Hereditary Transthyretin Amyloidosis
Identification and Diagnosis

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Disclosures

- Consulting: Pfizer, Inc.
- Advisory Board: Alnylam Pharmaceuticals, Inc.; Eidos Therapeutics, Inc.
- Speakers Bureau: Alnylam Pharmaceuticals, Inc.
- Research (Institutional): Pfizer, Inc.; Alnylam Pharmaceuticals, Inc.; Eidos Therapeutics, Inc.; Ionis-Akcea, Inc.

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Outline

- Overview and Prevalence of Hereditary ATTR
- Clinical Features
- Clinical Presentations
- Diagnosing Hereditary ATTR
- Future Directions

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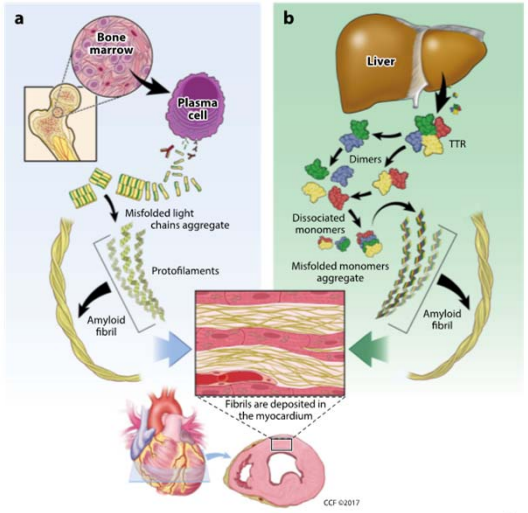
Overview and Prevalence of Hereditary ATTR

Amyloid comes in a variety of "flavors"

- Amyloidosis is a disorder of protein folding
- Misfolded proteins deposit in organs resulting in organ dysfunction
- AL & ATTR most common (~95%) cardiac involvement

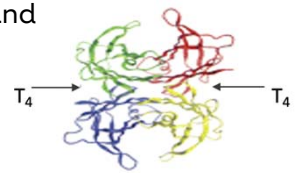
Amyloid protein	Precursor	Main features	Myocardial involvement
AL	Immunoglobulin light chain	Primary/myeloma associated	Frequent
ATTR	Transthyretin	Familial	Variable according to genotype
ATTR	Transthyretin	Wild type	Constant
AApo AI	Apolipoprotein AI	Familial	Occasional but severe
AApo AII	Apolipoprotein AII	Familial	Exceptional
AFib	Fibrinogen α chain	Familial	Exceptional
ALys	Lysozyme	Familial	Exceptional
AA	Serum AA	Secondary, reactive	Exceptional
A β2 M	β2 microglobulin	Hemodyalisis associated	Exceptional
IAA	Atrial natriuretic factor	Atrial fibrillation	Atrial tissue

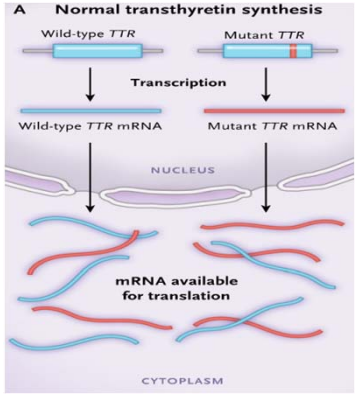


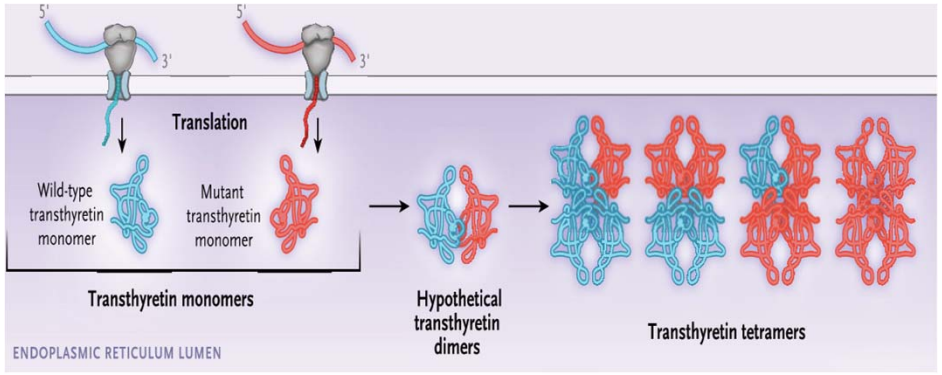
Adapted from Rubin, et al. Annu. Rev. Med. 2020. 71:203–19

TTR: Structure & Physiologic Binding

- Transthyretin (**Prealbumin**) transports thyroxine (T_4) and retinol (Vit A) in plasma and CSF
  - Homotetramer – 4 identical 127 amino acid monomers
- Variant forms of TTR protein are encoded by amyloidogenic TTR mutations
  - TTR gene located on long arm of chromosome 18
  - >120 TTR variants described: single amino acid substitutions → mutant subunits
  - Tetramers with ≥ 1 mutant subunits are kinetically or thermodynamically unstable
  - Dissociate under physiologic conditions to release monomers prone to misfolding

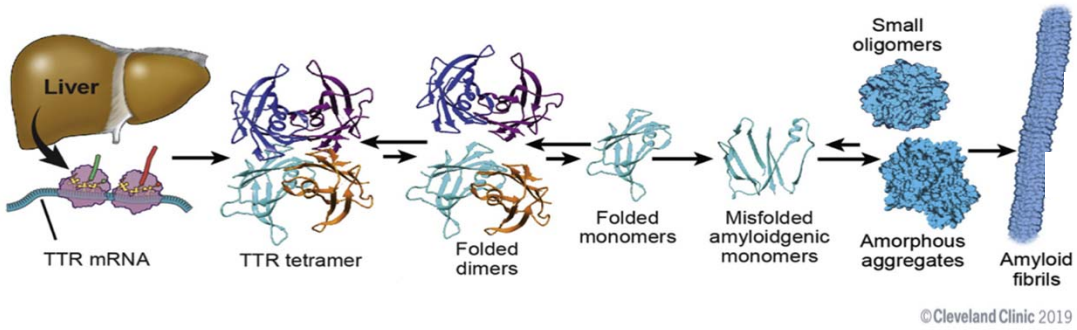






Adapted from Buxbaum *NEJM* 2018

TTR Amyloidosis: Amyloidogenic Cascade

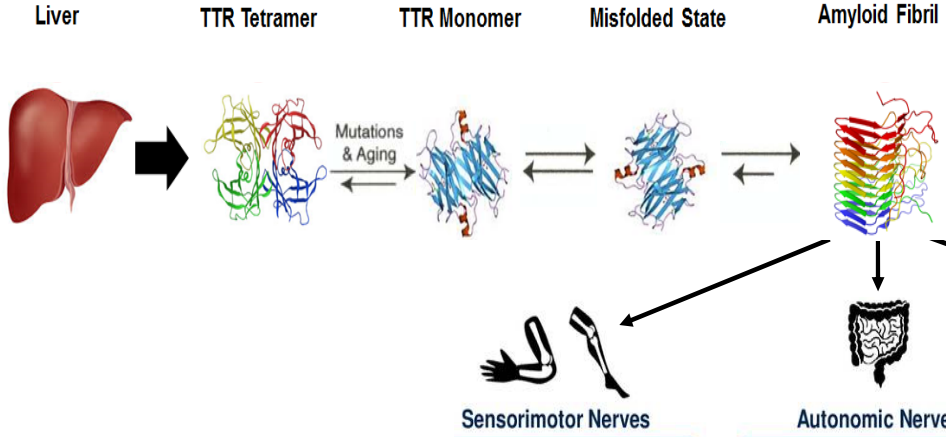


Functional TTR structure ⇢ Pathologic TTR structures

- Mutations
- Aging

Adapted from *Canadian Journal of Cardiology* 2020 36322-334DOI: (10.1016/j.cjca.2019.12.034)

hATTR: Pathogenesis & Classification



Clinical Manifestations	Loss of sensation Muscle weakness Impaired ambulation	Orthostatic hypotension Syncope/falls Constipation/diarrhea Urinary retention/UTIs	Heart failure Arrhythmias/syncope Impaired exercise capacity
	TTR Amyloid Polyneuropathy (ATTR-PN or FAP)		TTR Amyloid Cardiomyopathy (ATTR-CM or FAC)

