

Overview of Hereditary Transthyretin Amyloidosis (hATTR)

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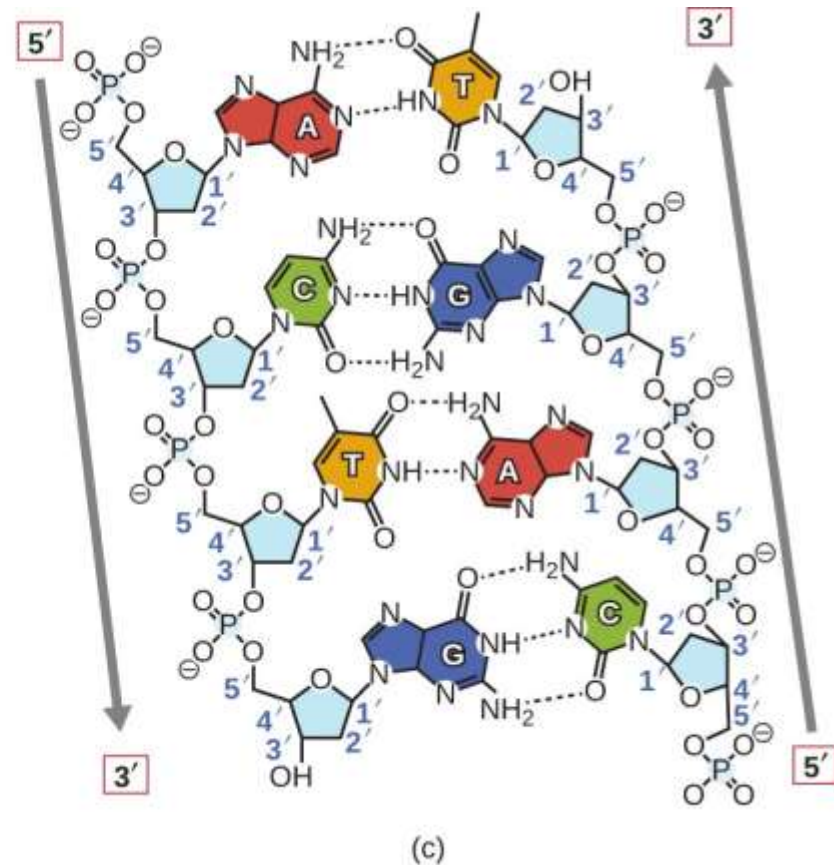
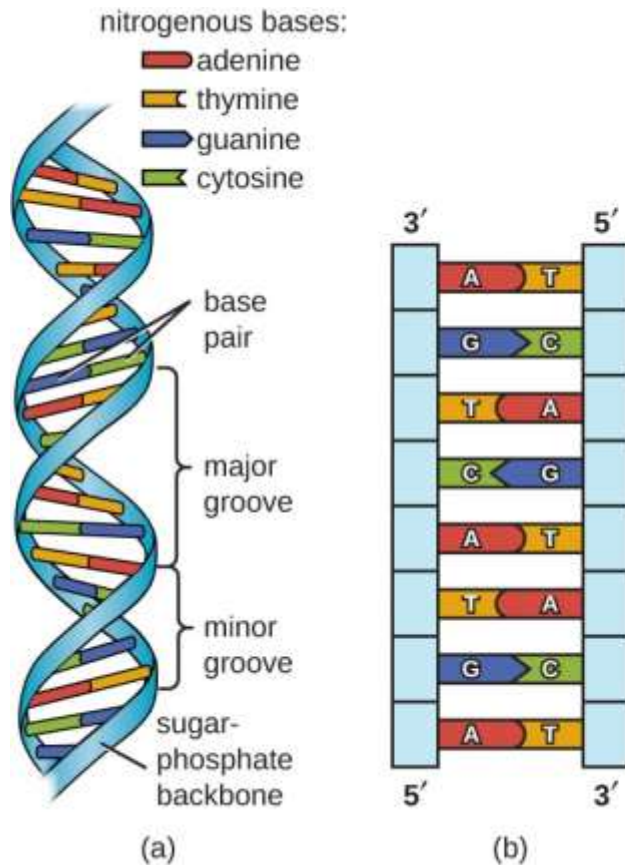


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DISCLOSURES

- Grant support – NIH (NHLBI), Eidos Therapeutics, Akcea Therapeutics (pending), Pfizer
- Consulting – Pfizer

