PDHA1, PDHB Gene Analysis in Pyruvate Dehydrogenase Deficiency

Mendelian Inheritance in Man Numbers: 312170 – Pyruvate dehydrogenase deficiency; 300502 – PDHA1, PDHB gene

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 Features of PDH deficiency due to mutations in the PDHB gene, that encodes the E1 beta-subunit of pyruvate dehydrogenase, are similar to those seen in patients with PDHA1 mutations except that ataxia appears to be more frequent in PDHA1 cases. Consanguinity is more common in the families with PDHB gene mutations.

Inheritance pattern: PDHA1: X-linked, PDHB: Autosomal Recessive

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 E1α 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 and PDHB genes 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.\textsuperscript{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%)\textsuperscript{1}. There have been only a few reports of patients with PDH deficiency with mutations in the PDHB gene. In one study of 83 patients with PDH deficiency diagnosed by low E1 activity with normal E2 and E3 activities, PDHB mutations were identified in 4 patients.\textsuperscript{5}

**Mutation spectrum:**
To date, over 100 mutations including missense, nonsense, splicing, small deletions/insertions, and large deletions/insertions 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.\textsuperscript{3} Three recurrent mutations at codons R72, R263 and R378 account for half of the mutations identified in affected males, while affected females most commonly are found with insertion/deletion mutations.\textsuperscript{3} In patients with PDHA1 mutations, it has been reported that 5%-25% of the mothers were found to be carriers.\textsuperscript{1,3} Somatic mosaicism for a PDHA1 mutation has also been described in affected individuals.\textsuperscript{1,4} At this time, seven missense mutations in the PDHB gene have been reported: Each mutation has been found in only a single family.\textsuperscript{5,6}

**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:** 10 mL amniotic fluid, 5 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

**Required Forms:**
Sample Submission (Requisition) Form – complete all pages

**Prices and Turn-Around Time - Fees are subject to change without notice:**
Test# 533 PDHA1, PDHB Sequencing $ Inquire Approx. 4 weeks

**CPT codes for mutation detection in a new patient - All codes and units apply:**

- #533 PDHA1, PDHB Sequencing
  - 83891 x 1 unit
  - 83892 x 1 unit
  - 83894 x 22 units
  - 83900 x 1 unit
  - 83901 x 19 unit
  - 83904 x 42 units
  - 83912 x 1 unit
  - 84311 x 1 unit

**TOTAL** Please Inquire

**ICD9 codes that might apply to new patients having this diagnostic test:**
277.87 Disorder of mitochondrial metabolism, 276.2 Lactic acidosis, 330.8 Leigh syndrome

**References:**