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

**Mendelian Inheritance in Man Numbers:** 312170 – Pyruvate dehydrogenase deficiency; 300502 – PDHA1

**Clinical features:**
Pyruvate dehydrogenase complex (PDHc) deficiency due to mutations in the PDHA1 gene is an X-linked inborn error of mitochondrial energy metabolism. Defects in the PDH complex are an important cause of primary lactic acidosis, and clinical symptoms of patients with a PDH complex deficiency vary considerably, ranging from intermittent ataxia to a progressive disease with mental retardation and neurological complications to an early neonatal presentation with severe lactic acidosis and early death. Dysmorphic features including hypertelorism, a long narrow prominent forehead, long philtrum, thin lips, scarce eyelashes, cranial asymmetry, small hands and feet; short inferior limbs and hypospadias have also been described.\(^1\) 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 and is 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.\(^1\)

**Inheritance pattern:** X-linked

**Genetics and biochemical features:**
The PDHc is located in the mitochondrial matrix and catalyzes the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA. The majority (>80%) of PDHc deficiencies result from mutations in the E1\(\alpha\) subunit that is encoded by the PDHA1 gene.\(^2\) 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.

**Reasons for referral:**
1. Confirmation of biochemical diagnosis
2. Carrier testing
3. Genetic counseling
4. Prenatal diagnosis in at risk pregnancies

**Test method:**
Mutation 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 mutation 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. Mutations 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 mutation in the PDHA1 gene was identified in 19.\(^1\) 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 mutation in PDHA1 was identified in 17 (53%)\(^1\). In a second study of 82 PDHc deficient patients, a mutation in the
PDHA1 gene was identified in 65. Of these 65 patients, 3 (4.6%) females harbored a large deletion involving PDHA1.

**Mutation spectrum:**
To date, over 100 mutations including missense, nonsense, splicing, small deletions/insertions, and large deletions have been described in the PDHA1 gene. Mutations that completely abolish PDHc activity are not found in males, probably because they are not compatible with survival. However, null mutations can be tolerated in males who are mosaic. In one study, three recurrent mutations R72C, R263G and R378H were identified in affected males. In patients with PDHA1 mutations, it has been reported that 5%-25% of the mothers were found to be carriers. Somatic mosaicism for a PDHA1 mutation has also been described in affected individuals.

**Specimen Requirements and Shipping/Handling:**
- **Blood:** A single tube with 1-5 mL whole blood in EDTA (1-2mL for infants). Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for one week prior to shipping.
- **Buccal Brushes:** CANNOT be accepted for this test
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the PDHA1 gene, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Pyruvate dehydrogenase E1-alpha deficiency” page on our website: [www.genedx.com](http://www.genedx.com)

**Required Forms:**
- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions