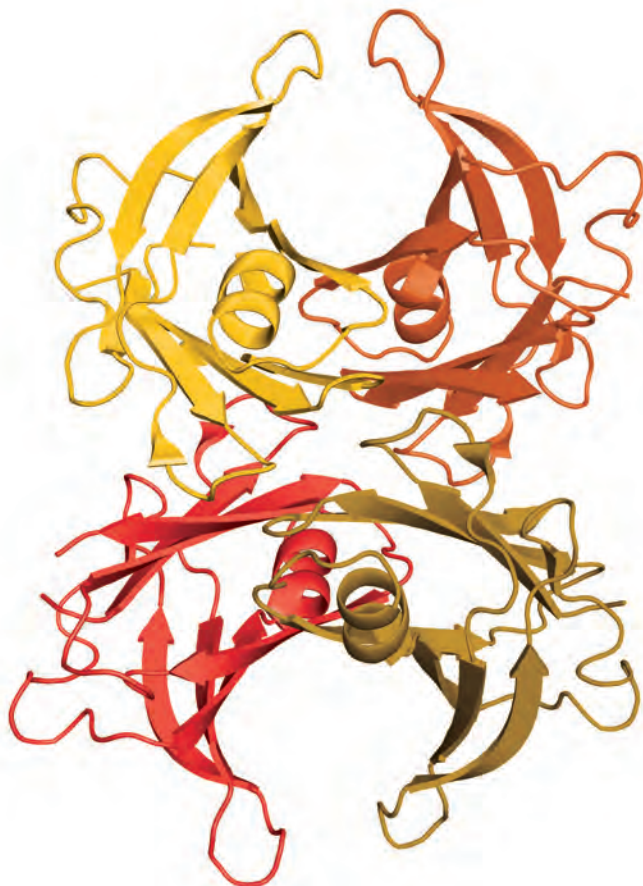


Hereditary Transthyretin Amyloidosis

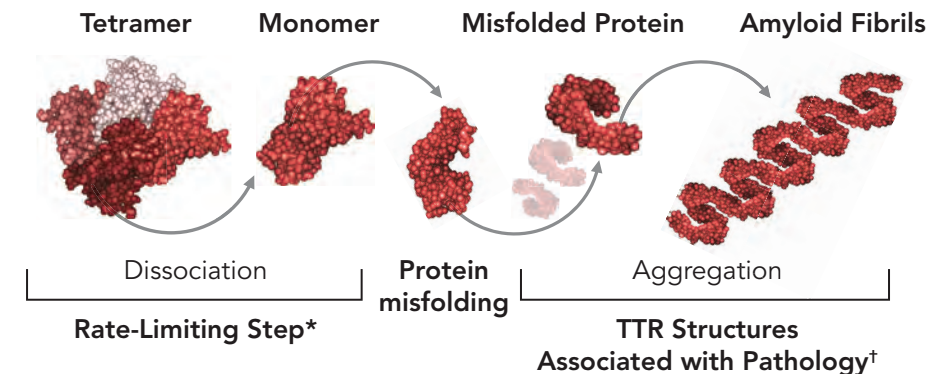
AN OVERVIEW



TRANSTHYRETIN AMYLOIDOSIS (ATTR)

- ATTR amyloidosis is a progressive and fatal disease that manifests clinically with sensorimotor polyneuropathy, autonomic neuropathy, gastrointestinal disturbances, and cardiomyopathy¹⁻³
- ATTR amyloidosis is caused by the buildup of amyloid fibrils in organs and tissues in the body⁴
- The amyloidogenic precursor in ATTR amyloidosis is transthyretin (TTR), a transport protein synthesized primarily by the liver^{2,5,6}
- Normally, TTR comprises 4 single-chain monomers arranged as a tetramer⁵
- In hereditary ATTR amyloidosis, mutations in the *TTR* gene are thought to disrupt the tetrameric structure of TTR resulting in weaker interactions between monomer subunits^{5,7-10}
 - Weakened interactions promote dissociation into monomers that misfold and have a greater propensity for aggregation
 - Misfolded protein accumulates, forming fibrils that deposit in tissues and organs

MECHANISM OF AMYLOID FIBRIL FORMATION¹⁰



TTR, transthyretin.

*Rate-limiting step involves dissociation of tetrameric TTR to a pair of dimeric TTR which rapidly progresses to monomeric TTR.

†Misfolded protein can form a variety of toxic intermediates, including amyloid fibrils (shown here) as well as small oligomers and amorphous aggregates.

GENETICS

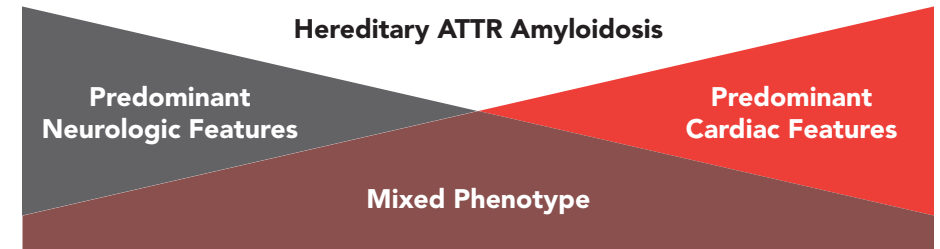
- TTR is encoded by a single-copy gene; however, >130 mutations have been identified¹¹
- Hereditary ATTR amyloidosis is typically associated with a single amino acid substitution caused by a point mutation in the *TTR* gene^{2,12,13}
 - For example, valine to methionine substitution at position 50 (p. Val50Met; formerly Val30Met)
- Most *TTR* mutations are amyloidogenic and promote instability of TTR tetramers⁹
- Hereditary ATTR amyloidosis is transmitted in an autosomal dominant manner, with variable penetrance²

GENOTYPE-PHENOTYPE CORRELATION

- Specific genotypes are associated with predominant polyneuropathic or cardiomyopathic features; however, most mutations affect multiple organs, and there is considerable heterogeneity in disease manifestations¹
- Although p. Val50Met is commonly associated with polyneuropathy, many patients with p. Val50Met have symptoms of cardiomyopathy as well¹
 - The highest occurrence of p. Val50Met is in northern Portugal (incidence, 1 in 538 individuals); however, this mutation is also common in other regions of world^{1,2}
- Although many patients with p. Val142Ile (previously Val122Ile) have polyneuropathy, this genotype is largely associated with a cardiomyopathy phenotype¹
 - In the United States, p. Val142Ile is the most common mutation and primarily occurs in African American individuals^{1,14}
 - 3%-4% of African American individuals are p. Val142Ile carriers²
- Due to the multisystem nature of hereditary ATTR amyloidosis, it is imperative to perform a full neurologic and cardiac workup of a diagnosed patient regardless of the presenting phenotype or genotype

