SLC25A13 Gene Analysis in Citrin Deficiency

Disorder also known as: Citrullinemia type II (CTLN2); neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD)

Clinical Features:
The two phenotypes of citrin deficiency are citrullinemia type II (CTLN2) and neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). CTLN2 typically presents in adulthood with recurring neuropsychiatric symptoms associated with episodic hyperammonemia, including disorientation, irritability, delusions, delirium, seizures, and coma that can lead to death from brain edema. Onset is sudden usually between the ages of 20-50 and often prompted by medication, alcohol, or surgery. The symptoms of NICCD are milder and present in children under one year of age as transient intrahepatic cholestasis, hypoproteinemia, growth retardation, hypoglycemia, fatty liver, mild liver dysfunction, and/or high levels of plasma alpha-fetoprotein.[1] A few NICCD patients have a severe form of the disorder with liver damage associated with tyrosinemia and require liver transplantation.[2] Most NICCD patients' symptoms disappear by one year of age; however, some NICCD patients later develop CTLN2 with neuropsychiatric symptoms several decades later. Patients with both CTLN2 and NICCD tend to have a preference for protein-rich and lipid-rich foods and avoid sugar-rich and carbohydrate-rich foods. Some individuals with NICCD later develop severe CTLN2. The male to female ratio in CTLN2 is 2.4 to 1, while the ratio in NICCD is roughly equal.[7] Citrin deficiency was once thought to be restricted to Japan where the carrier rate is 1 in 65.[7] However, affected individuals in other countries have now been identified.[3] The carrier rate is also high in the East Asian population: China (1 in 65), Taiwan (1 in 48) and Korea (1 in 112).[3]

Inheritance Pattern:
Autosomal Recessive

Genetics:
The *SLC25A13* gene encodes the citrin protein, which is a calcium-binding mitochondrial solute carrier localized in the inner mitochondrial membrane that functions as a calcium-stimulated aspartate-glutamate carrier. This protein plays a role in various metabolic pathways, including aerobic glycolysis, gluconeogenesis, the urea cycle, and protein and nucleotide synthesis. Patients with CTLN2 and NICCD show hyperammonemia and increases in plasma citrulline, arginine, threonine to serine ratio, and serum pancreatic secretory trypsin inhibitor levels. In CTLN2, decreased hepatic argininosuccinate synthetase activity is also observed, while NICCD patients exhibit multiple aminoacidemias (including citrulline, threonine, methionine, phenylalanine, tyrosine and arginine), galactosemia, hypoproteinemia,

hypoglycemia, cholestasis, fatty liver and elevated plasma alpha-fetoprotein. The *SLC25A13* gene is located on chromosome 7q21.3 and has 18 exons.

Test Methods:

Variant analysis of the *SLC25A13* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *SLC25A13* 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:

In patients with citrin deficiency, variant analysis of the *SLC25A13* gene is expected to identify variants in greater than 95% of patients.[2-6] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

The majority of variants in the *SLC25A13* gene are nonsense, frameshift and splice-site variants.[5] Missense variants and large deletions and duplications have also been reported. Common variants in patients with citrin deficiency have been identified in Asian populations.[8] At this time, genotype-phenotype correlations have not been established.[9]

References:

1. Radha et al. (2018) Gene 668 :190-195 (PMID: 29787821)
2. Lu et al., (2005) J Hum Genet 50:338-346 (PMID: 16059747).
3. Tabata et al., (2008) J Hum Genet 53:534-545 (PMID: 18392553).
4. Kobayashi et al., (1999) Nat Genet 22:159-163 (PMID: 10369257).
5. Ko et al., (2007) Int J Mol Med 20:809-815 (PMID: 17982687).
6. Yamaguchi et al., (2002) Hum Mutat 19:122-130 (PMID: 11793471).
7. Kobayashi, K. (Updated [July 2, 2008]) Citrin Deficiency In: GeneReviews at Genetests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010. Available at http://www.genetests.org.
8. Oh et al. (2017) J. Hum. Genet. 62 (2):305-307 (PMID: 27829683)
9. Yasuda et al., (2000) Hum Genet 107:537-545 (PMID: 11153906).