

## Familial Transthyretin Amyloidosis (TTR) Sequencing

Familial transthyretin (ATTR) amyloidosis is a genetic disorder that is caused by pathogenic variants in the *TTR* gene and results in amyloid deposits consisting of mutated TTR.<sup>1</sup> It is characterized by progressive peripheral sensorimotor or autonomic neuropathy, with nonneuropathic changes including cardiomyopathy, nephropathy, vitreous opacities, and central nervous system amyloidosis.<sup>1,2</sup> ATTR amyloidosis is inherited in an autosomal dominant manner and accounts for the majority of hereditary amyloidosis cases. Genetic testing is indicated to confirm a clinical diagnosis of ATTR amyloidosis by distinguishing it from other types of amyloidosis, cardiomyopathy, or neuropathy and as a predictive test for individuals at risk for ATTR amyloidosis.

### Disease Overview

### Associated Phenotypes

### Tests to Consider

**Familial Transthyretin Amyloidosis (TTR) Sequencing 3004531**

**Method:** Massively Parallel Sequencing

Preferred test for genetic confirmation of ATTR amyloidosis

**Familial Mutation, Targeted Sequencing 2001961**

**Method:** Polymerase Chain Reaction/Sequencing

- Useful for confirming a diagnosis when a pathogenic sequence variant has been identified in a family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED.

### TTR Amyloidosis Phenotypes

Phenotype	ATTR Amyloid Neuropathy (Familial Amyloid Polyneuropathy)	ATTR Cardiac Amyloidosis (Familial Amyloid Cardiomyopathy)	ATTR Leptomeningeal Amyloidosis/ Cerebral Amyloid Angiopathy
<b>Symptoms</b>	<p>Early signs</p> <ul style="list-style-type: none"> <li>• Autonomic dysfunction</li> <li>• Carpal tunnel</li> <li>• Constipation/diarrhea</li> <li>• Impotence</li> <li>• Sensorimotor polyneuropathy of the legs</li> </ul> <p>Late signs</p> <ul style="list-style-type: none"> <li>• Cardiomyopathy</li> <li>• CNS symptoms</li> <li>• Glaucoma</li> <li>• Nephropathy</li> <li>• Vitreous opacities</li> </ul>	<p>Anginal pain</p> <p>Arrhythmia</p> <p>Cardiomegaly</p> <p>Conduction block</p> <p>Congestive heart failure</p> <p>Sudden death</p>	<p>Ataxia</p> <p>Dementia</p> <p>Hemorrhage (subarachnoid or intracerebral)</p> <p>Hydrocephalus</p> <p>Psychosis</p> <p>Seizures</p> <p>Spasticity</p> <p>Transient focal neurologic episodes</p>

CNS, central nervous system

Source: Sekijima, 2001<sup>1</sup>

### Familial Euthyroid Hyperthyroxinemia

- Asymptomatic increase in total serum thyroxine concentration<sup>1</sup>
- Caused by benign *TTR* variants

## Typical Age of Onset

- Between 20-50 years in those of Japanese or Portuguese descent<sup>1</sup>
- Later age of onset for those with Swedish, French, or British ancestry<sup>1</sup>

## Epidemiology

- 1/100,000 in individuals of northern European descent in the U.S.<sup>1</sup>
- Up to 1/538 in individuals of Portuguese descent<sup>1</sup>
- The frequency of p.Val142Ile, associated with late-onset cardiac amyloidosis, is 3.0-3.9% in African Americans<sup>1</sup>

## Genetics

### Etiology

Pathogenic *TTR* germline variants

### Penetrance

Incomplete, but varies greatly depending on<sup>1</sup>:

- Ethnic groups
- Geographic regions
- Variants

### Inheritance

Autosomal dominant<sup>1</sup>

### Variants

There are two primary founder variants, c.148G>A (p.Val50Met) and c.424G>A (p.Val142Ile). Gain-of-function sequence variants account for >99% of pathogenic variants detected, though missense, nonsense, and splice-site variants may also be causative for disease.<sup>1</sup> ATTR amyloidosis has a poor phenotype-genotype correlation.

### Screening Issues

Presymptomatic genetic testing is useful to diagnose ATTR 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.<sup>2</sup>

## Test Description

### Clinical Sensitivity

Approximately 99% for ATTR amyloidosis

### Analytical Sensitivity

Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%) and 95% Credibility Region (%)	Analytical Specificity (NPA) (%)
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<sup>a</sup>Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

<sup>b</sup>Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

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

Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%) and 95% Credibility Region (%)	Analytical Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp <sup>b</sup>	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp <sup>b</sup>	94.8 (86.8-98.5)	>99.9

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## Limitations

- A negative result does not exclude a diagnosis of hereditary amyloidosis.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the *TTR* coding regions and intron-exon boundaries
  - Regulatory region and deep intronic variants
  - Noncoding transcripts
  - Large exonic deletions/duplications/inversions
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes or repetitive/homologous regions

## Results

Result	Variant(s) Detected	Clinical Significance
Positive	One or more pathogenic <i>TTR</i> variant(s) detected	Confirms a clinical diagnosis of ATTR amyloidosis
Negative	No pathogenic <i>TTR</i> variants detected	Decreases likelihood of, but does not exclude, a diagnosis of ATTR amyloidosis
Inconclusive	Variant of uncertain significance detected	Diagnosis of ATTR amyloidosis is uncertain

## References

1. Sekijima Y. [Hereditary transthyretin amyloidosis](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2021. [Last Update: Jun 2021; Accessed: Dec 2021]
2. Obici L, Kuks JB, Buades J, et al. [Recommendations for presymptomatic genetic testing and management of individuals at risk for hereditary transthyretin amyloidosis](#). *Curr Opin Neurol*. 2016;29 Suppl 1:S27-S35.

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