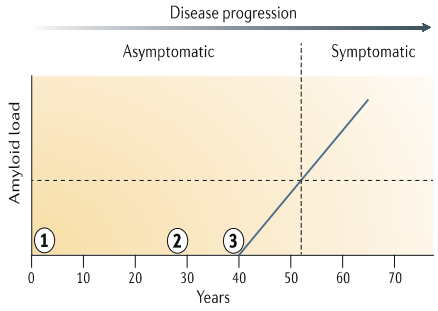
hATTR: Genotype-Phenotype Correlation

Mutations Causing Disease

Inheritance: Autosomal dominant

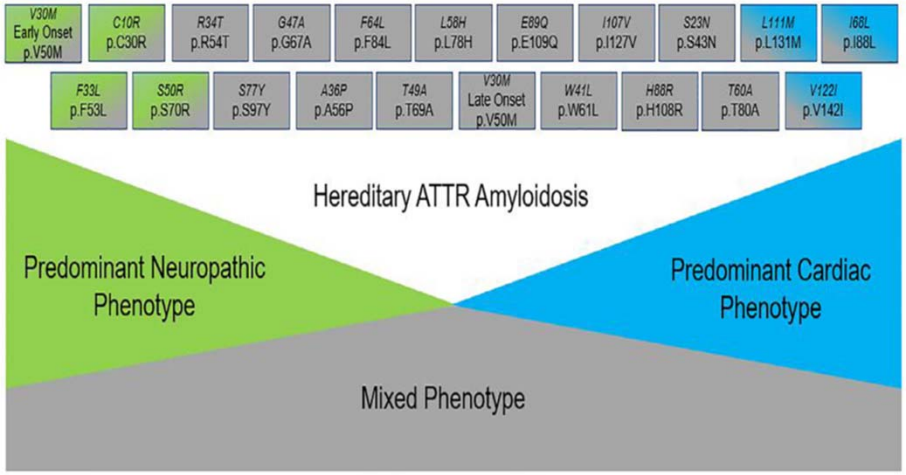
Penetrance: Incomplete; multi-factorial determinants incompletely understood

Symptom onset: Presenting age varies by mutation, environmental factors



1. Production of mutant TTR
2. Initiation of non-fibrillar TTR deposition
3. Initiation of amyloid deposition

Adams, et al. *Nature Reviews Neurol* 2019

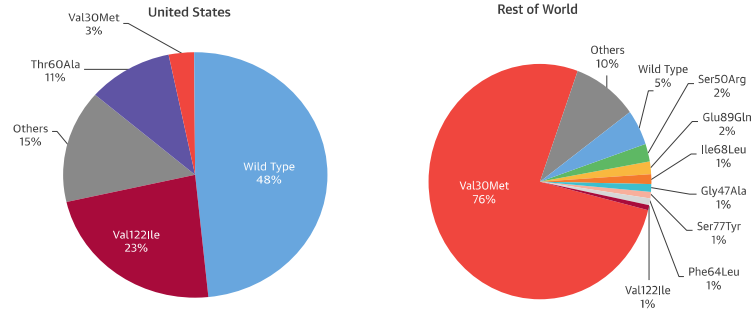


Griffin, et al. *Trends in Cardiovasc Med* 2021

ATTR: Worldwide Distribution & Characteristics

Transthyretin Amyloid Outcomes Survey (THAOS)

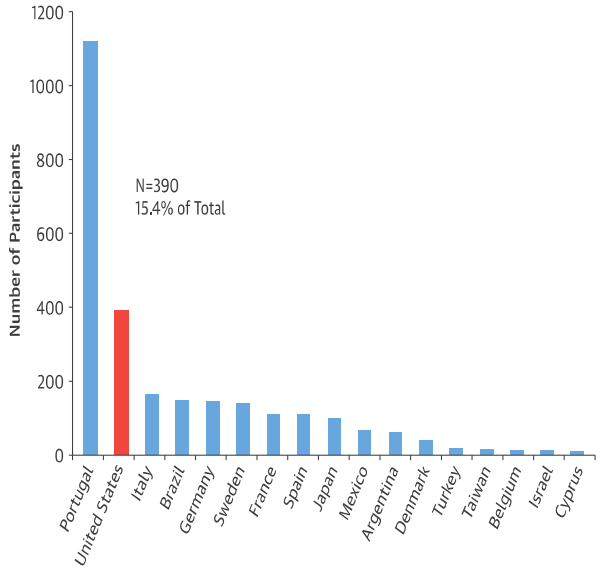
Maurer, M.S. et al. J Am Coll Cardiol. 2016;68(2):161-72.



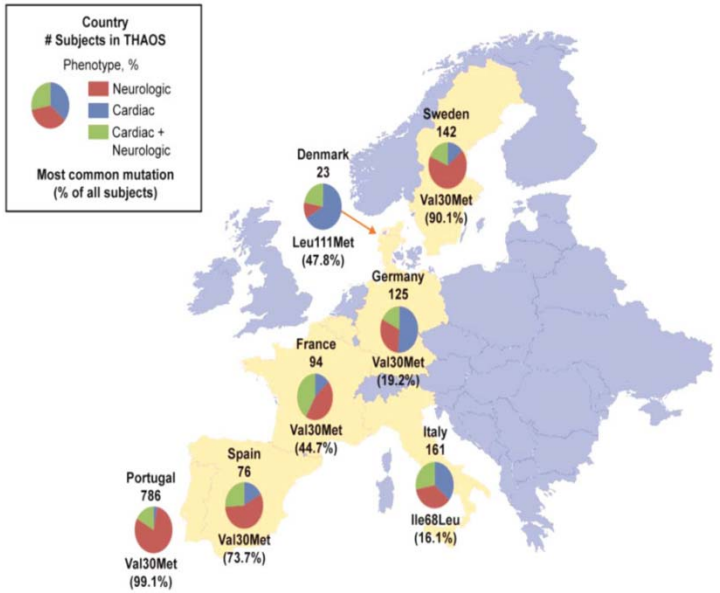
Disease	Mutation	Population & Age of Onset
wtATTR-CM	None (Wild Type)	Accumulations in >20% of >80yo Male predominant (9:1) >70 years
hATTR-CM (FAC)	V122I (V141I)	3-4% African Americans (West African Descent) Male predominant (3:1; Gene+ 1:1) >60 years
hATTR-CM and/or -PN (or mixed FAC-FAP)	T60A (T80A)	Northern Ireland descent Male predominant (2:1) >45 years

ATTR: Distribution in Europe (THAOS)

FIGURE 1 THAOS Enrollment According to Country

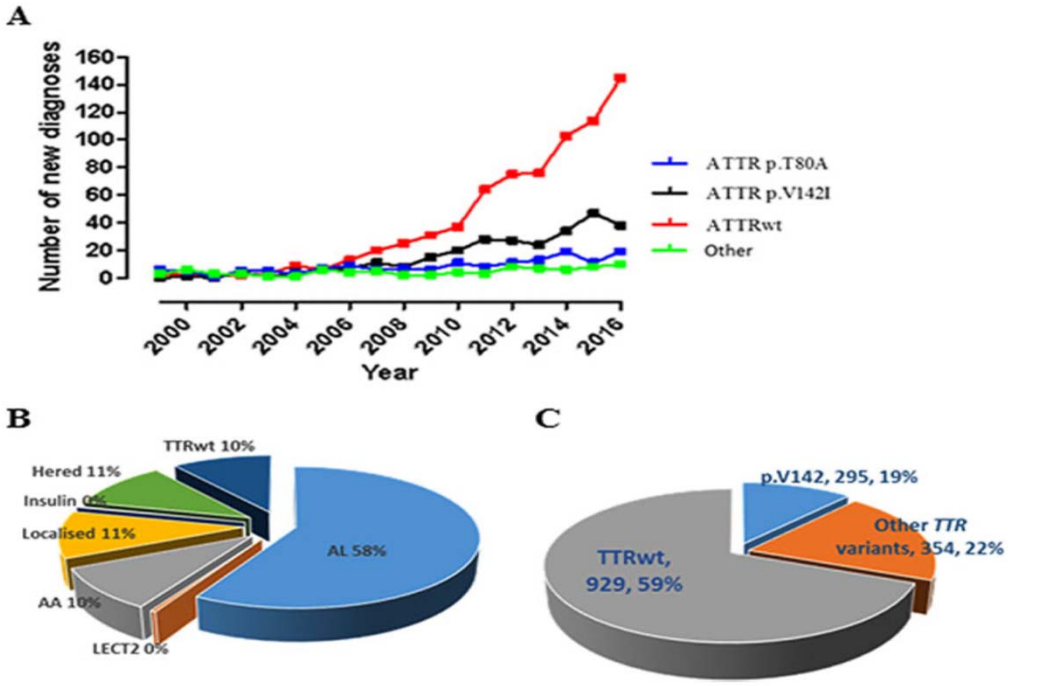


Maurer, M.S. et al. J Am Coll Cardiol. 2016;68(2):161-72.



