**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).

For patients with suspected pyruvate dehydrogenase deficiency, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

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
- Carrier testing in adult females with a family history of pyruvate dehydrogenase deficiency

**Methodology**

PCR amplification of 11 exons contained in the PDHA1 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.
Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

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

- Deletion/duplication analysis of the PDHA1 gene by CGH array is available for those individuals in whom sequence analysis is negative (YO).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- **Custom diagnostic mutation analysis (KM)** is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- 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.