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.[1,2] Antenatally, neurodevelopmental lesions, and craniofacial dysmorphisms may be present.[5] 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).[1,2] 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.[2]

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:

1. Brown et al. (2006) Dev Med Child Neurol 48 (9):756-60 (PMID: 16904023)
2. Okajima et al. (2008) Mol. Genet. Metab. 93 (4):371-80 (PMID: 18164639)
3. Imbard et al. (2011) Molecular Genetics And Metabolism 104 (4):507-16 (PMID: 21914562)
4. Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)
5. Pirot et al. (2016) J. Neuropathol. Exp. Neurol. 75 (3):227-38 (PMID: 26865159)