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

Clinical presentation

<table>
<thead>
<tr>
<th></th>
<th>NICCD</th>
<th>FTTDCD</th>
<th>CTLN2</th>
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<tbody>
<tr>
<td>Age of onset</td>
<td>Infancy (&lt;1 year)</td>
<td>&gt;1 year-11 years</td>
<td>&gt;11 years</td>
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</tbody>
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| 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
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<td><strong>Age of onset</strong></td>
<td>Infant (&lt;1 year)</td>
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<tr>
<td><strong>Provocation of symptoms</strong></td>
<td>• Hyperammonemia</td>
<td>• Hypoglycemia</td>
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<tr>
<td></td>
<td>• Elevated</td>
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<td></td>
<td>• Alpha fetoprotein</td>
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<td></td>
<td>• Arginine</td>
<td>• Arginine</td>
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<td></td>
<td>• Bile acids</td>
<td>• Bile acids</td>
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<tr>
<td></td>
<td>• Bilirubin</td>
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<tr>
<td></td>
<td>• Citrulline</td>
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<tr>
<td></td>
<td>• Galactose</td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>• Methionine</td>
<td>• Ammonia and citrulline – normal or slightly elevated</td>
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<tr>
<td></td>
<td>• Threonine</td>
<td>• Arginine – usually normal</td>
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<tr>
<td></td>
<td>• Tyrosine</td>
<td>• Lactate:pyruvate ratio – elevated</td>
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<td>• Urine succinylacetone – normal</td>
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<tr>
<td><strong>Metabolic derangements</strong></td>
<td></td>
<td>• Hyperammonemia</td>
</tr>
<tr>
<td></td>
<td>• Hemolytic anemia</td>
<td>• Elevated</td>
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<tr>
<td></td>
<td>• Hypoglycemia</td>
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<tr>
<td></td>
<td>• Coagulation factor deficiencies</td>
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<td></td>
<td>• 40% have abnormal newborn screen (elevated galactose and/or citrulline/methionine on second screen)</td>
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**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