Understanding ATTR: Pathophysiology and Disease Prevalence

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ATTR Disease State Slide Deck

- This resource provides information about ATTR.
- This resource is intended to be viewed in its entirety to support scientific exchange and is not intended as recommendations for clinical practice.
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Introduction to ATTR

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Amyloidosis Overview

More than 30 amyloidogenic proteins have been identified in humans[1]

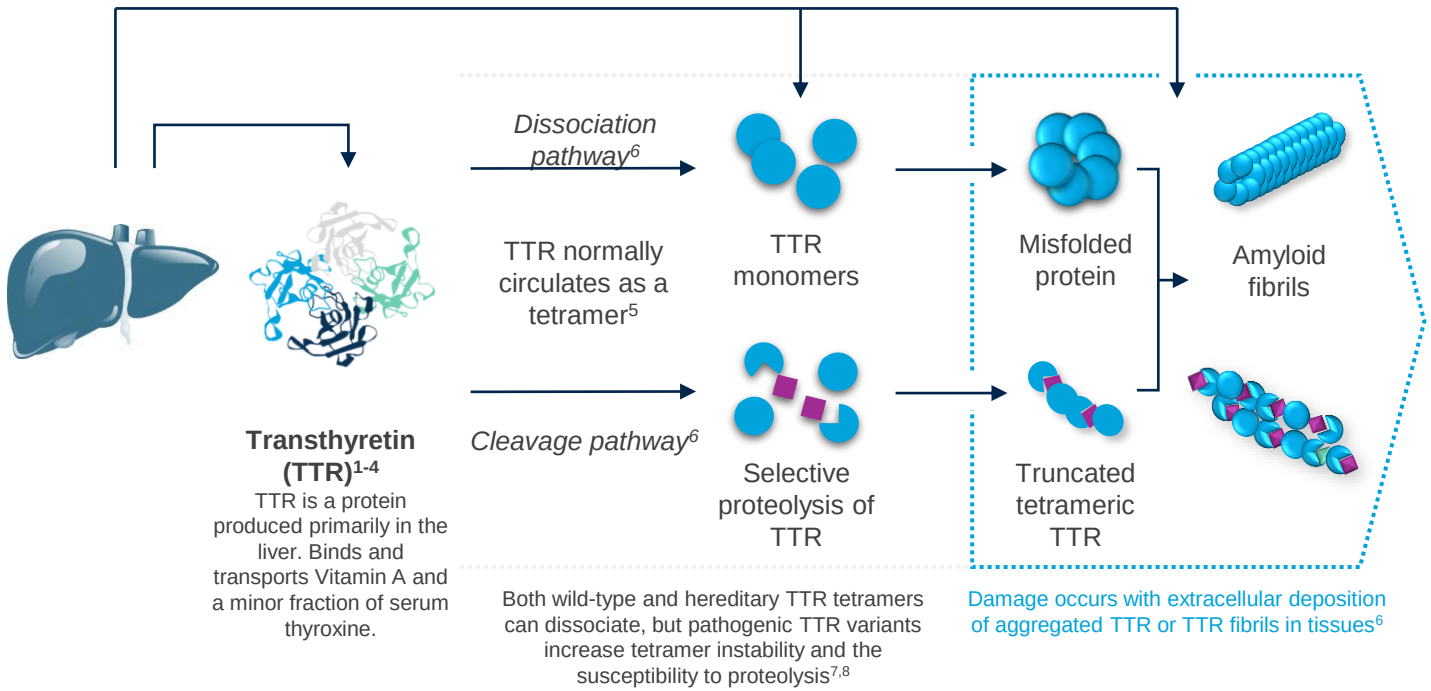
Summary of the most common amyloid types and their fibrillary precursor protein, underlying cause, clinical phenotype, and management and treatment

Amyloid type	Fibrillary precursor protein	Underlying cause	Most common organs involved	Management/Treatment*
AL amyloidosis	Monoclonal immunoglobulin light chain	B cell dyscrasia	Kidneys, heart, liver, peripheral NS, autonomic NS, soft tissues, gastrointestinal system	Chemotherapy and/or autologous stem cell transplantation
Wild-type ATTR amyloidosis	Wild-type transthyretin	Unknown, associated with aging	Heart, soft tissues	TTR stabilizer
Hereditary ATTR amyloidosis	Variant transthyretin, wild-type transthyretin	*TTR* gene mutation	Heart, peripheral NS, autonomic NS, soft tissues	TTR stabilizer, gene silencing therapy
Systemic AA amyloidosis	Serum amyloid A	Chronic inflammatory conditions	Kidneys, liver, spleen, heart (<1%)	Management of underlying cause of inflammation
LECT2 amyloidosis	LECT2	Unknown	Kidneys, liver	Supportive
Fibrinogen Aα-chain amyloidosis	Variant fibrinogen	Fibrinogen gene mutation	Kidneys, liver	Supportive
AApoA1 amyloidosis	Variant *ApoA1*	*AApoA1* gene mutation	Kidneys, liver, heart	Supportive
Lysozyme	Variant lysozyme	Lysozyme gene mutation	Liver, kidneys, gastrointestinal tract, skin, lacrimal and salivary glands	Supportive
Gelsolin amyloidosis	Variant gelsolin	Gelsolin gene mutation	Peripheral NS, autonomic NS, cranial nerves, kidneys	Supportive

