

Citrullinemia: ASS1 Gene Sequencing

Test Code: JG

Turnaround time: 4 weeks

CPT Codes: 81479 x1

Condition Description

Citrullinemia type I (CTLN1) is an autosomal recessive disorder resulting from a deficiency of the enzyme argininosuccinate synthase (ASS), the third step in the urea cycle, in which citrulline is condensed with aspartate to form argininosuccinic acid. Laboratory findings include hyperammonemia (ammonia concentration 1000-3000 mol/L in plasma), while analysis of plasma quantitative amino acids shows an absence of argininosuccinic acid and a concentration of citrulline usually greater than 1000 mol/L (normal: <50 mol/L). Argininosuccinate synthase enzyme activity, measured in fibroblasts, liver, and in all tissues in which ASS is expressed, is decreased.

The disease presents as a clinical spectrum that includes an acute neonatal form (the "classic" form), a milder late-onset form, and a form in which women have onset of severe symptoms during pregnancy or postpartum. Individuals remaining asymptomatic up to at least age ten have also been reported. Distinction between the clinical forms is based on clinical findings and is not clear-cut. Classic neonatal-onset citrullinemia type I is suspected in infants who have been on a full protein diet and who present in the first week of life with hyperammonemia, lethargy, refusal to feed, and vomiting. Hyperammonemia may lead to increased intracranial pressure, which can cause increased neuromuscular tone, spasticity, ankle clonus, seizures, loss of consciousness, and death. Children with the severe form who are treated promptly may survive for an indeterminate period of time, but usually with significant neurologic deficits. Milder, adult-onset citrullinemia type I is suspected in individuals with recurrent lethargy, somnolence, mental retardation, and chronic or recurrent hyperammonemia. CTLN1 occurs in 1:57,000 births.

Citrullinemia type I is caused by mutations in the ASS1 gene (9q34.1). Sequencing of the ASS1 gene is recommended after a biochemical diagnosis of CTLN1, and provides a complementary method to confirm the presence of mutations in a proband, identify carriers among the proband's relatives, and provide prenatal diagnosis in families with known mutations.

References:

- [OMIM #215700](#): Citrullinemia, Classic

Genes

[ASS1](#)

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of citrullinemia type I
- Carrier testing in adults with a family history of citrullinemia type I

Methodology

PCR amplification of 16 exons contained in the ASS1 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

Clinical Sensitivity: It is estimated that sequencing will detect 96% of mutations in the ASS1 gene. 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

Type: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

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: 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.

Type: Saliva**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ 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.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample. 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

Plasma amino acid analysis (AA) is used in the diagnosis of a patient with citrullinemia type I.

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (JH).

[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.