Amyloidosis
Research
Consortium

Hereditary ATTR Amyloidosis Overview

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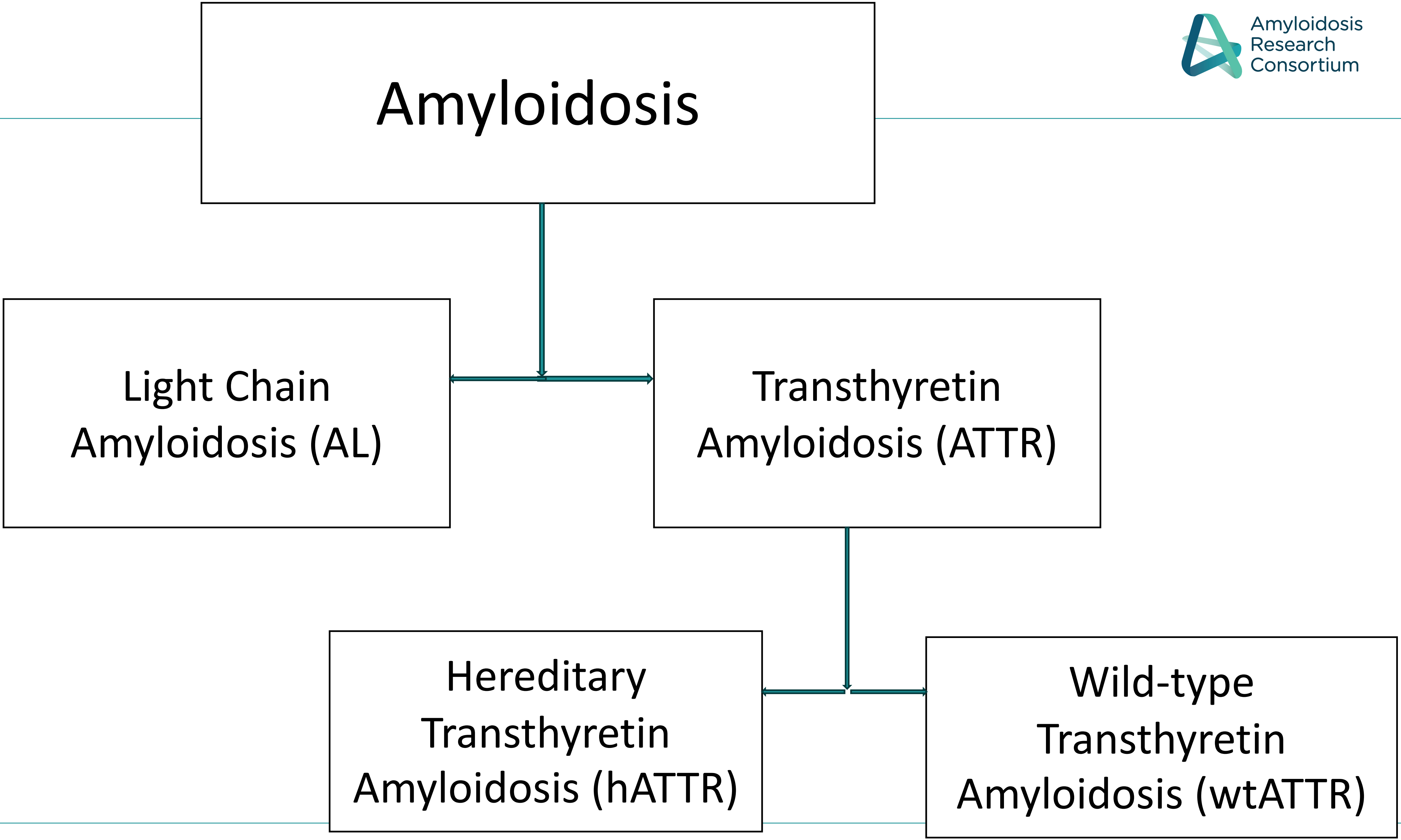
April 2025



