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 affected individuals have only exhibited neurologic signs. Individuals with late-onset disease have been reported to have a milder course, and variable presentations, including isolated-dilated cardiomyopathy, have been reported. [1-4]

Inheritance Pattern

Autosomal Recessive

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, affected individuals may have hyperammonemia, hyperglycinemia/uria, mild to moderate elevation of lactate, low free and total carnitine and 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. Molecular analysis by gene sequencing and deletion/duplication testing is the preferred method to diagnose PA. However, in some cases measurement of reduced activity of the PCC enzyme in lymphocytes or fibroblasts may be useful. Enzyme activity cannot reliably identify heterozygotes. 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]

Test Methods

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the PCCA and/or PCCB genes are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Variant spectrum

Missense, nonsense and splicing variants and small insertions or deletions have been identified in *PCCA* and *PCCB*. In one cohort, 20% of individuals with PCCA molecular analysis were found to have a large deletion on one allele that was not detectable by standard sequencing. [7] A recent study demonstrated correlation of enzyme activity with disease severity for many variants, however exceptions were noted.[8] Three variants in the *PCCA* gene and three variants in the *PCCB* gene account for 56% and 70%, respectively, of mutant alleles in individuals of Japanese descent. Among the Inuit population in Greenland, the A513_R514insP variant is common, with a carrier frequency of 5%.[1,5,6] The G142D variant in PCCA has been reported as a likely founder pathogenic variant associated with a severe phenotype in Saudi Arabian population.[9]

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