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Hereditary Transthyretin Amyloidosis

Synonyms: ATTRv Amyloidosis, Familial Amyloid Polyneuropathy, Familial Transthyretin Amyloidosis, hATTR, Hereditary Amyloidogenic Transthyretin Amyloidosis, Hereditary ATTR Amyloidosis, Hereditary Transthyretin-Mediated Amyloidosis

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Summary

Clinical characteristics

Hereditary transthyretin amyloidosis (ATTRv amyloidosis) is characterized by a slowly progressive peripheral sensorimotor and/or autonomic neuropathy. Amyloidosis can involve the heart, central nervous system (CNS), eyes, and kidneys. The disease usually begins in the third to fifth decade in persons from endemic foci in Portugal and Japan; onset is later in persons from other areas. Typically, sensory neuropathy starts in the lower extremities with paresthesia and hypesthesia of the feet, followed within a few years by motor neuropathy. In some persons, particularly those with early-onset disease, autonomic neuropathy is the first manifestation of the condition; findings can include orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Cardiac amyloidosis is mainly characterized by progressive restrictive cardiomyopathy. Individuals with leptomeningeal amyloidosis may have the following CNS findings: dementia, psychosis, visual impairment, headache, seizures, motor paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage. Ocular involvement includes vitreous opacity, glaucoma, dry eye, and ocular amyloid angiopathy. Mild-to-severe kidney disease can develop.

Diagnosis/testing

The diagnosis of ATTRv amyloidosis is established in a proband with characteristic clinical features, including imaging or histopathology findings of amyloidosis, and a heterozygous pathogenic variant in *TTR* identified by molecular genetic testing.

Management

Targeted therapies: Pharmacotherapeutics (e.g., gene-silencing therapies, transthyretin tetramer stabilizers) are first-line therapy for all individuals with ATTRv amyloidosis. There is limited indication for orthotopic liver transplantation.

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Treatment of manifestations: Pharmacologic treatments for neuropathic pain; surgical release for carpal tunnel syndrome; ankle-foot orthoses and physical therapy for motor neuropathy; standard treatments for autonomic dysfunction and CNS manifestations. In those with sick sinus syndrome or second- or third-degree atrioventricular block, a cardiac pacemaker may be indicated. Vitrectomy for vitreous opacification; surgical treatment for glaucoma; ocular lubrication for dry eye; erythropoietin or intravenous iron for normocytic normochromic anemia; hemodialysis as needed for end-stage kidney disease.

Surveillance: Abdominal wall fat aspiration or gastrointestinal tract biopsy annually to identify disease onset in asymptomatic individuals; systematic neurologic screening at least annually; nerve conduction studies annually; clinical assessment for manifestations of cardiac disease and serum B-type natriuretic peptide levels annually; electrocardiogram and echocardiography at least annually; ^{99m}Tc-PYP myocardial scintigraphy every three to five years; clinical assessment for dementia, psychosis, headache, seizures, motor paresis, and ataxia annually; ophthalmology examination including assessment for glaucoma at least annually; laboratory assessment of kidney function annually; modified body mass index annually; assessment of psychological manifestations as needed.

Agents/circumstances to avoid: Local heating appliances, such as hot-water bottles, which can cause low-temperature burn injuries in those with decreased temperature and pain perception.

Evaluation of relatives at risk: Clarify the genetic status of at-risk relatives by molecular genetic testing for the *TTR* pathogenic variant(s) in the family in order to identify as early as possible those who would benefit from prompt early diagnosis and treatment.

Genetic counseling

ATTRv amyloidosis is inherited in an autosomal dominant manner. Each child of an individual who is heterozygous for a *TTR* pathogenic variant has a 50% risk of inheriting the *TTR* pathogenic variant. All offspring of an individual who has biallelic *TTR* pathogenic variants will inherit a pathogenic variant. Once the *TTR* pathogenic variant(s) has been identified in an affected family member, predictive testing for at-risk family members and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Hereditary transthyretin amyloidosis (ATTRv amyloidosis) **should be suspected** in adults with the following clinical, imaging, and histopathology findings and family history.

Clinical findings. Slowly progressive sensorimotor and/or autonomic neuropathy that is frequently accompanied by one or more of the following:

- Cardiac conduction blocks
- Cardiomyopathy
- Nephropathy
- Vitreous opacities
- Glaucoma

Imaging findings

- Echocardiogram may show left ventricular or biventricular thickening with speckled myocardium.
- Gadolinium contrast-guided cardiac MRI can show characteristic gadolinium distribution. Note: Gadolinium administration in those with ATTRv amyloidosis-related nephropathy can lead to nephrogenic systemic fibrosis.

- Bone scintigraphy using ^{99m}technetium-3,3-diphosphono-1-2-propanodicarboxylic acid (Tc-DPD), ^{99m}Tc-pyrophosphate (Tc-PYP), and/or ^{99m}Tc-hydroxymethylene-diphosphonate (Tc-HMDP) can show cardiac amyloid [Gillmore et al 2016]. Note: Bone scintigraphy is negative in young individuals with the *TTR* p.Val50Met pathogenic variant.
- Amyloid PET imaging using Pittsburgh compound B is useful for detecting amyloid in individuals with early-onset ATTRv amyloidosis due to the *TTR* p.Val50Met pathogenic variant [Takasone et al 2020].

Histopathology findings

- **Tissue biopsy to identify amyloid deposits.** Tissues suitable for biopsy include subcutaneous fatty tissue of the abdominal wall, skin, gastric or rectal mucosa, sural nerve, endocardium, and peritendinous fat from specimens obtained at carpal tunnel surgery. With Congo red staining, amyloid deposits show a characteristic yellow-green birefringence under polarized light.

