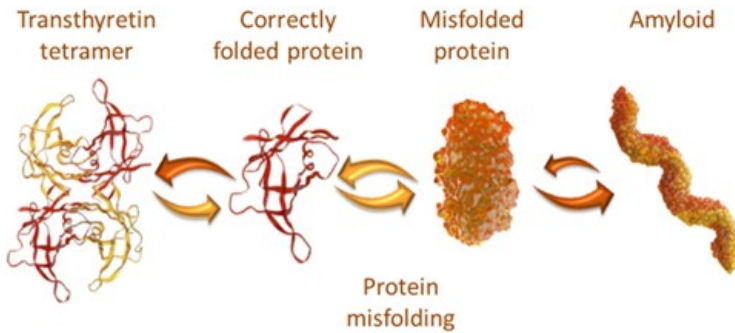


# A Guide to Transthyretin Amyloidosis



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# What is amyloidosis?

Amyloidosis is a systemic disorder characterized by extra cellular deposition of a protein-derived material, known as amyloid, in multiple organs. Amyloidosis occurs when native or mutant polypeptides misfold and aggregate as fibrils. The amyloid deposits cause local damage to the cells around which they are deposited leading to a variety of clinical symptoms. There are at least 23 different proteins associated with the amyloidoses.

The most well-known type of amyloidosis is associated with a hematological disorder, in which amyloid fibrils are derived from monoclonal immunoglobulin light-chains (AL amyloidosis). This is associated with a clonal plasma cell disorder, closely related to and not uncommonly co-existing with multiple myeloma.

Chronic inflammatory conditions such as rheumatoid arthritis or chronic infections such as bronchiectasis are associated with chronically elevated levels of the inflammatory protein, serum amyloid A, which may misfold and cause AA amyloidosis.

The hereditary forms of amyloidosis are autosomal dominant diseases characterized by deposition of variant proteins, in distinctive tissues. The most common hereditary form is transthyretin amyloidosis (ATTR) caused by the misfolding of protein monomers derived from the tetrameric protein transthyretin (TTR). Mutations in the gene for TTR frequently result in instability of TTR and subsequent fibril formation. Closely related is wild-type TTR in which the native TTR protein, particularly in the elderly, can destabilize and re-aggregate causing non-familial cases of TTR amyloidosis.

Other proteins that have been associated with forms of hereditary amyloidosis include apolipoproteins AI and AII, cystatin C, lysozyme, fibrinogen A $\alpha$ -chain and gelsolin.

This pamphlet will concentrate on the most common form of hereditary amyloidosis – ATTR, including a discussion of the non-hereditary wild-type TTR disease.

## **What is transthyretin (TTR)?**

(TTR) is a 127 amino acid protein, which forms a tetrameric, 55 kDa transport protein primarily synthesized in the liver. The protein is a carrier of thyroxine and retinol (vitamin A)-retinol binding protein complex. It is the tertiary carrier of thyroxine in plasma, carrying less  $T_4$  than thyroxine-binding globulin (TBG) and albumin. In its native state TTR is a tetramer, i.e. four single chain TTR monomers form a tetrameric complex.

## **What is transthyretin amyloidosis (ATTR)?**

ATTR is caused by deposition of TTR amyloid fibrils in various tissues.

The hereditary form of ATTR is caused by autosomal dominant mutations in the TTR gene. The prevailing theory for amyloid formation associated with the amyloidogenic mutations is based on the observations that changes of amino acids are associated with destabilization and dissociation of the TTR tetramer, leading to abnormally folded monomers that ultimately self-assemble to amyloid fibrils (Fig. 1). These TTR amyloid fibrils are then deposited extracellularly in various tissues. There are more than 120 reported TTR single point mutations that have been associated with hereditary ATTR.

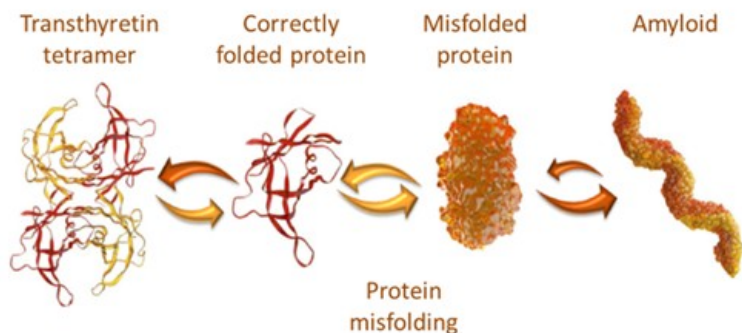


Figure 1. Non-hereditary ATTR is caused by spontaneous fibril formation of wild-type TTR, a disease primarily affecting the heart and clinically occurring predominantly in elderly (>65-70 years) men.

## How frequent is hereditary TTR amyloidosis (ATTR)?

Familial ATTR is a rare disorder, with unequal distribution around the world. Certain clusters (predominately causing familial amyloid polyneuropathy) have been described, mainly in Portugal, Japan, and Northern Sweden. This form of the disease (related to the Val30Met mutation) was first described in the Porto area of Portugal and is sometimes referred to as the Portuguese type of amyloidosis. Estimates have been made for the incidence and prevalence of this type of ATTR. In Europe, the incidence is estimated as 0.003 cases per 10,000 per year (or 0.3 new cases per year per 1 million inhabitants), with a prevalence estimate of 0.052 per 10,000 (or 5.2 cases per 1 million inhabitants). In the endemic area of Northern Sweden with a population of 600,000 individuals, the frequency of the gene is 1.5%, however, the penetrance is relatively low, and most patients develop the disease after the age of 50 years. The size of the patient population

in the US is estimated to not exceed 6,400 patients. In Japan, approximately 400 patients with hereditary ATTR have been reported.

The prevalence of ATTR dominated by cardiomyopathy is less well known, but is almost certainly underdiagnosed. The two most well documented mutations leading to cardiomyopathy are Val122Ile and Thr60Ala. Val122Ile is seen in populations of West-African descent, with a carrier frequency as high as 3.5-4%. This West-African lineage is particularly common in the African American population. Recent data suggest that the penetrance of the Val122Ile mutation is less than 50% by the age of 80. This would mean that among the Val122Ile carrier population who are older than age 60 (approximately 150,000 individuals), potential caseload in the US may be up to 75,000. The Thr60Ala mutation, known as Ala60, is found in populations of Irish descent. The carrier frequency is unknown. The penetrance of Thr60Ala is less well known but thought to be very high. This mutation results in a more pronounced manifestation of neuropathic phenotype than Val122Ile in addition to a cardiomyopathy.

## **Clinical aspects of ATTR**

ATTR is a systemic disorder resulting in polyneuropathy, autonomic neuropathy, cardiomyopathy and often a mixture of these manifestations.

### ***Polyneuropathy***

The main neuropathic feature of ATTR is a progressive sensorimotor and autonomic neuropathy. Val30Met (valine in position 30 is replaced by methionine) is the most common TTR mutation in patients presenting with neuropathy. The disease onset is usually in the third or fourth decade, but can occur later. The disease initially affects small unmyelinated nerve fibers which mediate pain and temperature sensations, and autonomic nerve func-

tions. Typically, sensory neuropathy with paresthesia (numbness and tingling) and hypesthesia starts in the feet and progresses proximally. By the time the sensory neuropathy has progressed to the knee level, the hands have usually become involved. With progression of the neuropathy, larger myelinated fibers become involved, impacting position and vibratory sensations, and reflexes. Carpal tunnel syndrome with median nerve compression is common and may be the first presenting symptom.

Motor neuropathy usually follows within a few years. Footdrop, wristdrop and disability of the hands and feet are frequent symptoms of motor neuropathy leading to difficulties in walking and performing fine hand movements.

Subjects with the Val30Met mutation also have evidence of cardiac involvement with conduction disease manifestation early in the course of the disease. As the disease progresses, features of a restrictive cardiomyopathy develop with resulting heart failure and atrial arrhythmias.

### ***Autonomic Neuropathy***

Autonomic neuropathy often accompanies the sensory and motor deficits and may represent the initial disease presentation. Symptoms include orthostatic hypotension, constipation alternating with diarrhea, nausea, vomiting, delayed gastric emptying, erectile dysfunction, anhidrosis, urinary retention and incontinence. The gastrointestinal involvement results in weight loss and ultimately in cachexia.

Symptoms from the central nervous system (CNS) are rarely found in ATTR except in very rare forms of familial leptomeningeal amyloidosis, in which there may be cerebral hemorrhage with stroke like symptoms.

### ***Cardiomyopathy***

Cardiomyopathy may be the predominant feature of ATTR for some patients or may develop after the onset of neuropathy in patients with familial amyloid polyneuropathy. ATTR cardio-

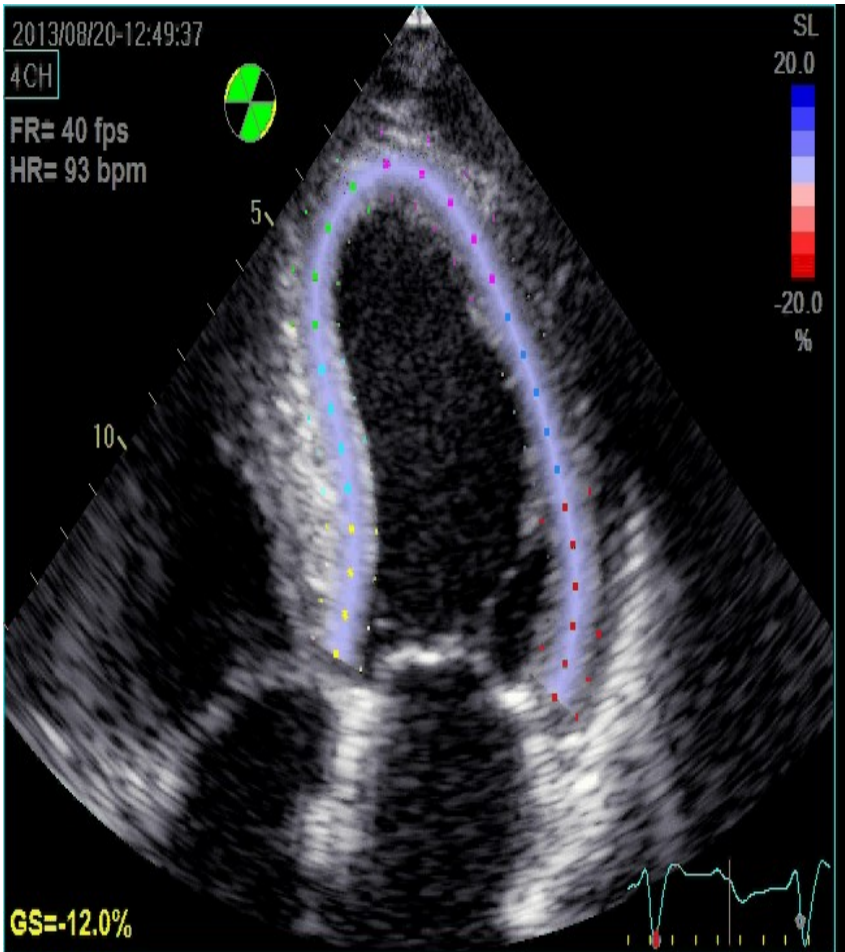
myopathy occurs when TTR amyloid fibrils infiltrate the myocardium, causing myocardial stiffness, reduction in chamber capacitance and restrictive filling patterns seen on Doppler echocardiography. This initially results in diastolic dysfunction, and without treatment will progress to symptomatic heart failure typical of restrictive cardiomyopathy.

The phenotype is characterized by progressive heart failure, often with severe right-sided symptoms. When a low cardiac output supervenes, renal impairment may occur, although autopsy studies have not shown renal involvement by amyloid deposits.

The onset of ATTR cardiomyopathy may occur at any age from the third decade onward, with the typical age of onset > 55 in patients with the Val122Ile mutation. Cardiac involvement can present with conduction system disease (sinus node or atrioventricular node dysfunction) or congestive heart failure including shortness of breath, peripheral edema, syncope, exertional dyspnea, generalized fatigue or with heart block. The echocardiographic findings often show thicker ventricular walls than in AL amyloidosis and include thickened ventricular walls (concentric hypertrophy, both right and left) with a normal to small left ventricular cavity, increased myocardial echogenicity, normal or mildly reduced ejection fraction, often with evidence of diastolic dysfunction and severe impairment of contraction along the longitudinal axis, and bi-atrial dilation with impaired atrial contraction (see figure 2). Subjects with TTR amyloid usually have more severe left ventricular thickening than those with AL amyloid.

Similar to AL amyloidosis, the voltage on the ECG may be normal, although low voltage may be seen despite the increased wall thickness on echocardiography. Low voltage is a marker of advanced disease and lacks sensitivity in isolation for identification of the phenotype. As many as 15% of subjects with TTR amyloid can have electrocardiographic evidence of left ventricular hypertrophy. Clinicians are encouraged to measure the voltage to mass ratio as this is a more sensitive marker than the EKG voltage alone. Also, poor precordial R wave progression and

pseudoinfarcts (q waves in the absence of previous myocardial infarctions) are quite common in subjects with TTR amyloid and provides clues to the diagnosis. Marked axis deviation, bundle branch block and AV block is common, as is atrial fibrillation.



An emerging echocardiographic pattern that is strongly suggestive of cardiac amyloid is a preserved apical strain.



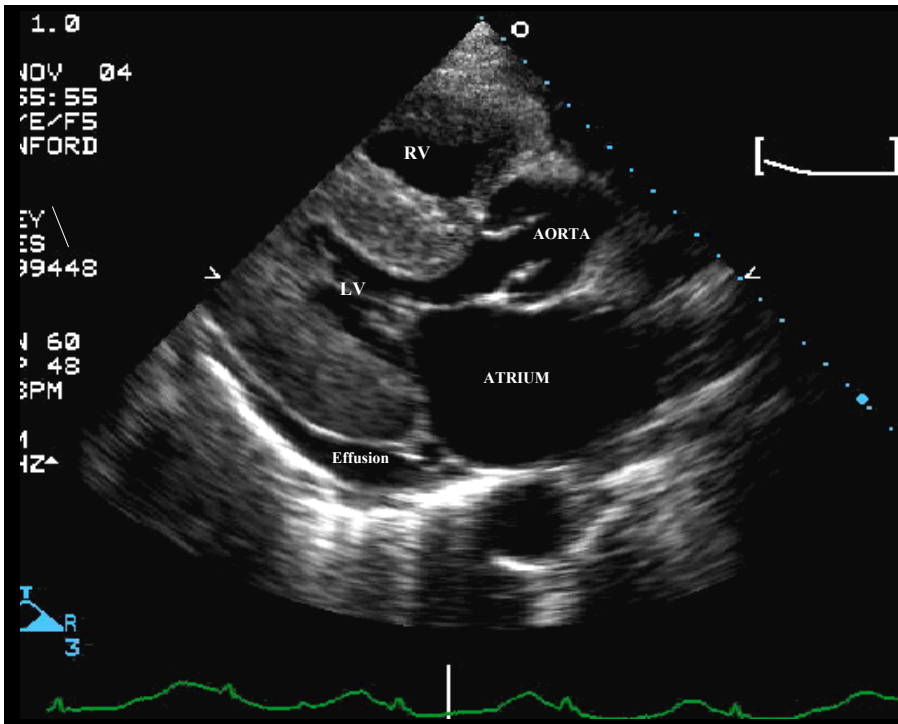
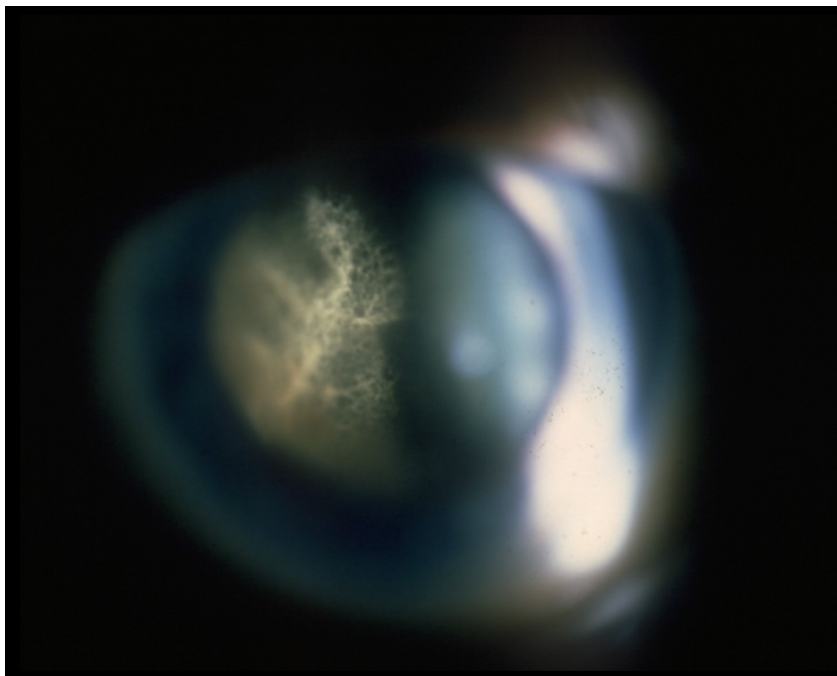


Figure 2. Echocardiographic Findings of Cardiac Amyloid (Courtesy of R. Falk, MD) a parasternal long-axis view in systole in a patient with severe cardiac amyloidosis. The LV walls are thickened and echogenic. The left atrium is enlarged. The aortic valve is particularly well seen due to infiltration.

### ***Ocular manifestations***

The TTR gene is also expressed in the retinal pigment epithelium of the eye, and approximately 20% of amyloidogenic TTR mutations are associated with vitreous opacities derived from amyloid, and may lead to visual impairment. TTR amyloid can be visualized in the vitreous body with typical cotton wool inclusions (Fig. 3). Demonstration of such deposits is helpful for the diagnosis of ATTR.

Figure 3. TTR amyloid deposits in vitreous body (cotton wool inclusions). Reproduced with permission from R. Andersson & T. Kassmann.



### ***Other organs***

Unlike AL amyloidosis, renal involvement is rare in ATTR except for patients with TTR V30M, which it may be a presenting feature. When renal involvement is present, proteinuria is the usual manifestation. Very rarely the renal involvement leads to end-stage renal disease requiring dialysis or renal transplantation.

### **Non-hereditary ATTR**

Wild-type ATTR cardiomyopathy occurs when wild-type TTR forms fibrils, which then deposit as amyloid, primarily in cardiac tissue, primarily in men. This deposition proceeds gradually and becomes clinically manifested (and is thereby usually diagnosed) in the 6<sup>th</sup> or 7<sup>th</sup> decade. Other than carpal tunnel syndrome and possibly the lumbar or cervical spine and tendons, deposition is clinically limited to the heart. The clinical presentation is similar to that described for the hereditary form of ATTR cardiomyopathy. The clinical prevalence of wild-type ATTR cardiomyopathy is

unknown, but autopsy studies suggest that up to 22-25% of individuals >80 years old have demonstrable TTR amyloid deposits in cardiac tissue, although in most cases the degree of deposition is mild. 10-15% of patients who have heart failure and a preserved EF have TTR cardiac amyloid demonstrated by non-invasive scanning with DPD or PYP scanning.

## **When should a physician suspect ATTR?**

The multisystemic involvement in hereditary or familial ATTR makes the disease a possible differential diagnosis in many instances. It would be particularly important to consider the diagnosis when one, or especially several of the following symptoms are present:

- when there is a known family history of neuro-pathic disease, especially if associated with heart failure
- in cases of neuropathic pain or sensory disturbances of unknown etiology
- when there is a history of carpal tunnel syndrome (without obvious cause), particularly if bilateral and requiring decompression
- in patients with gastro-intestinal motility disturbances or autonomic nerve dysfunction of unknown etiology
- if there is cardiac disease characterized by thickened ventricular walls, diastolic dysfunction, or overt cardiomyopathy, particularly in the presence of normal or preserved ejection fraction and in the absence of hypertension
- when a patient presents with complete heart block of unknown origin and echocardiographic abnormalities

- when there are vitreous body inclusions of cotton wool type

As there are many pitfalls in the diagnosis of ATTR, it is generally recommended that patients with possible ATTR are referred to a specialist center with experience in the diagnosis and management of amyloidosis.

## **Diagnosis of TTR amyloidosis**

TTR amyloidosis is a systemic disease in which amyloid deposits can be visualized in most tissues such as skin, fat pad, rectal mucosa, gastric mucosa, nerve tissue or, myocardium. Tissue biopsy should be performed, ideally of an affected organ. Staining with Congo red, which gives a characteristic apple green color when viewed under polarizing microscopy, can confirm amyloidosis. Confirmation of the precursor protein being TTR can be made with either immunohistochemistry (though this method is highly dependent on pathologist experience) or by mass spectroscopy (considered the gold standard). As the distribution of amyloid may be patchy in certain tissues, a negative biopsy does not rule out the diagnosis of amyloidosis, although it is almost universally positive in cardiac amyloidosis if the echocardiogram shows typical findings.

Once amyloid is demonstrated, then the type of precursor protein should be identified. If a tissue biopsy is negative for amyloid staining but the clinical suspicion for hereditary ATTR is high, the investigator may proceed directly with genotyping. However, it should be kept in mind that the penetrance of the underlying trait varies and therefore, demonstration of amyloid deposits is generally required.

Diagnosis of the hereditary form of ATTR requires demonstration of a TTR gene mutation. A history of familial disease is helpful but many patients seen with ATTR do not have a documented family history.

For the diagnosis of non-hereditary ATTR in a patient with suspicious echocardiogram, a cardiac biopsy demonstrating amyloid deposits which are positive for TTR, combined with lack of identifiable mutation in the TTR gene is generally required. Even though non-hereditary ATTR is a systemic disease, it may be difficult to demonstrate amyloid deposits in tissues other than the heart.

More recently, nuclear imaging using bone isotopes (DPD, PYP, and HMDP) has been demonstrated to have high sensitivity and specificity for identifying TTR amyloid non-invasively. These imaging techniques are easy to perform (usually in < 1.5 hours), involve minimal radiation exposure and are highly sensitive and specific (~90%) for TTR cardiac amyloid.

## **Treatment of ATTR**

Since there have been no US approved pharmacologic therapy available for ATTR; therapy has been symptomatic, e.g. analgesics for painful neuropathy, pacemaker implantation for heart conduction problems, diuretics for congestive heart failure, etc. Treatment with certain calcium channel blockers and possibly digitalis, should be avoided since it may accumulate in the amyloid deposits and increase the risk of heart complications.

As TTR is primarily formed in the liver, orthotopic liver transplantation has been the disease modifying treatment available to most patients with hereditary ATTR. This procedure can remove approximately 95% of the production of variant TTR and slow or halt the progression of the disease. Improvement of nerve function, and in particular of autonomic disturbances, has been reported, but has not been documented in systematic follow-up studies in liver transplant recipients. Cardiac disease may progress after liver transplantation, due to deposition of wild-type TTR-derived amyloid. Because of this possibility, combined liver and heart transplantation has been performed in patients with TTR amyloid cardiomyopathy. Eye opacities may develop or progress after liver transplantation as they are due to local ocular

amyloid formation. It is generally considered that the best outcome of orthotopic liver transplantation is achieved when it is performed before the disease has become too advanced. Overall patient survival rate at 5 years is reported to be above 77%.

New therapies aimed at stabilizing TTR tetramers or silencing their production in order to avoid fibril formation are being tested in clinical trials. Further information about clinical trials, is available at

**<http://www.clinicaltrials.gov/>**.

Ongoing trials include studies with several compounds. Diflunisal is a non-steroidal anti inflammatory drug with reported TTR stabilization properties. It was studied in a population of patients with familial amyloid polyneuropathy (FAP) due to mutations in the TTR gene. About half of subjects had concomitant TTR cardiac amyloidosis. The drug was well tolerated despite its NSAIDs properties and was shown to reduce disease progression in a placebo controlled trial published in JAMA in 2014. Tafamidis is a specific and potent TTR stabilizing compound with no NSAID activity. Already approved in Japan and Europe, the final phase III trial of this Pfizer drug has completed enrollment, with expected results in 2017.

Another method to silence TTR employs oligonucleotides, and is currently being tested in a phase III trial for familial amyloid polyneuropathy.

## **Prognosis of ATTR**

All forms of ATTR are progressive, but the rate of progression is variable and may be dependent on the clinical phenotype and the mutation. Generally patients with the ATTR V30M mutation have a mean life expectancy of 9-11 years from symptom onset. Death is due primarily to malnutrition and cachexia, renal failure, cardiac disease or sudden death. For other more rare mutations, survival is less well documented.

The progression of ATTR when cardiomyopathy is the predominant clinical manifestation is less well documented but the prognosis is often poor with mean life expectancy from symptom onset of 5-6 years, and death due primarily from heart failure or sudden death.

## Relevant reading

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## **Important links and contacts**

[www.amyloidosis.org](http://www.amyloidosis.org)

[www.fapwtr.org](http://www.fapwtr.org)

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

## ***Hereditary ATTR***

### **Mutated ATTR**

More than 120 Different mutations described leading to instability of TTR and amyloid fibril formation and deposit and many organs and tissues

#### *Polyneuropathy*

Progressive disease which affects

- Peripheral sensory and motor nerves
- Autonomic nervous system

causing pain, sensory and motor deficits and autonomic nerve dysfunction like orthostatic hypo-tension, gastro-intestinal symptoms (obstipation alternating with diarrhea) and anhydrosis.

Cardiac and renal manifestations may appear at any time during the course of the disease.

Also known as Familial Amyloid Polyneuropathy (FAP)

#### *Cardiomyopathy*

Cardiomyopathy with conduction disturbances and impaired function, mostly restrictive cardiomyopathy.

Patients may develop neuropathy

Also known as Familial Amyloid Cardiomyopathy (FAC)

## ***Non-hereditary ATTR***

### **Wild Type TTR**

Cardiomyopathy is the dominating clinical feature and a disease primarily affecting elderly men (>65-70 years)

Formerly known as Senile Systemic Amyloidosis (SSA)

**To Locate an Amyloidosis Clinic please visit  
our website**

**<http://www.amyloidosis.org/resources/#treatment-centers>**

Or give us a call—1-877-AMYLOID

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