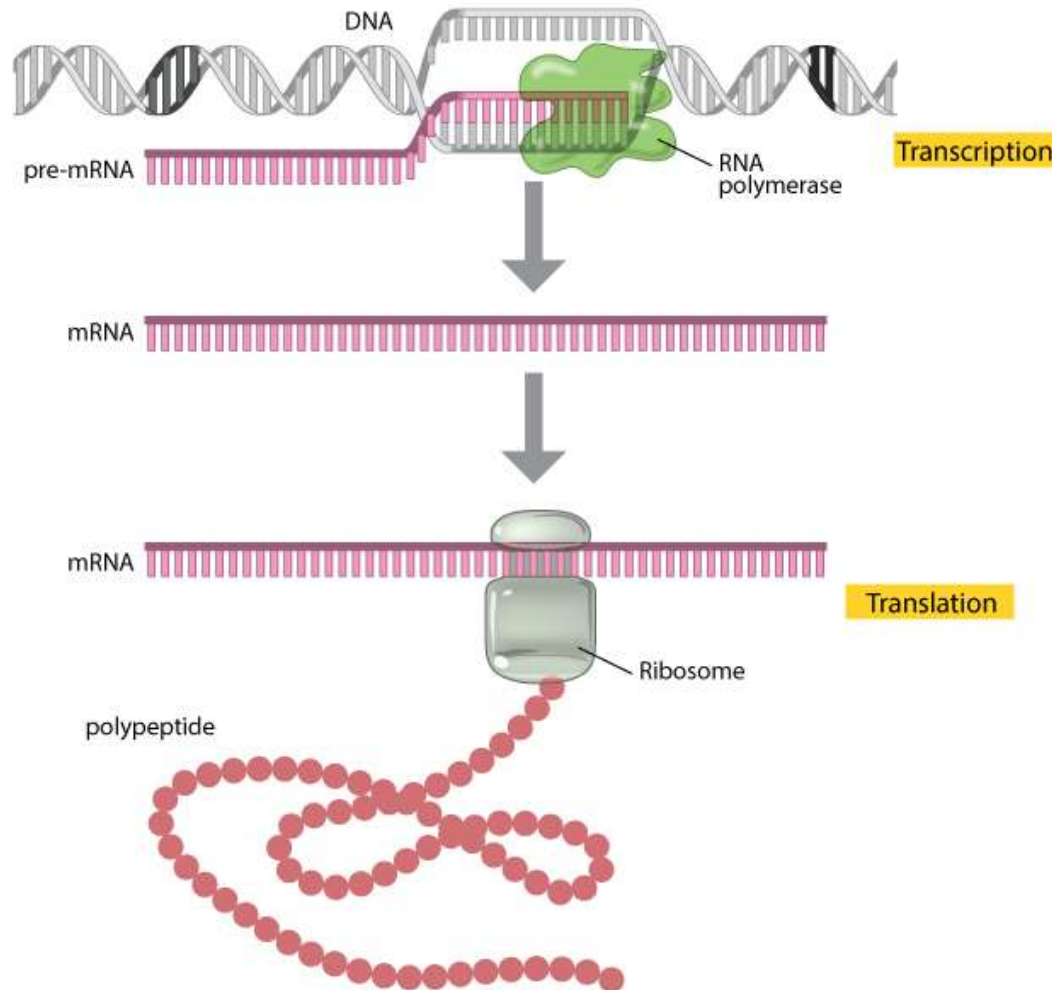
GENETICS: BASIC BIOLOGY – DNA STRUCTURE



GENETICS: BASIC BIOLOGY – AMINO ACID CODES

		Second Letter				
		U	C	A	G	
1st letter	U	UUU Phe UUC UUA Leu UUG	UCU Ser UCC UCA UCG	UAU Tyr UAC UAA Stop UAG Stop	UGU Cys UGC UGA Stop UGG Trp	U C A G
	C	CUU Leu CUC CUA CUG	CCU Pro CCC CCA CCG	CAU His CAC CAA Gln CAG	CGU Arg CGC CGA CGG	U C A G
	A	AUU Ile AUC AUA AUG Met	ACU Thr ACC ACA ACG	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG	U C A G
	G	GUU Val GUC GUA GUG	GCU Ala GCC GCA GCG	GAU Asp GAC GAA Glu GAG	GGU Gly GGC GGA GGG	U C A G

