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

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

### Provocation of symptoms
- • Alcohol/carbohydrate intake
- • Medication
- • Surgery

### Metabolic derangements
<table>
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<th>NICCD</th>
<th>FTTDCD</th>
<th>CTLN2</th>
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</table>
| • 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