PCCA and *PCCB* Gene Analysis in Propionic Acidemia

Clinical Features:
Propionic acidemia (PA) is a disorder of organic acid metabolism caused by deficient activity of mitochondrial propionyl-CoA carboxylase. Onset often occurs in the neonatal period and is associated with developmental delay and early death. The common clinical presentation includes severe ketoacidosis, vomiting, poor feeding, lethargy, hypotonia and coma. Hyperammonemia, seizures and hepatomegaly may also be present. A small number of patients have only exhibited neurologic signs. Late-onset patients have been reported to have a milder course, and variable presentations, including isolated-dilated cardiomyopathy have been reported.[1-4]

Genetics:
Pathogenic variants in *PCCA* and *PCCB* cause propionic acidemia. The propionyl-CoA carboxylase (PCC) enzyme is a heteropolymer of 4 alpha and 4 beta subunits encoded by the *PCCA* and *PCCB* genes respectively. PCC catalyzes the carboxylation of propionyl-CoA to *D*-methylmalonyl-CoA in the catabolism of odd-chain fatty acids and the amino acids isoleucine, valine, threonine and methionine. In addition to mild to severe ketoacidosis patients may have hyperammonemia, hyperglycinemia/uria, mild to moderate elevation of lactate, low free and total carnitine, high levels of plasma odd-chain fatty acids. Typically the urine organic acid profile consists of elevations in 3-hydroxypropionate, methylcitrate, propionylglycine, and tiglyglycine. *PCCA* is located on chromosome 13q32 and has 24 exons. *PCCB* is on chromosome 3q13.3-q22 and has 15 exons. Heterozygotes are not reliably detected by fibroblast enzyme assay alone. The worldwide incidence of PA is estimated at approximately 1 in 50,000; however, the incidence appears to be much higher in specific populations due to founder effects and genetic drift.[1]

Inheritance:
Autosomal Recessive

Test Methods:
Variant analysis of the *PCCA* and *PCCB* genes is performed on genomic DNA from the submitted specimen by bi-directional sequence analysis of coding exons and the corresponding intron/exon boundaries. If clinically indicated, for patients who have a single variant identified after full sequencing of both the *PCCA* and *PCCB* genes, GeneDx will perform reflex deletion/duplication testing (ExonArrayDx) at no additional charge. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. Testing of *PCCB* followed by *PCCA* may be ordered sequentially, or the genes may be sequenced simultaneously if a more rapid turnaround time is needed. If biochemical or complementation

studies have determined which subunit is defective, sequencing of that gene alone may be ordered.

Test Sensitivity:

In two separate studies of patients with PA from diverse ethnic backgrounds, sequencing was able to identify 100% (40/40) of variant alleles in *PCCB* and 92-95% of variant alleles in *PCCA*.[6,7] In a recent study, sequence analysis of the *PCCA* and *PCCB* genes in a cohort of patients with PA from Indian background detected variants in 100% (50/50) of variant alleles (Gupta et al., 2016). The method employed by GeneDx is expected to identify >99% of variants that are detectable by sequencing.

Variant spectrum:

Missense, nonsense and splicing variants and small insertions or deletions have been identified in *PCCA* and *PCCB*. In one study of 66 patients with PA, large deletions were detected on 21% of *PCCA* alleles of patients with no variant identified by sequencing on one or both alleles.[8] Genotype-phenotype correlations have been reported. Three variants in the *PCCA* gene and three variants in the *PCCB* gene account for 56% and 70%, respectively, of mutant alleles in Japanese patients. Among the Inuit population in Greenland, the A513_R514insP variant is common, with a carrier frequency of 5%.[1,5,6]

References:

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