Damy, et al. *Eur Heart J* 2019

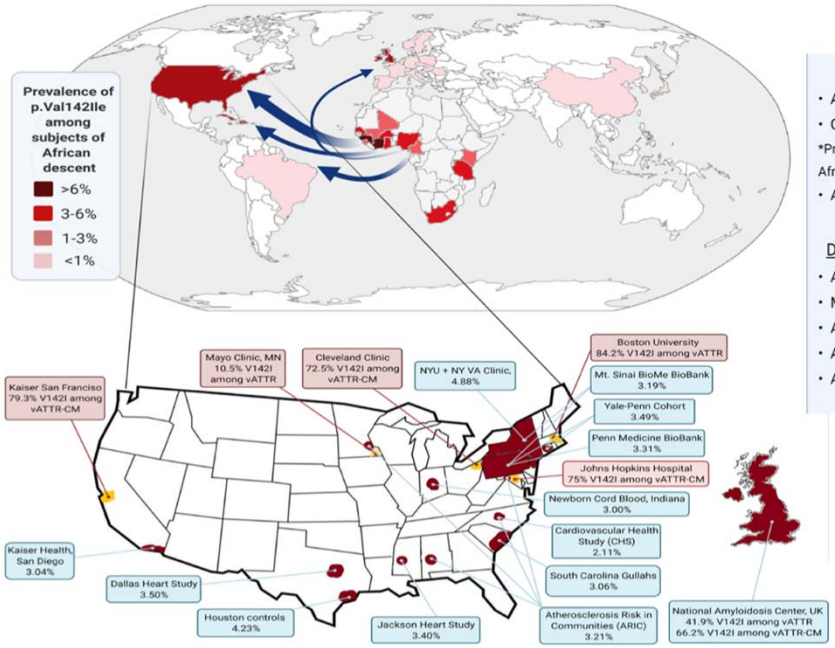
ATTR at National Amyloidosis Center, UK



Rowczenio, et al. *Human Mutation* 2019

hATTR Amyloidosis in the United States

Prominence of TTR V122I (p.V142I) mutation



Prevalence of p.Val142Ile Variant

- Among African Descent: 3.0% - 3.5%
- General Population*: 0.3% - 1.6%

*Proportionate to percentage of population that is of African descent

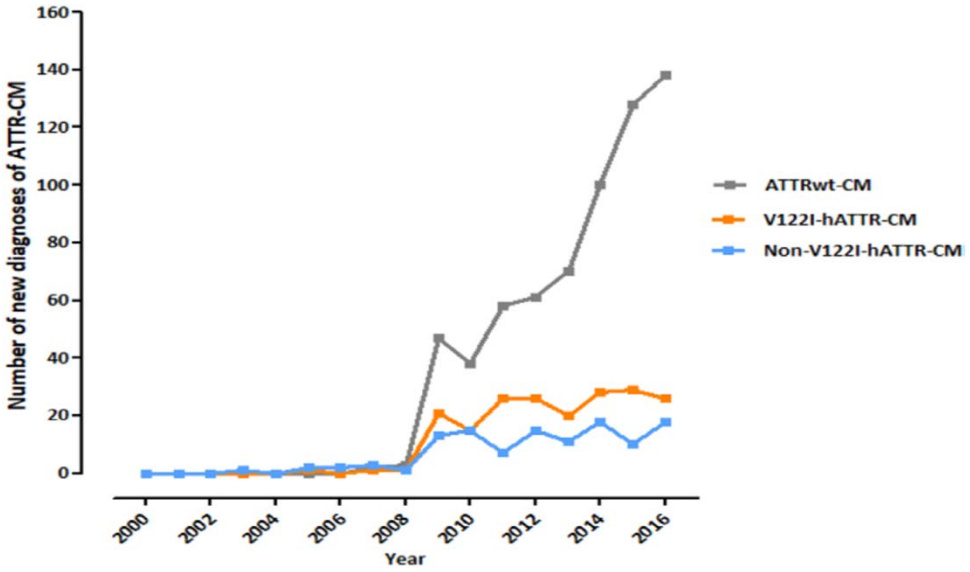
- Among vATTR-CM: 66% - 79%

Demographics of p.Val142Ile vATTR-CM

- African descent: 75% - 100%
- Male predominance: 73% - 96%
- Age of symptom onset: 63 years
- Age of diagnosis: 67 - 71 years
- Atrial fibrillation: 25% - 38%

Chandrashekar, et al. *Circ Genom Precis Med* 2021

Increasing Recognition of ATTR-CM



- Increased awareness (with emergence of therapies)
- Validated non-invasive diagnostic techniques
- Increased access to genetic testing / screening

Adapted from Lane, et al. Circulation 2019

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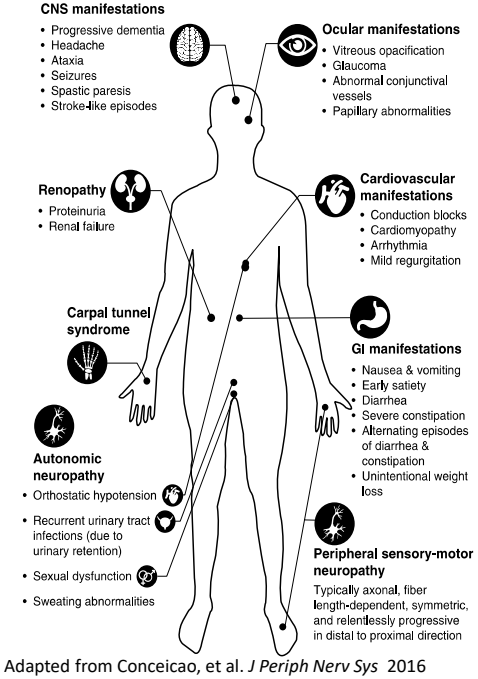
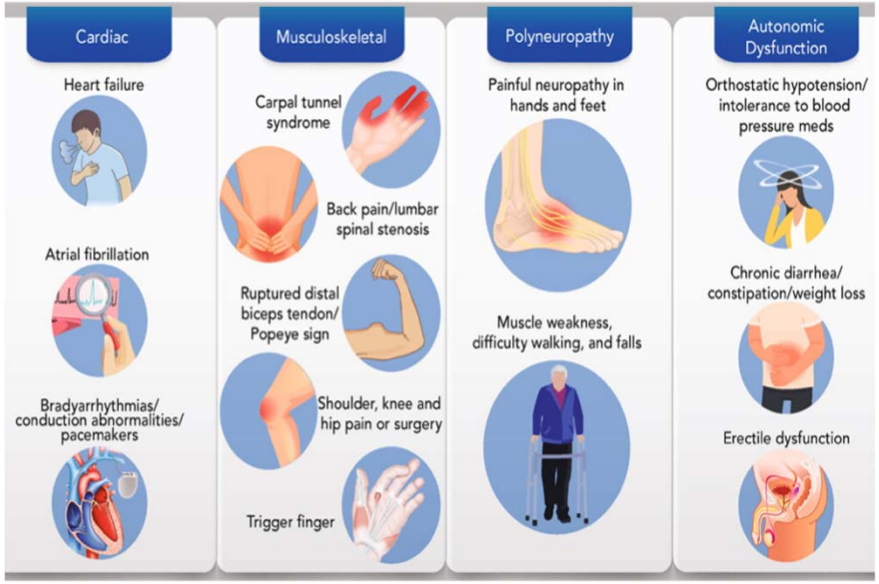
Clinical Features

hATTR: Systemic Manifestations

Clinical history / Physical exam



Adapted from Conceicao, et al. *J Periph Nerv Sys* 2016

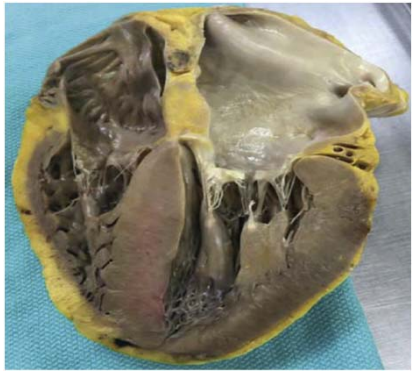


Adapted from Nativi-Nicolau, et al. *HF Reviews*, 2021

ATTR-CM: Infiltrative & Restrictive

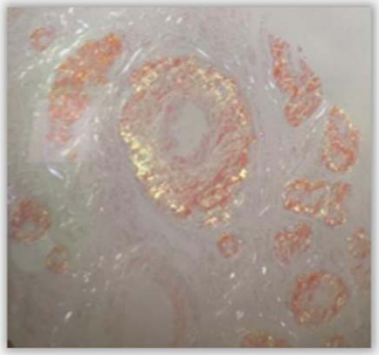
Restrictive CMP

- Increased mass (LVH & RVH) without dilatation
- Stiff, poorly compliant
- Progressive diastolic filling abnormalities
- Atrial infiltration impairs atrial contraction