Table taken from Law and Gillmore. 2022[1]

*There may be other management or treatment options not listed.
AA, serum amyloid A; AL, primary/light chain; ATTR, amyloidosis; LECT2, leukocyte chemotactic factor 2; NS, nervous system.
1. Law and Gillmore. *Am J Med.* 2022;135:S2−8.

ATTR Pathophysiology Overview



Clinical manifestations[6]

Extracellular amyloid deposition in nerves and soft tissue

- Carpal tunnel syndrome
- Orthostatic hypotension
- Syncope
- Pins and needles sensations
- Painful sensation
- Erectile dysfunction
- Bowel disorders

Extracellular amyloid deposition between cardiomyocytes

- Signs and symptoms of HF
- Diastolic dysfunction
- Impaired longitudinal contraction
- Arrhythmias
- Increased NT-proBNP
- Increased troponin T
- Increased troponin I

ATTR results from damage caused to cells and tissues by TTR amyloid deposition.[9]
ATTR is rapidly progressive, with significant morbidity and mortality.[10-12]

ATTR, transthyretin amyloidosis; HF, heart failure; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; TTR, transthyretin; wt, wild-type.

1. Eisele et al. *Nat Rev Drug Discov.* 2015;14:759–80; 2. Sekijima. *J Clin Pharm Ther.* 2014;39:225–33; 3. Soprano et al. *J. Biol. Chem.* 1985; 260:11793–98; 4. Hennebry et al. *Proteins.* 2006;64:1024–45; 5. Monaco et al. *Science* 1995;268:1039–41; 6. Porcari et al. *Cardiovasc Res.* 2022;cvac119. doi:10.1093/cvr/cvac119; 7. Kelly. *Structure* 1997;5:595–600; 8. Mangione et al. *J Biol Chem.* 2018;293:14192–9; 9. Koike & Katsuno. *Biomedicines.* 2019;7:11; 10. Lane et al. *Orphanet J Rare Dis.* 2015;10(Suppl. 1):O26; 11. Adams et al. *Neurology.* 2015;85:675–82; 12. Adams et al. *Curr Opin Neurol.* 2016;29(Suppl.1):S14–26.

Differentiating Hereditary and Wild-Type ATTR

	hATTR	wtATTR
Genetics[1]	Autosomal dominant, at least one *TTR* gene variant is present	Non-hereditary, no *TTR* gene variant
Global prevalence	~50,000[2]	~200,000-300,000[a]
Age at symptom onset[3]	>20 years	>50 years
Male, %[3]	76-86	91-97
Median survival following diagnosis, years	4.7[4]	2.5-5.5[5-7]
Clinical manifestations[3]		
Cardiac	Yes	Yes
Peripheral nerves	Yes	Occasionally
Autonomic nerves (including GI)	Yes	Rare
Kidney	Yes	Rare
Ophthalmologic	Vitreous deposition	Not prominent
Musculoskeletal	Yes	Yes

Table adapted from Gertz et al. 2020[3]

[a]Information based on Alnylam modeling data.

ATTR, transthyretin amyloidosis; GI, gastrointestinal; hATTR/hATTR, hereditary ATTR; TTR, transthyretin; wtATTR/wtATTR, wild-type ATTR.

