Citrin Deficiency (*SLC25A13*) Sequencing

Indications for Ordering

- Abnormal newborn screen suggestive of neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD)
- Diagnostic testing for individuals with
  - Clinical and/or biochemical evidence of citrullinemia type II (CTNL2)
  - Failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD) or NICCD
- Carrier testing for the reproductive partner of an individual affected with, or a carrier of, CTNL2 or NICCD
- Useful when
  - Phenotype is unclear
  - Biochemical values are borderline
  - Need to distinguish citrin deficiency from citrullinemia type I (due to variants in *ASS1* gene)

Test Description

Polymerase chain reaction followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *SLC25A13* gene

Tests to Consider

Typical testing strategy

- Biochemical testing
  - Amino Acids Quantitative, Plasma
  - Ammonia, Plasma
  - Galactose-1-Phosphate in Red Blood Cells
  - Orotic Acid and Orotidine, Urine
- Molecular testing
  - Citrin Deficiency (*SLC25A13*) Sequencing

Primary test

Citrin Deficiency (*SLC25A13*) Sequencing 2006261

- Use to confirm a diagnosis of citrullinemia type II (or citrin deficiency) following clinical and/or biochemical findings

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence/prevalence – varies by population

- Asian – 1/65 carrier
- Prevalence in those of Japanese descent
  - CTLN2 phenotype – 1/100,000
  - NICCD phenotype – 1/19,000

Pathophysiology

- Citrin is a mitochondrial aspartate-glutamate carrier in the inner mitochondrial membrane
  - Involved in both the urea cycle and the aspartate/malate NADH shuttle
- Deficiency results in
  - Decreased aspartate transport
  - Decreased ability of enzyme argininosuccinate synthase to produce argininosuccinate
  - Increased NADH:NAD+ ratio
    - Impacts
      - Glycolysis
      - Gluconeogenesis
      - Fatty acid synthesis

Clinical presentation

	NICCD	FTTDCD	CTLN2
Age of onset	**Infancy (<1 year)**	**>1 year-11 years**	**>11 years**
Symptoms	• Transient intrahepatic cholestasis • Symptoms often disappear by age 1 o Some will develop CTNL2 o ~40% have abnormal newborn screen ▪ Galactose ▪ Methionine ▪ Phenylalanine • Growth retardation • Hepatomegaly • Echinocytosis	• Aversion to carbohydrates develops as the child ages • Growth retardation • Fatigue • Pancreatitis • Fatty liver • Hepatoma • Dyslipidemia	• Recurrent episodes of neuropsychiatric symptoms o Loss of memory o Disorientation o Flapping tremor o Aberrant behaviors o Seizures • Fatty liver infiltration • Pancreatitis • Hyperlipidemia • Carbohydrate aversion

	NICCD	FTTDCD	CTLN2
Age of onset	**Infancy (<1 year)**	**>1 year-11 years**	**>11 years**
Provocation of symptoms			• Alcohol/carbohydrate intake • Medication • Surgery
Metabolic derangements	• Hyperammonemia • Elevated o Alpha fetoprotein o Arginine o Bile acids o Bilirubin o Citrulline o Galactose o Methionine o Threonine o Tyrosine • Urine succinylacetone – normal • Hemolytic anemia • Hypoglycemia • Coagulation factor deficiencies • 40% have abnormal newborn screen (elevated galactose and/or citrulline/methionine on second screen)	• Hypoglycemia • Ammonia and citrulline – normal or slightly elevated • Arginine – usually normal • Lactate:pyruvate ratio – elevated	• Hyperammonemia • Elevated o Plasma citrulline o Arginine o Threonine:serine ratio o Pancreatic secretory trypsin inhibitor • Liver-specific argininosuccinate synthetase – deficient

Genetics

Gene – *SLC25A13*

Inheritance – autosomal recessive

Variants

- >50 pathogenic variants identified
- Two variants account for 70% of gene variants in individuals of Japanese descent
  - c.1177+G>A
  - c.851_854del
- No genotype/phenotype correlations

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – >95%
- Analytical sensitivity/specificity – 99%

Results

- Two pathogenic *SLC25A13* gene variants detected
  - Predicts citrin deficiency
- One pathogenic *SLC25A13* gene variant detected
  - Individual is at least a carrier for citrin deficiency
  - If individual is clinically affected, an undetected variant may be present on opposite chromosome
- Lack of gene variant reduces the likelihood of citrin deficiency or carrier state
- Variants of unknown clinical significance may be identified

Limitations

- Diagnostic errors can occur due to rare sequence variants
- Not detected
  - Regulatory region or deep intronic variants
  - Large deletions and/or duplications
- Other genes associated with urea cycle disorders are not evaluated