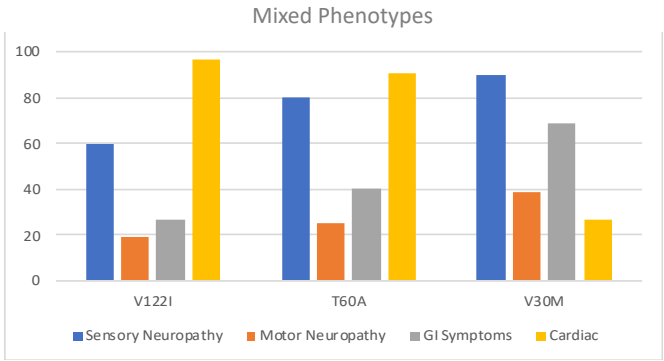


Amyloid Deposits

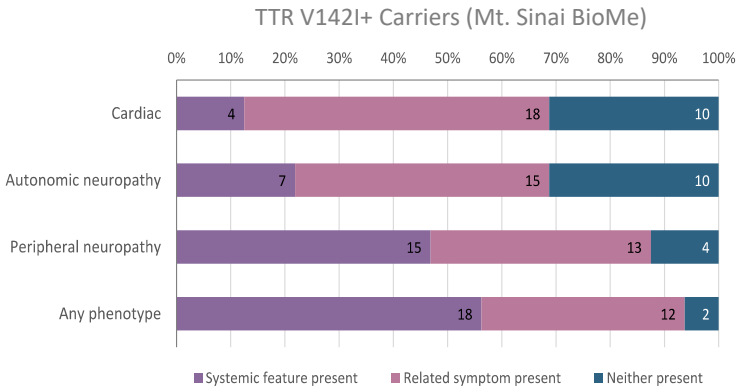
- Deposition into the extracellular space
  - Stiffened extracellular space
  - Myocyte compression
  - Microvascular ischemia
  - Direct myocyte damage
- Dysfunction – myocardial, conduction, valvular



hATTR: Mixed Phenotypic Presentations



Adapted from Wixner, et al. *Orphanet J Rare Dis* 2014

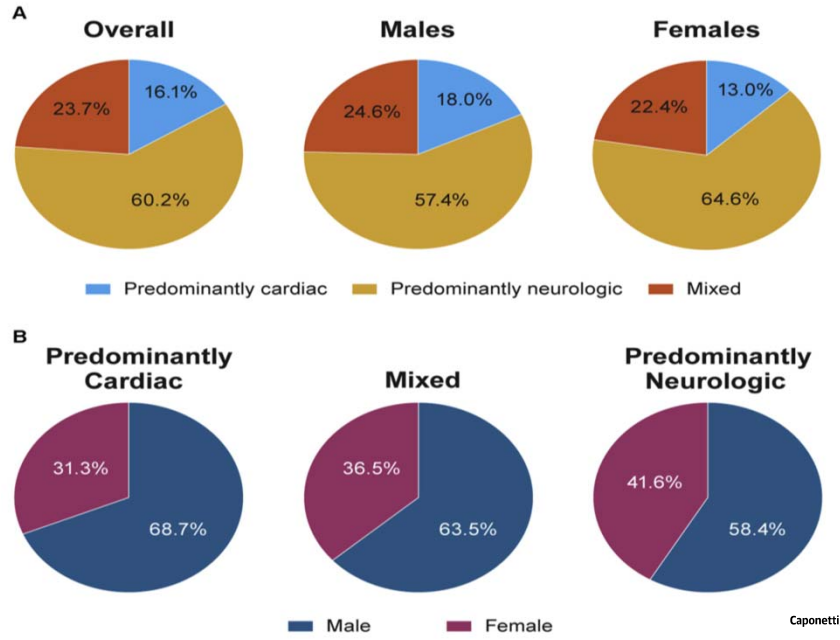


Soper, et al. *J Pers Med* 2021

hATTR: Mixed Phenotypic Presentations

Distribution by Gender

FIGURE 1 Association Between Sex and Phenotypes in Patients With ATTRv Amyloidosis



Caponetti, A.G. et al. J Am Coll Cardiol HF. 2021;9(10):736–746.

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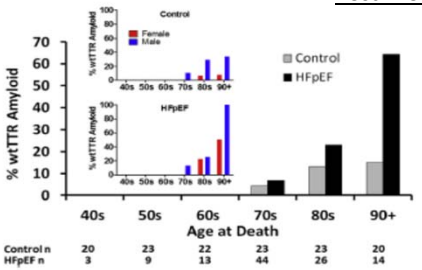
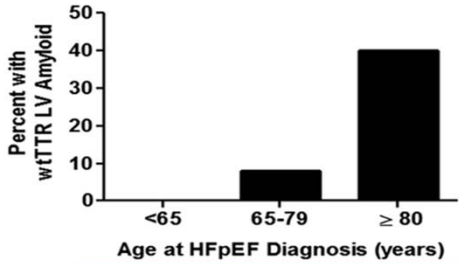
Clinical Presentations

ATTR-CM: Underrecognized cause of HFpEF

Post-Mortem (Histopathology)



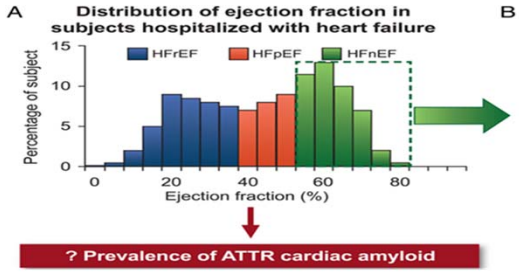
Prevalence of LV wtTTR Amyloid in Control (n = 131) and HFpEF (n = 109) Patients by Age



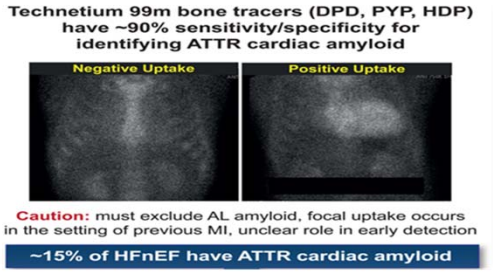
Prevalence of wtTTR Amyloid at Autopsy According to Age at HFpEF Diagnosis

Mohammed, et al. J Am Coll Cardiol HF 2014;2:113–22

Hospital Admission (Imaging)



? Prevalence of ATTR cardiac amyloid



Caution: must exclude AL amyloid, focal uptake occurs in the setting of previous MI, unclear role in early detection

~15% of HFnEF have ATTR cardiac amyloid

Castano, et al. European Heart Journal (2015) 36, 2595–2597

ATTR-CM: Other associated conditions

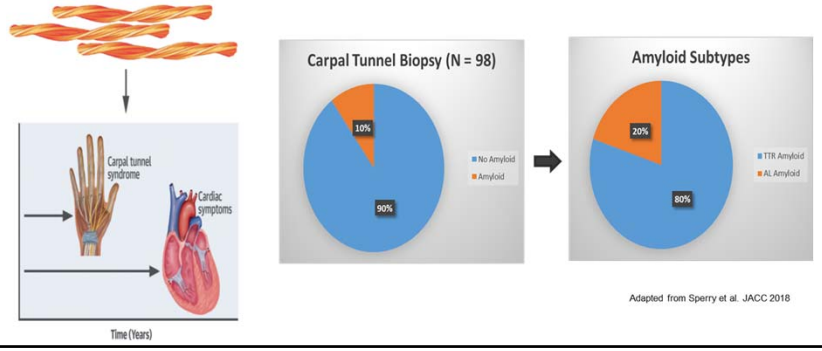
Atrial fibrillation

Table I Frequency of atrial fibrillation in different types of cardiac amyloidosis

	N	AL amyloidosis (%)	ATTRm (%)	ATTRwt (%)
Rapezzi *et al.*[10]	233	12	5	27
Longhi *et al.*[11]	262	9	11	40
Pinney *et al.*[12]	138	16	NA	43
Kristen *et al.*[13]	216	16	18	30
Grogan *et al.*[14]	360	NA	NA	62

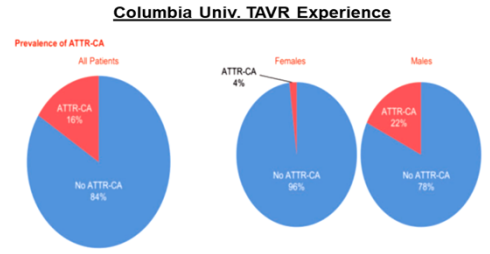
Adapted from van den Berg, et al. Eur Heart J 2019

Carpal Tunnel Syndrome (10%)



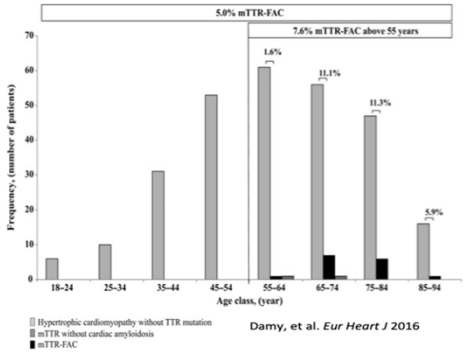
Adapted from Sperry et al. JACC 2018

Aortic Stenosis (16%)