Genotype-Phenotype Relationship in Hereditary ATTR Amyloidosis^{15,16}

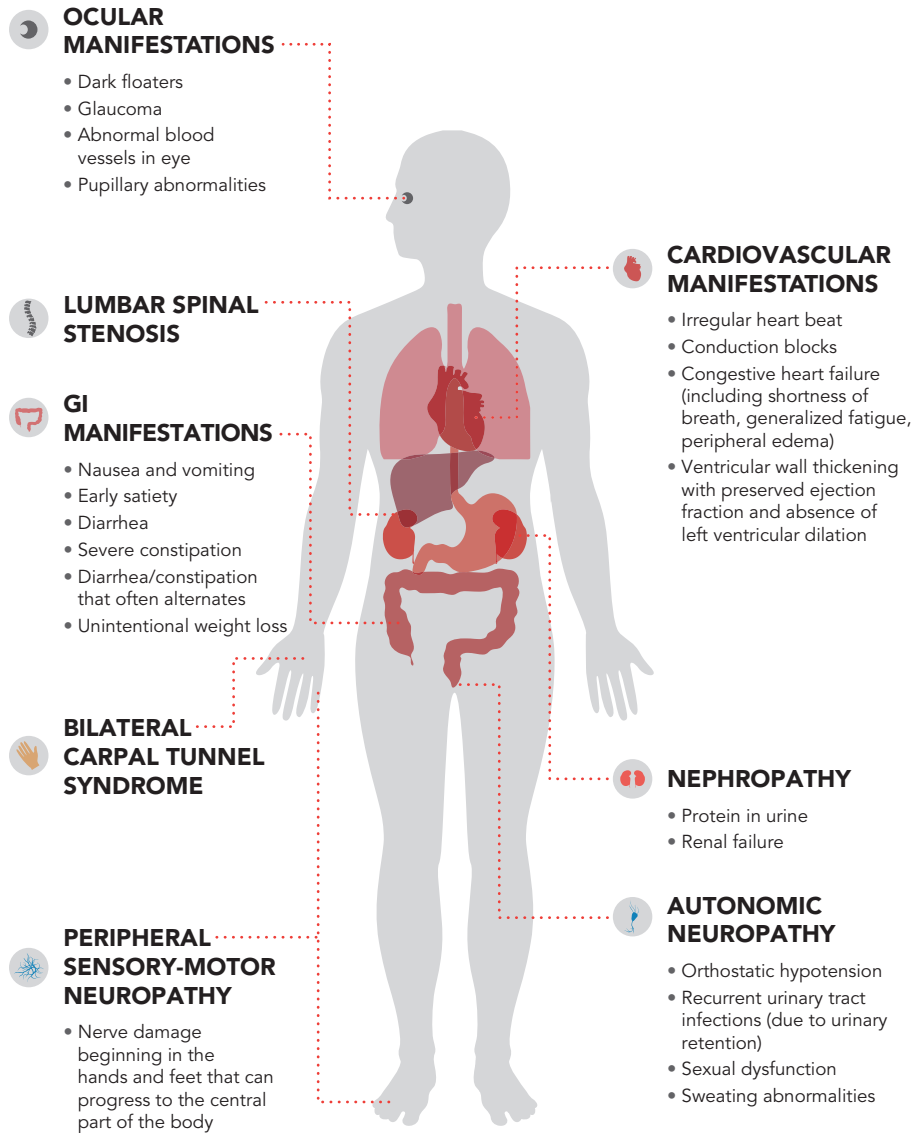
Val50Met Early Onset	Cys30Arg	Arg54Thr	Gly67Ala	Phe84Leu	Leu78His	Glu109Gln	Ile127Val	Ser43Asn	Leu131Met	Ile88Leu
Phe53Leu	Ser70Arg	Ser97Tyr	Ala56Pro	Thr69Ala	Val50Met Late Onset	Trp61Leu	His108Arg	Thr80Ala	Val142Ile	



CLINICAL PRESENTATION

- Hereditary ATTR amyloidosis causes sensorimotor neuropathy, autonomic neuropathy, cardiomyopathy, gastrointestinal disturbances, and nephropathy^{1,8}
- Length-dependent peripheral sensory-motor neuropathy is a characteristic feature of hereditary ATTR amyloidosis^{7,17}
- Bilateral carpal tunnel syndrome may be an early, nonspecific symptom of hereditary ATTR amyloidosis, presenting as early as 12 years before the appearance of other symptoms^{18,19}
- Lumbar spinal stenosis has been detected in patients with hereditary ATTR amyloidosis and is a common early presenting manifestation in patients with hereditary ATTR amyloidosis²⁰
- Recognizing hereditary ATTR amyloidosis can be challenging because of the substantial clinical heterogeneity and nonspecific symptoms/manifestations that overlap with more common disorders

Clinical Manifestations of Hereditary ATTR Amyloidosis, a Multisystem Disease^{*,8,18,19,21-25}



CNS, central nervous system; GI, gastrointestinal.

