Glutaric Aciduria Type I (GA-I): GCDH Gene Sequencing

Condition Description

Glutaric aciduria type I (GA-I) is an autosomal recessive inborn error of lysine, hydroxyllysine, and tryptophan metabolism caused by deficiency of the enzyme glutaryl-CoA dehydrogenase [1]. Frequent laboratory findings include hypoglycemia, ketonuria, and metabolic acidosis. Urinary 3-hydroxyglutaric acid is the diagnostic metabolite with glutaric acid and glutarylcarnitine frequently but not always elevated [2]. The buildup of metabolites may lead to basal ganglia injury.

The clinical manifestations of GA-1 can vary considerably between individual patients, but most have macrocephaly at birth or shortly thereafter. Affected individuals may experience motor difficulty, abnormal gait, spasms, jerking, rigidity, hypotonia, and seizures. Some individuals with glutaric acidemia have developed subdural or retinal hemorrhage. MRI or CT of the brain may show an underdeveloped neocortex with fronto-operculo-temporal hypoplasia and communicating hydrocephalus, creating a distinct radiologic appearance that characterizes GA-I. The presentation of distinctive acute striatal necrosis is a major cause of morbidity and mortality. Acute neurological deterioration usually occurs between 6 and 18 months of age and can be triggered by a febrile illness or dehydration.

GA-1 is caused by mutations in the glutaryl-CoA dehydrogenase gene (GCDH) located on 19p13 [3]. Gene sequence analysis is available to test for mutations in the GCDH gene (FX). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (NL).

References:

- Tortorelli et al. The urinary excretion of glutarylcarnitine is an informative tool in the biochemical diagnosis of glutaric acidemia type I. Mol Genet Metab 84 (2005) 137-143.

Genes

GCDH

Indications

This test is indicated for:
- Confirmation of a clinical/biochemical diagnosis of GA-I
- Carrier testing in adults with a family history of GA-I

Methodology

PCR amplification of 11 exons contained in the GCDH gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then 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. Large deletions are not detected by this analysis.

Detection

The majority of patients with a clinical and biochemical diagnosis will have an abnormal DNA test.
Clinical Sensitivity: 24/24 mutations identified in 12 patients [4], 38/40 mutations identified in 20 patients [5].
Analytical Sensitivity: ~99%

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype. Prevalence: The incidence of GA-I is estimated to be 1:83,300 [6]. It is inherited in an autosomal recessive manner, therefore the recurrence risk for carrier parents of an affected child is 25%.

Specimen Requirements

Submit only 1 of the following specimen types
Type: DNA, Isolated

Specimen Requirements:
Microtainer
8ug
Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old: 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Special Instructions
Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

Related Tests
- Urine Organic Acid Analysis (OA) showing elevation of glutaric and 3-hydroxyglutaric acids
- Plasma/Urine Acylcarnitine Profile showing increased concentration of glutarylcarnitine.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by sequencing.
- For comprehensive testing, a Deletion/Duplication Assay is available separately. This test is indicated for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- 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.