Glutaric Aciduria Type I (GA-I): GCDH Gene Deletion/Duplication

Condition Description

Glutaric aciduria type I (GA-I) is an autosomal recessive inborn error of lysine, hydroxylysine, 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 fronoto-oculotemporal 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).

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

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.

Detection

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must 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: 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 uncotted cord or cardiac blood

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

**Type: DNA, Isolated**

Specimen Requirements:
Microtainer
3µg
Isolation using the Perkin Elmer™ 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.

**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.
- 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.