  Note: Sensitivity of endoscopic biopsy of gastrointestinal mucosa is approximately 85%; biopsy of the sural nerve is less sensitive because amyloid deposition is often patchy [Hund et al 2001, Koike et al 2004, Vital et al 2004].

- **Immunohistochemistry of tissue biopsies with anti-transthyretin antibodies** can identify amyloid deposits.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Family history can include rapidly progressive polyneuropathy of unknown cause, cardiac failure, sudden cardiac death, or cardiac arrhythmia. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of ATTRv amyloidosis **is established** in a proband with suggestive findings (including imaging or histopathology findings of ATTRv amyloidosis) and a heterozygous pathogenic (or likely pathogenic) variant in *TTR* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *TTR* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *TTR* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: ATTRv amyloidosis occurs through a gain-of-function mechanism and testing for intragenic deletions or duplications is unlikely to identify a disease-causing variant.

Note: Targeted analysis for the most common pathogenic variant, c.148G>A (p.Val50Met), can be performed first.

A multigene panel that includes *TTR* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance

and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of ATTRv amyloidosis has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *TTR* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Hereditary Transthyretin Amyloidosis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TTR	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. The most common pathogenic variant, c.148G>A (p.Val50Met), has been identified in many individuals of different ethnic backgrounds; it is found in large clusters in Portugal, Sweden, and Japan.
5. TTR has four exons; all pathogenic variants identified to date are in exon 2, 3, or 4.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Since ATTRv amyloidosis occurs through a gain-of-function mechanism and large intragenic deletions or duplications have not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Clinical Characteristics

Clinical Description

Clinical features of hereditary transthyretin amyloidosis (ATTRv amyloidosis) can include peripheral sensorimotor neuropathy and autonomic neuropathy, as well as non-neuropathic changes. Cardiac amyloidosis (e.g., restrictive cardiomyopathy, arrhythmia), leptomeningeal amyloidosis (e.g., transient focal neurologic episodes, intracerebral and/or subarachnoid hemorrhages), ophthalmopathy (e.g., vitreous opacities, glaucoma), and nephropathy are frequently seen in the advanced stage of the disease (see Table 2). Affected individuals can also present with non-neuropathic forms of ATTRv amyloidosis in which polyneuropathy is less evident.

Table 2. Hereditary Transthyretin Amyloidosis: Frequency of Select Features

Feature	% of Persons w/Feature		
	Persons w/early onset & p.Val50Met	Persons w/late onset & p.Val50Met	Persons w/other *TTR* pathogenic variants
Sensory neuropathy	82%	84%	60%
Motor neuropathy	36%	52%	29%
Autonomic dysfunction	74%	60%	45%
Gastrointestinal manifestations	68%	47%	33%
Cardiac manifestations	22%	39%	59%

Gentile et al [2023]

Onset. The disease usually begins earlier in persons from endemic foci in Portugal and Japan. In Japanese individuals from two large endemic foci (Ogawa and Arao) heterozygous for *TTR* pathogenic variant p.Val50Met, the mean age at onset is 40.1 ± 12.8 years (range: age 22-74 years) [Nakazato 1998]. In persons of Portuguese ancestry with *TTR* pathogenic variant p.Val50Met, the mean age at onset is 33.5 ± 9.4 years (range: age 17-78 years). In persons of Japanese ancestry with p.Val50Met who are unrelated to the two large endemic foci, the mean age at onset is much later (62.7 ± 6.6 years; range: age 52-80 years) [Misu et al 1999, Ikeda et al 2002]. In persons of Swedish, French, or British ancestry, the mean age at onset is much later than that in individuals of Japanese or Portuguese ancestry [Planté-Bordeneuve et al 1998]. Individuals with pathogenic variant p.Val50Met and early-onset disease have type B amyloid fibrils composed of full-length transthyretin (TTR), whereas individuals with p.Val50Met and late-onset disease have type A amyloid fibrils composed of both full-length TTR and TTR fragments [Ihse et al 2008, Ihse et al 2013].

Neuropathy. The cardinal feature of ATTRv amyloidosis neuropathy is slowly progressive sensorimotor and autonomic neuropathy [Ando et al 2005]. Typically, sensory neuropathy starts in the lower extremities and is followed by motor neuropathy within a few years. The initial symptoms are paresthesia (sense of burning, shooting pain) or hypoesthesia of the feet. Temperature and pain sensation are impaired earlier than vibration and position sensation. By the time sensory neuropathy progresses to the level of the knees, the hands have usually become affected. Individuals with *TTR* pathogenic variants p.Leu78His, p.Leu78Arg, p.Lys90Asn, p.Ile104Ser, p.Ile127Val, and p.Tyr134His tend to develop carpal tunnel syndrome as an initial manifestation [Nakazato 1998, Connors et al 2000, Benson 2001, Hund et al 2001, Connors et al 2003]. Due to sensory neuropathy, trophic ulcers on the lower extremities are common.

Motor neuropathy (muscle atrophy and weakness) of the extremities develops with foot drop, wrist drop, and disability of the hands and fingers. Eventually sensorimotor neuropathy shows a glove-and-stocking distribution.

Autonomic neuropathy may be the presenting manifestation of ATTRv amyloidosis, including orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, impotence, anhidrosis, and urinary retention or incontinence. Frequently, the autonomic neuropathy produces the most significant morbidity of the disorder. Amyloid deposition in the gastrointestinal tract wall, especially with involvement of the gastrointestinal autonomic nerves, is common [Ikeda et al 1982, Ikeda et al 1983].

Cardiac amyloidosis. Most individuals develop cardiac manifestations after age 50 years. Cardiac manifestations include arrhythmias such as atrioventricular block, sick sinus syndrome, and atrial fibrillation due to amyloid deposition in the heart. Amyloid deposition in the myocardium causes progressive restrictive cardiomyopathy and heart failure, and it is thought that ventricular diastolic dysfunction precedes systolic dysfunction. In some individuals, cardiomyopathy is the predominant feature and peripheral neuropathy is not present.

