Familial Transthyretin Amyloidosis (TTR) Sequencing

Familial transthyretin (TTR) amyloidosis is a genetic disorder resulting in amyloid deposits consisting of mutated TTR and characterized by progressive neuropathy.\(^1\) TTR amyloidosis, along with several genetically related disorders, is caused by pathogenic variants in the TTR gene.\(^1\) Genetic testing is indicated to confirm a clinical diagnosis of familial TTR amyloidosis, familial euthyroid hyperthyroxinemia, or wild-type amyloid TTR (ATTR) amyloidosis, and as a predictive test for individuals at risk for TTR amyloidosis.

**Disease Overview**

**Prevalence**
- ~1/100,000 in individuals of northern European descent in the U.S.\(^1\)
- Up to 1/568 in Portuguese\(^1\)

**Typical Age of Onset**
- Between 20-50 years in those of Japanese or Portuguese descent\(^1\)
- Later age of onset for those with Swedish, French, or British ancestry\(^1\)

**Symptoms**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>ATTR Amyloid Neuropathy (Familial Amyloid Polyneuropathy)</th>
<th>ATTR Cardiac Amyloidosis (Familial Amyloid Cardiomyopathy)</th>
<th>ATTR Leptomeningeal Amyloidosis/Cerebral Amyloid Angiopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early signs</td>
<td>Autonomic dysfunction</td>
<td>Angina (\text{pain})</td>
<td>Ataxia</td>
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<td></td>
<td>Carpal tunnel</td>
<td>Arrhythmia</td>
<td>Dementia</td>
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<td>Constipation/diarrhea</td>
<td>Cardiomegaly</td>
<td>Hemorrhage (subarachnoid or intracerebral)</td>
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<tr>
<td></td>
<td>Impotence</td>
<td>Conduction block</td>
<td>Hydrocephalus</td>
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<td></td>
<td>Sensorimotor polyneuropathy of the legs</td>
<td>Congestive heart failure</td>
<td>Psychosis</td>
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<td></td>
<td>Sudden death</td>
<td>Seizures</td>
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<tr>
<td>Late signs</td>
<td>Cardiomyopathy</td>
<td></td>
<td>Spasticity</td>
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<tr>
<td></td>
<td>Nephropathy</td>
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<td></td>
<td>Vitreous opacities</td>
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<td>Glaucoma</td>
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</table>

Source: Sekijima, 2001\(^1\)
Familial Euthyroid Hyperthyroxinemia

- Asymptomatic increase in total serum thyroxine concentration (1-Sekijima)
- Caused by benign TTR variants

Wild-Type ATTR Amyloidosis (Senile Systemic Amyloidosis)

- Typically presents in elderly individuals with carpal tunnel syndrome followed by cardiac symptoms\(^1\)
- Some develop mild peripheral neuropathy
- Results from pathogenic deposition of TTR primarily in the heart but no pathogenic TTR variants are present

Genetics

Gene

*TTR*

Inheritance

Autosomal dominant\(^1\)

Penetrance

Incomplete, but varies greatly among\(^1\):

- Ethnic groups
- Geographic regions
- Variants

Variants

- Gain of function sequence variants account for >99% of pathogenic variants detected\(^1\)
- Missense, nonsense, and splice-site variants may be causative for disease\(^1\)
- Poor phenotype-genotype correlation

Screening Issues

Presymptomatic genetic testing is useful to diagnose familial TTR amyloidosis because early treatment may delay disease progression. However, it should only be performed for at-risk individuals >18 years of age and should be accompanied by genetic counseling.\(^2\)

Test Interpretation

Sensitivity

- Clinical sensitivity: ~99% for familial TTR amyloidosis
- Analytical sensitivity: 99%

Results
<table>
<thead>
<tr>
<th>Result</th>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>One or more pathogenic TTR variant(s)</td>
<td>Confirms a clinical diagnosis of familial TTR amyloidosis</td>
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<tr>
<td></td>
<td>detected</td>
<td></td>
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<tr>
<td>Negative</td>
<td>No pathogenic TTR variants detected</td>
<td>Decreases, but does not exclude, risk of familial TTR amyloidosis</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Variant of unknown significance detected</td>
<td>Diagnosis of familial TTR amyloidosis is uncertain</td>
</tr>
</tbody>
</table>

**Limitations**

- Not detected:
  - Regulatory region or deep intronic variants
  - Large deletions or duplications
- Diagnostic errors can occur due to rare sequence variants

**References**
