MAYO CLINIC LABORATORIES

Test Definition: TTRX

Amyloidosis, Transthyretin-Associated Familial, Reflex, Blood

Overview

Useful For

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

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
TTRZ	TTR Gene, Full Gene Analysis	Yes	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No

Genetics Test Information

Mass spectrometry to evaluate transthyretin (TTR) protein structure is performed first. In all cases demonstrating a structural change, the *TTR* gene will be further analyzed by DNA sequence analysis. If no alterations are detected, full gene analysis will not be performed unless a specific request for TTRZ / *TTR* Gene, Full Gene Analysis, Varies is submitted by the ordering healthcare professional or client.

Testing Algorithm

If familial amyloidosis by liquid chromatography-mass spectrometry is abnormal, DNA sequencing will be performed at an additional charge.

For more information see Amyloidosis (Familial) Test Algorithm.

Special Instructions

- Amyloidosis (Familial) Test Algorithm

Method Name

Affinity Chromatography/Mass Spectrometry (MS)

NY State Available

Yes

Specimen

Specimen Type

Whole blood

Shipping Instructions

Specimen must arrive within 4 days of collection. Specimens are stabilized upon receipt and stored until testing is performed.

Specimen Required

Container/Tube:

Preferred: Lavender top (EDTA)

Acceptable: Yellow top (ACD)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**

Forms

If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

-Hematopathology/Cytogenetics Test Request (T726)

-Biochemical Genetics Test Request (T798)

Specimen Minimum Volume

0.5 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Refrigerated (preferred)	4 days	
	Ambient	4 days	

Clinical & Interpretive

Clinical Information

The amyloidoses are a group of diseases that result from the abnormal deposition of amyloid in various tissues of the body. They have been classified into 3 major types: primary, secondary, and hereditary. The most common form of amyloidosis (AL) is a disease of the bone marrow called primary systemic AL (immunoglobulin light chain). Secondary AL usually occurs in tandem with chronic infectious or inflammatory diseases, such as rheumatoid arthritis, tuberculosis, or osteomyelitis. Familial or hereditary AL is the least common form. Determining the specific type of AL is imperative in order to provide both an accurate prognosis and appropriate therapies.

Familial or hereditary transthyretin AL is an autosomal dominant disorder caused by variants in the transthyretin gene (*TTR*). The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic transthyretin (TTR) protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Affected individuals may present with a variety of symptoms including sensorimotor and autonomic neuropathy, vitreous opacities, cardiomyopathy, nephropathy, and gastrointestinal dysfunction. TTR-associated AL is progressive over a course of 5 to 15 years and usually ends in death from cardiac or kidney failure or malnutrition. Orthotopic liver transplantation is a treatment option for some patients who are diagnosed in early stages of the disease. Other treatment options include the use of TTR tetramer stabilizer medications and gene-silencing therapies (RNA interference/RNAi) approved for use in several countries including the United States.

Mayo Clinic Laboratories recommends a testing strategy that includes both protein analysis by mass spectrometry (MS) and *TTR* gene analysis by DNA sequencing for patients in whom TTR-associated familial AL is suspected. The structure of TTR protein in plasma is first determined by MS. The presence of a disease-causing variant in the *TTR* gene leads to conformational changes in the TTR protein. This ultimately disrupts the stability of the mature TTR protein tetramer, leading to increased amounts of pro-amyloidogenic TTR monomers in the plasma of affected individuals. MS technology can identify the mass difference between wildtype TTR and variant TTR protein. Only the transthyretin (also known as prealbumin) is analyzed for amino acid substitutions. Other proteins involved in other less common forms of familial amyloidosis are not examined. If no alterations are detected, gene analysis will not be performed unless requested by the provider (ie, when the diagnosis is still strongly suspected; to rule out the possibility of a false-negative by MS). In all cases demonstrating a structural change by MS, DNA sequence analysis will be performed on the *TTR* gene to identify and characterize the observed alteration (disease-causing or benign variant). More than 90 variants that cause TTR-associated familial AL have now been identified within the *TTR* gene. Most of the variants described to date are single base pair changes that result in an amino acid substitution. Some of these variants correlate with the clinical presentation of AL.

