Transthyretin-Related Amyloidosis

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Background

The amyloidoses are a wide range of diseases of secondary protein structure, in which a normally soluble protein forms insoluble extracellular fibril deposits, causing organ dysfunction. All types of amyloid contain a major fibril protein that defines the type of amyloid, plus minor components. Over 20 different fibril proteins have been described in human amyloidosis, each with a different clinical picture (see Amyloidosis, Overview). One such protein that forms human amyloid fibrils is transthyretin (TTR).

TTR acts as a transport protein for thyroxine in plasma. TRR also transports retinol (vitamin A) through its association with the retinol-binding protein. It circulates as a tetramer of 4 identical subunits of 127 amino acids each. TTR was once called prealbumin because it migrates anodally to albumin on serum protein electrophoresis, but this name was misleading, as TTR is not a precursor of albumin. The TTR monomer contains 8 antiparallel beta pleated sheet domains. TTR can be found in plasma and in cerebrospinal fluid and is synthesized primarily by the liver and the choroid plexus of the brain and, to a lesser degree, by the retina. Its gene is located on the long arm of chromosome 18 and contains 4 exons and 3 introns.[1]

The systemic amyloidoses are designated by a capital A (for amyloid) followed by the abbreviation for the chemical identity of the fibril protein. Thus, for example, TTR amyloidosis is abbreviated ATTR, and amyloidosis of the immunoglobulin light chain type is abbreviated AL.

Pathophysiology

Both normal-sequence TTR and variant-sequence TTR form amyloidosis. Normal-sequence TTR forms cardiac amyloidosis in elderly people, termed senile cardiac amyloidosis (SCA). When it was recognized that SCA is often accompanied by microscopic deposits in many other organs, the alternative name senile systemic amyloidosis (SSA) was proposed. Both terms are now used.[1]

TTR mutations accelerate the process of TTR amyloid formation and are the most important risk factor for the development of clinically significant ATTR. More than 85 amyloidogenic *TTR* variants cause systemic familial amyloidosis. The age at symptom onset, pattern of organ involvement, and disease course vary, but most mutations are associated with cardiac and/or nerve involvement. The gastrointestinal tract, vitreous, lungs, and carpal ligament are also frequently affected.[1]

Amyloidogenic *TTR* mutations destabilize TTR monomers or tetramers, allowing the molecule to more easily attain an amyloidogenic intermediate conformation. Other unknown factors also play a role in TTR amyloid formation, as the clinical manifestations of the disease vary widely among people carrying the same *TTR* variant.

When the peripheral nerves are prominently affected, the disease is termed familial amyloidotic polyneuropathy (FAP). When the heart is involved heavily but the nerves are not, the disease is called familial amyloid cardiomyopathy (FAC). Regardless of which organ is primarily targeted, the general term is simply amyloidosis-transthyretin type, abbreviated ATTR.

Most variants that cause familial ATTR are rare, but a few are common in certain populations. *TTR* variants are written, according to convention, by the normal amino acid found at a position in the mature protein, followed by

the number of the amino acid from the amino terminal end, and the variant amino acid found, using either the 3-letter or single-letter amino acid code. The most widely recognized *TTR* variants are as follows:

- *TTR* V30M: This was the first *TTR* variant discovered. The role of TTR in amyloidosis was first established when TTR was found in the fibrils in several kindreds with autosomal dominant amyloidosis affecting the peripheral nerves, heart, and other organs. This syndrome was first described in Portugal in the 1950s and later in Japan and Sweden.[2] The fibrils in patients in all 3 endemic areas were found to contain TTR that carried a substitution of methionine for valine at position 30, arising from a point mutation. This variant has now been found worldwide, is the most widely studied *TTR* variant, and has served as a prototype for variant-sequence ATTR. The disease in the *TTR* V30M kindreds was termed FAP because early symptoms arose from peripheral neuropathy, but these patients actually have systemic amyloidosis, with widespread deposits often involving the heart, gastrointestinal tract, eye, and other organs.[3]
- *TTR* V122I: This variant, carried by 3.9% of African Americans and over 5% of the population in some areas of West Africa, increases the risk of late-onset (after age 60 years) cardiac amyloidosis. It appears to be the most common amyloid-associated *TTR* variant worldwide. Affected patients usually do not have peripheral neuropathy.[4]
- *TTR* T60A: This variant causes late-onset systemic amyloidosis with cardiac, and sometimes neuropathic, involvement. This variant originated in northwest Ireland and is found in Irish and Irish American patients.[5]
- *TTR* L58H: Typically affecting the carpal ligament and nerves of the upper extremities, this variant originated in Germany. It has spread throughout the United States but is most common in the mid-Atlantic region.[5]
- *TTR* G6S: This is the most common *TTR* variant, but it appears to be a neutral polymorphism not associated with amyloidosis. It is carried by about 10% of people of white European descent.[5]

