# *ASS1* Gene Analysis in Classic Citrullinemia

**Clinical Features:**
Classic citrullinemia (CTLN1) is a disorder of the urea cycle characterized by neonatal or intermittent onset of hyperammonemia caused by a deficiency of the enzyme argininosuccinate synthetase. An acute neonatal form is the most common. Infants are normal at birth followed by an acute illness characterized by hyperammonemia, anorexia, vomiting, lethargy, and hepatomegaly in some cases, increased intracranial pressure, seizures and coma. A later onset presentation is less frequent and may be similar to or milder than the neonatal form and present with feeding difficulties, vomiting, episodic hyperammonemia, lethargy, seizures and cerebral atrophy on CT scans or MRI. CTLN1 has been diagnosed in adult women who developed severe symptoms such as psychosis during pregnancy or postpartum.[1] Another late onset form, common in Japan, has been reported in individuals as late as 20 years of age with milder presentation including slurred speech, irritability and insomnia as presenting signs. Asymptomatic individuals have also been described.

**Genetics:**
CTLN1 is caused by variants in the *ASS1* gene that encodes argininosuccinate synthetase, the third enzyme of the urea cycle catalyzing the formation of argininosuccinic acid from citrulline and aspartic acid. The enzyme is widely distributed in tissues including liver and fibroblasts. Enzyme deficiency leads to hyperammonemia, low serum arginine and elevated serum and urine citrulline. Newborn screening for citrullinemia is available and performed in almost all states using tandem mass spectrometry. The *ASS1* gene is located on chromosome 9q34.1 and has 16 exons. The incidence of CTLN1 is estimated to be 1 in 57,000.[2]

Patients with citrullinemia type II have a secondary deficiency of argininosuccinate synthetase, however, citrullinemia type II is a distinct disorder due to the deficiency of citrin, a glutamate-aspartate transporter localized to the inner mitochondrial membrane. The gene for citrin is *SLC25A13*. This disorder is typically of adult onset, although neonatal and childhood forms have been described.

**Inheritance Pattern:**
Autosomal recessive

**Test Methods:**
Variant analysis of the *ASS1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons (3-16), and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *ASS1* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no

additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test Sensitivity:**

Sequence analysis of the *ASS1* gene in patients with CTLN1, detected 154 of 160 (96%) abnormal alleles.[7] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

**Variant Spectrum:**

*ASS1* variants are mostly private and occur throughout the gene with a somewhat higher concentration of variants in exons 5 and 12-14.[1] Most reported variants are missense variants; splice site, nonsense variants, small deletions, and gross deletions have also been reported in several patients.[4] A single splice site variant (IVS6-2 A>G) accounts for over 50% of mutated alleles in Japanese patients.[5] Some genotype-phenotype correlation has been reported.[1,2,6]

**References:**

1. Gao, et al. (2003) Hum Mutat 22:24-34
2. Haberle, et al. (2002) Hum Genet 110:327-333
3. GeneTests http://www.genetests.org/
4. Human Gene Mutation Database: www.hgmd.cf.ac.uk
5. Kobayashi, et al. (1995) Hum Genet 96:454-463
6. Engel et al. (2009) Hum Mutat 30:300-307
7. Thoene, J. (Updated [Aug 11, 2011]) Citrullinemia Type I. In: GeneReviews at Genetests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2012