The typical electrocardiogram shows a pseudoinfarction pattern with prominent Q wave in leads II, III, $_{a}V_{F}$, and V_{1}-V_{3}, presumably resulting from dense amyloid deposition in the anterobasal or anteroseptal wall of the left

ventricle. The echocardiogram reveals left ventricular hypertrophy with preserved systolic function. The thickened walls show a "granular sparkling appearance."

Leptomeningeal amyloidosis / cerebral amyloid angiopathy. Liver transplant and disease-modifying drugs do not affect TTR production in the choroid plexus, and TTR production in the cranial nervous system (CNS) continues in those on therapy. This results in the emergence of CNS manifestations. The most common include transient focal neurologic episodes (TFNEs), in which affected individuals have short, self-limited episodes of focal cortical dysfunction, including hemiparesis, hemisensory disturbance, and motor aphasia. TFNEs are common, particularly in individuals with *TTR* pathogenic variant p.Val50Met and long-standing disease [Sekijima et al 2016, Taipa et al 2023, Takahashi et al 2023]. Following TFNEs, dementia and intracranial hemorrhage can develop approximately 20 years after the onset of ATTRv amyloidosis [Takahashi et al 2023].

Amyloid deposition is seen in the pial and arachnoid membrane, as well as in the walls of blood vessels in the subarachnoid space. Amyloid in the blood vessels disappears as the vessels penetrate the brain parenchyma. More rarely, a few individuals have developed myelopathy, caused by amyloid deposition in the blood vessel walls in the spinal cord [Dowell et al 2007].

In leptomeningeal amyloidosis, protein concentration in the cerebrospinal fluid is usually high, and gadolinium-enhanced MRI typically shows extensive enhancement of the surface of the brain, ventricles, and spinal cord [Brett et al 1999]. CNS amyloid deposition can also be detected by amyloid PET, using Pittsburgh compound B (PiB) [Sekijima et al 2016].

Ophthalmopathy. Ocular involvement, including vitreous opacity, glaucoma, dry eye, and ocular amyloid angiopathy, is common and occurs in most individuals with *TTR* pathogenic variant p.Val50Met [Ando et al 1997]. Vitreous opacification has been reported in approximately 20% of individuals with ATTRv amyloidosis. Four of 43 individuals with *TTR* pathogenic variant p.Val50Met developed vitreous amyloidosis as the first manifestation of ATTRv amyloidosis [Kawaji et al 2004]. In one individual vitreous opacification was the only evidence of ATTRv amyloidosis [Yazaki et al 2002].

Nephropathy. The kidney is consistently involved, with marked deposition of amyloid demonstrated at postmortem examination. Mild-to-severe kidney involvement is usually seen in the advanced stage [Haagsma et al 2004, Lobato et al 2004]. Kidney involvement is preceded by proteinuria. Kidney failure occurs in about one third of individuals of Portuguese descent with early-onset ATTRv amyloidosis caused by *TTR* pathogenic variant p.Val50Met [Lobato et al 2004]; however, severe kidney dysfunction rarely occurs in individuals with late-onset disease. Anemia with low erythropoietin has been reported in 25% of individuals [Beirão et al 2004].

Other

- Nodular cutaneous amyloidosis has been reported in one individual [Mochizuki et al 2001].
- Shortness of breath induced by diffuse pulmonary amyloid deposition has been reported in two individuals [Yazaki et al 2000].

Prognosis. Sensorimotor and autonomic neuropathy progress over ten to 20 years. Cachexia is a common feature at the late stage of the disease. Affected individuals usually die of cardiac failure, kidney failure, or infection.

Homozygotes / compound heterozygotes. Homozygosity for *TTR* pathogenic variant p.Val50Met has been reported in at least 19 individuals from 14 families [Tojo et al 2008]. Individuals homozygous and compound heterozygous for other *TTR* pathogenic variants have also been reported. Individuals with biallelic *TTR* pathogenic variants have increased penetrance and earlier onset than heterozygotes within the same family [Reddi et al 2014]; amyloid deposition is also more widespread in those with biallelic pathogenic variants than in heterozygotes [Yoshinaga et al 2004]. However, there are some reported homozygous individuals from non-

endemic areas with p.Val50Met or p.Val142Ile with disease onset at the same age as heterozygotes [Uchida et al 2015, Micaglio et al 2023].

Genotype-Phenotype Correlations

Despite intensive investigation, few genotype-phenotype correlations have been detected. Most *TTR* pathogenic variants result in peripheral and autonomic neuropathy; but some pathogenic variants have been associated with phenotypes in which peripheral or autonomic neuropathy is clinically absent or less prominent:

- A cardiac-dominant phenotype is associated with p.Asp38Asn, p.Val40Ile, p.Pro44Ser, Ala65Ser, p.Ala65Thr, p.His76Arg, p.Gly77Arg, p.Ile88Leu, p.Ala101Thr, p.Ala101Val, p.His108Arg, p.Glu112Lys, p.Arg123Ser, p.Leu131Met, or p.Val142Ile [Nakazato 1998, Benson 2001, Saraiva 2001, Connors et al 2003, Benson & Kincaid 2007]. Peripheral and autonomic neuropathy are absent or less evident in persons with these variants.
- A leptomeningeal-dominant phenotype is associated with p.Leu32Pro, p.Asp38Gly, p.Ala45Thr, p.Val50Gly, p.Ala56Pro, p.Gly73Glu, p.Gly73Ala, p.Phe84Ser, p.Tyr89His, or p.Tyr134Cys [Petersen et al 1997, Nakazato 1998, Brett et al 1999, Mascalchi et al 1999, Uemichi et al 1999, Connors et al 2000, Benson 2001, Ellie et al 2001, Saraiva 2001, Ikeda et al 2002, Blevins et al 2003, Connors et al 2003, Hammarström et al 2003, Sekijima et al 2003]. It has been demonstrated that highly destabilizing *TTR* pathogenic variants induce leptomeningeal amyloidosis [Hammarström et al 2001, Sekijima et al 2003, Sekijima et al 2005].
- A leptomeningeal- and ocular-dominant phenotype are the first and primary manifestations in individuals with *TTR* pathogenic variants p.Ala45Thr, p.Gly73Arg, p.Gly73Glu, p.Tyr89His, and p.Tyr134Cys [Sousa et al 2021].