Adapted from Castano, et al. Eur Heart J 2017

Increased LV wall thickness (5-10%)



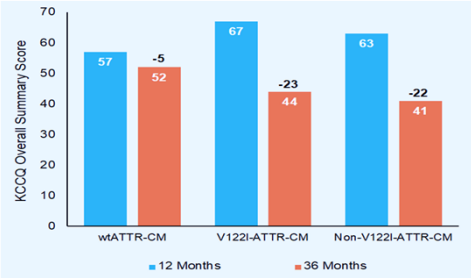
Damy, et al. *Eur Heart J* 2016

ATTR-CM: Severity & Relevance to Practice

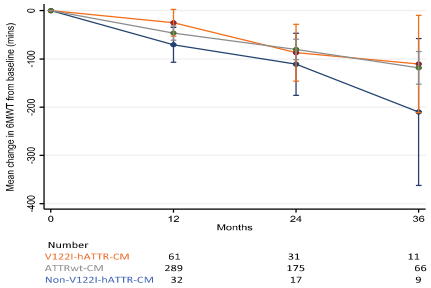
Diagnostic delays are common and diagnosis in ATTR-CM and diagnosis is often made at a more advanced stage

- Median diagnostic delay: 39 months
- 42% of patients had diagnostic delay >4 years
- 23% of patients waited 6 months to 4 years for diagnosis

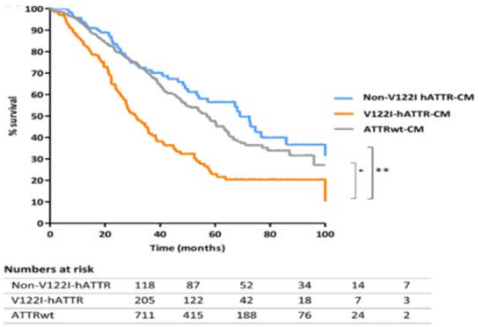
QOL (KCCQ)



Functional Capacity (6MWD)



Survival



Adapted from Lane, et al. Circulation. 2019;140:16–26.

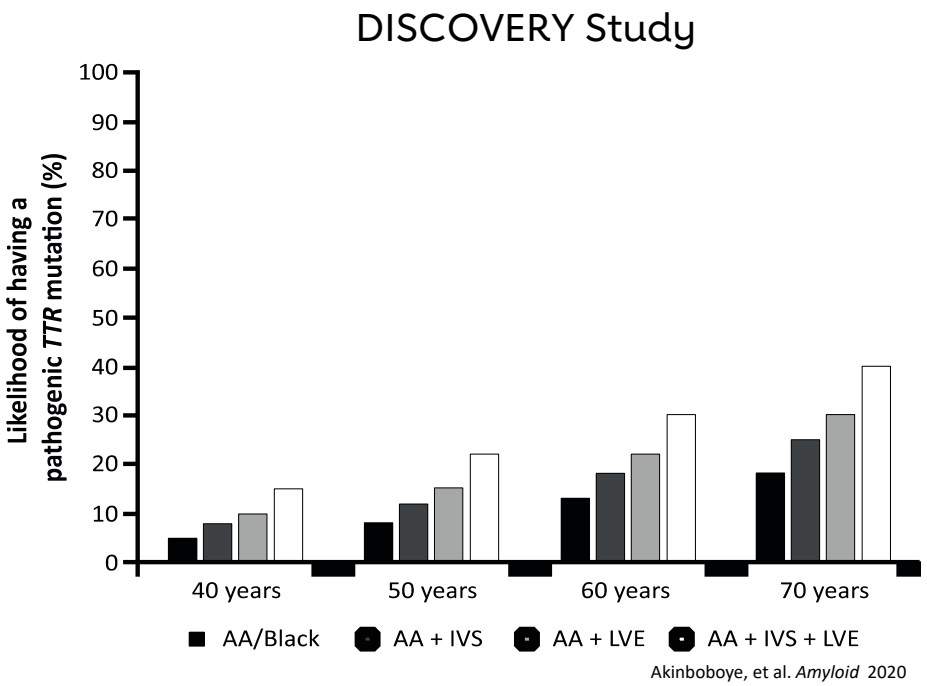
Hereditary ATTR

'Red flag' presenting features and diagnostic testing for Cardiologist

	Clinical signs / symptoms		Diagnostic testing	
Cardiac	• Biventricular HF presentation (dyspnea, orthopnea, edema) • Intolerance to HF GDMT • Low-normal BP; prior HTN • Late-onset LVH w/o HTN • Atrial fibrillation / flutter • SSS / AV block • Aortic stenosis		• Elevated natriuretic peptides • Chronic mild troponin elevation • Negative monoclonal proteins (i.e., sIFE, uIFE, sFLC)	**Basic Labs**
Nerves	• Carpal tunnel syndrome • Lumbar spinal stenosis • Peripheral neuropathy • Orthostatic hypotension		• Discordant LVH on imaging vs. relative low voltage on ECG	**ECG**
Kidney	• Renal impairment		• Concentric LV hypertrophy • Biventricular hypertrophy • Longitudinal strain (globally impaired, relative apical sparing)	**TTE**
GI	• Weight loss • Nausea, early satiety • Diarrhea/constipation		• Diffuse subendocardial LGE • Prolonged T1 relaxation times • Increased ECV	**CMR**

Adapted from Zhang, et al. *Am J Med* 2021

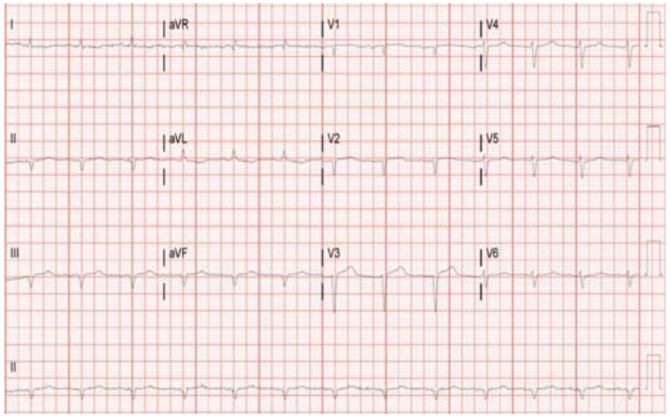
‘Red flags’ facilitate identification of hATTR-CM