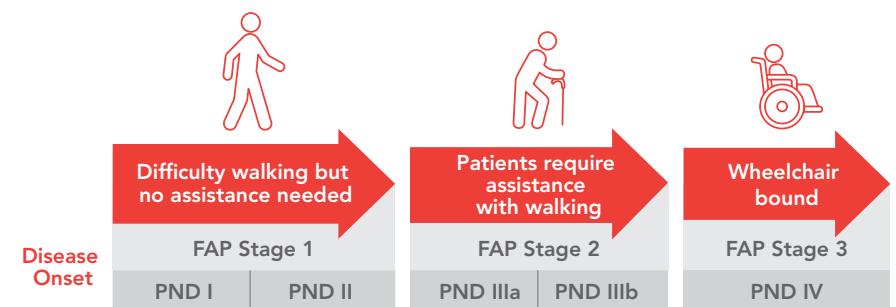
*CNS symptoms can occur with certain TTR mutations but are not a common manifestation.

Modified with permission from Conceição et al.⁸

BURDEN OF DISEASE - POLYNEUROPATHY

- Hereditary ATTR amyloidosis with polyneuropathy is a devastating, progressive disease that results in a rapid decline in quality of life
- Symptoms of hereditary ATTR amyloidosis impact multiple aspects of daily life, and disease burden increases with illness progression^{26,27}
- If left untreated, patients experience a progressive reduction in ambulation and daily function, that ultimately results in premature death²⁸⁻³⁰
- The clinical course and degree of ambulation disability can be assessed using two staging systems: Familial Amyloid Polyneuropathy stage and Polyneuropathy Disability (PND) score²⁹
 - Both staging systems can be used to assess the progression of the disease on ambulation
- Continued disease progression can lead to worsening and life-threatening autonomic dysfunction, with symptoms including orthostatic hypotension and uncontrolled diarrhea^{2,31}
- Patients report difficulty with activities of daily living, an inability to stand for a significant amount of time, run, or work^{26,27}
- Health care resource use is high among patients with hereditary ATTR amyloidosis, ranging from outpatient visits to in-patient hospitalization lasting multiple nights, as well as emergency room visits^{26,27}
- More than half (55%) of patients with hereditary ATTR amyloidosis report that their mental health/outlook on life is impacted by amyloidosis and that they have anxiety (71%), stress (62%), and depression (43%)³²

Hereditary ATTR Amyloidosis With Polyneuropathy Is a Progressive, Disabling Disease²⁹



FAP, Familial Amyloid Polyneuropathy; PND, Polyneuropathy Disability.

DIAGNOSIS

Diagnostic challenges in patients with hereditary ATTR amyloidosis with polyneuropathy

- Low index of clinical suspicion coupled with disease unawareness impedes early and accurate diagnosis. Additional impediments to timely diagnosis include substantial clinical heterogeneity, nonspecific symptoms, and overlap with more common medical conditions
- Substantial delays between initial symptoms and diagnosis as well as misdiagnosis are common in patients with hereditary ATTR amyloidosis²⁰
- Patients visit multiple physicians, as many as 10 with some patients required to visit >20, across a broad range of clinical specialties before receiving a diagnosis³²
- Clinical presentation of hereditary ATTR amyloidosis is often indistinguishable from acquired monoclonal immunoglobulin light chain (AL amyloidosis), and patients may receive ineffective and harmful treatments^{13,20}
- Hereditary ATTR amyloidosis with polyneuropathy is commonly misdiagnosed as CIDP (chronic inflammatory demyelinating polyneuropathy)²⁰

