Familial Transthyretin Amyloidosis (\textit{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 \textit{TTR} gene

**Tests to Consider**

- **Primary test**
  Familial Transthyretin Amyloidosis (\textit{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 systemic 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 $\geq$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
  o 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
  o Cardiac conduction blocks
  o Cardiomyopathy
  o Nephropathy
  o 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
  o 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
  o Confirms a clinical diagnosis of familial TTR amyloidosis
• Negative – no pathogenic TTR variants detected
  o Decreases, but does not exclude, a diagnosis of familial TTR amyloidosis
• Inconclusive – variant of uncertain clinical significance detected
  o Diagnosis of familial TTR amyloidosis can be neither confirmed nor excluded

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

Reference