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. TTR amyloidosis, along with several genetically related disorders, is caused by pathogenic variants in the TTR gene. 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 Portuguese¹

Typical Age of Onset
- Between 20-50 years in those of Japanese or Portuguese descent¹
- Later age of onset for those with Swedish, French, or British ancestry¹

Symptoms

<table>
<thead>
<tr>
<th>TTR Amyloidosis</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>
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</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Early signs</td>
<td>Autonomic dysfunction</td>
<td>Anginal pain</td>
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<td></td>
<td>Autonomic dysfunction</td>
<td>Carpal tunnel</td>
<td>Arrhythmia</td>
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<tr>
<td></td>
<td>Carpal tunnel</td>
<td>Constipation/diarrhea</td>
<td>Cardiomegaly</td>
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<td>Constipation/diarrhea</td>
<td>Impotence</td>
<td>Conduction block</td>
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<td>Impotence</td>
<td>Sensorimotor polyneuropathy of the legs</td>
<td>Congestive heart failure</td>
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<td>Sensorimotor polyneuropathy of the legs</td>
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<td>Sudden death</td>
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<td>Ataxia</td>
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<td>Dementia</td>
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<td>Hemorrhage (subarachnoid or intracerebral)</td>
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<td>Hydrocephalus</td>
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<td>Psychosis</td>
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<td>Seizures</td>
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<td>Spasticity</td>
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<td>Transient focal neurologic episodes</td>
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</tbody>
</table>

Source: Sekijima, 2001¹

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 symptoms¹
- 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 dominant¹

Related Test
Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing
Useful when a pathogenic familial variant identifiable by sequencing is known
Penetrance
Incomplete, but varies greatly among:
- Ethnic groups
- Geographic regions
- Variants

Variants
- Gain of function sequence variants account for >99% of pathogenic variants detected
- Missense, nonsense, and splice-site variants may be causative for disease
- 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.

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>
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<tbody>
<tr>
<td>Positive</td>
<td>One or more pathogenic TTR variant(s) detected</td>
<td>Confirms a clinical diagnosis of familial TTR amyloidosis</td>
</tr>
<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>
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</table>

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

REFERENCES