The benign *TTR* variant c.416C>T (p.Thr139Met) has a protective effect on amyloidogenesis in individuals who also have *TTR* pathogenic variant p.Val50Met [Hammarström et al 2001, Sebastião et al 2001].

Penetrance

Penetrance for ATTRv amyloidosis is not 100%; an individual with a *TTR* pathogenic variant may remain symptom-free until late adulthood. The penetrance may vary by pathogenic variant, geographic region, or ethnic group.

The penetrance appears to be much higher in individuals in endemic foci than outside of endemic foci [Misu et al 1999]. In Portugal, cumulative disease risk in individuals with *TTR* pathogenic variant p.Val50Met is estimated at 80% by age 50 years and 91% by age 70 years, whereas the risk in French heterozygotes is 14% by age 50 years and 50% by age 70 years [Planté-Bordeneuve et al 2003]. In Sweden, the penetrance is much lower: 1.7% by age 30, 5% by age 40, 11% by age 50, 22% by age 60, 36% by age 70, 52% by age 80, and 69% by age 90 years, respectively [Hellman et al 2008].

Some p.Val50Met homozygotes remain asymptomatic.

Nomenclature

Historical protein numbering was based on the mature protein after cleavage of a 20-amino-acid signal sequence (e.g., p.Val50Met would be referred to as Val30Met). Standard nomenclature uses numbering beginning at the Met initiation codon. Variants reported in older literature may use historical nomenclature.

ATTRv amyloidosis-related neuropathy was formerly referred to as one of the following:

- Familial amyloid polyneuropathy type I (or the Portuguese-Swedish-Japanese type)
- Familial amyloid polyneuropathy type II (or the Indiana/Swiss or Maryland/German type)

The abbreviation "ATTRv" refers to hereditary transthyretin-related amyloid protein [Ando et al 2022]; "v" stands for variant and is the recommended abbreviation in the International Society of Amyloidosis (ISA) nomenclature committee [Buxbaum et al 2022].

Prevalence

TTR pathogenic variant p.Val50Met is the most common pathogenic variant in Portugal, Sweden, and Japan; p.Val50Met is also one of the most common pathogenic variants worldwide. The frequency of ATTRv amyloidosis caused by p.Val50Met is estimated at 1:538 in northern Portugal (Povoa do Varzim and Vila do Conde), the largest cluster worldwide of individuals with ATTRv amyloidosis. The frequency of p.Val50Met heterozygotes is 1.5% in the northern part of Sweden [Holmgren et al 1994]; however, the penetrance is very low in this area [Hellman et al 2008] (see Penetrance). In individuals of northern European origin in the United States, the frequency of p.Val50Met-related ATTRv amyloidosis is estimated at 1:100,000 [Benson 2001].

The frequency of p.Val142Ile in the African American population is 3.0%-3.9%; most heterozygous individuals develop late-onset cardiac amyloidosis. More than 5% of the population in some areas of West Africa is heterozygous for this variant. The high frequency of p.Val142Ile in the African American population partly explains the observation that in individuals in the US older than age 60 years, cardiac amyloidosis is four times more common among Blacks than Whites [Akinboboye et al 2020].

Genetically Related (Allelic) Disorders

Familial euthyroid hyperthyroxinemia is associated with benign variants in *TTR* [Pappa et al 2015]. Transthyretin (TTR) binds approximately 15% of serum thyroxine. Euthyroid hyperthyroxinemia-related *TTR* variants increase total serum thyroxine concentration because of their increased affinity for thyroxine; however, they increase neither free thyroxine nor free triiodothyronine. Therefore, individuals with these variants develop no clinical symptoms (i.e., they are euthyroid).

Wild type ATTR (previously called senile systemic amyloidosis, or senile cardiac amyloidosis) results from the pathologic deposition of wild type TTR predominantly in the heart. Pathologic deposits are also seen in the lungs, blood vessels, and the renal medulla of the kidneys [Westermark et al 2003]. Wild type ATTR affects mainly the elderly but is rarely diagnosed during life [Sekijima et al 2018]. Thus, the precise prevalence of wild type ATTR is still unknown, but the examination of autopsy samples revealed a prevalence of 10%-25% in the elderly (age >80 years) [Cornwell et al 1988, Ueda et al 2011].

Wild type ATTR is associated with cardiac amyloidosis but typically does not cause features such as kidney and autonomic dysfunction that are common in hereditary transthyretin amyloidosis (ATTRv amyloidosis). The majority of individuals with wild type ATTR present with carpal tunnel syndrome [Nakagawa et al 2016]. Wild type ATTR should be distinguished from ATTRv amyloidosis and other forms of amyloidosis such as primary (AL) amyloidosis. In contrast to the rapid progression of heart failure in AL amyloidosis, wild type ATTR results in slowly progressive heart failure [Ng et al 2005]. The lung may be a more reliable tissue for amyloid detection than the heart [Westermark et al 2003].

Differential Diagnosis

Genetic disorders. Genes of interest in the differential diagnosis of hereditary transthyretin amyloidosis (ATTRv amyloidosis) are listed in Table 3a.

Note: A total of 35 amyloidogenic proteins including transthyretin (TTR) have been identified in human amyloidoses [Sipe et al 2016]. Among the hereditary amyloidoses, ATTRv amyloidosis is the most prevalent [Benson 2001, Hund et al 2001, Benson 2005].

