PDHA1 Gene Analysis in Pyruvate Dehydrogenase E1-Alpha Deficiency

CLINICAL FEATURES

Pyruvate dehydrogenase complex (PDHc) deficiency is an inborn error of mitochondrial energy metabolism. Defects in the PDH complex are an important cause of primary lactic acidosis. Pyruvate dehydrogenase complex is a multienzyme complex comprised of multiple subunits each encoded by different genes. Mutations in any of the genes of this complex can cause a similar phenotype. Mutations in the *PDHA1* gene cause pyruvate dehydrogenase L-1 alpha deficiency that is the most common cause of PDHc deficiency and is the only gene that causes X-linked PDHc deficiency. The phenotype of patients with PDHA1 deficiency include an early neonatal presentation with severe lactic acidosis, encephalopathy and early death, and a progressive disease course with neurological complications including hypotonia, seizures, episodic dystonia, or intermittent ataxia. [1] Recurrent acute proximal muscle weakness of upper and lower extremities was also reported as the presenting feature in one affected individual. [9] Reported craniofacial features include microcephaly, hypertelorism, a long narrow prominent forehead, broad nasal bridge, long philtrum, thin lips, sparse eyelashes, and cranial asymmetry. [1] Small hands and feet, short inferior limbs, and hypospadias have also been described.[1] Antenatally, corpus callosum, brain stem hypoplasia and cystic lesions, migration abnormalities, and craniofacial dysmorphism, may be present; [2] in one case, fetal akinesia deformation sequence was reported. [3]

Equal numbers of affected males and females have been identified.[1] Males typically present with severe neonatal lactic acidosis while the presentation in females is more variable, dependent upon the pattern of X-inactivation.[1,11] Females have been reported with a severe phenotype that included microcephaly, spastic quadriplegia, severe epilepsy, and cortical/subcortical atrophy.[1]

GENETICS

The PDHc is located in the mitochondrial matrix and catalyzes the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA. The majority (>80%) of cases of PDHc deficiency result from pathogenic variants in the E1α subunit that is encoded by the *PDHA1* gene.[4] Biochemically, patients with a PDHc deficiency have elevated lactate and pyruvate levels in blood and cerebrospinal fluid, with normal or low lactate to pyruvate ratio. Measurement of enzyme activity in cultured skin fibroblasts or muscle is not always unequivocal because some affected males have a high residual PDHc activity and females may have normal levels of enzyme activity in fibroblasts.[1] The *PDHA1* gene is located on chromosome Xp22.1 and has 11 exons

INHERITANCE PATTERN

X-linked

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *PDHA1* 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.

VARIANT SPECTRUM

To date, almost 200 variants including missense, nonsense, splicing, small deletions/insertions, and large deletions have been described in the *PDHA1* gene.[6] In one review three recurrent variants R72C, R263G and R378H were reported that had been identified in affected males.[7] Variants that completely abolish PDHc activity in fibroblasts are generally not found in males, and are likely due to somatic mosacism or variations in activity between tissues. [7] Somatic mosaicism for a *PDHA1* variant has been described in affected males and females.[1,8,10] It has been estimated that 5%-25% of mothers of patients with *PDHA1* variants are carriers.[1,5,7]

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