1. Sekijima. *GeneReviews. [Internet]* 2001. Last updated June 17, 2021. Accessed October 5, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1194/ 2. Hawkins et al. *Ann Med.* 2015;47:625–38; 3. Gertz et al. *BMC Fam Pract.* 2020;21:198; 4. Swiecicki et al. *Amyloid.* 2015;22:123–31; 5. Lane et al. *Circulation.* 2019;140:16–26; 6. Aus dem Siepen et al. *Clin Res Cardiol.* 2018;107(2):158–69; 7. Givens et al. *Aging health.* 2013;9(2):229–35.

wtATTR: Reported and Expected Prevalence

- wtATTR is considered **largely underdiagnosed**, but recognition of this disease is increasing rapidly due to developments in diagnostic techniques[1]
  - Growing recognition of wtATTR is highlighted by the recent rise in the number of new diagnoses[2]
- Based on the projected aging of the worldwide population, wtATTR is predicted to be recognized as the most common form of cardiac amyloidosis[1,3]

New diagnoses from 2000-2016 at the UK National Amyloidosis Center[2]

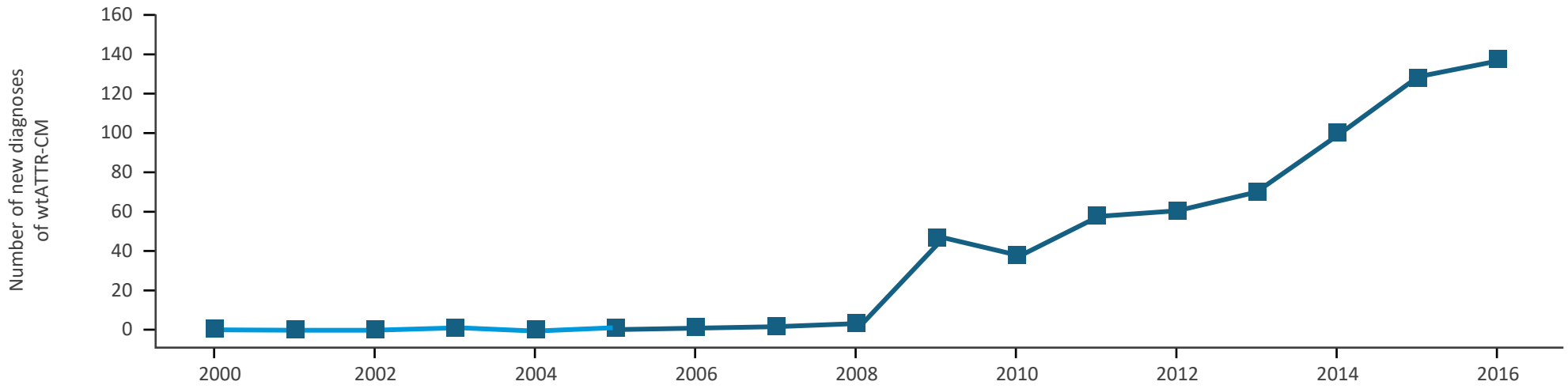


Figure adapted from Lane et al. 2019[2]

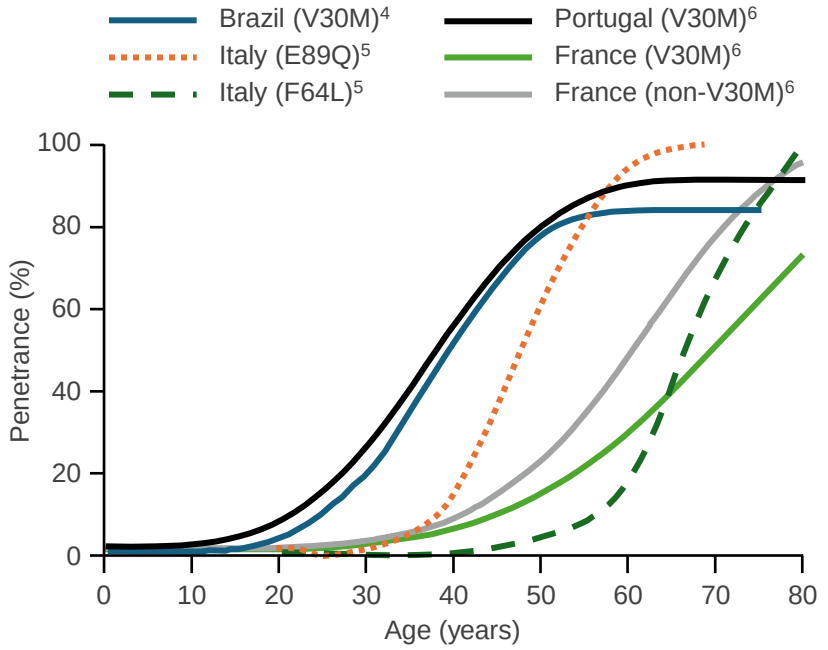
wtATTR, wild-type ATTR; wtATTR-CM, wild-type ATTR with cardiomyopathy; UK, United Kingdom.