GENETICS: BASIC BIOLOGY – DNA, RNA, AND PROTEINS

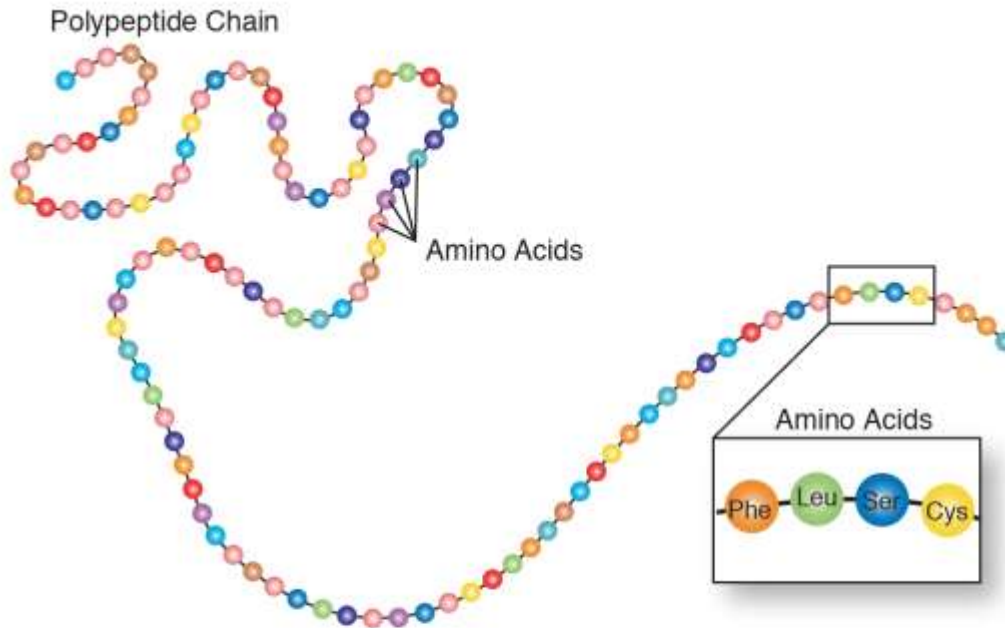


DNA

mRNA

Protein

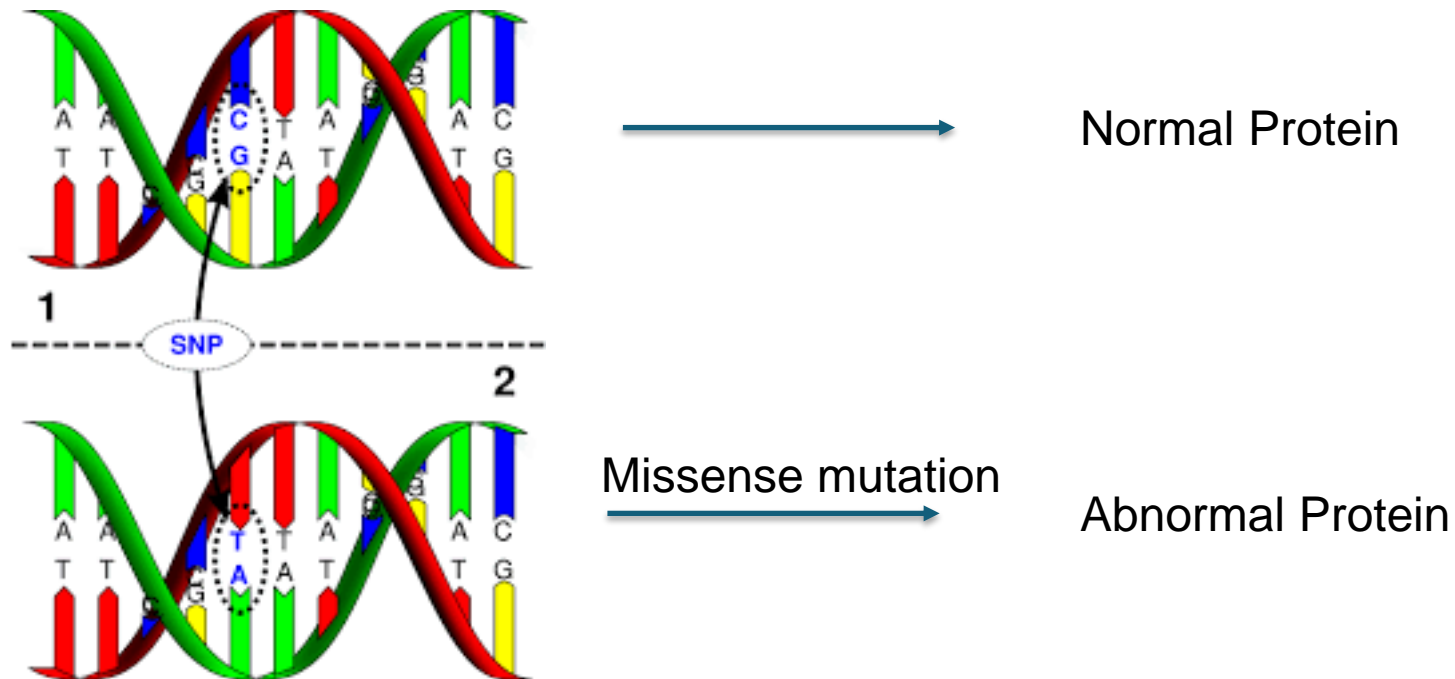
GENETICS: BASIC BIOLOGY – PROTEIN STRUCTURE



Amino Acids

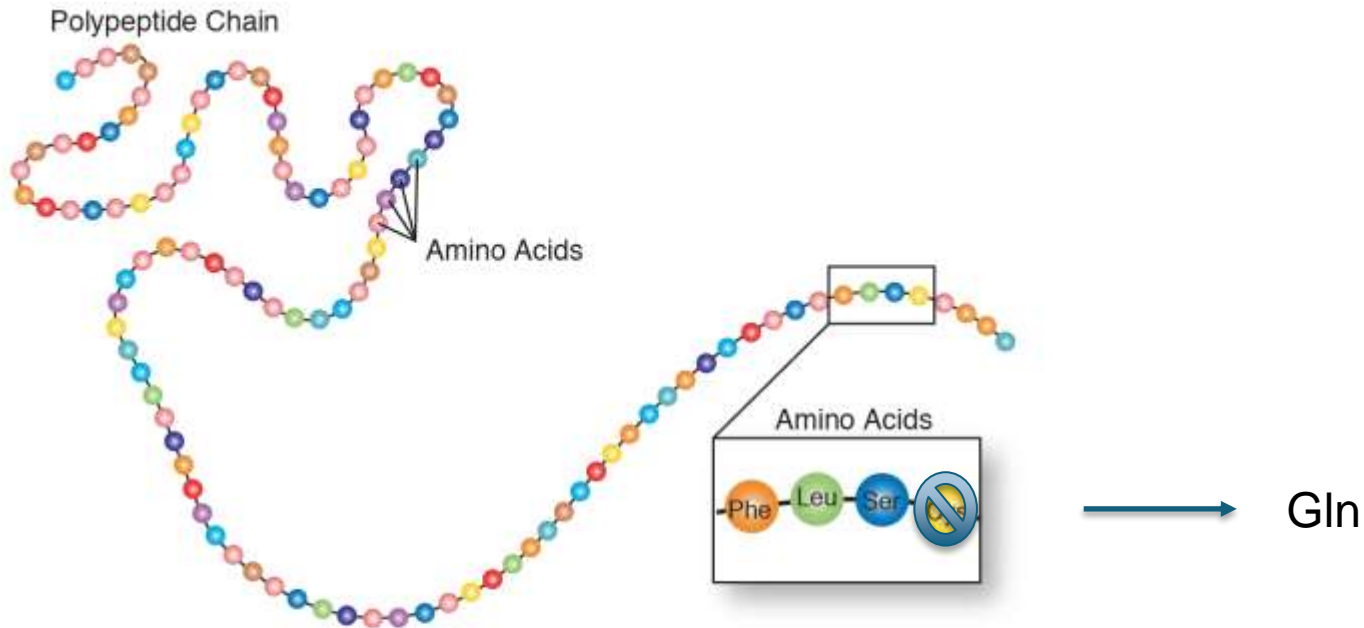
Ala: Alanine	Gln: Glutamine	Leu: Leucine	Ser: Serine
Arg: Arginine	Glu: Glutamic acid	Lys: Lysine	Thr: Threonine
Asn: Asparagine	Gly: Glycine	Met: Methionine	Trp: Tryptophane
Asp: Aspartic acid	His: Histidine	Phe: Phenylalanine	Tyr: Tyrosine
Cys: Cysteine	Ile: Isoleucine	Pro: Proline	Val: Valine

