

## *PDHA1* Gene Analysis in Pyruvate Dehydrogenase E1-Alpha Deficiency

### **Clinical Features:**

Pyruvate dehydrogenase complex (PDHc) deficiency is an X-linked inborn error of mitochondrial energy metabolism. Defects in the PDH complex are an important cause of primary lactic acidosis. The phenotype of patients with a PDH complex deficiency include an early neonatal presentation with severe lactic acidosis and early death, a progressive disease with mental retardation and neurological complications, or intermittent ataxia.<sup>1</sup> Recurrent acute proximal muscle weakness of upper and lower extremities has also been reported as the presenting feature in one affected individual.<sup>9</sup> Dysmorphic features including hypertelorism, a long narrow prominent forehead, long philtrum, thin lips, sparse eyelashes, cranial asymmetry, small hands and feet, short inferior limbs, and hypospadias have also been described.<sup>1</sup> Antenatally, neurodevelopmental lesions, craniofacial dysmorphisms, and fetal akinesia deformation sequence/ arthrogryposis multiplex congenita may be present.<sup>2,3</sup>

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

### **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 E1 $\alpha$  subunit that is encoded by the *PDHA1* gene.<sup>4</sup> 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.<sup>1</sup> The *PDHA1* gene is located on chromosome Xp22.1 and has 11 exons.

### **Inheritance Pattern:**

X-linked

## Test Methods:

Variant analysis of the *PDHA1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. In addition, if no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available for females to evaluate for a deletion or 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 38 patients with biochemically demonstrated PDHc deficiency or abnormal pyruvate oxidation studies, a variant in the *PDHA1* gene was identified in 19.<sup>1</sup> Thirty-two patients from this group showed specific deficiency of the PDH-E1 component in muscle and/or fibroblasts and of these 32 individuals a variant in *PDHA1* was identified in 17 (53%)<sup>1</sup>. In a second study of 82 PDHc deficient patients, a variant in the *PDHA1* gene was identified in 65.<sup>5</sup> Of these 65 patients, 3 (4.6%) females harbored a large deletion involving *PDHA1*.<sup>5</sup> The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

## Variant Spectrum:

To date, almost 200 variants including missense, nonsense, splicing, small deletions/insertions, and large deletions have been described in the *PDHA1* gene.<sup>6</sup> In one study, three recurrent variants R72C, R263G and R378H were identified in affected males.<sup>7</sup> Variants that completely abolish PDHc activity are not found in males, likely because they are not compatible with survival.<sup>7</sup> However, males have been reported to be mosaic for null variants. It has been reported that 5%-25% of the mothers of patients with *PDHA1* variants were carriers.<sup>1,5,7</sup> Somatic mosaicism for a *PDHA1* variant has been described in affected individuals.<sup>1,8,10</sup>

## References:

1. Quintana et al. (2010) *Clinical Genetics* 77 (5):474-82 (PMID: 20002461)
2. Pirot et al. (2016) *J. Neuropathol. Exp. Neurol.* 75 (3):227-38 (PMID: 26865159)
3. Winters et al. (2017) *Eur. J. Paediatr. Neurol.* 21 (5):745-753 (PMID: 28495245)
4. Brown et al. (2006) *Dev Med Child Neurol* 48 (9):756-60 (PMID: 16904023)
5. Imbard et al. (2011) *Molecular Genetics And Metabolism* 104 (4):507-16 (PMID: 21914562)
6. Stenson et al. (2014) *Human Genetics* 133 (1):1-9 (PMID: 24077912)
7. Lissens et al. (2000) *Human Mutation* 15 (3):209-19 (PMID: 10679936)
8. Ridout et al. (2008) *Hum. Genet.* 124 (2):187-93 (PMID: 18709504)
9. Kara et al. (2017) *Neuromuscul. Disord.* 27 (1):94-97 (PMID: 27894792)
10. Qin et al. (2016) *J Mol Diagn* 18 (3):446-53 (PMID: 26944031)