1. Narotsky et al. *Can J Cardiol.* 2016;32:1166.e1–1166.e10; 2. Lane et al. *Circulation.* 2019;140:16–26; 3. Ruberg & Berk. *Circulation.* 2012;126:1286–300.

hATTR: Symptom Onset and Penetrance

- Age of onset can vary by geography[1]
- EO: <50 years of age
  - Patients frequently exhibit sensory, motor, and autonomic neuropathy; more prevalent in endemic populations and patients with V30M[1,2]
  - Nearly always associated with a positive family history, less severe disease course, and longer survival[3]
- LO: ≥50 years of age
  - Patients exhibit sensory and motor neuropathy, and mild autonomic dysfunction that often includes cardiac dysfunction—commonly seen in Sweden and non-endemic regions[2]
    - Sensory and motor symptoms begin in lower extremities with mixed sensory loss (superficial and deep sensation)[3]
  - Disease tends to occur sporadically, with male predominance in families with LO disease[3]

Penetrance and age of onset



Average age of onset (years)	
Sweden (V30M)[7,a]	56
Portugal (V30M)[8]	34
Brazil (V30M)[4]	35
Italy (E89Q)[5]	49
Cyprus[a] (V30M)[9]	46
Mallorca[a] (V30M)[10]	46

- **Genotype**: Penetrance differs within and across genetic variants
- **Age:** Gene penetrance of >50% by age 70 in almost all regions, regardless of variant[11]
- Additional factors that impact penetrance are geography and inheritance (paternal vs. maternal)[12]

Penetrance of V122I in the US

[a]Penetrance by age not available
hATTR, hereditary ATTR; EO, early-onset; LO, late-onset.

- 1. Parman et al. *Curr Opin Neurol.* 2016;29:S3–13; 2. Plante-Bordeneuve et al. *Lancet Neurol.* 2011;10:1086–97; 3. Adams et al. *J Neurol* 2021;268:2109–22; 4. Saporta et al. *Eur J Neurol* 2009;337–41; 5. Mazzeo et al. *J Neuromuscul Dis* 2015;2:S39–48; 6. Planté-Bordeneuve et al. *J Med Genet.* 2003;40:120; 7. Holmgren et al. *J Med Genet.* 1994;31:351–4; 8. Sousa et al. *Am J Med Genet.* 1995;60:512–21; 9. Dardiotis et al. *Amyloid.* 2009;16:32–7; 10. Munar-Ques et al. *Amyloid.* 2005;12:54–61; 11. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 12. Hellman et al. *Amyloid.* 2008;15:181–6.

SCAN-MP Study: Determining the Clinical Penetrance of the V122I Variant in the US With Nuclear Imaging

Study population: 278 self-identified Black and Caribbean Hispanic participants ≥60 years of age with a history of HF

- LVEF >30%
- LV septal or inferolateral wall thickness ≥12 mm

Of the participants with ATTR-CM (n=19):

- 63% had wild-type ATTR-CM
- 37% had hereditary ATTR-CM attributable to the V122I variant

The overall clinical ATTR-CM penetrance of the V122I variant in this study was **39%**

- Penetrance for participants <75 years: 20%
- Penetrance for participants ≥75 years: 63%

Median age of individuals with penetrant ATTR-CM was **82 years**

- ATTR-CM, ATTR with cardiomyopathy; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction.
- 1. Madhani et al. *J Am Heart Assoc.* 2023;12(15):e028973.

hATTR: Common Variants and Frequency[1]

V122I

- Most common pathogenic variant in the US[2,3] and common in African Americans (prevalence of 3-4%) and West Africans (up to 5%)[3-5]
- Common cause of heart failure among elderly African patients,[2,6] although V122I carriers have reported symptoms of neuropathy[1,7,a]

T60A

- Originated in the UK and endemic to NW Ireland; reported to present with both polyneuropathy and cardiomyopathy[8,9]

V30M

- Most common variant across majority of European countries[2,10] and endemic to Portugal, Sweden, Brazil, and Japan[10-13]
- EO typically presents with polyneuropathy; LO typically presents with both polyneuropathy and cardiomyopathy[10,11]

Genetic and clinical characteristics of *TTR* variants

[a]Polyneuropathy was defined by International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD10) diagnosis code G62 or G63, or ICD9 diagnosis code 357. Phenome-wide association studies identified an association between polyneuropathy and the V122I variant.

hATTR, hereditary ATTR; EO, early-onset; LO, late-onset; NW, northwest; TTR, transthyretin; UK, United Kingdom; US, United States.