GENETICS: BASIC BIOLOGY – SINGLE NUCLEOTIDE POLYMORPHISMS (SNP)



Common diseases caused by SNPs – sickle cell anemia, cystic fibrosis

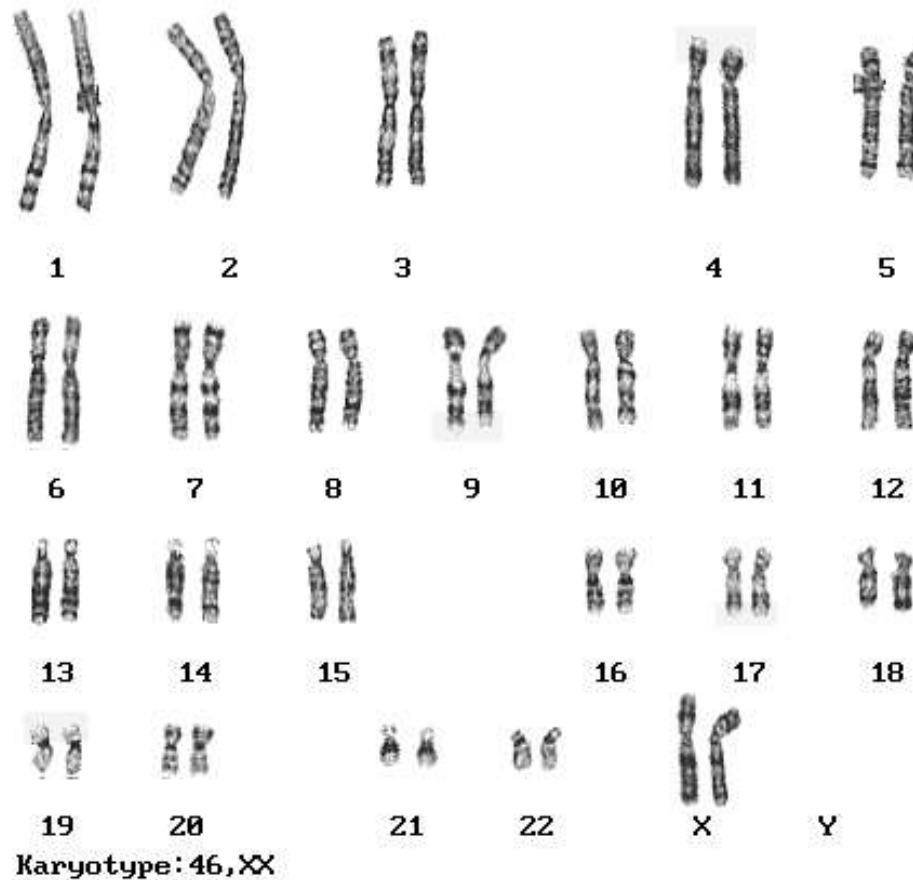
GENETICS: BASIC BIOLOGY – PROTEIN STRUCTURE WITH SNP