Table 3a. Genes of Interest in the Differential Diagnosis of Hereditary Transthyretin Amyloidosis

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/ATTRv amyloidosis	Distinguishing from ATTRv amyloidosis
Neuropathic amyloidoses				
APOA1 *B2M* *FGA* *LYZ*	Familial amyloidosis (OMIM 105200)	AD	• Nephropathy • Peripheral neuropathy • Cardiomyopathy	• Hepatomegaly • Swelling of testes
GSN	Gelsolin (AGel) amyloidosis (OMIM 105120)	AD	• Peripheral neuropathy • Kidney failure • Cranial neuropathy	• Corneal lattice dystrophy • Cutis laxa
Non-amyloidotic neuropathies				
>80 genes incl: *GDAP1* *GJB1* *HINT1* *MFN2* *MPZ* *PMP22* *SH3TC2* *SORD*	Charcot-Marie-Tooth hereditary neuropathy	AD AR XL	Affected persons present w/peripheral neuropathy	• No cardiomyopathy • Disease progression is slower than in ATTRv amyloidosis.
GLA	Fabry disease	XL	Affected persons present w/ cardiomyopathy, nephropathy, & peripheral neuropathy	• Usually juvenile onset, esp in males • Angiokeratoma • Low alpha-galactosidase A activity
>350 genes [1]	Mitochondrial disorders incl MELAS (See Primary Mitochondrial Disorders Overview.)	AD AR Mat XL	• Cardiomyopathy • Neuropathy &/or nephropathy variably present • Myopathy	• Diabetes • Deafness • High serum lactate & pyruvate levels
Many genes incl: *ACTC1* *MYBPC3* *MYH7* *MYL2* *MYL3* *PLN* *TNNI3* *TNNT2* *TPM1*	Hereditary hypertrophic cardiomyopathy	AD [2]	Cardiomyopathy	No peripheral/autonomic neuropathy

AD = autosomal dominant; AR = autosomal recessive; ATTRv amyloidosis = hereditary transthyretin amyloidosis; Mat = maternal; MOI = mode of inheritance; XL = X-linked

1. McCormick et al [2018]

2. Nonsyndromic hereditary hypertrophic cardiomyopathy is typically inherited in an autosomal dominant manner; pathogenic variants in genes associated with autosomal recessive inheritance have been rarely reported.

Acquired disorders of interest in the differential diagnosis of ATTRv amyloidosis are listed in Table 3b. Of note, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common misdiagnosis in individuals with ATTRv amyloidosis who represent simplex cases (i.e., the only family member known to be affected) [Planté-Bordeneuve et al 2007, Koike et al 2011].

Table 3b. Acquired Conditions to Consider in the Differential Diagnosis of Hereditary Transthyretin Amyloidosis

Disorder		Features of Disorder	
		Overlapping w/ATTRv amyloidosis	Distinguishing from ATTRv amyloidosis
Amyloidoses	Wild type amyloidosis (senile systemic amyloidosis)	• Cardiomyopathy • Carpal tunnel syndrome	Severe peripheral neuropathy is rare.
	Immunoglobulin light chain (AL) amyloidosis	• Neuropathic symptoms incl polyneuropathy, carpal tunnel syndrome, & autonomic neuropathy in ~1/3 of affected persons. • Cardiomyopathy • Kidney failure	• May be difficult to distinguish clinically • Immunohistochemical study or mass spectrometry of biopsied tissue required for diagnosis. • Positive serum &/or urine monoclonal protein • Negative myocardial ^{99m}Tc-PYP scintigraphy
	ATTR following liver transplant [1]	Neuropathic symptoms incl polyneuropathy, carpal tunnel syndrome	History of liver transplant from donor w/ ATTRv amyloidosis
Cardiac sarcoidosis		• Cardiomyopathy • Peripheral neuropathy &/or nephropathy variably present	• Uveitis • Hilar lymphadenopathy • High serum angiotensin-converting enzyme level
Chronic inflammatory demyelinating polyradiculoneuropathy [2]		Peripheral neuropathy	No cardiomyopathy
POEMS syndrome		• Peripheral neuropathy • Impotence	• Positive serum &/or urine monoclonal protein • High serum vascular endothelial growth factor level
Diabetic neuropathy		Peripheral neuropathy	History of diabetes mellitus & high blood sugar levels

^{99m}Tc-PYP = ^{99m}technetium pyrophosphate; ATTR = transthyretin amyloidosis; POEMS = plasma cell neoplasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes

1. Individuals who received a liver graft from a donor with ATTRv amyloidosis have developed clinical manifestations of ATTR [Stangou et al 2005, Goto et al 2006, Barreiros et al 2010, Lladó et al 2010, Adams et al 2011, Obayashi et al 2011].

2. Eighteen of 90 individuals with ATTRv amyloidosis without a family history were mistakenly diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [Planté-Bordeneuve et al 2007]. Seven of 15 individuals with ATTRv amyloidosis who represented simplex cases were initially diagnosed with CIDP [Koike et al 2011]. Thirteen of 102 (12.7%) individuals with ATTRv amyloidosis showed electrophysiologic demyelinating features and satisfied the definite European Federation of Neurological Societies / Peripheral Nerve Society electrodiagnostic criteria for CIDP [Ohashi et al 2019].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary transthyretin amyloidosis (ATTRv amyloidosis), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Hereditary Transthyretin Amyloidosis: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic assessment incl baseline nerve conduction studies	
Cardiac	Echocardiogram	To evaluate ventricular wall thickness, ventricular septal thickness, diastolic & systolic function, & longitudinal strain
	Electrocardiogram	To evaluate for low voltage in standard limb leads & QS pattern in right precordial leads w/ or w/o conduction blocks
	Myocardial ^{99m}Tc-PYP scintigraphy	To visualize amyloid deposition in heart
CNS	• Gadolinium-enhanced MRI of brain & spinal cord • Amyloid PET imaging using PiB	To evaluate CNS amyloidosis
Ophthalmologic	Ophthalmologic eval	To evaluate for vitreous opacities & glaucoma
Renal	Blood & urine testing	To assess kidney function
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of ATTRv amyloidosis to facilitate medical & personal decision making

