MAYO CLINIC LABORATORIES

Test Definition: ATTRZ

TTR Gene, Full Gene Analysis

Overview

Useful For

Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

Testing Algorithm

See Amyloidosis (Familial) Test Algorithm in Special Instructions.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Amyloidosis (Familial) Test Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) Amplification/DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send specimen in original tube.

Additional Information: To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on

file. The following documents are available in Special Instructions:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521) in Special Instructions
3. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-Hematopathology/Cytogenetics Test Request (T726)
-Renal Diagnostics Test Request (T830)

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Minimum Volume

0.5 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical & Interpretive

Clinical Information

The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions.
The most common hereditary amyloidosis is familial transthyretin amyloidosis; an autosomal dominant disorder caused by mutations in the transthyretin (*TTR*) gene. The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic TTR protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Typically, TTR-associated amyloidosis is progressive over a course of 5 to 15 years and the most common cause of death is cardiomyopathy. Affected individuals may present with a variety of symptoms, including peripheral neuropathy, blindness, cardiomyopathy, nephropathy, autonomic nervous dysfunction, or bowel dysfunction.
More than 90 mutations have now been identified within the *TTR* gene, which cause TTR-associated familial amyloidosis. Most of the mutations described to date are single base pair changes that result in an amino acid substitution. Some of these mutations correlate with the clinical presentation of amyloidosis. However, several different mutations have been identified which exhibit considerable clinical overlap.
It is important to note that this assay does not detect mutations associated with non-TTR forms of familial amyloidosis. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific mutation in the family before testing at risk individuals.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of transthyretin (TTR)-associated amyloidosis may have a mutation that is not identified by this method (eg, large genomic deletions/ duplications, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of TTR-associated amyloidosis. For carrier testing, it is important to first document the presence of a *TTR* gene mutation in an affected family member.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Mutations in other genes, such as lysozyme, apolipoprotein AII, gelsolin, and others, have been shown to cause other forms of familial amyloidosis. Abnormalities in these genes are not detected by this assay.

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently unvalidated.

Unless reported or predicted to cause disease, alterations in protein coding genes that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review likely pathogenic alterations or variants of uncertain significance that have been previously detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Supportive Data

DNA sequence analysis was performed on 196 specimens (17 patients with a known transthyretin mutation, 48 patients tested by mass spectrometry, 91 patients with amyloidosis, and 40 normal individuals).

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular

Pathology. Genet Med 2015 May;17(5):405-424
2. Benson MD: The hereditary amyloidoses. Best Pract Res Clin Rhematol 2003;17:909-927
3. Eneqvist T, Sauer-Eriksson AE: Structural distribution of mutations associated with familial amyloidotic polyneuropathy in human transthyretin. Amyloid 2001;8:149-168
4. Connors LH, Lim A, Prokaeva VA, et al: Tabulation of human transthyretin (TTR) variants, 2003. Amyloid 2003;10:160-184

Performance

Method Description
Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the transthyretin (*TTR*) gene.(Bergen RH 3rd, Zeldenrust SR, Butz ML, et al: Identification of transthyretin variants by sequential proteomic and genomic analysis. Clin Chem 2004;50:1544-1552)

PDF Report
No

Specimen Retention Time
Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees & Codes

Test Classification
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81404-*TTR (transthyretin)* (eg, familial transthyretin amyloidosis), full gene sequence

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
ATTRZ	TTR Gene, Full Gene Analysis	94225-0

Result ID	Test Result Name	Result LOINC Value
53018	Result Summary	50397-9
53019	Result	82939-0
53020	Interpretation	69047-9
53021	Additional Information	48767-8

53022	Specimen	31208-2
53023	Source	31208-2
53024	Released By	18771-6