

Propionic Acidemia Testing via *PCCB* Gene Sequencing (Test #392)

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 70 different causative mutations 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). Causative mutations are about equally split between missense and gene disruption (frameshift, splicing, and nonsense). Mutations are located throughout the length of the gene. A frameshift mutation in exon 12 (c.1218 del14 ins12) is apparently the most frequent mutation in Caucasians.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 15 exons of the *PCCB* gene. Sequencing includes about 50 bp of flanking non-coding DNA of either side of the coding region of each exon.

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).

When 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 this gene in family members of patients with known mutations, and to confirm research results (\$190-340 charge).

Sensitivity of Test: PA patients are about equally split between those with mutations in *PCCA* and those with mutations in *PCCB*. Rodriguez-Pombo et al. (Am J Hum Genet 63:360-369, 1998) reported detection of 56 out of 58 possible causative mutations in a series of 29 unrelated patients within the *PCCB* complementation group. It therefore appears that at least one likely causative mutation will be detected in virtually all *PCCB* complementation group patients, and two causative mutations in a high fraction (roughly 90%).

Turn Around Time: Maximum of 40 days.

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

Price: Sequencing of *PCCB* Exons 1-15

\$ 790

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x14	83898	\$210	Sequencing x14	83904	\$370
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 90

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