PC Gene Analysis in Pyruvate Carboxylase Deficiency

Clinical Features:
Pyruvate carboxylase (PC) deficiency is a rare inborn error of metabolism. Three clinical presentations have been reported. An infantile form (Type A) is characterized by onset between two and five months of age with lactic acidemia and delayed mental and motor development, failure to thrive, pyramidal tract signs, ataxia, nystagmus, convulsions and often death in infancy or early childhood. This form has been seen primarily in North American Indians. A neonatal form (Type B), first described in France though occurring worldwide, is characterized by severe lactic acidosis, anorexia, lethargy, hypotonia, hepatomegaly, convulsions, pyramidal tract signs, and severely delayed psychomotor development with the majority of infants dying within the first three months of life. The intermittent or benign form (Type C) has only been reported in a few cases, and is characterized by normal or mildly delayed neurological development and episodes of metabolic acidosis. Intermediate cases of moderate-severe PC deficiency have also been described that do not fit into one of these three categories, including cases of somatic mosaicism.[1,3] PC deficiency is reported to have an approximate incidence in most populations of 1 in 250,000 births.[1] In native North American Ojibwa, Cree, and Micmac tribes of the Algonquin-speaking peoples, the carrier frequency may be as high as 1 in 10.[1]

Genetics:
PC deficiency is caused by pathogenic variants in the *PC* gene that encodes the pyruvate carboxylase enzyme: a biotin dependent enzyme located in the mitochondria which catalyzes the ATP-dependent carboxylation of pyruvate to oxaloacetate. The enzyme plays a key role in intermediary metabolism being involved in gluconeogenesis, lipogenesis, the biosynthesis of neurotransmitters and the replenishment of Krebs cycle intermediates. The PC enzyme is expressed in a tissue specific manner, with highest activity in liver, kidney, adipose tissue, pancreas and lactating mammary gland. The diagnosis of PC deficiency involves enzymatic assay, which usually shows a residual activity of less than 5% of normal PC activity in cultured fibroblasts. The level of residual enzyme activity is not correlated with the severity of the phenotype.[2] The *PC* gene is located on chromosome 11q13.4-q13.5 and has 20 coding exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *PC* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If full sequencing identifies a variant on only one allele of the *PC* gene, and if

clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. 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.

Test Sensitivity:

In three small studies of patients with PC deficiency, variants were identified on all the *PC* alleles (56/56 alleles).[2,3,4] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

At this time, more than 20 variants have been described in the *PC* gene including missense, splicing, and small deletions and insertions. A c.1828 G>A (p.A610T) variant has been identified in 13 affected patients of native North American Ojibwa and Cree tribes.[4] Genotype-phenotype correlations have been reported, in that patients with the Type A infantile-onset form of PC deficiency harbor missense variants, whereas patients with the more severe neonatal form (Type B) are more likely to harbor at least one truncating variant.[2] However, the genotype-phenotype correlations can be complicated by somatic mosaicism.[3]

References:

1. Carbone et al., (2002) Hum Mutat 20:48-56 (PMID: 12112657).
2. Monnot et al., (2009) Hum Mutat 30: 734-740 (PMID: 19306334).
3. Wang et al., (2008) Mol Genet Metab 95:31-38 (PMID: 18676167).
4. Carbone et al., (1998) Am J Hum Genet 62:1312-1319 (PMID: 9585612).