Citrullinemia: *ASS1* Gene Deletion/Duplication

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

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. 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.

### Specimen Requirements

Submit only 1 of the following specimen types

* 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™ 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. 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.

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.