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.¹,² 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

**Inheritance Pattern/Genetics:**
Autosomal Recessive

PC deficiency is caused by pathogenic variants in the PC gene that encodes the pyruvate carboxylase (PC) enzyme: a biotin dependent enzyme, located in the mitochondria, that 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. PC 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.

**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).²³⁴

References: