Wilson Disease (ATP7B) Sequencing

Wilson disease (WD) is a rare inherited genetic disorder caused by pathogenic variants in the ATP7B gene, resulting in excessive amounts of copper accumulating in the body, particularly in the liver, brain, and eyes. Signs and symptoms most often appear during the teens but may appear as early as age 6 or as late as the mid-40s. Liver disease is typically the initial feature of Wilson disease in affected children and young adults. Nervous system or psychiatric problems are often the initial features in individuals diagnosed in adulthood, and commonly occur in young adults. For additional details on diagnostic testing for WD, refer to the ARUP Consult Wilson Disease topic and the Wilson Disease Testing Algorithm.

Disease Overview

Symptoms

- Neurologic: clumsiness, tremors, difficulty walking, speech problems
- Psychiatric: impaired thinking, depression, anxiety, mood swings
- Other: Kayser-Fleischer ring, abnormalities in eye movement

Diagnostic Issues

- Affected individuals occasionally have normal biochemical test results
- Up to 20% of WD carriers have equivocal biochemical findings

Genetics

Gene

ATP7B

Inheritance

Autosomal recessive

Penetration

Age dependent, may be reduced

Test Interpretation

Clinical Sensitivity

98%\(^1\)

Analytic Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate(^a) (%)</th>
<th>Analytic Sensitivity (PPA) 95% Credibility Region(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99</td>
<td>96.9-99.4</td>
</tr>
</tbody>
</table>

\(^a\)Gene included on this test is a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants
### Variant Class

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Analytic Sensitivity (PPA) 95% Credibility Region&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
</tr>
<tr>
<td>Deletions 11-44 bp</td>
<td>&gt;99</td>
<td>87.8-100</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
</tr>
<tr>
<td>Insertions 11-23 bp</td>
<td>&gt;99</td>
<td>62.1-100</td>
</tr>
</tbody>
</table>

<sup>a</sup>Gene included on this test is a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

### Results

<table>
<thead>
<tr>
<th>Results as Reported in Patient Chart</th>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Two pathogenic ATP7B gene variants detected on opposite chromosomes</td>
<td>Consistent with a diagnosis of WD</td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic ATP7B variants detected</td>
<td>Significantly reduces the likelihood of being affected with or a carrier of WD</td>
</tr>
<tr>
<td>See note</td>
<td>One pathogenic ATP7B gene variant detected</td>
<td>Individual is at least a carrier of WD and may be affected with WD if an undetected variant is present on the opposite chromosome</td>
</tr>
<tr>
<td></td>
<td>Variants of uncertain clinical significance may be identified</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

### Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated:
  - Regulatory region variants, including the Sardinian founder variant, c.-436_-422del15
  - Deep intronic variants
  - Large deletions/duplications
  - Variants in genes other than ATP7B

### References


### Related Information

- **Wilson Disease**
- **Wilson Disease Testing Algorithm**

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