**PDHB Gene Analysis in Pyruvate Dehydrogenase E1-Beta Deficiency**

**Clinical Features:**
Pyruvate dehydrogenase (PDH) deficiency is a highly heterogeneous disorder that is one of the major causes of severe primary lactic acidosis in the newborn period and infancy. It can also present as a more chronic neurodegenerative disease with extensive cerebral atrophy and structural anomalies in the brain, as Leigh syndrome or as episodic ataxia. Antenatally, neurodevelopmental lesions, and craniofacial dysmorphisms may be present. The majority of cases of PDH deficiency (~60% to >80%) are due to pathogenic variants in the PDHA1 gene that encodes the pyruvate dehydrogenase E1 α-subunit (see separate information sheet for details on PDHA1 gene analysis). A very rare cause of PDH deficiency is due to variants in the PDHB gene, that encodes the E1-beta subunit of pyruvate dehydrogenase. Features of PDH deficiency due to variants in the PDHB gene are similar to those seen in individuals with PDHA1 deficiency except that ataxia appears to be more frequent in PDHA1 cases. Consanguinity is more common in the families with PDHB gene variants.

**Genetics:**
Pyruvate dehydrogenase (PDH) is a multienzyme complex located in the mitochondrial matrix that catalyzes the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA. The PDH complex is comprised of three catalytic components: pyruvate dehydrogenase (E1), dihydrolipoamide acetyltransferase (E2) and dihydrolipoamide dehydrogenase (E3), and two regulatory components: E1-kinase and phospho E1-phosphatase, together with a sixth component, E3-binding protein. The E1 enzyme is a heterotetramer of two α subunits and two β subunits. The PDHB gene encodes the β-subunit of the E1 enzyme. PDHB is located on chromosome 3p14.3 and has 10 exons.

**Inheritance:**
Autosomal Recessive

**Test Methods:**
Variant analysis of the PDHB gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the PDHB 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:
There have been only a few reports of patients with PDH deficiency due to pathogenic varinats in the PDHB gene. In two large studies, 11 out of a total of 165 patients had PDH deficiency due to variants in the PDHB gene.²,³ The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:
At this time, fewer than 20 variants in the PDHB gene have been reported. Variants include missense and splice-site.⁴ The p.Met101Val variant has been identified as a founder mutation in patients of North-African descent.³

References: