Citrullinemia Type I (*ASS1*) Sequencing

DIAGNOSTIC TESTING FOR CITRULLINEMIA TYPE I

Disease Overview

- Citrullinemia type I (CTLN1) is a urea-cycle disorder resulting from a deficiency of the enzyme argininosuccinate synthase 1 (ASS1), caused by mutations in the *ASS1* gene. The enzyme ASS1 catalyzes the conversion of citrulline and aspartate to argininosuccinate in the third step of the urea cycle. The urea cycle is the body's primary system for removing waste nitrogen produced from the metabolism of protein and other nitrogen-containing molecules. Defects in the urea cycle can lead to life-threatening accumulations of ammonia.
- Most patients present with a severe neonatal form. Infants generally appear normal at birth, then at 1–2 days of age develop symptoms of hyperammonemia that include vomiting, lethargy, failure to thrive, seizures, stroke, hypertonia, increased intracranial pressure, and, ultimately, coma. Without prompt treatment, CTLN1 is fatal.
- Other patients may exhibit symptoms later in life. Late-onset CTLN1 symptoms tend to be more subtle and can include intense headache, scotomas, migraine-like episodes, cyclic vomiting, hepatomegaly, liver failure, ataxia, slurred speech, lethargy, and somnolence.
- A diagnosis of CTLN1 is suspected in the presence of abnormal newborn-screen test results that include elevated plasma ammonia concentration and elevated plasma citrulline concentration.
- Molecular testing is helpful when the phenotype is unclear, when biochemical values are borderline, or to distinguish citrullinemia type 1 from citrullinemia type II (citrin deficiency due to mutations in the *SLC25A13* gene).
- Treatment of CTLN1 includes a protein-restricted diet, arginine supplements, and sodium phenylbutyrate scavenger therapy. Regular patient attendance at a metabolic clinic is essential for proper management of the condition.
- Acute hyperammonemia requires administration of IV fluids containing calories as sugars and fats, careful management of fluids and electrolytes to avoid hyponatremia and brain edema, administration of IV scavenger drugs (sodium phenylacetate and sodium benzoate), and, in many cases, emergency use of hemodialysis to reduce the plasma ammonia concentration.

Epidemiology

Incidence in the United States is approximately 1/57,000 births.

Genetics

- Autosomal recessive inheritance
- *ASS1* is the only gene associated with CTNL1. The majority of causative mutations in the gene are sequence variants, but large deletions have been reported.

Indications for Ordering

- Abnormal newborn-screen test results suggestive of CTNL1
- Diagnostic testing for individuals with clinical and/or biochemical evidence of CTNL1
- Carrier testing for the reproductive partner of an individual affected with, or known to be a carrier of, CTNL1

Additional Ordering Notes

If there is a family history of CTNL1 and the specific familial mutations have already been identified, testing can be performed on at-risk family members by contacting one of ARUP's genetic counselors and requesting targeted sequencing for the familial mutation.

Interpretation

- The detection of two pathogenic *ASS1* gene mutations on opposite chromosomes predicts CTNL1.
- When one pathogenic *ASS1* gene mutation is detected in a clinically unaffected individual, the patient is predicted to be at least a carrier of CTNL1. If the patient is clinically affected, an undetected mutation may be present on the opposite chromosome.
- When no pathogenic mutations are detected by sequencing, the possibility is reduced that the individual is a carrier of or affected with CTNL1. Medical management of the patient should rely on clinical and biochemical findings.
- Variations of unknown clinical significance in the *ASS1* gene may be detected by this assay.
- Clinical sensitivity may be as high as 95%.
- Analytical sensitivity and specificity are 99%.

Methodology

PCR followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *ASS1* gene

Limitations

- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Regulatory-region mutations, large deletions and duplications, and deep intronic mutations will not be detected.
- Genes other than *ASS1* that are associated with urea-cycle disorders will not be evaluated.

Related Tests

- Amino Acids Quantitative, Plasma (0080710)
- Organic Acids, Urine (0098389)
- Orotic Acid and Orotidine, Urine (0092458)
- Citrin Deficiency (*SLC25A13*) Sequencing (2006261)
- Familial Mutation, Targeted Sequencing (2001961)

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References

1. Thoene JG. Citrullinemia Type I. 2004 (Updated 2011). In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997–2012. Available at genetests.org. Accessed June 4, 2012.
2. Engel K, et al. Mutations and polymorphisms in the human argininosuccinate synthetase (ASS1) gene. *Hum Mut*. 2009;30:300–307.

Test Information

2007069 Citrullinemia Type I (*ASS1*) Sequencing

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.
For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

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