



## Hereditary Transthyretin Amyloidosis

Synonyms: Familial Amyloid Polyneuropathy, Familial Transthyretin Amyloidosis, Hereditary ATTR Amyloidosis

Yoshiki Sekijima, MD, PhD<sup>1</sup>

Created: November 5, 2001; Revised: June 17, 2021.

### Summary

#### Clinical characteristics

Hereditary transthyretin (ATTR) amyloidosis is characterized by a slowly progressive peripheral sensorimotor and/or autonomic neuropathy as well as non-neuropathic changes of cardiomyopathy, nephropathy, vitreous opacities, and CNS amyloidosis. 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 paresthesias and hypesthesias 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 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.

#### Diagnosis/testing

The diagnosis of hereditary ATTR amyloidosis is established in a proband with characteristic clinical features, amyloid deposits identified on biopsy that bind to anti-TTR antibodies, and identification of a heterozygous pathogenic variant in *TTR* by molecular genetic testing.

#### Management

*Treatment of manifestations:* Therapeutic approach based on the characteristics of each therapy and the affected individual's severity of amyloidosis, general condition, and social environment. Pharmacotherapeutics (e.g., TTR tetramer stabilizers, gene-silencing therapies) are first-line therapy for all individuals with hereditary ATTR amyloidosis. Limited indication for orthotopic liver transplantation, which is highly invasive and does not address non-neuropathic forms of ATTR amyloidosis. Surgery indicated for carpal tunnel syndrome, vitrectomy

for vitreous involvement, and surgical treatment for glaucoma. In those with sick sinus syndrome or second-degree or third-degree AV block, a cardiac pacemaker may be indicated.

*Surveillance:* Serial nerve conduction studies to monitor polyneuropathy; serial electrocardiogram, echocardiography, and serum B-type natriuretic peptide levels to monitor cardiomyopathy and conduction block; follow modified body mass index to monitor nutritional status.

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

*Evaluation of relatives at risk:* If the family-specific pathogenic variant is known, molecular genetic testing ensures early diagnosis and treatment. If the familial variant is not known, clinical evaluations ensure early diagnosis and treatment.

## Genetic counseling

Hereditary ATTR amyloidosis is inherited in an autosomal dominant manner. Each child of an affected individual (who is heterozygous for one *TTR* pathogenic variant) has a 50% chance of inheriting the *TTR* variant. For affected individuals homozygous for *TTR* pathogenic variants:

- Each sib is at a 50% risk of inheriting one *TTR* pathogenic variant and a 25% risk of inheriting two *TTR* pathogenic variants;
- All offspring will inherit a pathogenic variant.

Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant has been identified in the family. Requests for prenatal testing for adult-onset conditions that (like hereditary ATTR amyloidosis) do not affect intellect and have some treatment available are not common.

## GeneReview Scope

Hereditary Transthyretin (ATTR) Amyloidosis: Included Phenotypes
<ul style="list-style-type: none"> <li>• ATTR amyloid neuropathy</li> <li>• ATTR cardiac amyloidosis</li> <li>• ATTR leptomeningeal/CNS amyloidosis</li> </ul>

For synonyms and outdated names see Nomenclature.

## Diagnosis

### Suggestive Findings

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

**Clinical features.** 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

**Family history** is consistent with autosomal dominant inheritance.

Note: While family history supports the diagnosis, absence of other affected individuals in the family does not preclude the diagnosis of hereditary ATTR amyloidosis, especially in persons older than age 50 years.

## Histopathology

- **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, 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-TTR antibodies** to identify amyloid deposits associated with ATTR amyloidosis

## Establishing the Diagnosis

The diagnosis of hereditary ATTR amyloidosis **is established** in a proband with the above clinical features, biopsy showing amyloid deposits that bind to anti-TTR antibodies, and identification of a heterozygous pathogenic variant in *TTR* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TTR* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.  
Note: (1) Targeted analysis for pathogenic variants can be performed first for the most common pathogenic variant, c.148G>A (p.Val50Met). (2) Since hereditary ATTR amyloidosis occurs through a gain-of-function mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.
- **A multigene panel** that includes *TTR* and other genes of interest (see Differential Diagnosis) is most likely 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](#).

**Table 1.** Molecular Genetic Testing Used in Hereditary Transthyretin (ATTR) Amyloidosis

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
TTR	Sequence analysis <sup>3</sup>	>99% <sup>4, 5</sup>
	Gene-targeted deletion/duplication analysis <sup>6</sup>	None reported <sup>7</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; 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. The gene 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 hereditary ATTR amyloidosis occurs through a gain-of-function mechanism and large intragenic deletion or duplication has 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 (ATTR) amyloidosis can include peripheral sensorimotor neuropathy and autonomic neuropathy, as well as non-neuropathic changes (cardiomyopathy, nephropathy, vitreous opacities, and CNS amyloidosis) (see Table 2).

**Table 2.** Phenotypes Associated with Hereditary Transthyretin (ATTR) Amyloidosis

Phenotype		Representative Genotype
Type	Features	
ATTR amyloid neuropathy (familial amyloid polyneuropathy)	<p>Early:</p> <ul style="list-style-type: none"> <li>• Sensorimotor polyneuropathy of the legs</li> <li>• Carpal tunnel syndrome</li> <li>• Autonomic dysfunction</li> <li>• Constipation &amp;/or diarrhea</li> <li>• Impotence</li> </ul> <p>Late:</p> <ul style="list-style-type: none"> <li>• Cardiomyopathy</li> <li>• Vitreous opacities</li> <li>• Glaucoma</li> <li>• Nephropathy</li> <li>• CNS symptoms</li> </ul>	p.Val50Met <sup>1</sup>
ATTR cardiac amyloidosis (familial amyloid cardiomyopathy)	<ul style="list-style-type: none"> <li>• Cardiomegaly</li> <li>• Conduction block</li> <li>• Arrhythmia</li> <li>• Anginal pain</li> <li>• Congestive heart failure</li> <li>• Sudden death</li> </ul>	p.Val142Ile

Table 2. continued from previous page.

