# Familial Transthyretin Amyloidosis (TTR) Sequencing

Last Literature Review: December 2021 Last Update: August 2023

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.[1] It is characterized by progressive peripheral sensorimotor or autonomic neuropathy, with nonneuropathic changes including cardiomyopathy, nephropathy, vitreous opacities, and central nervous system amyloidosis.[1,2] 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.

## Featured ARUP Testing

Familial Transthyretin Amyloidosis (TTR) Sequencing 3004531

**Method:** Massively Parallel Sequencing

Preferred test for genetic confirmation of ATTR amyloidosis

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

# Disease Overview

## Associated Phenotypes

**TTR Amyloidosis Phenotypes**

| Phenotype | ATTR Amyloid Neuropathy (Familial Amyloid Polyneuropathy) | ATTR Cardiac Amyloidosis (Familial Amyloid Cardiomyopathy) | ATTR Leptomeningeal Amyloidosis/ Cerebral Amyloid Angiopathy |
|---|---|---|---|
| Symptoms | Early signs<br>• Autonomic dysfunction<br>• Carpal tunnel<br>• Constipation/diarrhea<br>• Impotence<br>• Sensorimotor polyneuropathy of the legs<br><br>Late signs<br>• Cardiomyopathy<br>• CNS symptoms<br>• Glaucoma<br>• Nephropathy<br>• Vitreous opacities | Anginal pain<br>Arrhythmia<br>Cardiomegaly<br>Conduction block<br>Congestive heart failure<br>Sudden death | Ataxia<br>Dementia<br>Hemorrhage (subarachnoid or intracerebral)<br>Hydrocephalus<br>Psychosis<br>Seizures<br>Spasticity<br>Transient focal neurologic episodes |

CNS, central nervous system

Source: Sekijima, 2001[1]

## Familial Euthyroid Hyperthyroxinemia

- Asymptomatic increase in total serum thyroxine concentration[1]
- Caused by benign *TTR* variants

## 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]

## Epidemiology

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

# Genetics

## Etiology

Pathogenic *TTR* germline variants

## Penetrance

Incomplete, but varies greatly depending on[1]:

- Ethnic groups
- Geographic regions
- Variants

## Inheritance

Autosomal dominant[1]

## 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.[1] 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.[2]

# Test Description

## Clinical Sensitivity

Approximately 99% for ATTR amyloidosis

## Analytic Sensitivity

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

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

[b]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

## 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 *TTR* variant(s) detected | Confirms a clinical diagnosis of ATTR amyloidosis |
| Negative | No pathogenic *TTR* 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, eds. *GeneReviews.* University of Washington, Seattle. 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.



ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com