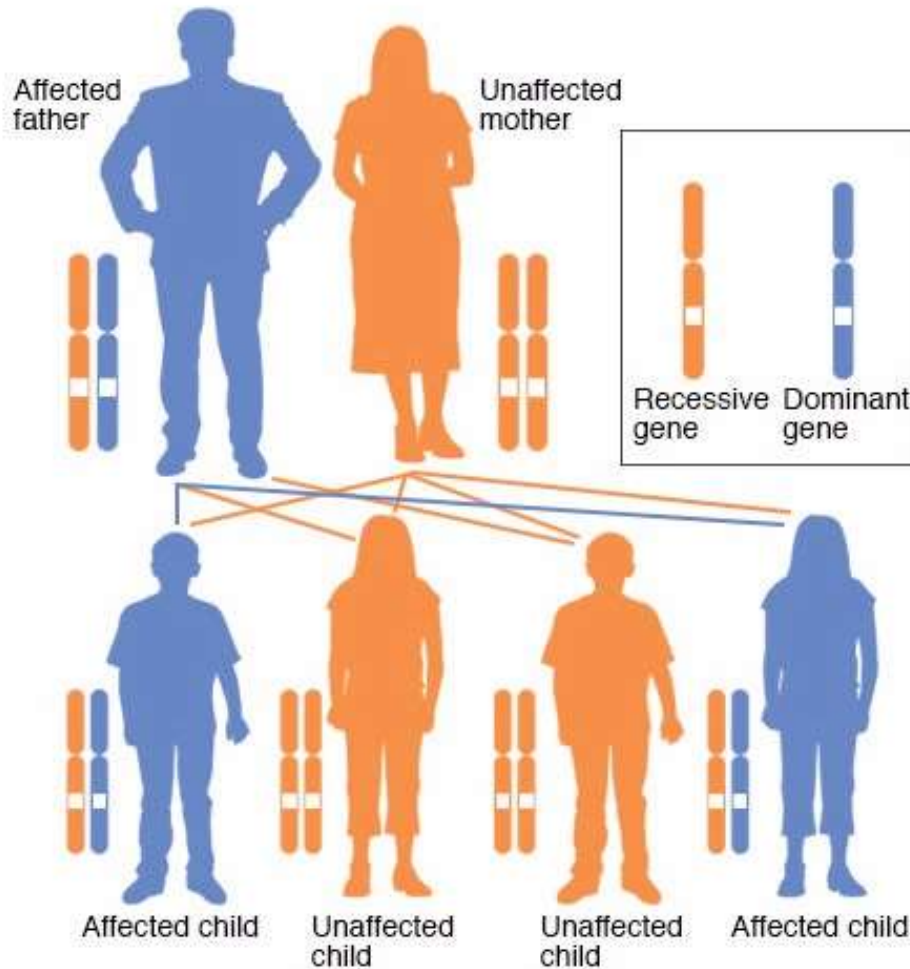
Amino Acids

Ala: Alanine	Gln: Glutamine	Leu: Leucine	Ser: Serine
Arg: Arginine	Glu: Glutamic acid	Lys: Lysine	Thr: Threonine
Asn: Asparagine	Gly: Glycine	Met: Methionine	Trp: Tryptophane
Asp: Aspartic acid	His: Histidine	Phe: Phenylalanine	Tyr: Tyrosine
Cys: Cysteine	Ile: Isoleucine	Pro: Proline	Val: Valine

GENETICS: BASIC BIOLOGY – DNA ORGANIZED INTO CHROMOSOMES



GENETICS: BASIC BIOLOGY – AUTOSOMAL DOMINANCE



HEREDITARY ATTR (hATTR) AMYLOIDOSIS

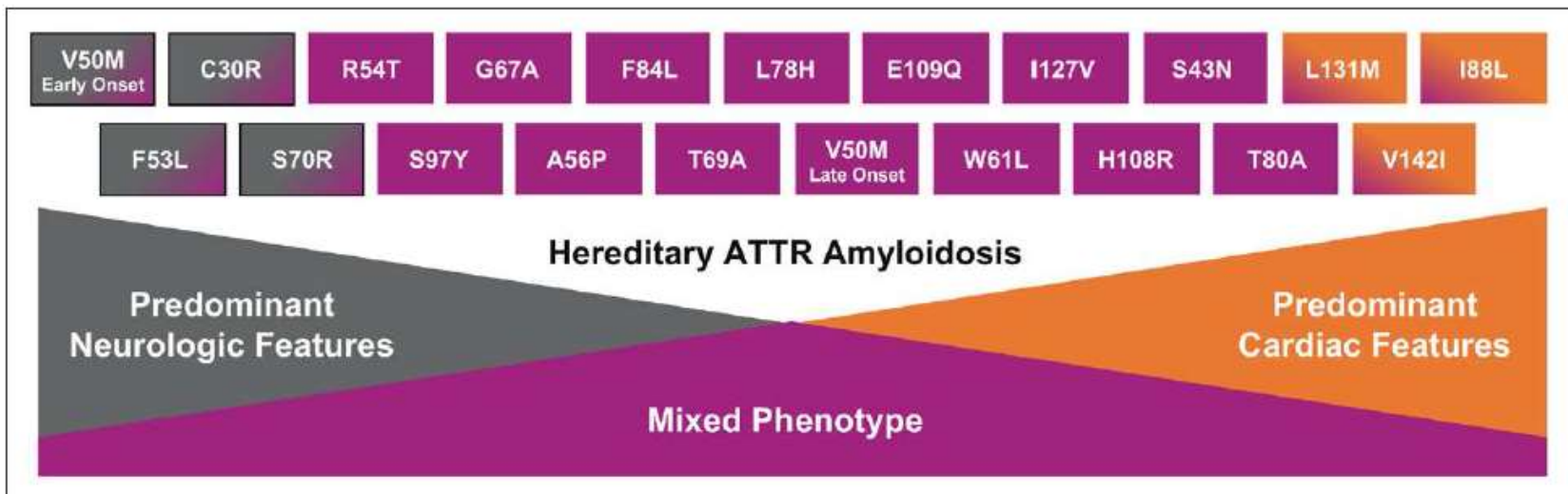
- Autosomal dominant (50% chance of passage to offspring)
 - AKA ATTRv (variant) or ATTm (mutant)
- Missense SNP – change in amino acid of TTR protein causing misfolding of the protein and amyloid deposits
- Present since birth, amyloidosis develops with age
- Naming – Normal amino acid-position in protein-Substituted amino acid
- Example Val122Val --> Val122Ile

JUST TO MAKE IT EXTRA CONFUSING...