Phenotype		Representative Genotype
Type	Features	
ATTR leptomeningeal amyloidosis / cerebral amyloid angiopathy	<ul style="list-style-type: none"> <li>• Transient focal neurologic episodes</li> <li>• Hemorrhage (intracerebral &amp;/or subarachnoid)</li> <li>• Dementia</li> <li>• Ataxia</li> <li>• Spasticity</li> <li>• Seizures</li> <li>• Psychosis</li> <li>• Hydrocephalus</li> </ul>	p.Asp38Gly

1. Historical protein numbering was based on the mature protein after cleavage of a 20-amino-acid signal sequence (i.e., 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.

**Neuropathy.** The cardinal feature of ATTR-amyloid 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 signs of this sensory neuropathy are paresthesias (sense of burning, shooting pain) and hypesthesias 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. In the full-blown stage of the disease, sensory loss, muscle atrophy, and weakness of the extremities show a glove and stocking distribution. Foot drop, wrist drop, and disability of the hands and fingers are common symptoms of motor neuropathy.

Autonomic neuropathy may occur as the first clinical symptom of the disease. The symptoms of autonomic dysfunction include: orthostatic hypotension [Vita et al 2005], constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Because of sensory loss and autonomic dysfunction, trophic ulcers on the lower extremities are common. Frequently, the autonomic neuropathy produces the most significant morbidity of the disorder.

The disease usually begins in the third, fourth, or fifth decade in persons from endemic foci in Portugal and Japan; onset is later in persons from other areas. The following findings indicate that age at onset varies greatly even within ethnically identical populations with the same *TTR* pathogenic variant:

- For persons of Japanese ancestry with the p.Val50Met variant who are related to two large endemic foci (Ogawa village and Arao city), the mean age at onset is 40.1±12.8 years (range 22-74 years) [Nakazato 1998].
- For 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 52-80 years) [Misu et al 1999, Ikeda et al 2002].
- For persons of Portuguese ancestry with the p.Val50Met variant, the mean age at onset is 33.5±9.4 years (range 17-78 years).
- For 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].

Sensorimotor neuropathy and autonomic neuropathy progress over ten to 20 years. Various types of cardiac conduction block frequently appear. Cachexia is a common feature at the late stage of the disease. Affected individuals usually die of cardiac failure, renal failure, or infection.

Individuals with specific *TTR* variants (e.g., p.Leu78His, p.Leu78Arg, p.Lys90Asn, p.Ile104Ser, p.Ile127Val, p.Tyr134His) tend to develop carpal tunnel syndrome as an initial symptom [Nakazato 1998, Connors et al 2000, Benson 2001, Hund et al 2001, Connors et al 2003].

Sensorimotor neuropathy and autonomic neuropathy are accompanied by visceral involvement. Cardiomyopathy (e.g., cardiac failure, arrhythmia, conduction block), ophthalmopathy (e.g., vitreous opacities, glaucoma), nephropathy, and/or CNS manifestations (e.g., transient focal neurologic episodes, intracerebral and/or subarachnoid hemorrhages) are frequently seen in the advanced stage of the disease.

**Non-neuropathic amyloidosis.** Individuals with hereditary ATTR amyloidosis do not necessarily present with polyneuropathy. Cardiac amyloidosis and leptomeningeal amyloidosis are well-known non-neuropathic forms of hereditary ATTR amyloidosis that are associated with specific *TTR* variants. In these types of hereditary ATTR amyloidosis, polyneuropathy is absent or, if present, less evident. Approximately one third of the *TTR* protein variants are accompanied by vitreous opacities.

**Cardiac amyloidosis**, mainly characterized by progressive cardiomyopathy, has been associated with more than two thirds of *TTR* pathogenic variants (see Table 6) [Nakazato 1998, Benson 2001, Saraiva 2001, Connors et al 2003, Hattori et al 2003, Benson & Kincaid 2007]. In some families with specific *TTR* variants, such as p.Asp38Asn, p.Val40Ile, p.Pro44Ser, p.Ala65Thr, p.Ala65Ser, p.His76Arg, p.Gly77Arg, p.Ile88Leu, p.Ala101Thr, p.Ala101Val, p.His108Arg, p.Glu112Lys, p.Arg123Ser, p.Leu131Met, or p.Val142Ile, cardiomyopathy without peripheral neuropathy is a main feature of the disease.

Cardiac amyloidosis is usually late onset. Most individuals develop cardiac symptoms after age 50 years; cardiac amyloidosis generally presents with restrictive cardiomyopathy. The typical electrocardiogram shows a pseudoinfarction pattern with prominent Q wave in leads II, III,  $aV_F$ , 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 present "a granular sparkling appearance."

Among the variants responsible for cardiac amyloidosis, p.Val142Ile is notable for its prevalence in African Americans. Approximately 3.0%-3.9% of African Americans are heterozygous for p.Val142Ile [Yamashita et al 2005]. The high frequency of p.Val142Ile 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 [Jacobson et al 1997].

**Leptomeningeal (oculoleptomeningeal) amyloidosis / cerebral amyloid angiopathy.** Amyloid deposition is seen in the pial and arachnoid membrane, as well as in the walls of vessels in the subarachnoid space associated with *TTR* pathogenic variants including p.Leu32Pro, p.Asp38Gly, p.Ala45Thr, p.Val50Gly, p.Ala56Pro, p.Gly73Glu, p.Gly73Ala, p.Phe84Ser, p.Tyr89His, or p.Tyr134Cys (see Table 6) [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]. Amyloid in the blood vessels disappears as the vessels penetrate the brain parenchyma.

Individuals with leptomeningeal amyloidosis show CNS signs and symptoms including: transient focal neurologic episodes, dementia, psychosis, visual impairment, headache, seizures, motor paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage.

When associated with vitreous amyloid deposits, leptomeningeal amyloidosis is known as *familial oculoleptomeningeal amyloidosis (FOLMA)* [Petersen et al 1997, Jin et al 2004].

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].

Although meningeal biopsy is necessary to confirm amyloid deposition in the meninges, characteristic MRI findings and the presence of a pathogenic variant in *TTR* strongly suggest this pathology [Mitsuhashi et al 2004]. CNS ATTR amyloid deposition can also be detected by amyloid PET, using Pittsburgh compound B (PiB) [Sekijima et al 2016].

**Ocular amyloidosis.** 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 families with various *TTR* pathogenic variants, including p.Val50Met [Benson 2001, Connors et al 2003, Kawaji et al 2004, Benson & Kincaid 2007]. Four of 43 individuals with the p.Val50Met variant developed vitreous amyloidosis as the first manifestation of hereditary ATTR amyloidosis [Kawaji et al 2004]. In one case report, vitreous opacification was the only evidence of amyloid deposit caused by the p.Trp61Leu variant [Yazaki et al 2002].

**Nephropathy.** The kidney is consistently involved with marked deposition of amyloid demonstrated at postmortem examination. Mild to severe renal involvement is usually seen in the advanced stage [Haagsma et al 2004, Lobato et al 2004]. Renal involvement, including nephritic syndrome and progressive renal failure, occurs in about one third of individuals of Portuguese descent with early-onset hereditary ATTR amyloidosis caused by *TTR* pathogenic variant p.Val50Met [Lobato et al 2004]; however, severe renal dysfunction rarely occurs in individuals with late-onset disease.

**Other.** Amyloid deposition on the gastrointestinal tract wall, especially with involvement of the gastrointestinal autonomic nerves, is common [Ikeda et al 1982, Ikeda et al 1983]. Nodular cutaneous amyloidosis has been reported in an individual with the p.Tyr134His variant [Mochizuki et al 2001]. Shortness of breath induced by diffuse pulmonary amyloid deposition has been reported in two individuals with the p.Asp58Ala variant [Yazaki et al 2000a]. Anemia with low erythropoietin has been reported in 25% of individuals [Beirão et al 2004].

## Genotype-Phenotype Correlations

**Heterozygotes.** Despite intensive investigation, few genotype-phenotype correlations have been detected.

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

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:

- Cardiac amyloidosis is caused by p.Asp38Asn, p.Val40Ile, p.Pro44Ser, p.Ala65Thr, Ala65Ser, 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.
- Leptomeningeal amyloidosis 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 destabilized *TTR* variants induce leptomeningeal amyloidosis [Hammarström et al 2001, Sekijima et al 2003, Sekijima et al 2005].

**Homozygosity** for the p.Val50Met variant has been reported in at least 19 individuals from 14 families [Munar-Qués et al 2001, Tojo et al 2008]. Eight homozygotes for variants p.Val142Ile (5), p.Leu78His (1), p.Phe84Leu (1), and p.Ile88Leu (1) have been reported [Jacobson et al 1990, Nichols et al 1991, Ferlini et al 1996, Askanas et al 2000, Jacob et al 2007, Perfetto et al 2011].

Homozygotes present with a slightly more severe clinical course (higher incidence rate and earlier onset) than heterozygotes within the same family [Tojo et al 2008]; amyloid deposition is more widespread in homozygotes

than in heterozygotes [Yoshinaga et al 2004]. Most homozygotes are members of families characterized by incomplete penetrance of hereditary ATTR amyloidosis.

## Penetrance

Because the penetrance for hereditary ATTR amyloidosis is not 100%, an individual with a *TTR* pathogenic variant may be symptom free until late adulthood. The penetrance may vary by 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 the p.Val50Met variant is estimated at 80% by age 50 and 91% by age 70 years, whereas the risk in French heterozygotes is 14% by age 50 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, 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.

The neuropathy associated with *TTR* pathogenic variants, now called hereditary ATTR amyloidosis, 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)

## Prevalence

The p.Val50Met pathogenic variant, found worldwide, is the most widely studied *TTR* variant and is responsible for the well-known large foci of individuals with TTR amyloid polyneuropathy in Portugal, Sweden, and Japan. Numerous families with various pathogenic variants other than p.Val50Met have also been identified worldwide.

The frequency of hereditary ATTR amyloidosis caused by the variant p.Val50Met is estimated at 1:538 in northern Portugal (Povoa do Varzim and Vila do Conde), the largest cluster worldwide of individuals with hereditary ATTR amyloidosis.

In individuals of northern European origin in the US, the frequency of p.Val50Met-related hereditary ATTR amyloidosis is estimated at 1:100,000 [Benson 2001].

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).

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. In the US, the frequency of p.Val142Ile in the white and Hispanic populations is 0.44% and 0.0%, respectively [Jacobson et al 1997, Yamashita et al 2005].

## Genetically Related (Allelic) Disorders

**Familial euthyroid hyperthyroxinemia** is caused by benign variants in *TTR*, including p.Gly26Ser, p.Ala129Thr, p.Ala129Val, and p.Thr139Met [Nakazato 1998, Benson 2001, Saraiva 2001]. The *TTR* protein

binds approximately 15% of serum thyroxine. These 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 sequence variants develop no clinical symptoms (i.e., they are euthyroid).

**Wild type ATTR amyloidosis** (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 [Westermarck et al 2003]. Wild type ATTR amyloidosis affects mainly the elderly but is rarely diagnosed during life [Sekijima et al 2018]. Thus, the precise prevalence of wild type ATTR amyloidosis 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 amyloidosis typically does not cause symptoms or can result in cardiac symptoms. The majority of individuals with wild type ATTR amyloidosis present with carpal tunnel syndrome [Nakagawa et al 2016]. Wild type ATTR amyloidosis should be distinguished from hereditary ATTR amyloidosis with variant TTR or other forms of amyloidosis such as primary (AL) amyloidosis. In contrast to the rapid progression of heart failure in AL amyloidosis, wild type ATTR amyloidosis results in slowly progressive heart failure [Ng et al 2005]. Westermarck et al [2003] have indicated that the lung may be a more reliable tissue for amyloid detection than the heart.

## Differential Diagnosis

**Table 3a.** Other Amyloidoses to Consider in the Differential Diagnosis of Hereditary Transthyretin (ATTR) Amyloidosis

DiffDx Disorder		Gene	MOI	Clinical Features of DiffDx Disorder	
				Overlapping	Distinguishing
Neuropathic amyloidoses	Apo AI (AAPoAI) amyloidosis (OMIM 105200)	<i>APOA1</i>	AD	<ul style="list-style-type: none"> <li>Nephropathy</li> <li>Peripheral neuropathy</li> <li>Cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>Hepatomegaly</li> <li>Swelling of testis</li> </ul>
	Gelsolin (AGel) amyloidosis (OMIM 105120)	<i>GSN</i>	AD	<ul style="list-style-type: none"> <li>Peripheral neuropathy</li> <li>Renal failure</li> </ul>	<ul style="list-style-type: none"> <li>Cranial neuropathy</li> <li>Corneal lattice dystrophy</li> <li>Cutis laxa</li> </ul>
Systemic amyloidoses	Wild type transthyretin amyloidosis (senile systemic amyloidosis)	NA (acquired disorders)		<ul style="list-style-type: none"> <li>Cardiomyopathy</li> <li>Carpal tunnel syndrome</li> <li>Peripheral neuropathy (mild or absent)</li> </ul>	<ul style="list-style-type: none"> <li>No <i>TTR</i> pathogenic variants</li> <li>Severe peripheral neuropathy is rare</li> </ul>
	Immunoglobulin (AL) amyloidosis			<ul style="list-style-type: none"> <li>Neuropathic symptoms incl polyneuropathy, autonomic neuropathy, &amp; carpal tunnel syndrome in ~1/3 of affected individuals</li> <li>Cardiomyopathy</li> <li>Renal failure</li> </ul>	<ul style="list-style-type: none"> <li>May be difficult to distinguish clinically</li> <li>Immunohisto-chemical study or mass spectrometry of biopsied tissue required for diagnosis</li> <li>Positive serum &amp;/or urine monoclonal protein</li> <li>Negative myocardial technetium-99m-pyrophosphate scintigraphy</li> </ul>

AD = autosomal dominant; DiffDx = differential diagnosis; MOI = mode of inheritance; NA = not applicable

A total of 35 amyloidogenic proteins including transthyretin (TTR) have been identified in human amyloidoses [Sipe et al 2016].

Among the hereditary amyloidoses, hereditary ATTR amyloidosis is the most prevalent [Benson 2001, Hund et al 2001, Benson 2005].

**Table 3b.** Non-Amyloidotic Neuropathies to Consider in the Differential Diagnosis of Hereditary Transthyretin (ATTR) Amyloidosis

DiffDx Disorder	Gene	MOI	Clinical Features of DiffDx Disorder	
			Overlapping	Distinguishing
<a href="#">Charcot-Marie-Tooth hereditary neuropathy</a>	Many <sup>1</sup>	AD AR XL	Present w/peripheral neuropathy	<ul style="list-style-type: none"> <li>No cardiomyopathy</li> <li>Disease progression is slower than in hereditary ATTR amyloidosis.</li> </ul>
<a href="#">Fabry disease</a>	<i>GLA</i>	XL	Present w/cardiomyopathy, nephropathy, & peripheral nephropathy	<ul style="list-style-type: none"> <li>Juvenile onset, esp in males</li> <li>Angiokeratoma</li> <li>↓ α galactosidase activity</li> </ul>
Mitochondrial disorders incl MELAS (See <a href="#">Mitochondrial Disorders Overview</a> .)	Many <sup>2</sup>	Mat AR AD	<ul style="list-style-type: none"> <li>Present w/ cardiomyopathy</li> <li>Neuropathy &amp;/or nephropathy variably present</li> </ul>	<ul style="list-style-type: none"> <li>Myopathy</li> <li>Diabetes</li> <li>Deafness</li> <li>↑ serum lactate &amp; pyruvate levels</li> </ul>
<a href="#">Hereditary hypertrophic cardiomyopathy</a>	Many <sup>3</sup>	AD	Present w/cardiomyopathy	No peripheral/autonomic neuropathy
<a href="#">Cardiac sarcoidosis</a>	NA (acquired disorders)		<ul style="list-style-type: none"> <li>Present w/ cardiomyopathy</li> <li>Peripheral neuropathy &amp;/or nephropathy variably present</li> </ul>	<ul style="list-style-type: none"> <li>Negative family history</li> <li>Uveitis</li> <li>Hilar lymphadenopathy</li> <li>↑ serum angiotensin-converting enzyme level</li> </ul>
<a href="#">Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)</a>			<ul style="list-style-type: none"> <li>Negative family history</li> <li>No cardiomyopathy</li> <li>Most common misdiagnosis in those w/ ATTR amyloidosis <sup>4</sup></li> </ul>	
<a href="#">Crow-Fukase syndrome (aka POEMS)</a>			Present w/peripheral neuropathy	<ul style="list-style-type: none"> <li>Negative family history</li> <li>Positive serum &amp;/or urine monoclonal protein</li> <li>↑ serum vascular endothelial growth factor level</li> </ul>
<a href="#">Diabetic neuropathy</a>			<ul style="list-style-type: none"> <li>Negative family history</li> <li>↑ blood sugar level</li> </ul>	

↑ = high; ↓ = low; AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; Mat = maternal; MOI = mode of inheritance; POEMS = plasma cell neoplasia w/polyneuropathy, organomegaly, endocrinopathy, M protein, & skin changes; NA = not applicable; XL = X-linked

1. More than 80 different genes are associated with CMT [Stojkovic 2016].

2. Pathogenic variants known to cause MELAS have been identified in mtDNA tRNA genes including *MT-TL1*, *MT-ND5*, *MT-TC*, *MT-TK*, *MT-TV*, *MT-TF*, *MT-TQ*, *MT-TS1*, *MT-TS2*, and *MT-TW*, and in the protein-encoding genes *MT-CO1*, *MT-CO2*, *MT-CO3*, *MT-CYB*, *MT-ND1*, *MT-ND3*, and *MT-ND6*. Pathogenic variants in many other genes cause mitochondrial disorders (see [Mitochondrial Disorders Overview](#)).

3. Pathogenic variants known to cause hereditary hypertrophic cardiomyopathy have been identified in *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, *CSRP3*, *ACTN2*, *MYH6*, *TCAP*, *TNNC1*, *PLN*, *MYOZ2*, and *NEXN* (see [Hypertrophic Cardiomyopathy Overview](#)).

4. 18/90 individuals with hereditary ATTR amyloidosis without a family history were mistakenly diagnosed with CIDP [Planté-Bordeneuve et al 2007].

## Management

### Evaluations Following Initial Diagnosis

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

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with Hereditary Transthyretin (ATTR) Amyloidosis

System/Concern	Evaluation	Comment
<b>Neurologic</b>	Complete neurologic assessment incl baseline nerve conduction studies	
<b>Cardiac</b>	Echocardiogram	To evaluate ventricular wall thickness, ventricular septal thickness, diastolic & systolic function, & longitudinal strain
	Electrocardiogram	To evaluate for low voltage in the standard limb leads & QS pattern in the right precordial leads w/ or w/out conduction blocks
	Myocardial technetium-99m-pyrophosphate scintigraphy	To visualize amyloid deposition in heart
<b>CNS</b>	<ul style="list-style-type: none"> <li>Gadolinium-enhanced MRI of brain &amp; spinal cord</li> <li>Amyloid PET imaging using PiB</li> </ul>	To evaluate CNS amyloidosis
<b>Ophthalmologic</b>	Ophthalmologic eval	Evaluate for vitreous opacities & glaucoma.
<b>Nephrologic</b>	Routine blood & urine exams for eval of renal function	
<b>Other</b>	Consultation w/clinical geneticist &/or genetic counselor	

PiB = Pittsburgh compound B

### Treatment of Manifestations

**Table 5.** Treatment of Manifestations in Individuals with Hereditary Transthyretin (ATTR) Amyloidosis

Manifestation/Concern	Treatment
<b>Peripheral &amp; autonomic neuropathy</b>	<ul style="list-style-type: none"> <li>Orthotopic liver transplantation</li> <li>TTR tetramer stabilizers</li> <li>Gene-silencing therapies</li> </ul>
<b>Cardiomyopathy</b>	TTR tetramer stabilizers
<b>Carpal tunnel syndrome</b>	Carpal tunnel release surgery
<b>Vitreous involvement</b>	Vitrectomy
<b>Glaucoma</b>	Glaucoma surgery
<b>2nd- or 3rd-degree AV block &amp; sick sinus syndrome</b>	Cardiac pacemaker implantation

**Orthotopic liver transplantation (OLT).** Orthotopic liver transplantation (OLT) provides a wild type gene expressing normal TTR in the liver, the main source of serum TTR protein. Successful OLT results in rapid disappearance of variant TTR protein from the serum and thus halts the progression of peripheral and/or autonomic neuropathy. It has been shown by pre- and postoperative sural nerve biopsy that myelinated nerve fibers regenerate after OLT [Ikeda et al 1997].

**Recommended clinical criteria for OLT** in individuals with TTR amyloid polyneuropathy [Takei et al 1999, Adams et al 2000] include the following:

- Age younger than 60 years
- Disease duration less than five years
- Either polyneuropathy that is restricted to the lower extremities or autonomic neuropathy alone
- No significant cardiac or renal dysfunction

As of the end of December 2017, 2,236 individuals with hereditary ATTR amyloidosis, approximately 90% of whom were heterozygous for the p.Val50Met variant, had undergone liver transplantation ([www.fapwtr.org/ram\\_fap.htm](http://www.fapwtr.org/ram_fap.htm)) [Ericzon et al 2000, Ikeda et al 2003, Herlenius et al 2004, Stangou & Hawkins 2004]. The five-year survival rate was significantly higher in individuals with the p.Val50Met variant than in those with other pathogenic variants (80% vs 57%,  $p=0.001$ ) [Ericzon et al 2000, Ikeda et al 2003]. The most common causes of postoperative death were cardiovascular events (29%) and septicemia (26%) [Ikeda et al 2003].

**Predictors of poor outcomes in transplanted individuals** include [Adams et al 2000, Ikeda et al 2003, Yamamoto et al 2007, Algalarrondo et al 2015, Ericzon et al 2015]:

- Poor nutritional condition (modified body mass index <600)
- Severe polyneuropathy (Norris score <55/81)
- Permanent urinary incontinence
- Marked postural hypotension
- A fixed pulse rate
- Age  $\geq 50$  years (especially in males)
- Pathogenic variants other than p.Val50Met
- Presence of cardiomyopathy

**OLT** is not effective in the non-neuropathic forms of hereditary ATTR amyloidosis (i.e., cardiac amyloidosis, leptomeningeal amyloidosis, and familial oculoleptomeningeal amyloidosis [FOLMA]).

Cardiomyopathy was reported to progress after OLT in some individuals with specific pathogenic variants other than p.Val50Met (e.g., p.Ala56Pro, p.Glu62Gly, and p.Ser97Tyr) [Dubrey et al 1997, Stangou et al 1998, Yazaki et al 2000b, Hörnsten et al 2004]. It is presumed that amyloid cardiomyopathy may accelerate after OLT by progressive deposition of wild type TTR on a template of amyloid derived from variant TTR [Yazaki et al 2000b, Hörnsten et al 2004]. Therefore, it is critical to assess the severity of cardiac amyloidosis when considering OLT [Coutinho et al 2004, Juneblad et al 2004].