Currently, about 100 *TTR* variants are known, with varying geographic distributions, degrees of amyloidogenicity, and organ predisposition. Currently known *TTR* variants are listed in the table below.[1] For organ involvement, the following abbreviations are used: PN = peripheral nerves, AN = autonomic nervous system, H = heart, L = liver, LM = leptomeninges, K = kidney, S = skin, E = eye, GI = gastrointestinal tract, CL = carpal ligament, and CNS = central nervous system.

Known *TTR* Variants (adapted from Connors et al)

(Open Table in a new window)

Variant	Geographic Focus (Ethnic Origin)	Organs Involved
Gly6Ser	Caucasian	None
Cys10Arg	United States (Hungarian)	H, PN, AN, E
Leu12Pro	United Kingdom	CNS, AN, L, LM
Asp18Gly	United States (Hungarian)	CNS, LM
Met13Ile	Germany	None
Asp18Asn	United States	H
Asp18Glu	South America	AN, PN
Val20Ile	United States, Germany	H, CL
Ser23Asn	United States (Portuguese)	H, E, PN
Pro24Ser	United States	PN, H, CL
Ala25Ser	United States	H, PN
Ala25Thr	Japan	CNS, PN
Val28Met	Portugal	AN, PN
Val30Met	Argentina, Brazil, China, Finland, France, Germany, Greece, Italy, Japan, Portugal, Sweden, Turkey, United States	PN, AN, E, LM
Val30Ala	United States (German)	AN, H
Val30Leu	Japan, United States	PN, AN, H, K
Val30Gly	United States	E, CNS, LM
Phe33Cys	United States	CL, E, K, H

Phe33Ile	Israel (Polish, Ashkenazi Jewish)	PN, E
Phe33Leu	United States (Polish, Lithuanian)	PN, AN
Arg34Thr	Italy	PN, H
Lys35Asn	France	PN, H, AN
Ala36Pro	Greece, Italy, United States (Jewish)	PN, E, CNS, CL
Asp38Ala	Japan	H, PN, AN
Trp41Leu	United States (Russian)	E
Glu42Gly	Japan, Russia, United States	PN, AN
Glu42Asp	France	H
Phe44Ser	United States, Japan	PN, H, AN, E
Ala45Thr	Italy, Ireland, United States	H
Ala45Asp	United States , Ireland, Italy	PN, H
Ala45Ser	Sweden	H
Gly47Ala	Italy, Germany, France	PN, H, AN
Gly47Arg	Japan	PN, AN
Gly47Val	Sri Lanka	H, AN, PN, CL
Gly47Glu	Germany, Italy	H, K, PN
Thr49Ala	France, Italy (Sicily)	PN, CL, H
Thr49Ile	Japan	PN, H
Thr49Pro	United States	H
Ser50Arg	Japan, France, Italy	PN, H, AN
Ser50Ile	Japan	PN, H, AN
Glu51Gly	United States	H
Ser52Pro	United Kingdom	PN, AN, H, K
Gly53Glu	Basque	CNS, LM, PN
Glu54Gly	United Kingdom	PN, E, AN
Glu54Lys	Japan	PN, AN, H
Leu55Pro	United States (Dutch, German), Taiwan	PN, E, H, AN
Leu55Arg	Germany	PN, LM
Leu55Gln	United States (Spanish)	AN, E, PN
Leu58His	United States, Germany	H, CL
His56Arg	United States	H
Leu58Arg	Japan	AN, E, CL, H
Thr59Lys	Italy, United States (Chinese)	H, PN, AN
Thr60Ala	Ireland, United States, Australia, Germany, United Kingdom, Japan	H, PN, GI, CL
Glu61Lys	Japan	PN
Phe64Leu	Italy, United States	PN, H, CL
Phe64Ser	Canada (Italian), United Kingdom	CNS, PN, E, LM
Ile68Leu	Germany, United States	H
Tyr69His	United States, Scotland	E
Tyr69Ile	Japan	CL, H
Lys70Asn	United States, Germany	CL, E, PN
Val71Ala	France, Spain	PN, E , CL
Ile73Val	Bangladesh	PN, AN

Asp74His	Germany	None
Ser77Tyr	Germany, France, United Kingdom	PN, H, K
Ser77Phe	France	PN, AN
Tyr78Phe	France (Italian)	PN, CL, S
Ala81Thr	United States	H
Ile84Ser	United States (Swiss), Hungary	H, CL, E, LM
Ile84Asn	Italy, United States	E, H, CL
Ile84Thr	Germany, United Kingdom	PN, AN, H
Glu89Gln	Sicily	PN, H, CL
Glu89Lys	United States	PN, H, AN
His90Asn	Portugal, Germany	None
Ala91Ser	France	PN, H, CL, AN
Arg104Cys	United States	None
Arg103Ser	United States	H
Pro102Arg	Germany	None
Ala97Ser	China, France, Taiwan	H,PN
Gln92Lys	Japan	H
Ala97Gly	Japan	PN,H
Gly101Ser	Japan	None
Arg104His	Japan, United States (Chinese)	None
Ile107Met	Germany	H, PN
Ile107Val	United States(German), Japan	PN, H, CL
Ala109Val	United States	None
Ala108Ala	Portugal	None
Ala109Thr	Portugal	None
Ala109Ser	Japan	PN
Leu111Met	Denmark	H, CL
Tyr114Cys	Holland	PN, E, H, LM, AN, CNS
Tyr114His	Japan	CL
Tyr116Ser	France	PN, CL, AN
Thr119Met	United States, Portugal	None
Ala120Ser	Afro-Caribbean	PN, H, AN
Val122Ile	Africa, United States, Portugal	H
Val122Ala	United States (Alaska), United Kingdom	PN, H, E
Deletion of 122Val	Ecuador, United States	PN, CNS, GI, CL, H
Pro125Ser	Italy	None

Genetic aspects of transthyretin-related amyloidosis

Familial ATTR is traditionally thought of as a group of autosomal-dominant diseases, but it is now known that disease expression is more complicated. The most abundant data pertain to *TTR* V30M; the following observations have been made:

- Variation in age of onset: The usual age of disease onset among *TTR* V30M gene carriers in Portugal, Brazil, and Japan is in the third to fourth decade of life. However, there are late-onset cases (as seen in Sweden) in which disease onset is in the fifth to sixth decade of life.

- Disease penetrance: In Portugal and Japan, more than 90% of *TTR* V30M gene carriers develop symptoms by middle age. However, in Sweden, disease penetrance is only 2%, and some V30M homozygous individuals remain asymptomatic.[3]
- Some atypical Portuguese and Japanese kindred follow the late-onset, low-penetrance Swedish pattern.[2]
- Some patients with no family history of amyloidosis and asymptomatic relatives with the variant gene carry the V30M variant.
- Disease onset is earlier in males than in females.[6]
- Age of symptom onset is progressively earlier in successive generations. This feature is referred to as anticipation. Anticipation in some neurologic disorders is caused by expansion of trinucleotide repeats. However, in ATTR, this mechanism seems not to apply.

