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.[1,2] 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.

Tests to Consider

Familial Transthyretin Amyloidosis (TTR) Sequencing 2014035

Method: Polymerase Chain Reaction/Sequencing

Preferred test for genetic confirmation of familial TTR amyloidosis

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

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

TTR Amyloidosis			
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 • Nephropathy • Vitreous opacities • Glaucoma	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

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

Result	Variant(s) Detected	Clinical Significance
Positive	One or more pathogenic *TTR* variant(s) detected	Confirms a clinical diagnosis of familial TTR amyloidosis
Negative	No pathogenic *TTR* variants detected	Decreases, but does not exclude, risk of familial TTR amyloidosis
Inconclusive	Variant of unknown significance detected	Diagnosis of familial TTR amyloidosis is uncertain

Limitations

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

References

1. Sekijima Y. Hereditary Transthyretin Amyloidosis. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Dec 2018; Accessed: Feb 2020]

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 S27-35. PubMed

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