1. Maurer et al. *J Am Coll Cardiol.* 2016;68(2):161–72; 2. Planté-Bordeneuve et al. *Lancet Neurol.* 2011;10:1086–97; 3. Dharmarajan et al. *J Am Geriatr Soc.* 2012;60:765–74; 4. Sekijima. *Gene Rev*. Last updated June 17, 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1194/#tfap.Molecular_Genetics (accessed October 5, 2022); 5. Jacobson et al. *Amyloid.* 2015;22:171–4; 6. Dungu et al. *Circ Heart Fail.* 2016;e0003352; 7. Parker et al. *Sci Rep.* 2021;11:11645; 8. Castano et al. *Heart Fail Rev* 2015;20:163–78; 9. Ruberg & Berk. *Circulation.* 2012;126:1286–300; 10. Parman et al. *Curr Opin Neurol.* 2016;29:S3–13; 11. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 12. Coelho et al. *Curr Med Res Opin.* 2013;29:63–76; 13. Sekijima et al. *Orphanet J Rare Dis.* 2018;13:6.

Genetic and Clinical Characteristics of *TTR* Variants

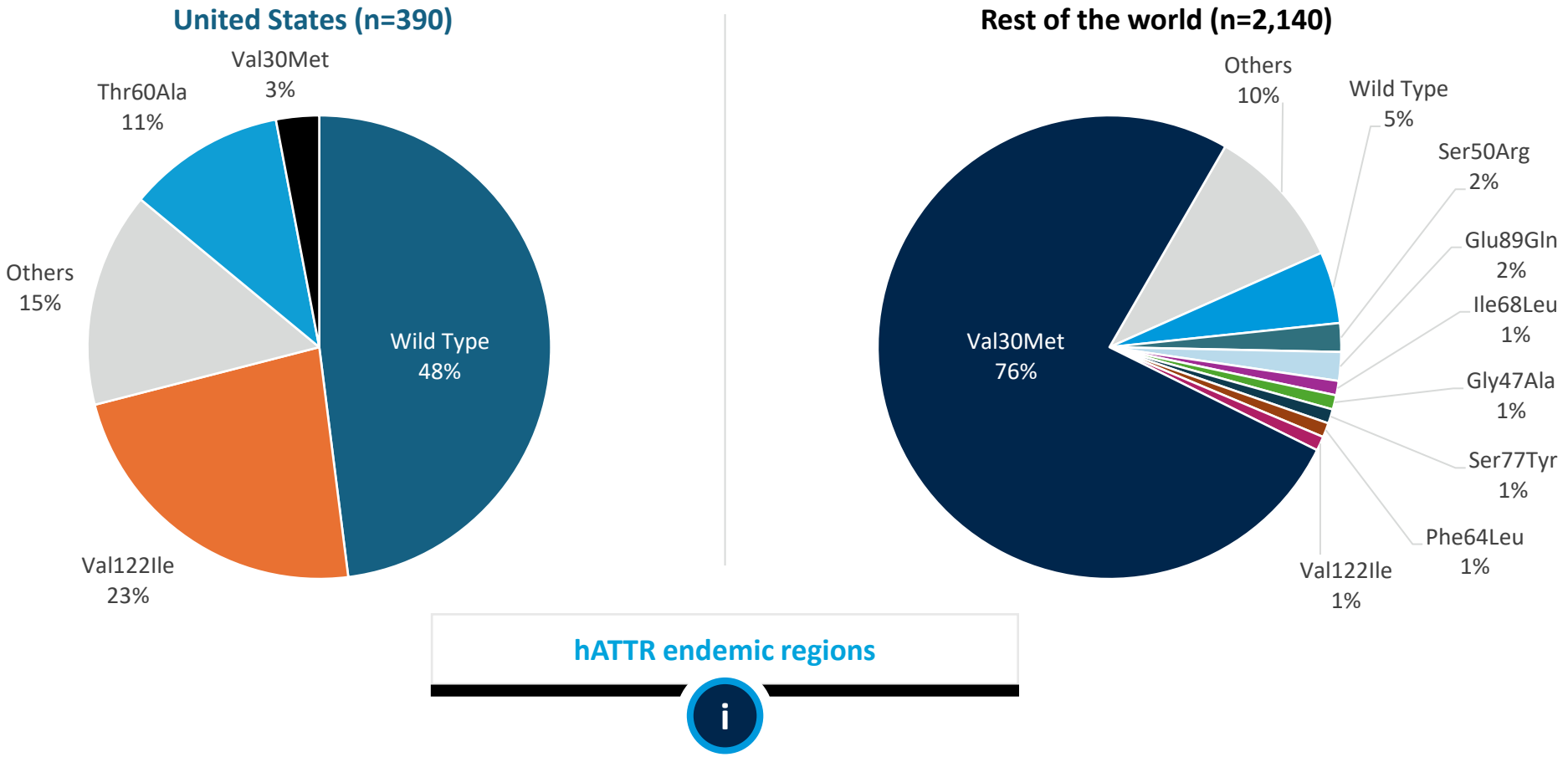
Variant	Frequency	Penetrance	Typical Age of Onset (y)	Cardiac Phenotype	Neurologic Phenotype	Race and/or Nationality	Country/Location
Val122Ile	3.5% in Blacks	37.4%, with carpal tunnel syndrome, polyneuropathy, cardiomyopathy, or heart failure by age 75 years	Late 60s	+++	+	Black and Caribbean Hispanics/West African ancestry	Worldwide
Val30Met (early onset)	Most common variant currently worldwide	>90%	<40	+	+++	Portuguese, Japanese, Swedish	Portugal, Sweden, Japan, Brazil, Cyprus, and Majorca
Val30Met (late onset)	1 per million in Japan	>60%	>50	++	++	Worldwide	Worldwide
Thr60Ala	1% in County Donegal, Ireland	>90%	>50	+++	++	Irish	Ireland, England, United States
Leu111Met	<1% of all *TTR* variants	>90%	30-40	+++	+	Danish	Denmark
Ile68Leu	<1% of all *TTR* variants	>90%	55	+++	+	Italian, German	Italy, Germany
Ser77Tyr	<1% of all *TTR* variants	>90%	55	++	++	French, German, American	United States, France, Spain
Glu89Gln	<1% of all *TTR* variants	>90%	55	++	++	Italian	Italy
Gly47Glu	<1% of all *TTR* variants	>90%	45	++	+++	Italian	Italy, Germany
Ile84Ser	<1% of all *TTR* variants	Unknown	40	++	+++	Swiss, German	United States
Phe64Leu	<1% of all *TTR* variants	Unknown	>50	++	+++	Italian	Italy, United States
Leu58His	<1% of all *TTR* variants	Unknown	>50	++	+++	German	United States, Germany
Ser50Arg	<1% of all *TTR* variants	Unknown	>40	++	+++	Asian, Mexican	Japan, Mexico
Gly47Ala	<1% of all *TTR* variants	Unknown	>40	+	+++	German, Italian, French, Mexico	Germany, Italy, France
Val20Ile	<1% of all *TTR* variants	Unknown	60s	++	+	German	Germany

