% of causative mutations), which would not be detected by our sequencing methods, have been reported (www.hgmd.cf.ac.uk).

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *PCCA* Exons 1-24

\$ 1240

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x24	83898	\$ 350	Sequencing x24	83904	\$ 630
Separation	83894	\$ 80	Interpretation/Report	83912	\$ 110

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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