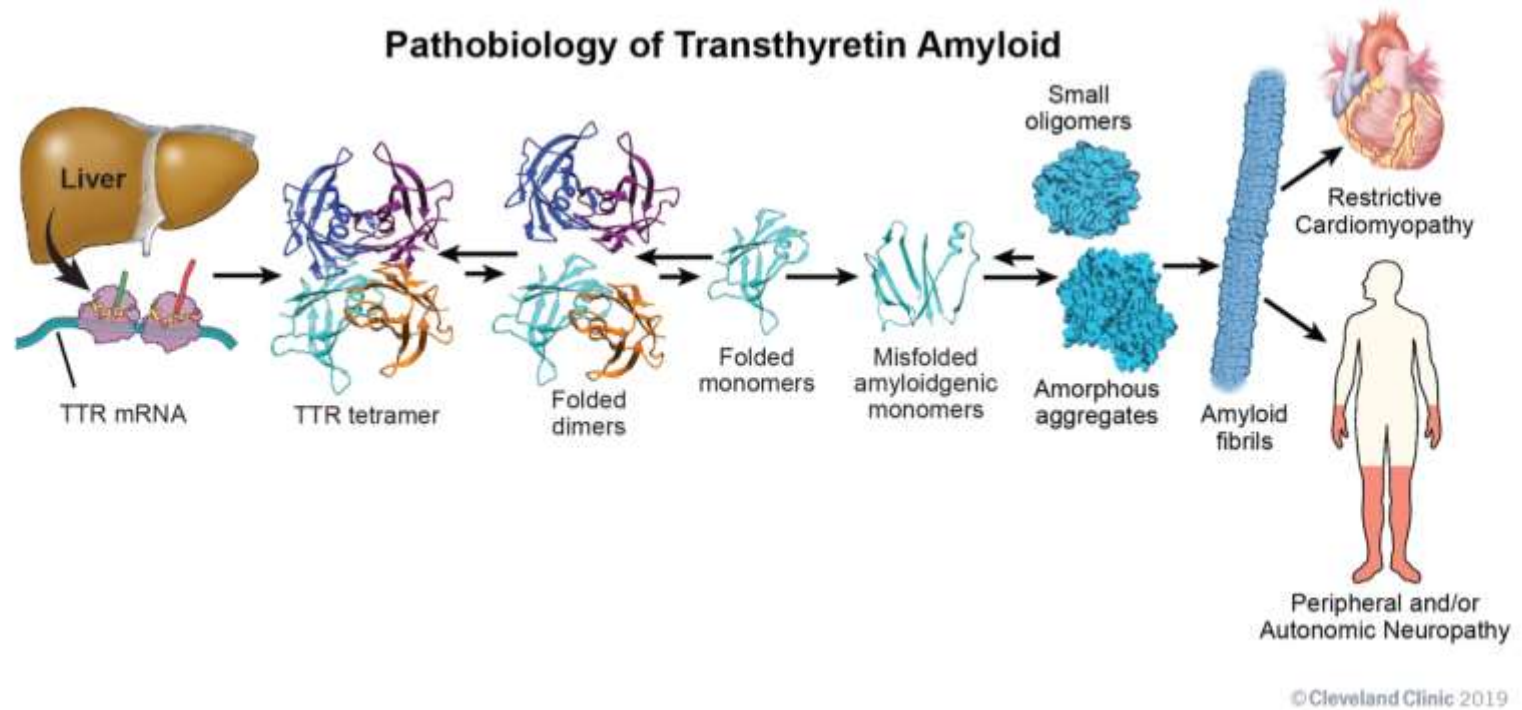
- Protein mutation locations now reported with 20 amino acid signal peptide at start
- So Val122Ile or V122I is now reported at pV142I
- And Val30Met or V30M is now reported at pV50M
- SO – Val122Ile or V122I = pVal142Ile or V142I

hATTR IS CAUSED BY SNP RESULTING IN AMYLOIDOSIS OF DIFFERENT ORGAN SYSTEMS

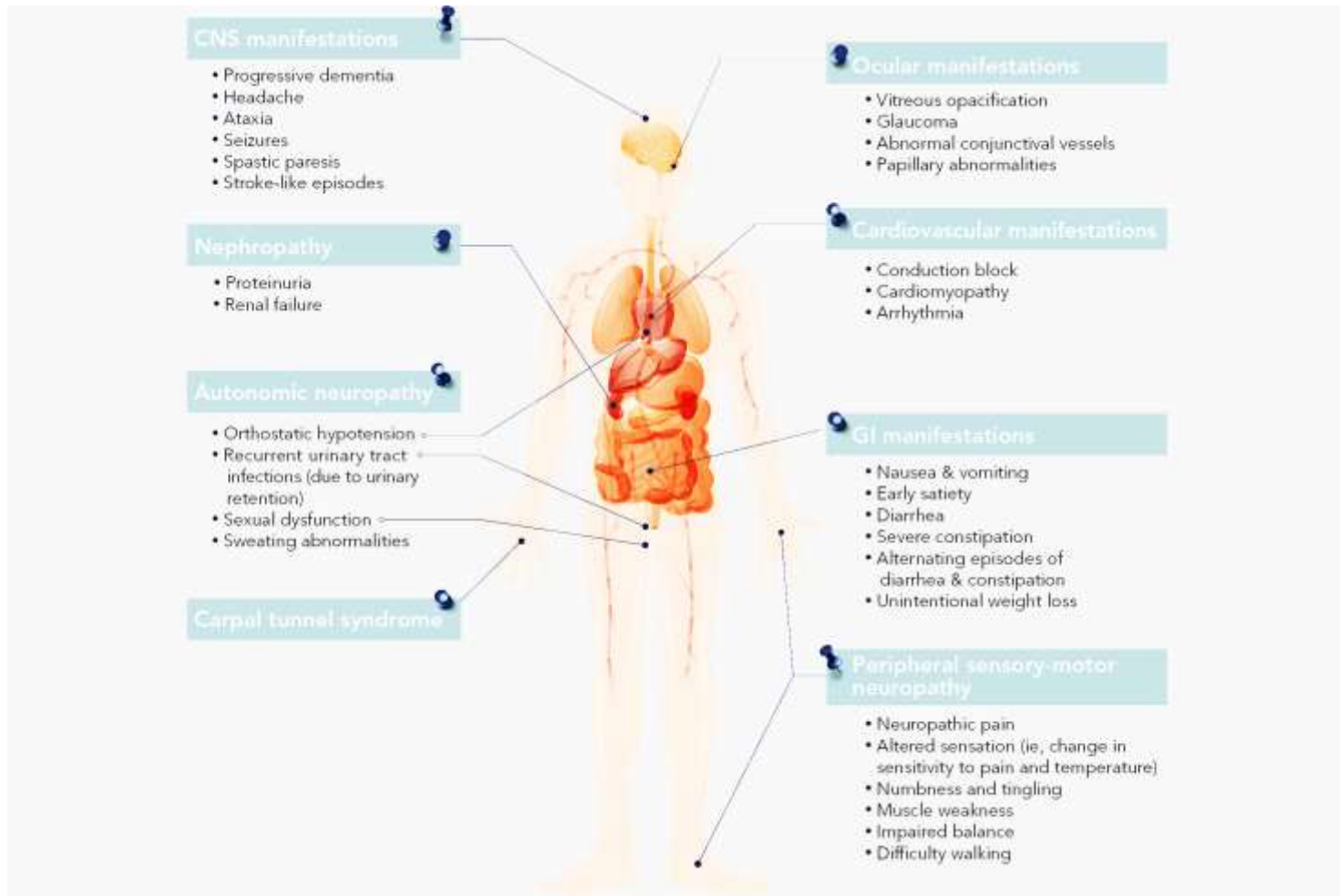
- Cardiac - Congestive heart failure, arrhythmia, conduction disease (previously called FAC)
- Neurological - peripheral sensory and autonomic neuropathy (previously called FAP)