1. Kittleson et al. *JACC.* 2023;81(11):1076–176.

+, less common; **++**, common; **+++**, more common.

Distribution of *TTR* Variants in the US vs. Globally

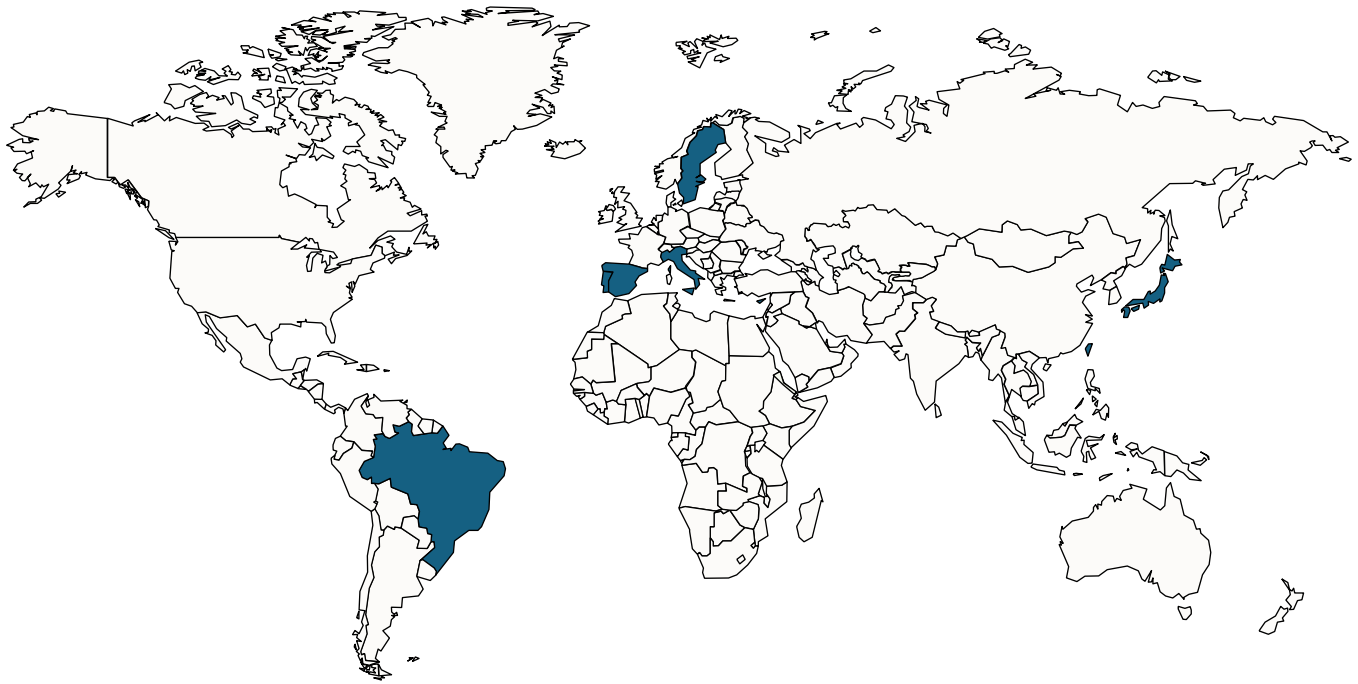
- THAOS is an **ongoing, multicenter, longitudinal, observational study** open to all ATTR patients
  - Individuals with *TTR* gene mutations without a diagnosis of hATTR (asymptomatic) are also eligible to submit data



ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; THAOS, Transthyretin Amyloid Outcome Survey; TTR, transthyretin.

1. Maurer et al. *J Am Coll Cardiol.* 2016;68(2):161–72.

hATTR: Endemic Regions



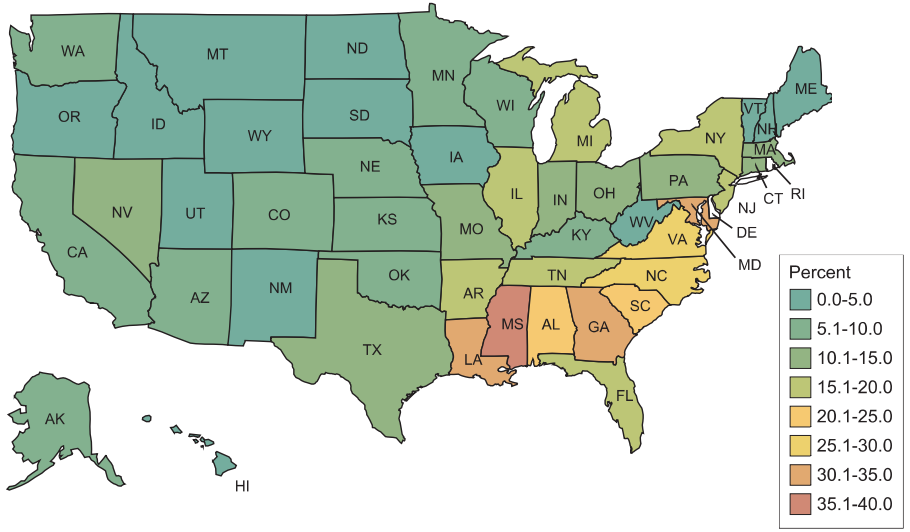
Cohort	Description	Prevalence (per 100,000)[1,2]
Portugal	~2000 diagnosed symptomatic V30M patients; EO with high penetrance	19.2
Spain	Endemic V30M populations in Mallorca, Huelva; significant cohorts in many regions	0.1
Sweden	LO V30M (~250 symptomatic); as many as 7500 carriers	2.6
Italy	Large population of E89Q patients in Sicily	1.0
Japan	EO and LO V30M populations (~125 symptomatic)	0.1
Brazil	Predominantly EO V30M populations[3]	2.4[a]
Cyprus	EO (~140 asymptomatic cases); V30M only reported variant in endemic areas	5.6
Taiwan	Endemic LO A97S population; ~90% of cases[4]	0.75[b]

[a]Calculated based on the highest estimated number of cases from two population subgroups: Luso-Brazilians and Portuguese non-Luso-Brazilians. [b]Based on the high prevalence estimate of 177 in a population of 23.5 million.
hATTR, hereditary ATTR; EO, early-onset; LO, late-onset.
1. Parman et al. *Curr Opin Neurol.* 2016;29(Suppl. 1):S3–13; 2. Schmidt et al. *Muscle Nerve.* 2018;57:829–37; 3. Waddington-Cruz et al. *Orphanet J Rare Dis.* 2019;14:34; 4. Chao et al. *Ann Clin Transl Neurol.* 2019;6:913–22.

