Pyruvate Dehydrogenase Deficiency: *PDHA1* Gene Deletion/Duplication

**Test Code:** YO  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81405 x1

### Condition Description

Mutation in the E1-alpha subunit gene *PDHA1* (Xp22.2-p22.1) of the pyruvate dehydrogenase complex (PDH) is one of the most common causes of primary lactic acidosis in children. The clinical spectrum of PDH deficiency is broad, ranging from fatal lactic acidosis in the newborn to chronic neurologic dysfunction with structural abnormalities in the CNS without systemic acidosis.

In general, there are two major presentations of PDH deficiency, metabolic and neurologic, which occur at equal frequency. The metabolic form presents as severe lactic acidosis in the newborn period, usually leading to death. Patients with the neurologic presentation are hypotonic and lethargic, and develop seizures, mental retardation, and spasticity. They often have structural abnormalities in the central nervous system with minimal or absent metabolic abnormalities. Between these two extremes, there is a continuous spectrum of intermediate forms characterized by intermittent episodes of lactic acidosis associated with cerebellar ataxia. Many patients fit into the category of Leigh syndrome.

A high proportion of heterozygous females manifest severe symptoms, although they may also be unaffected. Affected females may have severe developmental delay from an early age, agenesis of the corpus callosum, cortical atrophy, microcephaly, and spastic quadriplegia. The severity of the deficiency in affected females largely depends on the pattern of X inactivation in the brain. There are considerable difficulties in establishing the diagnosis in females based on measurements of enzyme activity and immunoreactive protein.

The sex ratio of PDH E1-alpha deficiency appears to be approximately 1:1, but most mutations identified in males have been missense mutations while most mutations found in females have been deletions or insertions. One study showed that in the parents of the affected patients, the mutation was never present in the somatic cells of the father; in 63 mothers studied, 16 (25%) were carriers. In four families, the origin of the mutation was determined to be twice paternal and twice maternal.

PDH deficiency can also be caused by mutation in other subunits of the PDH complex, including a form caused by mutation in the E3 gene (*DLD*) which is also associated with a variant form of maple syrup urine disease (MSUD).  

Click here for the OMIM summary on this condition.

### Genes

*PDHA1*

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of pyruvate dehydrogenase deficiency in individuals who have tested negative for sequence analysis  
- Carrier testing in adult females with a family history of pyruvate dehydrogenase deficiency who have tested negative for sequence analysis

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.
Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequencing analysis of the *PDHA1* gene is available (YN) and is required before deletion/duplication analysis.
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- Prenatal testing is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.