Familial Transthyretin Amyloidosis (*TTR*) Sequencing

Indications for Ordering

- Confirm a clinical diagnosis of
  - Familial transthyretin (TTR) amyloidosis
  - Familial euthyroid hyperthyroxinemia
  - Senile systemic amyloidosis
- Predictive test for individuals at risk for TTR amyloidosis

Test Description

Bidirectional sequencing of all coding regions and intron/exon boundaries of the *TTR* gene

Tests to Consider

Primary test

Familial Transthyretin Amyloidosis (*TTR*) Sequencing 2014035

- Preferred test for genetic confirmation of familial TTR amyloidosis

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence

- ~1/100,000 in general U.S. population
- Up to 1/568 in Portuguese

Age of onset

- Symptoms typically present between 20-50 years
- Highly variable and dependent on ethnicity, geographic region, and specific gene variant

Symptoms

TTR amyloidosis – neuropathic

- Type I
  - Early signs
    - Autonomic dysfunction
    - Carpal tunnel
    - Constipation/diarrhea
    - Impotence
    - Sensorimotor polyneuropathy of the legs
  - Late signs
    - Cardiomyopathy
    - Nephropathy
    - Vitreous opacities
- Type II
  - Early signs – carpal tunnel
  - Late signs
    - Autonomic dysfunction
    - Cardiomyopathy
    - Constipation/diarrhea
    - Impotence
    - Nephropathy
    - Sensorimotor polyneuropathy of the legs
    - Vitreous opacities

TTR amyloidosis – non-neuropathic

- Familial amyloid cardiomyopathy
  - Angina
  - Arrhythmia
  - Cardiomegaly
  - Conduction block
  - Congestive heart failure
  - Sudden death
- Familial leptomeningeal amyloidosis
  - Ataxia
  - Dementia
  - Hemorrhage
  - Hydrocephalus
  - Psychosis
  - Seizures
  - Spasticity

Familial euthyroid hyperthyroxinemia

- Increased affinity to thyroxine and total serum thyroxine concentration
- Asymptomatic

Senile systematic amyloidosis

- Pathogenic deposition of wild-type TTR in the heart and occasionally blood vessels, lungs, and renal medulla
- Affects 10-25% of individuals >80 years
- Rarely diagnosed

Diagnostic issues

Human amyloidosis can be caused by ≥20 different amyloidogenic proteins

- TTR is most common

Laboratory testing for TTR

- Tissue biopsy showing deposition of TTR by Congo red staining and immunohistochemistry
- Variant TTR protein found in serum using mass spectrometry

Treatment

Early diagnosis allows for more effective treatment

- Orthotopic liver transplantation halts progression of autonomic and peripheral neuropathy
  - Liver transplant is recommended for individuals <60 years with clinical symptoms <5 years, polyneuropathy of only lower extremities, and no significant renal or cardiac involvement

Clinical diagnostic criteria

- Slow, progressive sensorimotor and/or autonomic neuropathy accompanied by at least one of the following
  - Cardiac conduction blocks
  - Cardiomyopathy
  - Nephropathy
  - Vitreous opacities
- Family history of autosomal dominant TTR amyloidosis

Genetics

Gene – *TTR*

Inheritance – autosomal dominant

Penetrance – incomplete

- Varies greatly among ethnic groups
- Possibly higher through maternal transmission

Variants

- Sequence variants account for >99% of pathogenic variants detected
  - Missense, nonsense, and splice-site variants may be causative for disease

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – ~99% of pathogenic variants are detectable by *TTR* sequencing
- Analytical sensitivity – 99%

Results

- Positive – one pathogenic *TTR* variant detected
  - Confirms a clinical diagnosis of familial TTR amyloidosis
- Negative – no pathogenic *TTR* variants detected
  - Decreases, but does not exclude, a diagnosis of familial TTR amyloidosis
- Inconclusive – variant of uncertain clinical significance detected
  - Diagnosis of familial TTR amyloidosis can be neither confirmed nor excluded

Limitations

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

Reference

Sekijima Y, Yoshida K, et al. Familial Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2012 Jan 26]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. (www.ncbi.nlm.nih.gov/books/NBK1194/)