TTR STRUCTURE AND AMYLOID FIBRIL FORMATION



SIGNS AND SYMPTOMS OF hATTR



HOW COMMON IS hATTR AMYLOIDOSIS?

- Estimated world-wide prevalence of 50,000 people (predominantly with neuropathy)
- BUT V122I shown convincingly in about 3.5% US African Americans = 1,500,000 people with genotype
 - 150,000 are over age 65 y and at highest risk for hATTR
- Ongoing subject of active study (SCAN-MP, PI's Maurer/Ruberg, NHLBI)

ATTR AMYLOIDOSIS IS UNRECOGNIZED (EVEN AT BOSTON UNIVERSITY CARDIOLOGY CLINIC)



Amyloid
The Journal of Protein Folding Disorders



ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: <http://www.tandfonline.com/loi/iamy20>

Prevalence of mutant ATTR cardiac amyloidosis in elderly African Americans with heart failure

Marios Arvanitis, Gloria G. Chan, Daniel R. Jacobson, John L. Berk, Lawreen H. Connors & Frederick L. Ruberg

101 African Americans with HF, age > 60y, and wall thickness \geq 12 mm

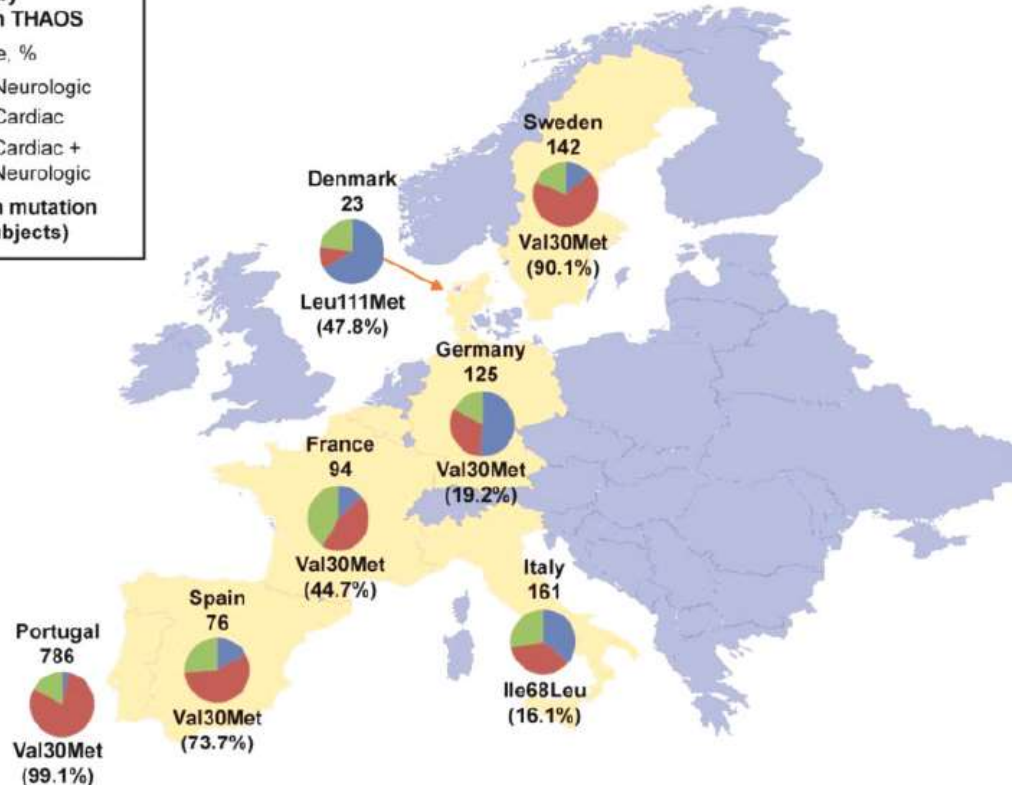
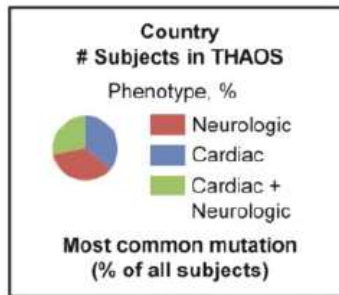


