Hyperinsulinemic Hypoglycemia: HADH Gene Sequencing

Test Code: SHADH  
Turnaround time: 4 weeks  
CPT Codes: 81479 x1

Condition Description

Congenital hyperinsulinemic hypoglycemia (HH) is a major cause of hypoglycemic brain injury and mental retardation and is caused by unregulated insulin secretion by pancreatic beta-cells. Neonatal-onset disease manifests within hours to 1-2 days after birth. Childhood-onset disease manifests during the first months or years of life. In the newborn period, presenting symptoms may be nonspecific, including seizures, hypotonia, poor feeding, and apnea. In severe cases, serum glucose concentrations are typically extremely low and thus easily recognized, whereas in milder cases, variable and mild hypoglycemia may make the diagnosis more difficult. Even within the same family, disease manifestations can range from mild to severe. Both sporadic and familial forms of congenital HH are known; the sporadic form has an incidence of 1 in 40-50,000 live births while the familial form has an incidence of 1 in 2500 in communities with high rates of consanguinity.

Mutations in seven genes involved in regulation of insulin secretion are responsible for about 50-60% of known cases of congenital HH. Loss-of-function mutations in the HADH gene (4q22-q26) can lead to relatively mild late onset intermittent HH or to severe neonatal hypoglycemia. Elevated urine 3-hydroxyglutaric acid and serum 3-hydroxybutyryl-carnitine have been shown to be diagnostically useful markers for HH due to HADH deficiency. HH caused by mutations in the HADH gene is inherited in an autosomal recessive manner.

The enzyme encoded by the HADH gene had been previously referred to as 'SCHAD.' Accordingly, some cases of human metabolic disorders previously reported as 'SCHAD deficiency' are in fact cases of 'HADH deficiency.'

This test includes only HADH gene sequencing, and does not include analysis of other genes associated with hyperinsulinemic hypoglycemia.

For patients with suspected HH, 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.

References:

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of HH in individuals with elevated urine 3-hydroxyglutaric acid and serum 3-hydroxybutyryl-carnitine
- Carrier testing in adults with a family history of HH with elevated urine 3-hydroxyglutaric acid and serum 3-hydroxybutyryl-carnitine

Methodology

PCR amplification of 8 exons contained in the HADH 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

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* 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\textsuperscript{TM} 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 \textit{HADH} gene by CGH array is available for those individuals in whom sequence analysis is negative.
- \textit{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 couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.