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.[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 • Autonomic dysfunction • Carpal tunnel • Constipation/diarrhea • Impotence • Sensorimotor polyneuropathy of the legs Late signs • Cardiomyopathy • CNS symptoms • Glaucoma • Nephropathy • Vitreous opacities	Anginal pain Arrhythmia Cardiomegaly Conduction block Congestive heart failure Sudden death	Ataxia Dementia Hemorrhage (subarachnoid or intracerebral) Hydrocephalus Psychosis Seizures Spasticity 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

[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

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
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, 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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