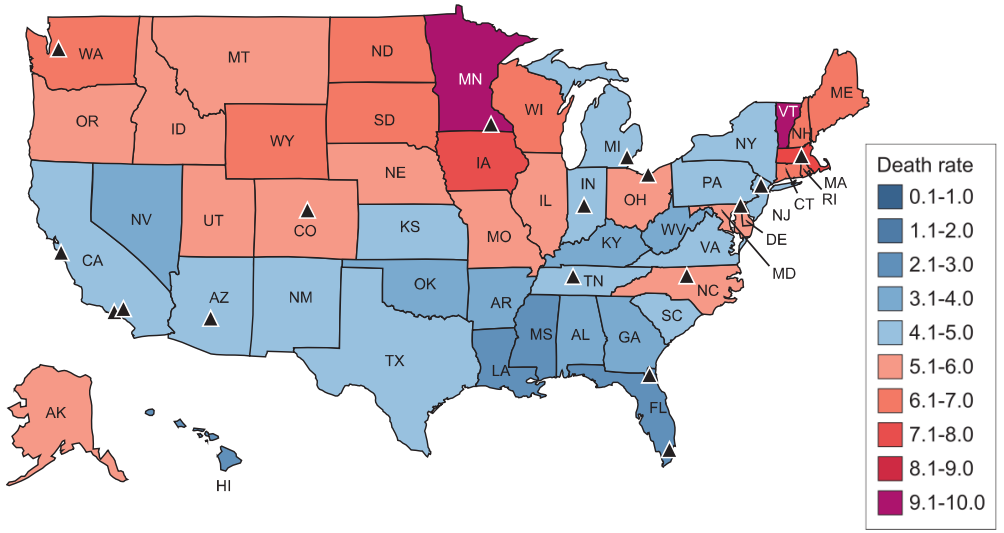
Potential Underdiagnosis of Cardiac Amyloidosis in the US

- An analysis based on a cohort study of death certificate data from 1979 to 2015[1]
- **Black men had the highest reported age-adjusted amyloidosis mortality rate in 1999-2015 at 12.36 per 1,000,000,** which was nearly twice the rate for white men
- States with higher proportions of black residents were not found to have higher amyloidosis mortality rates, despite black individuals being overrepresented in amyloidosis mortality, suggesting underdiagnosis of cardiac amyloidosis in these regions

A Proportion of black residents per state in 2014



B Amyloidosis death rates by state from 1979 to 2015



US, United States.

1. Alexander et al. *JAMA Cardiol.* 2018;3(9):865–70.

Summary

- ATTR is a multisystemic, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR accumulating as amyloid deposits in multiple organs and tissues including nerves, heart, and GI tract [1-4]
  - Patients diagnosed with hATTR and wtATTR have a median survival of 4.7[5] and 2.5-5.5 years,[6-8] respectively
- ATTR remains underdiagnosed or misdiagnosed[4,9,10]
- Patients with ATTR experience substantial burden, including reduced QoL[11-14] and functional impairment[6,15]

There remains a need for health care professionals to:

1	2	3	4
Recognize the constellation of red-flag symptoms of ATTR[16,17]	**Collaborate with a multidisciplinary team for a potential amyloidosis diagnosis[16,17]**	**Employ the diagnostic algorithm and confirmatory diagnostic tools to verify diagnosis[17-19]**	**Assess progression of disease following treatment and provide patient with holistic care (mental, physical, and social support)[20,21]**

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; GI, gastrointestinal; QoL, quality of life; TTR, transthyretin.

1. Hanna. *Curr Heart Fail Rep.* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis.* 2013;106:528–40; 3. Adams et al. *Neurology.* 2015;85:675–82; 4. Maurer et al. *Circ Heart Fail.* 2019;12:e006075; 5. Swiecicki et al. *Amyloid.* 2015;22:123–31; 6. Lane et al. *Circulation.* 2019;140:16–26; 7. Aus dem Siepen et al. *Clin Res Cardiol.* 2018;107(2):158–69; 8. Givens et al. *Aging health.* 2013;9(2):229–35; 9. Hawkins et al. *Ann Med.* 2015;47:625–38; 10. Castano et al. *Heart Fail Rev.* 2015;20:163–78; 11. Coehlo et al. *Muscle Nerve.* 2017;55:323–32; 12. Vinik et al. *J Peripher Nerv Syst.* 2014;19:104–14; 13. Ines et al. *ISPOR Congress* 2015. Poster N21; 14. Obici et al. *Amyloid.* 2020;27:153–62; 15. Bolte et al. *Orphanet J Rare Dis* 2020;15:287; 16. Nativi-Nicolau et al. *Heart Fail Rev*. 2022;27(3):785–93; 17. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 18. Namiranian and Geisler. *Am J Med.* 2022;135 Suppl 1:S13–19; 19. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 20. Adams et al. *Orphanet J Rare Dis.* 2021;16:411; 21. Obici et al. *BMJ Open.* 2023;13:e073130.

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