The explanation for the above observations is not well understood. Other genetic and/or environmental variables are thought to be at play. Anticipation, incomplete penetrance, and clinically sporadic cases in kindreds with unaffected allele carriers also have been observed with other *TTR* variants.[5]

Normal-sequence transthyretin-related amyloidosis

In contrast to variant ATTR, normal-sequence cardiac ATTR is associated with aging, usually in the seventh and eighth decade of life. This is commonly of little or no clinical significance. On the other hand, other elderly patients with normal-sequence ATTR develop extensive, symptomatic, and even fatal cardiac ATTR.

The stimuli that lead to normal-sequence ATTR are not understood. The clinical manifestations of severe SCA are similar to those observed in familial ATTR and in cardiac amyloidosis of the immunoglobulin light chain type (AL).

Epidemiology

Frequency

United States

The only *TTR* variant for which population-based prevalence studies have been conducted is *TTR* V122I; this variant has an allele prevalence of 0.02 (2%) in the African American population. Among African Americans, 3.9% of the population are heterozygous for this variant allele (about 1.3 million people). About 13,000 African Americans are homozygous for this variant. Limited data suggest that the latter group is at greater risk of developing clinical disease.

The other most common amyloidosis-associated *TTR* variants in the United States are as follows:

- *TTR* V30M - Also the most widespread variant worldwide
- *TTR* T60A - Most common in an area centered in West Virginia
- *TTR* L58H - Most commonly seen in Maryland but also throughout the United States
- *TTR* S77Y - Found in Europe and the United States
- *TTR* I84S - Found in an area centered in Indiana

Most other amyloid-associated *TTR* variants are rare. Many have been found in only one or a few families.

Cardiac ATTR amyloidosis has a progressive increase in prevalence in people older than 80 years and is seen in about 15% of autopsies. In this setting, the deposited TTR is usually of normal sequence.

International

A few amyloidosis-associated *TTR* variants are common in certain populations, although few data indicate population frequencies. The most common *TTR* variants include the following:

- *TTR* V30M is found throughout Europe, in North and South America, and Japan. It is most common in some areas of northern Sweden (where it is carried by more than 1% of the population), northern Portugal, and certain areas in Japan.[3]
- *TTR* V122I originated in West Africa. It is carried by 3.9% of African Americans and 5% or more of the population in some areas of West Africa.[4]

The other amyloid-associated *TTR* variants appear to be less common, although no firm data are available on

population prevalences.

Mortality/Morbidity

Morbidity and mortality from ATTR depends on whether a *TTR* variant is present and, if so, which variant. Some variants cause clinical disease by age 40 years in all gene carriers and are always fatal within a few years of symptom onset. Other variants typically cause much milder, later onset disease, and some carriers of the variant genes remain asymptomatic until late in life.[7]

Morbidity depends on the organ(s) involved. Neuropathy and cardiomyopathy are most common. The most common immediate cause of death is from cardiac failure or fatal arrhythmia.[8]

Race

TTR variants occur in all races.

- The most common variant worldwide, *TTR* V122I, apparently originated in West Africa, has spread throughout that area and the Americas, and is carried by 3.9% of African Americans. Therefore, cardiac amyloidosis is more prevalent among African Americans than among people of other races in the United States.[4]
- Other variants are documented to have originated in people of European, Japanese, and Chinese ancestry. *TTR* variants have probably originated in all races.[5]

Sex

All *TTR* variants encoded on chromosome 18 are inherited with equal frequency in males and females. For unknown reasons, disease penetrance is greater and age of onset earlier in males than in females. Individual case reports and several small series suggest that normal-sequence cardiac ATTR is more common in males than in females, although the sex ratio is unknown.[6]

Age

The age of onset varies widely, depending on the presence and identity of the *TTR* variant.

- Normal-sequence cardiac ATTR presents after age 60 years and usually after age 70 years.
- Variant-sequence ATTR presents in teenaged individuals and in people in their early 20s for the most aggressive variants and in people older than 50 years for many others.
- The average age of onset for ATTR V30M is 32 years in Japan and Portugal and 56 years in Sweden. The reason for this difference is not known.

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