Individuals with leptomeningeal involvement may not be candidates for liver transplantation because amyloidogenic TTR variants that cause intracranial amyloid deposits are considered to be derived from the choroid plexus. Leptomeningeal amyloidosis / cerebral amyloid angiopathy may develop after OLT as the choroid plexus continues to produce variant TTR [Maia et al 2015, Sekijima et al 2016].

Amyloid ophthalmopathy (e.g., vitreous opacities and glaucoma) may also progress after OLT, possibly as the result of *de novo* production of variant TTR in the retinal epithelium.

Note: Because liver involvement in hereditary ATTR amyloidosis is minimal, the liver of an individual with hereditary ATTR amyloidosis can be grafted into an individual with liver cancer or end-stage liver disease (so-called "domino" liver transplantation). Since 1995, 1,254 domino liver transplantations have been performed. Several individuals who received a liver graft from heterozygotes with hereditary ATTR amyloidosis developed symptomatic systemic ATTR amyloidosis [Stangou et al 2005, Goto et al 2006, Barreiros et al 2010, Lladó et al 2010, Adams et al 2011, Obayashi et al 2011].

**TTR tetramer stabilizers (tafamidis, diflunisal).** Another therapeutic option for ameliorating hereditary ATTR amyloidosis is to stabilize the native TTR tetramer structure, as tetramer dissociation is necessary for ATTR amyloid fibril formation. To date, clinical effect of two TTR tetramer stabilizers, tafamidis and diflunisal, has been confirmed:

- **Tafamidis.** In a Phase II/III study, tafamidis (Vyndaqel<sup>®</sup>) showed efficacy in delaying peripheral neurologic impairment compared with individuals treated with placebo. In addition, tafamidis resulted in improved nutritional status (modified body mass index) of the study participants [Coelho et al 2012].

In a Phase III clinical trial for ATTR cardiomyopathy including hereditary and wild type ATTR amyloidosis, tafamidis reduced mortality of all causes and cardiovascular-related hospitalizations, and reduced the decline in functional capacity and quality of life as compared with placebo [Maurer et al 2018].

Based on these findings, tafamidis was approved for hereditary ATTR amyloidosis treatment in more than 40 countries.

Among individuals with early-onset disease (age <50 years), tafamidis reduced the mortality risk over that of untreated individuals by 91%, and that of OLTX-treated individuals by 63%. Among individuals with late-onset disease (≥50 years), tafamidis reduced mortality risk over that of untreated individuals by 82% [Coelho et al 2018].

- **Diflunisal.** Phase III studies of diflunisal showed efficacy in delaying peripheral neurologic impairment compared with individuals treated with placebo [Berk et al 2013].

**Gene-silencing therapies (patisiran, inotersen).** Gene-silencing approaches using antisense oligonucleotides (ASOs) or small interfering RNAs (siRNAs) are promising therapeutic strategies for amelioration of hereditary ATTR amyloidosis, as reduction of amyloid fibril precursor protein level has proven to be effective in AL amyloidosis (chemotherapy to reduce amyloidogenic immunoglobulin light chain) and amyloid A protein (AA) amyloidosis (biologic agents and immunosuppressive agents to reduce serum amyloid A protein) [Sekijima 2015].

- **Patisiran.** In a Phase III clinical trial, patisiran (Onpattro<sup>™</sup>), a siRNA therapeutic agent, showed efficacy in halting peripheral neurologic impairment compared with placebo [Adams et al 2018]. In addition, patisiran decreased mean left ventricular wall thickness, global longitudinal strain, N-terminal prohormone of brain natriuretic peptide, and adverse cardiac outcomes compared with placebo [Solomon et al 2019].

Based on these findings, patisiran has been approved for hereditary ATTR amyloidosis treatment in the US, EU, Switzerland, Canada, Brazil, and Japan.

- **Inotersen.** In a Phase III clinical trial, inotersen (Tegsedi<sup>™</sup>), an ASO therapeutic agent, showed efficacy in delaying peripheral neurologic impairment compared with placebo [Benson et al 2018]. Based on these findings, inotersen has been approved for hereditary ATTR amyloidosis treatment in the US and EU.

## Surveillance

Serial nerve conduction studies can be used to objectively monitor the course of the polyneuropathy.

Serial electrocardiogram, echocardiography, and serum B-type natriuretic peptide levels can be used to monitor the course of cardiomyopathy and conduction block.

Modified body mass index can be used to monitor nutritional status.

## Agents/Circumstances to Avoid

Since most individuals with hereditary ATTR 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 injury.

## Evaluation of Relatives at Risk

It is appropriate to clarify the status of apparently asymptomatic older and younger at-risk relatives of an affected individual so that morbidity and mortality can be reduced by early diagnosis and treatment. Evaluations can include:

- Molecular genetic testing if the *TTR* pathogenic variant in the family is known;
- Clinical diagnostic evaluations if the pathogenic variant in the family is not known.

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

## Therapies Under Investigation

Strategies of potential molecular therapies for hereditary ATTR amyloidosis include the following:

- **Inhibition of synthesis of variant TTR.** Phase III clinical trials of a new siRNA therapeutic, vutrisiran, and a new ASO therapeutic agent, eplontersen, are under way.
- **Stabilization of variant TTR.** A Phase III clinical trial of a new TTR tetramer stabilizer, AG10, is under way.
- **Disruption of insoluble amyloid fibrils**
  - A Phase III study of combination therapy with doxycycline, an antibiotic that disrupts TTR amyloid fibrils, and tauroursodeoxycholic acid (TUDCA), a biliary acid that reduces nonfibrillar TTR aggregates, is under way.
  - A Phase I clinical trial of PRX004, an investigational antibody designed to target and clear the pathogenic, misfolded forms of the TTR protein found in ATTR amyloidosis without affecting the native, or normal, tetrameric form of the protein, is under way.
  - A Phase I clinical trial of NTLA-2001, an investigational gene-editing therapy using the CRISPR/Cas9 technology, is under way.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://european-clinical-trials-register.eu) 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 (ATTR) amyloidosis is inherited in an autosomal dominant manner.