^{99m}Tc-PYP = ^{99m}technetium pyrophosphate; ATTRv amyloidosis = hereditary transthyretin amyloidosis; CNS = central nervous system; MOI = mode of inheritance; PiB = Pittsburgh compound B

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Table 5. Hereditary Transthyretin Amyloidosis: Targeted Therapy

Mechanism of Action	Treatment Class	Specific Drug	Administration	Comment
Inhibit synthesis of amyloidogenic TTR	*TTR*-directed ASO gene therapy	Eplontersen (Wainua®)	Subcutaneous injection once monthly	• Halts peripheral neurologic impairment • Approved in US
		Inotersen (Tegsedi®)	Subcutaneous injection once weekly	• Delays peripheral neurologic impairment • Approved in US & EU
	TTR-directed siRNA gene therapy	Patisiran (Onpattro®)	Intravenous infusion once every 3 weeks	• Halts peripheral neurologic impairment & treats cardiac manifestations • Approved in US, EU, Switzerland, Canada, Brazil, & Japan
		Vutrisiran (Amvuttra®)	Subcutaneous injection once every 3 months	• Halts peripheral neurologic impairment • Approved in US, EU, Brazil, & Japan

Table 5. continued from previous page.

Mechanism of Action	Treatment Class	Specific Drug	Administration	Comment
	Liver transplant	NA	Consider in those w/*TTR* pathogenic variant p.Val50Met, age <60 yrs, disease duration <5 yrs, polyneuropathy restricted to lower extremities or autonomic neuropathy alone, & no significant cardiac or kidney dysfunction	• Halts progression of peripheral &/or autonomic neuropathy • Not effective for cardiac amyloidosis, leptomeningeal amyloidosis, or ophthalmopathy
Stabilize native TTR tetramer	Thyroxine mimetic	Diflunisal	Oral twice daily	• Delays peripheral neurologic impairment
		Tafamidis (Vyndaqel®, Vyndamax®)	Oral once daily	• Delays peripheral neurologic & cardiac impairment & reduces cardiac related mortality • Approved in >40 countries

ASO = antisense oligonucleotide; EU = European Union; siRNA = small interfering RNA; TTR = transthyretin; US = United States

Individuals with ATTRv amyloidosis and:

- **Pure neuropathy** should be treated either with second-generation *TTR* gene silencers (vutrisiran or eplontersen) or TTR tetramer stabilizers (tafamidis). The second-generation gene silencers are superior to the first-generation silencers (patisiran or inotersen) in terms of safety and efficacy. Liver transplantation is no longer first-line therapy for ATTRv amyloidosis.
- **Isolated cardiomyopathy** (New York Heart Association Classification [NYHA] I-III) should be treated with tafamidis, the only drug approved for cardiomyopathy. Efficacy of tafamidis in individuals with NYHA IV has not been proven.
- **Mixed phenotype of neuropathy and cardiomyopathy** (defined by evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm) can be treated with tafamidis or TTR gene silencers (patisiran, vutrisiran, or eplontersen). Tafamidis is the only drug approved for cardiomyopathy. Although patisiran has been shown to be effective against cardiomyopathy, it has not been approved for cardiomyopathy. Clinical trials of vutrisiran and eplontersen for cardiomyopathy are ongoing. Off-label use of diflunisal may be considered if other options are not available.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Hereditary Transthyretin Amyloidosis: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Peripheral neuropathy	See Targeted Therapies.	
Neuropathic pain	• Serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine, gabapentin, pregabalin) • Weak opioid analgesics (tramadol, tapentadol) • Topical medications (lidocaine, capsaicin patch)	
Carpal tunnel syndrome	Carpal tunnel release surgery	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Motor neuropathy	• AFO for foot drop • Physical therapy	
Orthostatic hypertension	• Compression stockings • Removal of hypotensive medications • Increasing water intake	
Impaired gastric emptying	• Small-volume meals w/low soluble fiber & low fat content • Prokinetic medications	
Severe constipation	• Osmotic laxatives • Polyethylene glycol • Linaclotide, lubiprostone, prucalopride	
Acute persistent vomiting	Metoclopramide (IV or IM) w/electrolyte & fluid supplementation	
Restrictive cardiomyopathy	TTR tetramer stabilizers & *TTR* silencing drugs (See Targeted Therapies.)	
2nd- or 3rd-degree AV block & sick sinus syndrome	Cardiac pacemaker implantation	
Leptomeningeal amyloidosis / Cerebral amyloid angiopathy	Supportive treatments for dementia, psychosis, headache, seizures, motor paresis, & ataxia per neurologist	
Vitreous opacification	Vitrectomy	
Glaucoma	Glaucoma surgery (e.g., trabeculectomy)	
Dry eye	Ocular lubrication	
Kidney disease	• Erythropoietin or IV iron in those w/normocytic normochromic anemia • Hemodialysis for those w/end-stage kidney disease	

AFO = ankle-foot orthoses; AV = atrioventricular; IM = intramuscular; IV = intravenous; TTR = transthyretin

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended [Ueda et al 2020, Ando et al 2022].

