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 βsubunit of the E1 enzyme. *PDHB* is located on chromosome 3p14.3 and has 10 exons.

INHERITANCE

Autosomal Recessive

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the PDHB gene 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.

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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)

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