## Risk to Family Members

### Parents of a proband

- Some individuals diagnosed with hereditary ATTR amyloidosis have an affected parent.

If the proband has biallelic *TTR* pathogenic variants (reported in at least 26 affected individuals), both parents may be affected and/or heterozygous for a *TTR* pathogenic variant.

- A proband with hereditary ATTR amyloidosis may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing if the pathogenic variant in *TTR* has been identified in the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with hereditary ATTR 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 appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of 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 affected and/or known to have a *TTR* pathogenic variant, the risk to sibs is 50%.
- If both parents of the proband are affected and/or known to have 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.
- If the proband has a known *TTR* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- Sibs of a proband with clinically unaffected parents are presumed to be at increased risk for hereditary ATTR amyloidosis because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

### Offspring of a proband

- Each child of a proband who is heterozygous for a *TTR* pathogenic variant has a 50% risk of inheriting the *TTR* pathogenic variant.
- All offspring of a proband who is homozygous for a *TTR* pathogenic variant will inherit the 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, his or her 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.

**Considerations in families with an apparent *de novo* pathogenic variant.** When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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

- Predictive testing for at-risk relatives is possible once the *TTR* pathogenic variant has 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.

### **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 hereditary ATTR amyloidosis, it is appropriate to consider testing of symptomatic individuals regardless of age.

**Related liver transplantation donors.** In Japan, where liver transplantation from living, related donors is the generally accepted therapy for hereditary ATTR amyloidosis, molecular genetic testing of asymptomatic adult relatives is always performed on family members volunteering to be donors.

### **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 has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for hereditary ATTR amyloidosis are possible.

Differences in perspective may exist among medical professionals and in 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.

## **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 (AF)**  
7151 North Main Street  
Suite 2  
Clarkston MI 48346  
**Email:** [info@amyloidosis.org](mailto:info@amyloidosis.org)  
[www.amyloidosisresearchfoundation.org](http://www.amyloidosisresearchfoundation.org)

- **American Liver Foundation**  
**Phone:** 800-465-4837 (HelpLine)  
[www.liverfoundation.org](http://www.liverfoundation.org)
- **Transthyretin Amyloidosis Outcomes Survey (THAOS)**  
**Phone:** 617-252-5500  
**Fax:** 617-252-5501  
**Email:** [THAOS@foldrx.com](mailto:THAOS@foldrx.com)  
[Transthyretin Amyloidosis Outcomes Survey](#)

## 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
<a href="#">TTR</a>	18q12.1	Transthyretin	<a href="#">TTR (transthyretin) gene homepage</a>	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](#))

<a href="#">105210</a>	AMYLOIDOSIS, HEREDITARY, TRANSTHYRETIN-RELATED
<a href="#">176300</a>	TRANSTHYRETIN; TTR

## Molecular Pathogenesis

The main component of amyloid is protein fibrils. In hereditary transthyretin (ATTR) amyloidosis, the fibrils are mainly composed of self-aggregated TTR protein. TTR protein is potentially amyloidogenic because of its extensive beta-sheet structure. The key factor in amyloidogenesis in hereditary ATTR amyloidosis is the stability of the TTR protein [Kelly 1998, Rochet & Lansbury 2000, Sekijima et al 2005]. The TTR protein normally circulates in plasma as a soluble protein having a tetrameric structure. The amyloidogenic process occurs in two steps:

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

It has been demonstrated that all disease-associated TTR variants are energetically (thermodynamically and kinetically) less stable than wild type TTR.

**Gene structure.** Human *TTR* contains four exons and spans approximately 7 kb. All exons but exon 1 consist of fewer than 200 base pairs. Exon 1 encodes a signal peptide and the first three amino acids of the mature protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** Nearly 150 *TTR* single-nucleotide variants and one in-frame microdeletion have been identified in individuals with hereditary ATTR amyloidosis [Connors et al 2000, Benson 2001, Saraiva 2001, Connors et al 2003, Benson & Kincaid 2007]. No pathogenic variant has been described in exon 1, which encodes amino acids 1 through 3.

The p.Val50Met pathogenic variant, found worldwide, is the most widely studied *TTR* variant and is responsible for the well-known large foci of individuals with TTR amyloid polyneuropathy in Portugal, Sweden, and Japan. Several haplotypes are associated with p.Val50Met in different ethnic groups, suggesting that multiple founders spontaneously occurred in each group.

The p.Val142Ile variant, present in 3.0%-3.9% of African Americans and more than 5.0% of the population in some areas of West Africa, is the most common amyloid-associated *TTR* variant worldwide [Jacobson et al 1997, Yamashita et al 2005].

Of note, suppressor variant p.Thr139Met is more stable than wild type TTR (e.g., individuals who were compound heterozygous for p.Thr139Met and another pathogenic variant showed milder clinical phenotype).