Table 7. Hereditary Transthyretin Amyloidosis: Recommended Surveillance

System/Concern	Evaluation	Frequency
Identification of disease onset	Abdominal wall fat aspiration or gastrointestinal tract biopsy (usually stomach, duodenum, or rectum) w/Congo red staining	Annually, if possible, in asymptomatic persons w/a *TTR* pathogenic variant to identify disease onset
Neuropathy	Systematic clinical screening for sensorimotor & autonomic neuropathy using tools such as NIS, PND score, 6-MWT or 10-MWT, COMPASS-31 questionnaire, & R-ODS [1]	At least annually
	Nerve conduction studies to assess sensorimotor neuropathy	Annually

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Cardiac amyloidosis	• Clinical assessment for signs & symptoms of cardiac disease • Serum B-type natriuretic peptide levels	Annually or at each visit
	• EKG • Echocardiogram	At least annually
	^{99m}Tc-PYP myocardial scintigraphy	Every 3-5 years
Leptomeningeal amyloidosis / Cerebral amyloid angiopathy	Assessment for dementia, psychosis, headache, seizures, motor paresis, & ataxia	Annually or at each visit
Ophthalmopathy	Ophthalmology exam incl assessment for glaucoma	At least annually
Nephropathy	Laboratory assessment of kidney function	Annually or at each visit
Nutritional status	Modified body mass index	
Genetic counseling	Assessment of psychological manifestations	As needed

6-MWT = six-minute walk test; 10-MWT = ten-minute walk test; COMPASS = composite autonomic symptom score; NIS = neuropathy impairment score; PND = polyneuropathy disability; R-ODS = Rasch-built overall disability scale
1. Ando et al [2022]

Agents/Circumstances to Avoid

Since most individuals with ATTRv amyloidosis have decreased temperature and pain perception, affected individuals should not use local heating appliances, such as hot-water bottles, which can cause low-temperature burn injuries.

Evaluation of Relatives at Risk

For early diagnosis and treatment. It is appropriate to clarify the genetic status of apparently asymptomatic adult at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures to reduce morbidity and mortality.

For liver donation. In Japan, where liver transplantation from living, related donors is the generally accepted therapy for ATTRv amyloidosis, molecular genetic testing is always performed on asymptomatic adult family members volunteering to be liver donors.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Strategies for potential molecular therapies for ATTRv amyloidosis include the following:

- **Stabilization of variant transthyretin (TTR).** A Phase III clinical trial of a new TTR tetramer stabilizer, acoramidis, showed greater TTR stabilization and clinical benefit in individuals with ATTRv amyloidosis-related cardiomyopathy [Gillmore et al 2024, Verbeeck et al 2024] (see NCT03860935). To date, acoramidis is not FDA approved.
- **Gene editing of *TTR*.** NTLA-2001, a new gene-editing therapy using the CRISPR/Cas9 technology, showed reducuction of serum TTR concentration comparable to gene silencers in a Phase I clinical trial [Gillmore et al 2021]. A Phase III clinical trial of NTLA-2001 is under way (see NCT04601051).
- **Disruption of insoluble amyloid fibrils**

- A Phase I clinical trial of NI006, an investigational antibody designed to target and clear the amyloid conformations of both wild type and variant TTR but not physiologically folded TTR, is completed [Garcia-Pavia et al 2023], and a Phase III trial is under way.
- A Phase II clinical trial of PRX004/NN6019, an investigational antibody designed to target and clear the pathogenic, misfolded forms of the TTR protein found in ATTR without affecting the native, or normal, tetrameric form of the protein, is under way (see NCT05442047).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hereditary transthyretin amyloidosis (ATTRv amyloidosis) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with ATTRv amyloidosis have an affected parent.

  Note: If an individual diagnosed with ATTRv amyloidosis has biallelic *TTR* pathogenic variants, both parents may be affected and/or heterozygous for a *TTR* pathogenic variant.
- A proband with ATTRv amyloidosis may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with a *de novo TTR* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with ATTRv amyloidosis may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has the pathogenic variant(s) identified in the proband.

Sibs of a proband. The risk to sibs depends on the genetic status of the parents:

- If one parent of the proband is known to be heterozygous for a *TTR* pathogenic variant, the risk to sibs of inheriting a *TTR* pathogenic variant is 50%.
- If both parents of the proband are known to be heterozygous for a *TTR* pathogenic variant, sibs of the proband have a 50% chance of inheriting one *TTR* pathogenic variant and a 25% chance of inheriting two *TTR* pathogenic variants (see Clinical Description, **Homozygotes / compound heterozygotes**).
- Significant clinical variability may be observed among affected family members, with age of onset differing by ten to 20 years or more.
- If the *TTR* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *TTR* pathogenic variant but are clinically unaffected, sibs of the proband are presumed to be at increased risk for ATTRv amyloidosis because of the possibility of reduced penetrance in a parent or the possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual who is heterozygous for a *TTR* pathogenic variant has a 50% risk of inheriting the *TTR* pathogenic variant.
- All offspring of an individual who has biallelic *TTR* pathogenic variants will inherit a *TTR* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *TTR* pathogenic variant(s) have been identified in an affected family member. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.
- In Japan, where liver transplantation from living, related donors is the generally accepted therapy for ATTRv amyloidosis, molecular genetic testing is always performed on asymptomatic adult family members volunteering to be liver donors.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American

College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of ATTRv amyloidosis, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TTR* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for ATTRv amyloidosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Amyloidosis Foundation**
  Phone: 248-922-9610
  Email: info@amyloidosis.org
  www.amyloidosis.org
- **American Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hereditary Transthyretin Amyloidosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TTR	18q12.1	Transthyretin	TTR (transthyretin) gene homepage	TTR	TTR

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hereditary Transthyretin Amyloidosis (View All in OMIM)

105210	AMYLOIDOSIS, HEREDITARY SYSTEMIC 1; AMYLD1

Table B. continued from previous page.