Amyloidosis

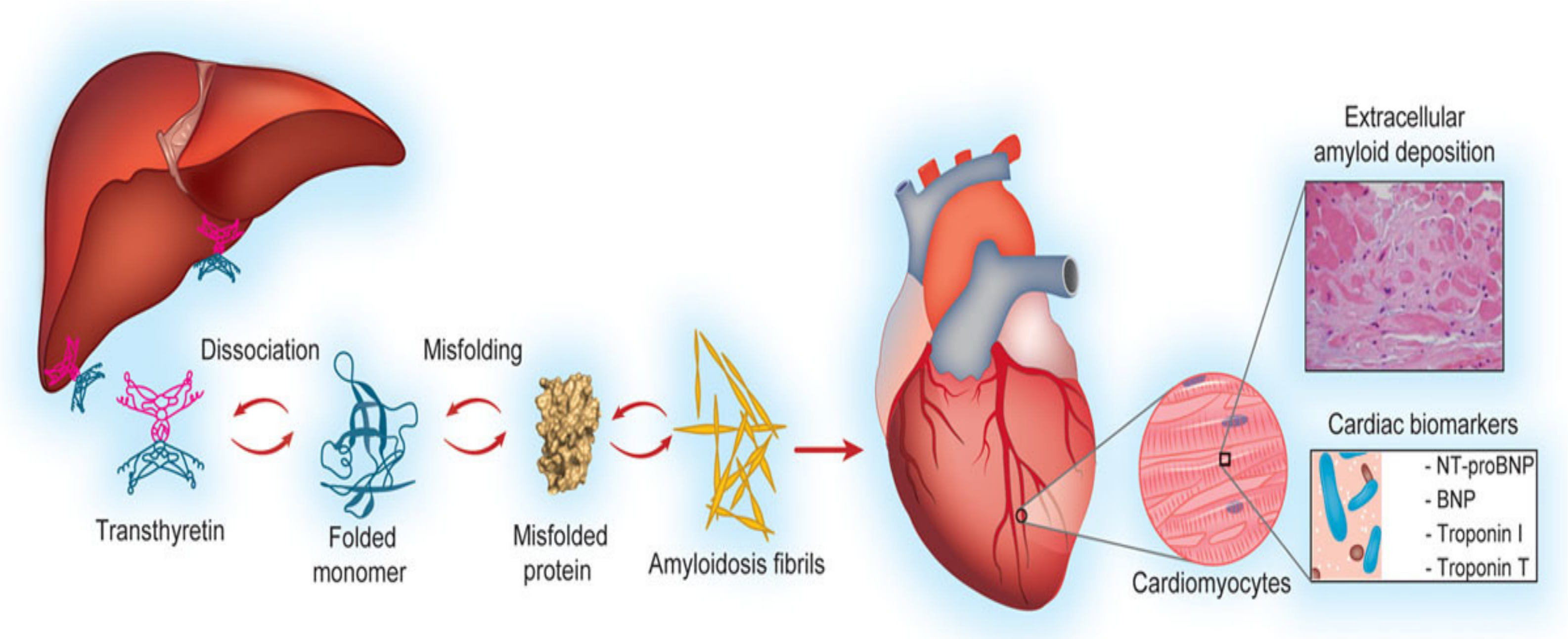
Light Chain Amyloidosis (AL)

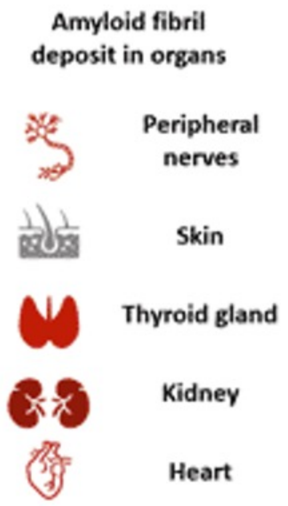
Transthyretin Amyloidosis (ATTR)

Hereditary Transthyretin Amyloidosis (hATTR)

Wild-type Transthyretin Amyloidosis (wtATTR)

TRANSTHYRETIN AMYLOIDOSIS





Credit: https://www.cusabio.com/c-20868.html

Jose Nativi-Nicolau. Circulation: Heart Failure. Serum Transthyretin, Volume: 11, Issue: 2, DOI: (10.1161/CIRCHEARTFAILURE.118.004802)

Hereditary Transthyretin Amyloidosis (hATTR)

- Autosomal dominant inheritance (50% chance to pass the mutation to each offspring).
- Substitution or deletion mutations.
- There are over 150 known TTR variants.
- Disease can have sensory-motor polyneuropathy, autonomic dysfunction, gastrointestinal and cardiac manifestations
- Most common in the United States is reported as Val122Ile or V122I.
  - The prevalence has shown to be 3.5% in the self-identified U.S. Black population (~approximately 1.5 million, 1 out of 25).