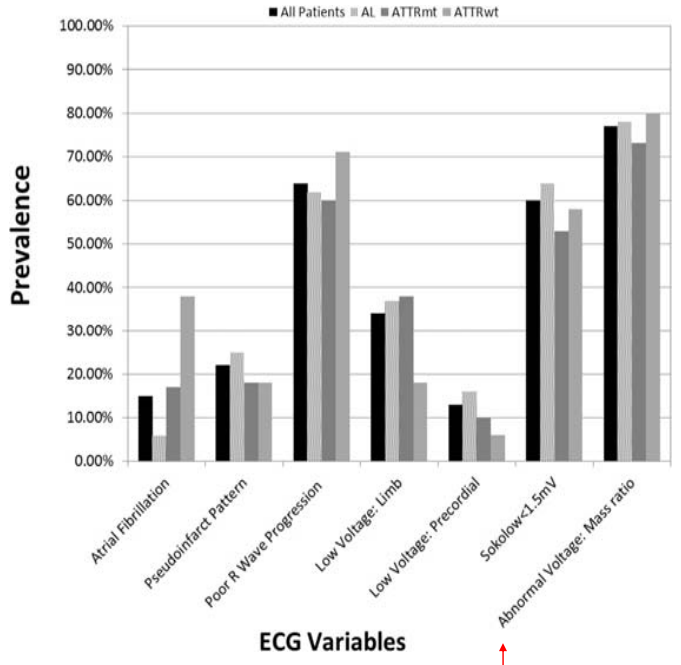
Akinboboye, et al. *Amyloid* 2020

Diagnosing hATTR Amyloidosis

ECG for Cardiac Amyloidosis



Common Misconception
Low voltage ECG = sensitive for cardiac amyloidosis

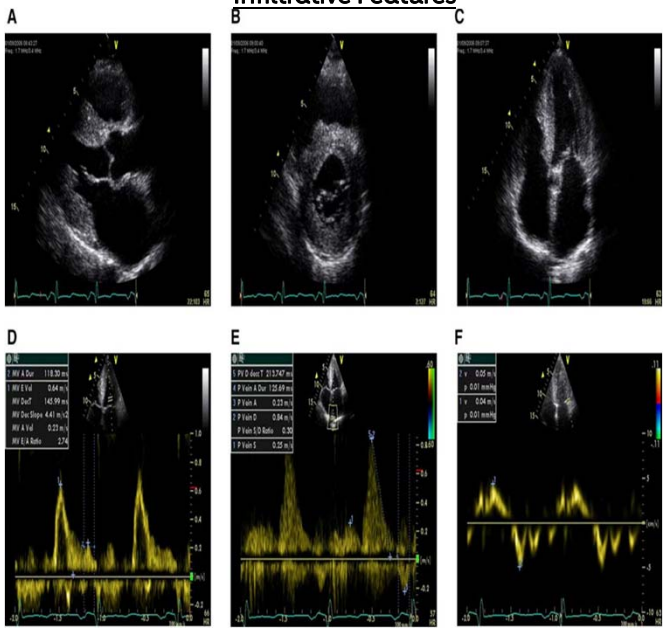


Adapted from Cyrille, et al. Am J Cardiol 2014

Echo for Cardiac Amyloidosis

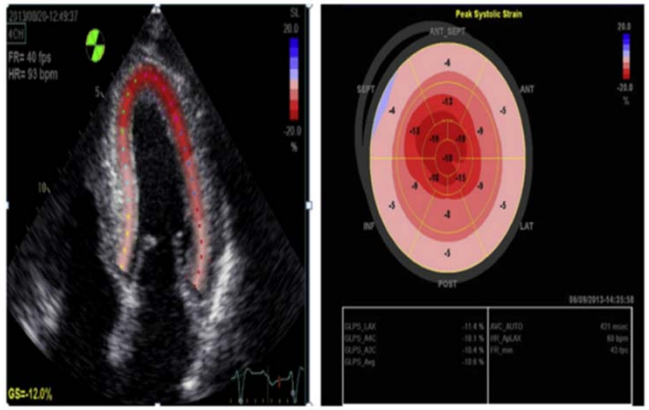
2D TTE

Infiltrative Features



Adapted from Maurer, et al. Circulation 2017

Longitudinal Strain

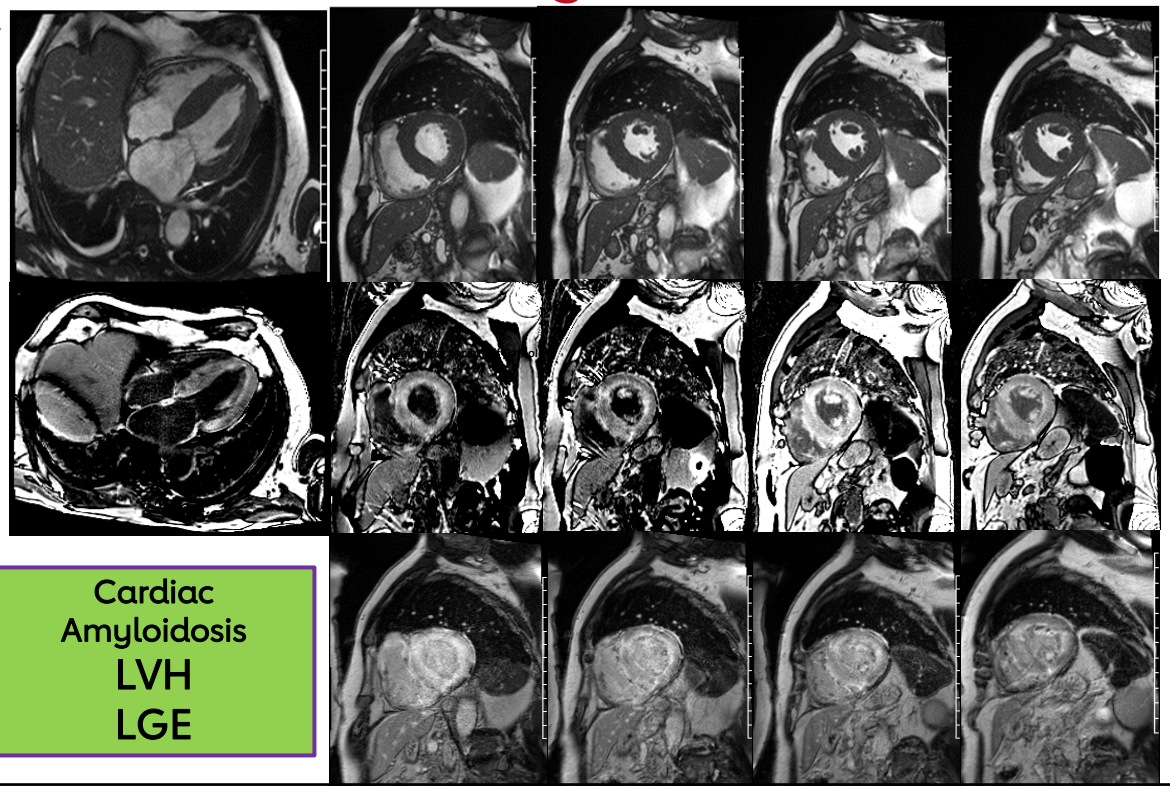


'Relative' Apical Sparing

$$\frac{\text{Apical}}{\text{Basal + Mid}} > 1.0$$

Narotsky, et al. Canadian J Cardiol 2016

CMR for Cardiac Amyloidosis



Cardiac Amyloidosis
LVH
LGE

Tc99m-PYP Scanning for ATTR-CM

Diagnostic scoring

Clinical Suspicion[1]

Heart failure, syncope, or bradyarrhythmia with ECG suggesting/indicating cardiac amyloid

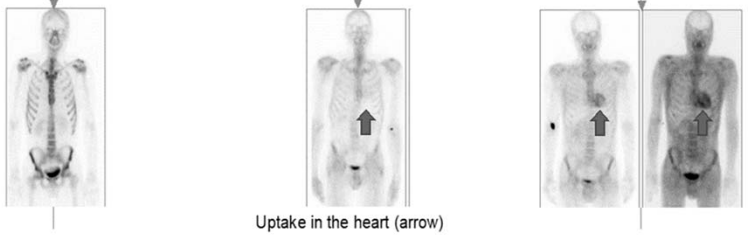
↓

Rule out plasma cell dyscrasia by serum and urine IFE & serum free light chains

↓

Bone Scintigraphy

with ^{99m}TC-DPD/HMDP/PYP



Uptake in the heart (arrow)

Grade 0	**Grade 1**	**Grade 2 to 3**
Absent cardiac uptake	Mild uptake less than bone	Moderate to higher uptake than bone

↓

Diagnosis*

In a subgroup of 374 patients with EMB:

Absence of a monoclonal protein by sFLC measurement

+

Grade 2 or 3 cardiac uptake on radionuclide scan

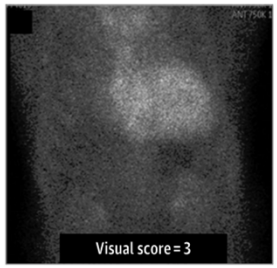
100% specific for presence of cardiac ATTR amyloid[1]

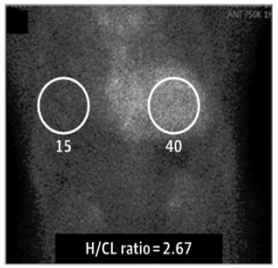
Adapted from Gillmore, et al. *Circulation* 2016

Tc99m-PYP Scanning for ATTR-CM

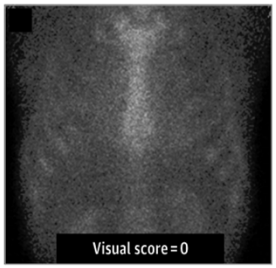
Diagnostic scoring

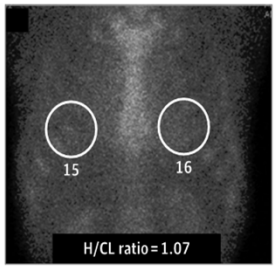
A Tc 99m scan of patient with ATTR cardiac amyloidosis





B Tc 99m scan of patient without ATTR cardiac amyloidosis





C Calculations

Visual score
0 = Myocardial uptake absent
1 = Myocardial uptake < rib
2 = Myocardial uptake = rib
3 = Myocardial uptake > rib