176300	TRANSTHYRETIN; TTR

Molecular Pathogenesis

TTR encodes transthyretin (TTR), a protein synthesized predominantly by the liver and secreted into plasma as a tetramer composed of four identical monomers. TTR is also synthesized in the retina and choroid plexus. *TTR* pathogenic variants reduce the stability of the TTR tetramer and produce a pro-amyloidogenic monomer. The amyloidogenic process occurs in two steps:

- Soluble TTR tetramers dissociate into pro-amyloidogenic monomers that in turn polymerize into amyloid fibrils in certain tissues [Kelly 1998, Rochet & Lansbury 2000].
- Pathogenic variants in *TTR* cause significant conformational change in TTR protein molecules, in turn disrupting the stability of the TTR tetramer. Tetramers containing abnormal TTR monomers more easily dissociate into pro-amyloidogenic monomers than do normal TTR tetramers [Sekijima et al 2005].

In vitro amyloidogenicity correlates with protein stability. All abnormal TTR proteins are energetically (thermodynamically and kinetically) less stable than wild type TTR. However, extremely destabilized (highly amyloidogenic in vitro) TTR protein does not result in severe systemic amyloidosis because serum concentrations of TTR are very low due to protein degradation before secretion. The most clinically severe *TTR* pathogenic variant (p.Leu75Pro), associated with the earliest disease onset, is the most destabilized variant that can be secreted at levels comparable to the wild type, consistent with disease-associated variants being missense rather than nonsense or deletion/duplication. *TTR* pathogenic variants that are predominantly associated with central nervous system (CNS) amyloidosis result in the least stable TTR protein. The choroid plexus secretes highly destabilized TTR more efficiently than hepatic cells, potentially accounting for CNS-selective amyloid deposition (leptomeningeal amyloidosis) [Hammarström et al 2003, Sekijima et al 2003, Mitsuhashi et al 2005, Sekijima et al 2005].

Mechanism of disease causation. Gain of function

Table 8. *TTR* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change [1]	Predicted Protein Change [1]	Phenotype	Comment [Reference]
NM_000371.4 NP_000362.1	c.95T>C	p.Leu32Pro	LM, liver	See Genotype-Phenotype Correlations.
	c.112G>A	p.Asp38Asn	Heart	
	c.113A>G	p.Asp38Gly	LM	
	c.118G>A	p.Val40Ile	Heart	
	c.130C>T	p.Pro44Ser	Heart, CTS, PN	
	c.133G>A	p.Ala45Thr	LM, eye, PN	
	c.148G>A	p.Val50Met	PN, AN, eye, LM	Founder variant in Portugal, Sweden, & Japan

Table 8. continued from previous page.

Reference Sequences	DNA Nucleotide Change [1]	Predicted Protein Change [1]	Phenotype	Comment [Reference]
	c.149T>G	p.Val50Gly	LM, eye	See Genotype-Phenotype Correlations.
	c.166G>C	p.Ala56Pro	LM, eye, CTS	
	c.193G>A	p.Ala65Thr	Heart	
	c.193G>T	p.Ala65Ser	Heart	
	c.217G>A	p.Gly73Arg	LM, eye	
	c.218G>A	p.Gly73Glu	LM, eye, heart	
	c.218G>C	p.Gly73Ala	LM, PN, kidney, eye, heart	
	c.224T>C	p.Leu75Pro	Heart, AN, eye	The most clinically severe *TTR* variant (See Molecular Pathogenesis.)
	c.227A>G	p.His76Arg	Heart	See Genotype-Phenotype Correlations.
	c.229G>A	p.Gly77Arg	Heart	
	c.233T>A	p.Leu78His	CTS, heart	Initial presentation is CTS
	c.233T>G	p.Leu78Arg	CTS	
	c.251T>C	p.Phe84Ser	LM, PN, eye	See Genotype-Phenotype Correlations.
	c.262A>T	p.Ile88Leu	Heart, PN	
	c.265T>C	p.Tyr89His	LM, eye	
	c.270A>C	p.Lys90Asn	CTS, eye, PN	Initial presentation is CTS
	c.301G>A	p.Ala101Thr	Heart	See Genotype-Phenotype Correlations.
	c.302C>T	p.Ala101Val	Heart	
	c.311T>G	p.Ile104Ser	CTS, heart, eye	Initial presentation is CTS
	c.323A>G	p.His108Arg	Heart	See Genotype-Phenotype Correlations.
	c.334G>A	p.Glu112Lys	Heart	
	c.367C>A	p.Arg123Ser	Heart	
	c.379A>G	p.Ile127Val	CTS, heart, PN	Initial presentation is CTS
	c.391C>A	p.Leu131Met	Heart	See Genotype-Phenotype Correlations.
	c.401A>G	p.Tyr134Cys	LM, eye, PN, AN	
	c.400T>C	p.Tyr134His	CTS, skin	Initial presentation is CTS
	c.416C>T	p.Thr139Met	Non-amyloid, FEH [2]	Suppressor variant that has a protective effect (See Genotype-Phenotype Correlations.)

Table 8. continued from previous page.

Reference Sequences	DNA Nucleotide Change [1]	Predicted Protein Change [1]	Phenotype	Comment [Reference]
	c.424G>A	p.Val142Ile	Heart	Most common *TTR* pathogenic variant worldwide; present in 3.0%-3.9% of African Americans & >5.0% of the population in some areas of West Africa [Jacobson et al 1997, Yamashita et al 2005]

AN = autonomic neuropathy; CTS = carpal tunnel syndrome; FEH = familial euthyroid hypertyroxinemia; LM = leptomeningeal amyloidosis; PN = peripheral neuropathy

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Historical protein numbering was based on the mature protein after cleavage of a 20-amino-acid signal sequence (e.g., p.Leu32Pro was historically referred to as Leu12Pro). Standard nomenclature uses numbering beginning at the Met initiation codon. Variants reported in older literature may use historical nomenclature.

2. See Genetically Related Disorders.

Chapter Notes

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