For predictive testing in cases where a familial variant is known, testing for the specific variant by DNA sequence analysis (FMTT / Familial Variant, Targeted Testing, Varies) is recommended. These assays do not detect alterations associated with non-*TTR* forms of familial AL. Therefore, it is important to first test an affected family member to determine if *TTR* is involved and to document a specific alteration in the family before testing at-risk individuals.

Reference Values

An interpretive report will be provided.

Interpretation

The presence of a structural change in transthyretin (TTR) is suggestive of a gene variant that requires confirmation by DNA sequence analysis. A negative result by mass spectrometry does not rule out a *TTR* variant. Mass spectrometric (MS) results are falsely negative if the amino acid substitution does not produce a measurable mass shift for the transthyretin variant. Approximately 90% of the *TTR* variants are positive by MS (see Cautions).

After identification of the variant at the DNA level, predictive testing for at-risk family members can be performed by molecular analysis (FMTT / Familial Variant, Targeted Testing, Varies).

Cautions

There are 3 circumstances where testing by mass spectrometry will not identify amyloid-causing variants:

-If the amino acid change results in a protein different by less than 10 atomic mass units (amu), the genetic variant will not be reliably detected.
-If an amino acid change results from a frequent nondisease-causing alteration (+30 amu). Since over 12% of the population has this innocuous alteration, it is an instance in which molecular testing must be done.
-Coinheritance of the alteration with a -30 amu variant would result in a transthyretin mass indistinguishable from normal.

Clinical Reference

1. Sekijima Y. Hereditary transthyretin amyloidosis. In: Adam MP, Bick S, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated May 30, 2024. Accessed February 23, 2026. Available at www.ncbi.nlm.nih.gov/books/NBK1194/
2. Finsterer J, Iglseder S, Wanschitz J, et al. Hereditary transthyretin-related amyloidosis. Acta Neurol Scand. 2019;139(2):92-105
3. Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry. 2015;86(9):1036-1043. doi:10.1136/jnnp-2014-308724
4. Manganelli F, Fabrizi GM, Luigetti M, et al. Hereditary transthyretin amyloidosis overview. Neurol Sci 43 (Suppl 2), 595–604 (2022). doi:10.1007/s10072-020-04889-2

Performance

Method Description

Transthyretin:
Transthyretin (TTR) is purified from plasma using online affinity chromatography coupled to a quadrupole time-of-flight mass spectrometer. The acquired ion spectra are deconvoluted and reviewed for TTR variants. After deconvolution, normal patients present with a single peak corresponding to wildtype (wt) TTR, which serves as a reference. When positive, amyloid patients are typically heterozygous and are detected by the presence of 2 peaks (ie, wt *TTR* and altered TTR) differing in mass.(Bergen HR 3rd, Zeldenrust SR, Butz ML, et al. Identification of transthyretin variants by sequential proteomic and genomic analysis. Clin Chem. 2004;50[9]:1544-1552; Trenchevska O, Yassine HN, Borges CR, et al. Development of quantitative mass spectrometric immunoassay for serum amyloid A. Biomarkers. 2016;21[8]:743-751)

TTR Gene Sequencing:
Next generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of *TTR*, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletion-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in *TTR*

There may be regions of *TTR* that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.(Unpublished Mayo method)

The reference transcript for *TTR* gene is NM_000371.3. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing.

PDF Report
No

Day(s) Performed
Wednesday

Report Available
3 to 9 days

Specimen Retention Time
2 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

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

CPT Code Information
82542
81404 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
TTRX	Familial Amyloidosis Reflex	94864-6

Result ID	Test Result Name	Result LOINC® Value
22668	Wild Type Mass	94860-4
22669	Wild Type Width at Half Height	94863-8
22670	Second Mass	94862-0

22671	Mass Difference	94861-2
22673	Abnormal result	51968-6
50944	Interpretation	69047-9
50946	Reviewed By	18771-6