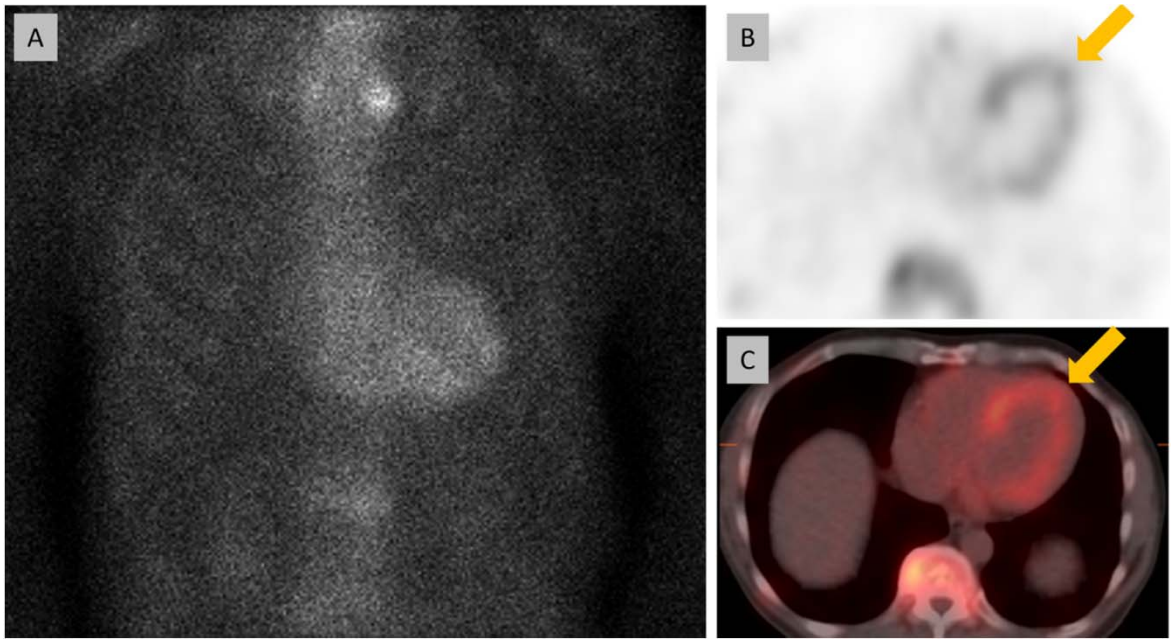
$$\text{H/CL ratio} = \frac{\text{(heart ROI mean counts/pixel)}}{\text{(contralateral ROI mean counts/pixel)}}$$

Positive Tc99m scan for ATTR	
Qualitative:	Visual score ≥ 2 (88% sens, 88% spec)
Quantitative:	H/CL ratio ≥ 1.5 (92% sens, 97% spec)

Adapted from Castano, et al. JAMA Cardiol 2016

Tc99m-PYP Scanning for ATTR-CM

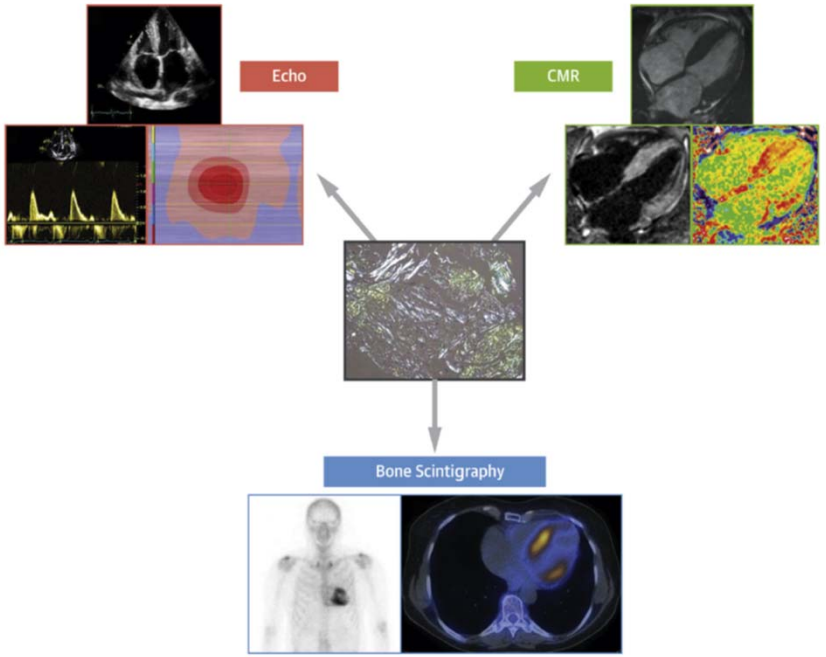
Importance of SPECT Imaging



Adapted from Zhang, et al. *Am J Med* 2021

Multi-modality Imaging for CA

CENTRAL ILLUSTRATION Imaging in Cardiac Amyloidosis



Fontana, M. et al. J Am Coll Cardiol Img. 2019;12(11):2345-56.

Diagnostic Tests for Cardiac Amyloidosis

Imaging / Blood Biomarkers	Diagnostic and Management Goals							
	Raise Suspicion	Early Diagnosis	Diagnosis	Subtyping	Ventricular Assessment	Prognosis	Amyloid Burden	Response to Therapy
2D TTE								
Speckle tracking strain								
Cardiac MRI								
Tc99m-PYP		TTR?		TTR				
PET								
Natriuretic peptides								AL

Key

Established Utility
- ✓ Multicenter experiences and/or
- ✓ Multiple publications and/or
- ✓ International expert consensus

Potential Utility
- ✓ Single-center experiences

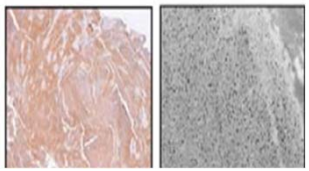
Low Utility
- ✓ Case reports and
- ✓ Cases series

Adapted from Castano, et al. Curr Cardiovasc Risk Rep 2017

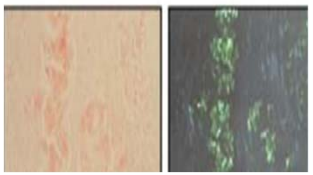
Diagnosing Cardiac Amyloidosis

Tissue biopsy

Identifying Amyloid

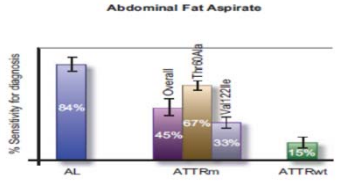


Typing Amyloid



Adapted from Connors LH, et al. Circulation 2016

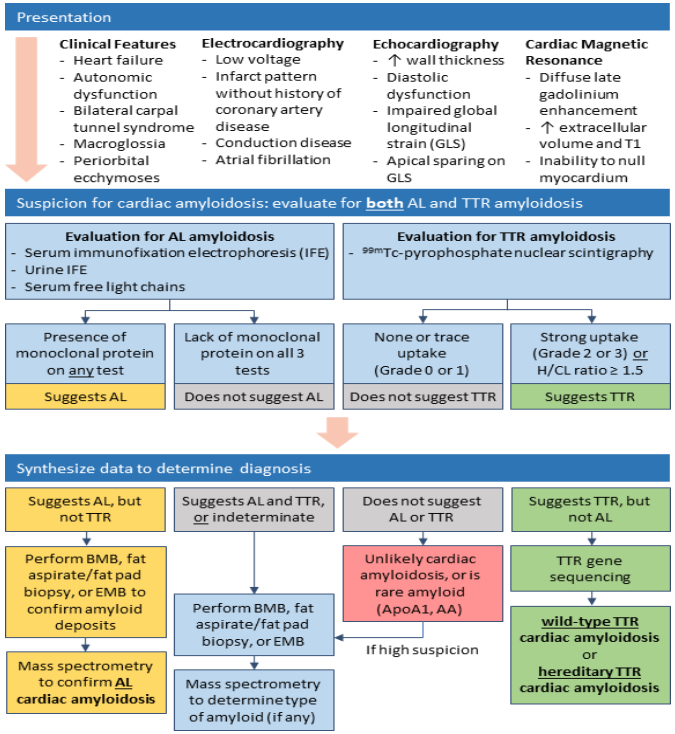
- Extra-cardiac biopsy
  - Bone marrow, abdominal fat pad, labial salivary gland
  - Yield: AL (>70%), ATTRm (50-70%) ATTRwt (20-25%)



Siddiqi, et al. EHJ 2017

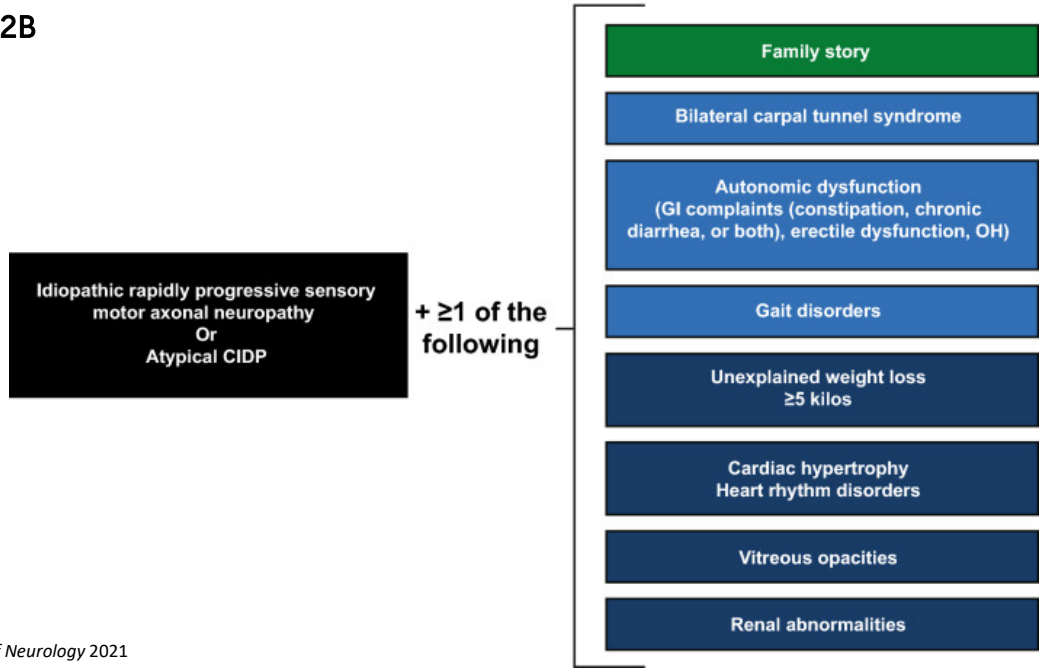
- Endomyocardial biopsy (EMB)
  - ~100% sensitive / specific
- Congo red stain to identify amyloid
  - Apple green birefringence (polarized light)
- Typing of amyloid
  - Immunohistochemistry (IHC)
    - Less accurate; problematic high background
  - Laser dissection mass spectrometry (mass spec)
    - Gold standard; Mayo Clinic Lab send out
- Genetic test to establish TTR genotype
  - Blood test - PCR

