Hyperinsulinemic Hypoglycemia: HADH Gene Deletion/Duplication

**Test Code:** DHADH  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 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:**

### Genes

HADH

### 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 who have tested negative for sequence analysis
- Carrier testing in adults who have a family history of HH with elevated urine 3-hydroxyglutaric acid and serum 3-hydroxybutyryl-carnitine and 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

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) or ACD (yellow 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 Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Sequence analysis of the \textit{HADH} gene is available and is required before deletion/duplication 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.