**Table 6.** *TTR* Variants Discussed in This GeneReview

DNA Nucleotide Change <sup>1, 2</sup>	Predicted Protein Change <sup>1, 2</sup>	Phenotype
c.76G>A	p.Gly26Ser <sup>3</sup>	Benign
c.95T>C	p.Leu32Pro	LM, liver
c.113A>G	p.Asp38Gly	LM
c.112G>A	p.Asp38Asn	Heart
c.118G>A	p.Val40Ile	Heart
c.130C>T	p.Pro44Ser	Heart, CTS, PN
c.133G>A	p.Ala45Thr	LM, PN
c.148G>A	p.Val50Met	PN, AN, eye, LM
c.149T>G	p.Val50Gly	LM, eye
c.166G>C	p.Ala56Pro	Eye, CTS
c.173A>C	p.Asp58Ala	PN, heart, lung
c.182G>T	p.Trp61Leu	Eye, PN
c.185A>G	p.Glu62Gly	PN, AN, heart
c.193G>A	p.Ala65Thr	Heart
c.193G>T	p.Ala65Ser	Heart
c.218G>A	p.Gly73Glu	LM, heart
c.218G>C	p.Gly73Ala	LM, PN, kidney, eye, heart
c.224T>C	p.Leu75Pro	Heart, AN, eye
c.227A>G	p.His76Arg	Heart
c.229G>A	p.Gly77Arg	Heart
c.233T>G	p.Leu78His	CTS, heart
c.250T>C	p.Phe84Leu	PN, CTS, heart
c.251T>C	p.Phe84Ser	LM, PN, eye
c.262A>T	p.Ile88Leu	Heart, PN
c.265T>C	p.Tyr89His	Eye, LM
c.270A>C	p.Lys90Asn	Eye, CTS, PN
c.290C>A	p.Ser97Tyr	Heart, kidney, PN
c.301G>A	p.Ala101Thr	Heart

Table 6. continued from previous page.

DNA Nucleotide Change <sup>1, 2</sup>	Predicted Protein Change <sup>1, 2</sup>	Phenotype
c.302C>T	p.Ala101Val	Heart
c.311T>G	p.Ile104Ser	Heart, CTS, eye
c.323A>G	p.His108Arg	Heart
c.334G>A	p.Glu112Lys	Heart
c.367C>A	p.Arg123Ser	Heart
c.379A>G	p.Ile127Val	CTS, heart, PN
c.385G>A	p.Ala129Thr <sup>3</sup>	Benign
c.386C>T	p.Ala129Val <sup>3</sup>	Benign
c.386C>T	p.Ala129Ser	PN, AN
c.391C>A	p.Leu131Met	Heart
c.401A>G	p.Tyr134Cys	PN, AN, eye, LM
c.400T>C	p.Tyr134His	CTS, skin
c.416C>T	p.Thr139Met	Non-amyloid, FEH
c.424G>A	p.Val142Ile	Heart

AN = autonomic neuropathy; CTS = carpal tunnel syndrome; FEH = familial euthyroid hyperthyroxinemia (see Genetically Related Disorders); LM = leptomeningeal; PN = peripheral neuropathy

Variants listed in the table have been provided by the author. *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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. The nucleotide naming conventions follow those of Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). For the DNA nucleotide change the numbering begins at the Met initiation codon.

2. Note: 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.

3. Causes familial euthyroid hyperthyroxinemia; see Genetically Related Disorders.

**Normal gene product.** The human *TTR* cDNA encodes a 20-amino-acid signal peptide plus a 127-amino-acid mature protein with molecular mass 14 kd. TTR is a normal plasma protein synthesized predominantly by the liver. TTR is secreted into plasma as a tetrameric form (Mw = 55 kd) composed of four identical monomers; its plasma half-life is approximately one to two days. TTR concentration in plasma normally ranges from 20 to 40 mg/dL.

TTR transports thyroxine and retinol-binding protein (RBP) coupled to vitamin A. TTR binds virtually all of serum RBP and approximately 15% of serum thyroxine. In the cerebrospinal fluid, TTR is required for transport of serum thyroxine across the blood-brain barrier.

The choroid plexus is the source of the cerebrospinal fluid TTR. The TTR concentration in cerebrospinal fluid ranges from 10 µg/mL to 40 µg/mL.

TTR is also synthesized in the retina.

**Abnormal gene product.** Amyloidogenic TTR variants reduce the stability of the physiologic TTR tetramer, and consequently produce a pro-amyloidogenic monomer more easily than normal TTR (see Molecular Pathogenesis) [Kelly 1998, Rochet & Lansbury 2000, Saraiva 2002, Sekijima et al 2005].

In vitro amyloidogenicity correlates very well with protein stability. However, extremely destabilized (highly amyloidogenic in vitro) TTR variants do not induce severe systemic amyloidosis because serum concentrations of these TTR variants are very low due to protein degradation before secretion. The most clinically severe TTR variant (p.Leu75Pro) exhibiting 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 variants that predominantly induce CNS amyloidosis are the least stable variants. The choroid plexus secretes highly destabilized TTR variants more efficiently than hepatic cells, thus, it is thought, accounting for CNS selective amyloid deposition (leptomeningeal amyloidosis) [Hammarström et al 2003, Sekijima et al 2003, Mitsuhashi et al 2005, Sekijima et al 2005].

## Chapter Notes

### Author History

Shu-ichi Ikeda, MD, PhD; Shinsu University Hospital (2001-2018)

Yoshiki Sekijima, MD, PhD (2006-present)

Takahiko Tokuda, MD, PhD; Kyoto Prefectural University Hospital (2001-2018)

Kunihiro Yoshida, MD, PhD; Shinsu University Hospital (2001-2018)

### Revision History

- 17 June 2021 (ys) Revision: updated Summary of treatment of manifestations
- 10 June 2021 (sw) Revision: updated information on tafamidis, patisiran, inotersen, and therapies under investigation (Management)
- 20 December 2018 (sw) Comprehensive update posted live
- 26 January 2012 (me) Comprehensive update posted live
- 15 September 2009 (me) Comprehensive update posted live
- 15 March 2006 (me) Comprehensive update posted live
- 2 March 2005 (cd) Revision: mutation scanning and sequencing of select exons no longer clinically available
- 5 March 2004 (ky) Revision: molecular genetic testing
- 9 January 2004 (me) Comprehensive update posted live
- 5 November 2001 (me) Review posted live
- 25 June 2001 (ky) Original submission

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