Cardiac Amyloidosis - Duke Diagnostic Algorithm



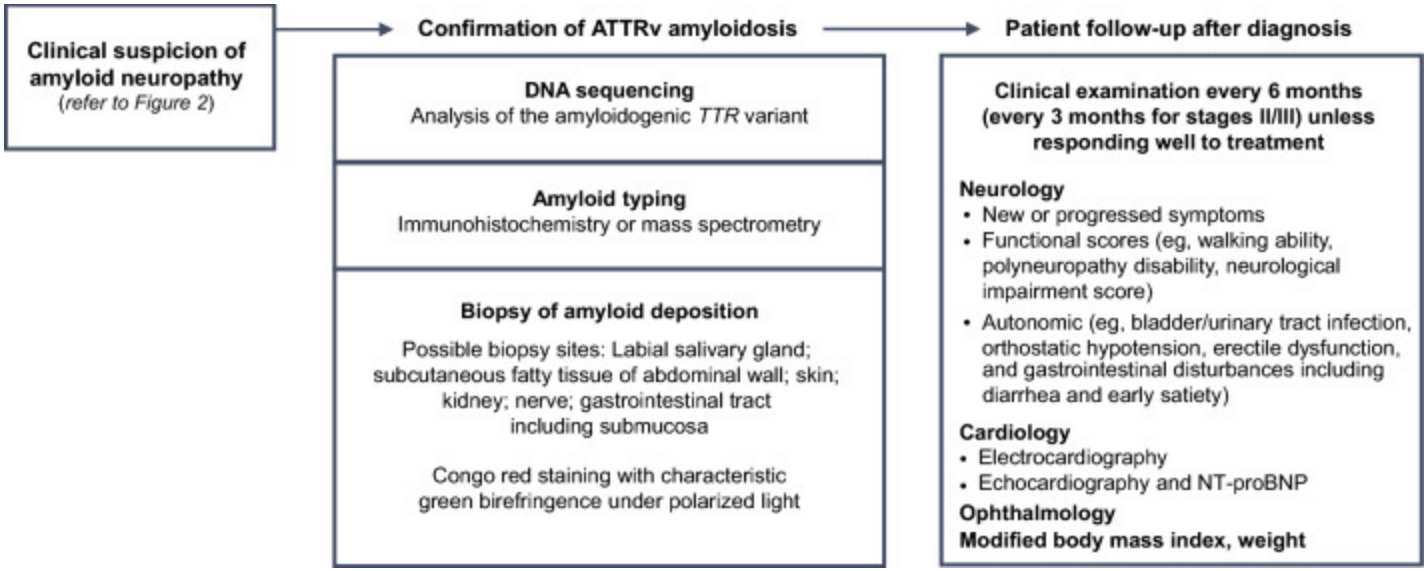
Hereditary ATTR with Neuropathy Diagnostic Algorithm

Figure 2B



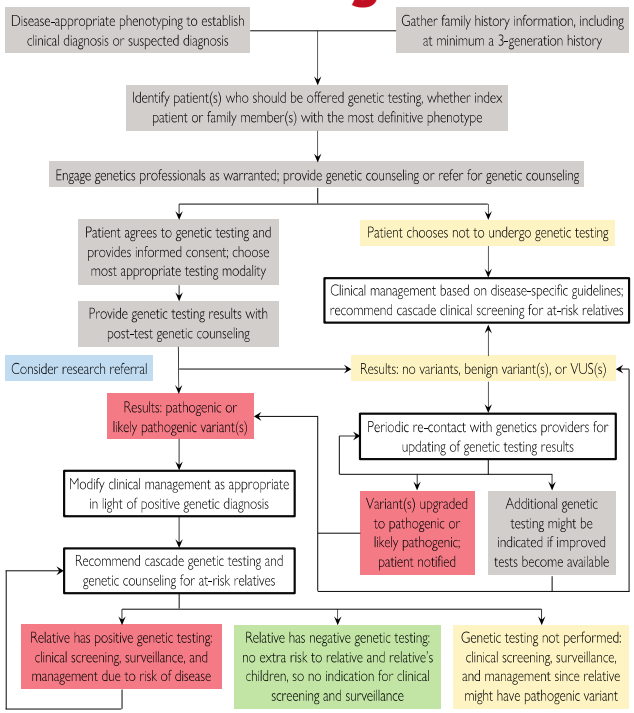
Adams, et al. *Journal of Neurology* 2021

Hereditary ATTR with Neuropathy Diagnostic Algorithm Continued



Adams, et al. *Journal of Neurology* 2021

Genetic Testing for Patients and Family



Musunuru, et al. *Circ Genom Precis Med* 2020

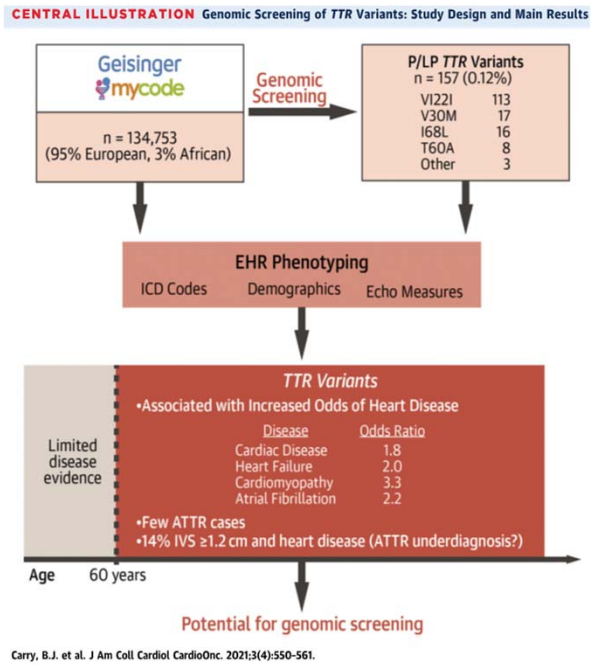
- Genetic testing availability:
  - Clinically directed testing
  - Health-system associated cohort projects
  - Direct-to-consumer genetic testing companies
- Professional genetics expertise and counseling is a necessity in the clinical setting
- Cascade clinical screening and genetic testing for first-degree family members should be offered, along with genetic counseling

American Heart Association.

Future Directions

Genomics-first model for hATTR Amyloidosis

Pre-symptomatic testing



Carry, B.J. et al. J Am Coll Cardiol CardioOnc. 2021;3(4):550-561.

Challenges

- Symptomatic disease attributable to TTR variants repeatedly underdiagnosed clinically
- Use of genetic analysis for identifying TTR variants in the diagnostic or pre-symptomatic setting remains uncommon
- Clinical penetrance is variable and incompletely understood; no clear genetic predictors of who will get symptomatic ATTR
- Pre-symptomatic testing for TTR variants (e.g., V122I) will need to be linked to clinical tests that reliably determine subclinical disease and response to therapy

American Heart Association.

Conclusions

Hereditary ATTR Take Home Points

- Hereditary ATTR presentations vary by genotype
  - Mixed neuro-cardiac presentations are common
- >120 pathogenic TTR mutations
  - TTR V122I variant = most prominent in US and worldwide
    - Affects 1 out of 25 people of African descent
- ATTR-CM is not an uncommon disease
  - There are many undiagnosed cases in HF, Afib, AS, etc.
- Increased awareness is needed to find patients
  - Be attentive to multi-systemic 'red flags'
- Cardiac imaging techniques can increase diagnostic yield
  - Biopsy no longer a necessity in hATTR-CM
- Genomic medicine may change natural history of hATTR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Thank You.
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