Diagnostic findings and testing

- Recognition of red-flag symptom clusters
 - In patients with signs, symptoms, or manifestations suggestive of hereditary ATTR amyloidosis, diagnostic and genetic tests should be performed
 - Patients presenting with progressive length-dependent neuropathy of unknown origin, particularly those with autonomic dysfunction and/or cardiac disorders, should be tested for hereditary ATTR amyloidosis^{8,33}
- Tissue biopsy and Congo red staining
 - Performed to confirm presence of amyloid deposits^{2,33}
 - Congo red staining of tissue with resultant green birefringence when viewed under polarized light is pathognomonic for amyloid^{2,33}
- Amyloid typing
 - With a positive Congo red stain biopsy, amyloid typing using laser microdissection followed by mass spectrometry can differentiate between different amyloid types (eg, ATTR vs AL amyloidosis) and give a specific diagnosis of ATTR amyloidosis³³

- Nuclear scintigraphy
 - Myocardial radiotracer uptake on bone scintigraphy with ^{99m}Tc-DPD or ^{99m}Tc-PYP can be used to detect TTR amyloid in the heart without a biopsy (if negative monoclonal antibody testing)^{2,34}
- Genetic testing
 - Required for confirmation and detection of specific *TTR* gene mutations, ultimately resulting in a diagnosis of hereditary ATTR amyloidosis with polyneuropathy^{2,33}
 - No-cost confidential genetic testing and counseling is available through the hereditary ATTR amyloidosis Compass program. Learn more at www.hATTRCompass.com

UNMET NEEDS



DIAGNOSIS

- Increased clinical suspicion and disease awareness are high unmet needs
- Increased efforts are needed to keep red-flag symptoms of hereditary ATTR amyloidosis “front of mind” among clinicians



PATIENT ACCESS TO COORDINATED CARE

- Access to and coordination of care between amyloidosis centers of excellence and academic specialists is greatly needed

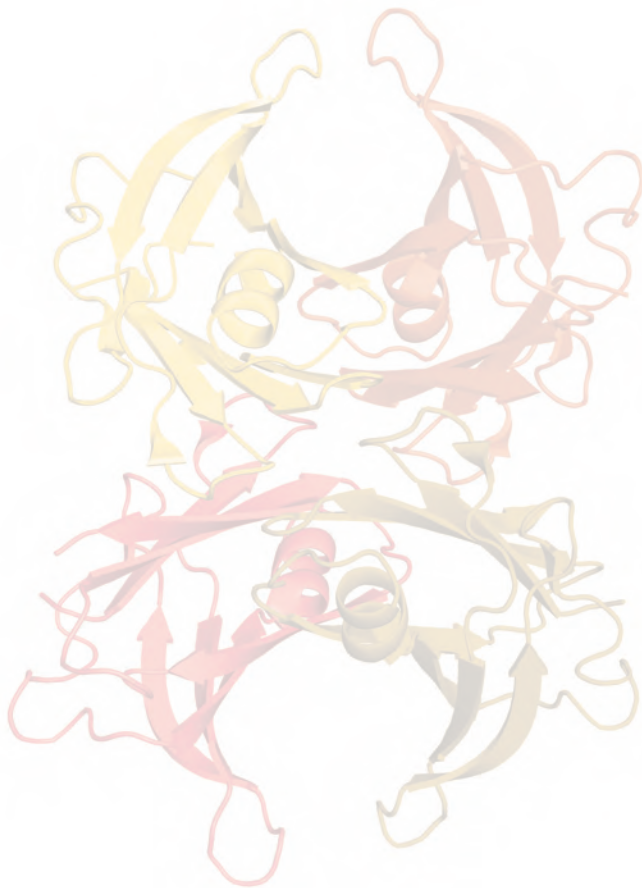


EARLY IMPLEMENTATION OF APPROPRIATE TREATMENT IS IMPERATIVE

- Due to the progressive nature of hereditary ATTR amyloidosis with polyneuropathy, disease awareness and early diagnosis are critical to optimal disease management

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