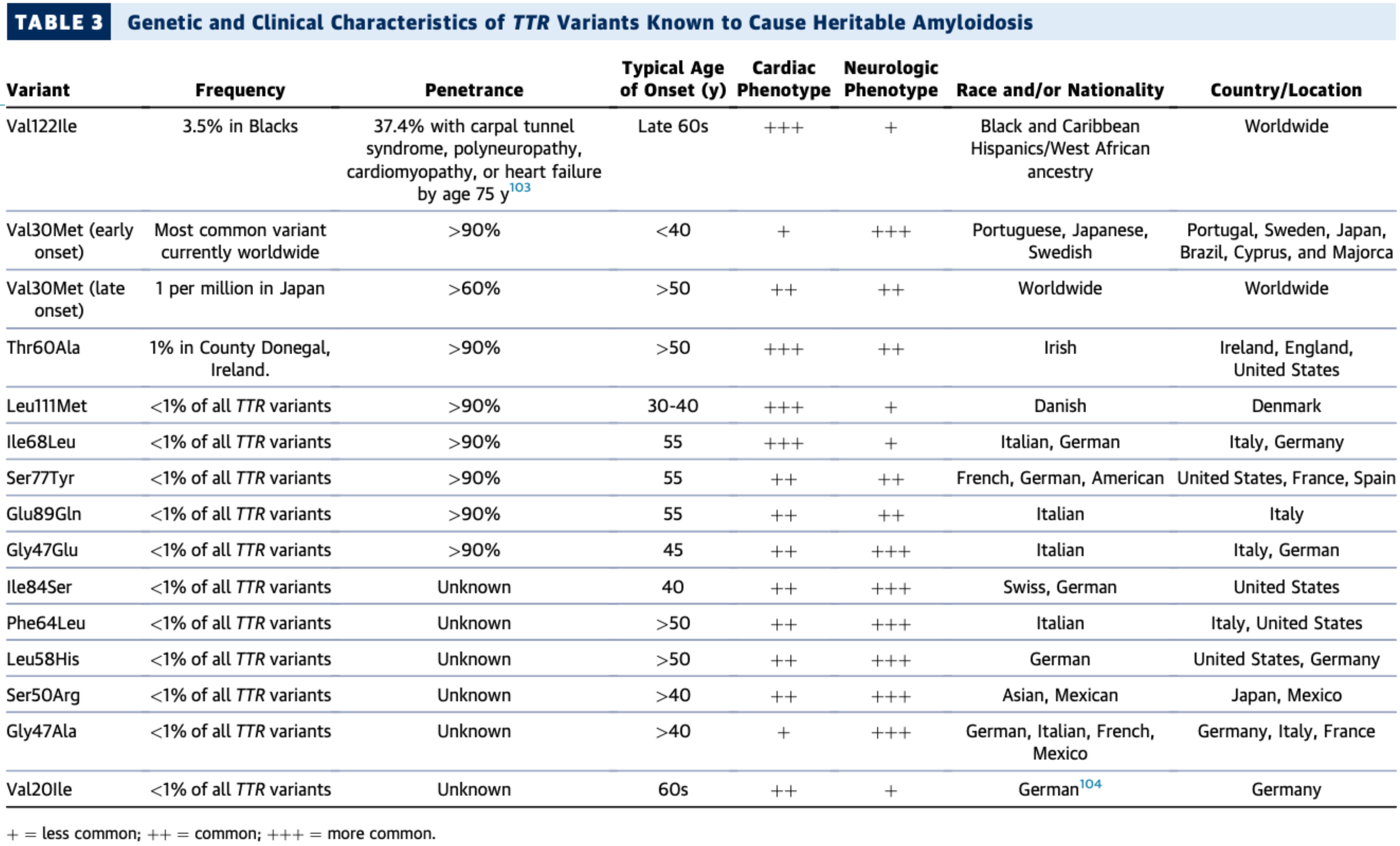


TABLE 3 **Genetic and Clinical Characteristics of *TTR* Variants Known to Cause Heritable Amyloidosis**

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 y[103]	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, German
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[104]	Germany

+ = less common; ++ = common; +++ = more common.

Kittleson et al JACC VOL. - , NO. - , 2022 2023 ACC Expert Consensus Decision Pathway on Cardiac Amyloidosis

GENETIC TESTING

Required to distinguish hereditary ATTR from wild-type ATTR.

Will determine specific gene variant of hATTR.

- Over 150+ gene variants

Important to identify the gene variant for cascade testing of family members.