6.7% males were V122I gene positive

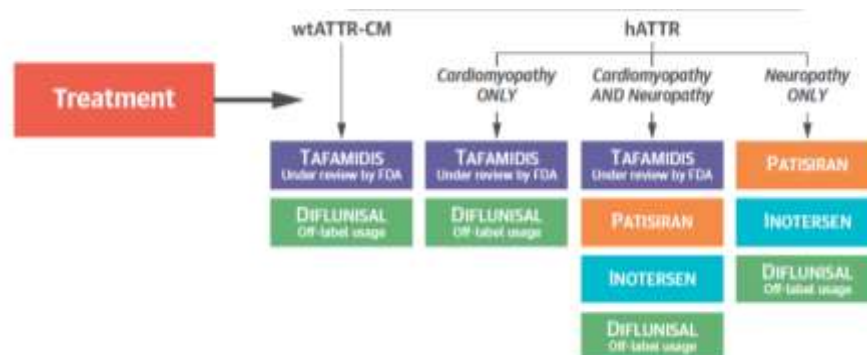
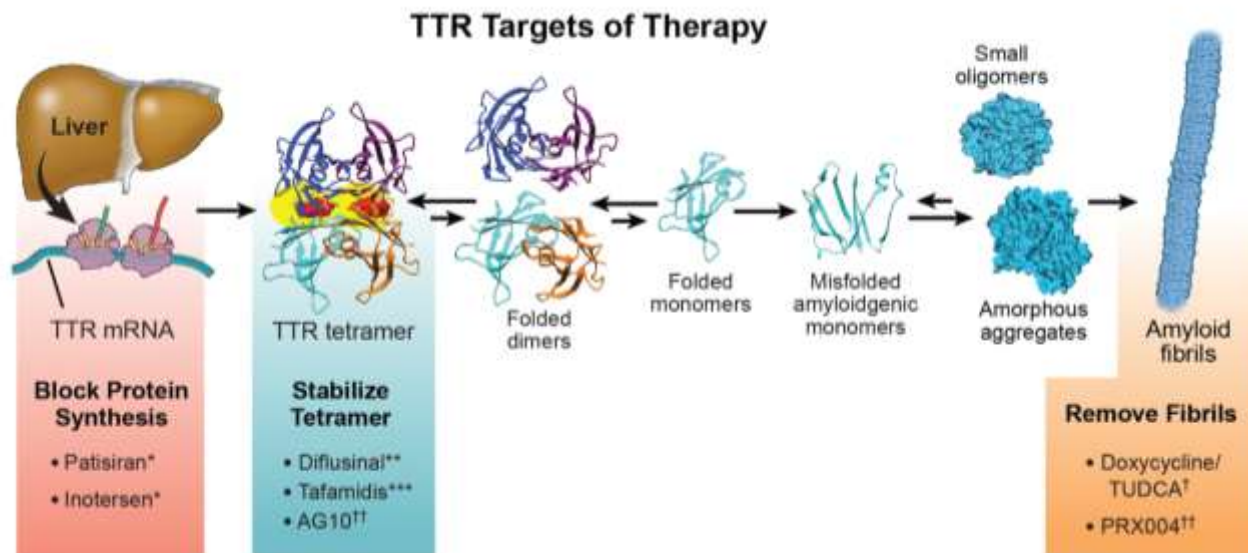


60% penetrance

hATTR ACROSS CONTINENTAL EUROPE – COUNTRY OF ORIGIN



DETERMINATION OF GENOTYPE IS CRITICAL TO TREATMENT



ANYONE CAN KNOW THEIR TTR GENOTYPE

23andMe

OUR SERVICES - HOW IT WORKS - REPORTS STORES SHOP

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BRCA1 (Breast Cancer)

HFE (Hemochromatosis)

CFTR (Cystic Fibrosis)

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ANYONE CAN KNOW THEIR TTR GENOTYPE – 23&ME

The screenshot shows the 23andMe website interface. At the top, there is a navigation bar with links for 'OUR SERVICES', 'HOW IT WORKS', 'REPORTS', 'STORES', 'SHOP', 'SIGN IN', 'MY ACCOUNT', and 'HELP'. Below this is a header with 'Genetic Health Risks' and 'Carrier Status'. A sidebar on the left titled 'Select a Condition' lists various genetic conditions, with 'Hereditary Amyloidosis (TTR-Related)' highlighted in green. The main content area is titled 'What to know about: Hereditary Amyloidosis (TTR-Related) and our test'. It includes a paragraph explaining the condition, followed by sections for 'Typical signs and symptoms', 'What do we test?', 'Relevant ethnicities', and 'Test performance summary'. The 'Typical signs and symptoms' section lists three types of neuropathy: Cardiomyopathy, Peripheral neuropathy, and Autonomic neuropathy. The 'What do we test?' section mentions testing for three variants in the TTR gene. The 'Relevant ethnicities' section lists V122I, V30M, and T60A variants and their prevalence in different populations. The 'Test performance summary' section states that the accuracy was determined by comparing results from the test with results from sequencing, with a greater than 99% accuracy rate.

Select a Condition

- Age-Related Macular Degeneration
- Alpha-1 Antitrypsin Deficiency
- BRCA1/BRCA2 (Selected Variants)
- Celiac Disease
- Familial Hypercholesterolemia
- G6PD Deficiency
- Hereditary Amyloidosis (TTR-Related)**
- Hereditary Hemochromatosis

[View sample report here](#)
[View package insert here](#)

What to know about: Hereditary Amyloidosis (TTR-Related) and our test

TTR-related hereditary amyloidosis is a genetic condition caused by the buildup of a protein called transthyretin (TTR) in the body's tissues and organs. This protein buildup, called amyloidosis, can damage the nerves, the heart, and other parts of the body. This test includes three of the most common genetic variants linked to TTR-related hereditary amyloidosis.

Typical signs and symptoms

Symptoms can vary widely depending on which TTR variant a person has and the location(s) of TTR protein buildup. Symptoms can vary even among people with the same variant. People with TTR-related hereditary amyloidosis may experience:

- **Cardiomyopathy** (heart damage), characterized by thickening of the walls of the heart, which can lead to heart failure.
- **Peripheral neuropathy** (damage to the nerves that connect the spinal cord to the rest of the body, including the arms and legs), characterized by symptoms including carpal tunnel syndrome as well as tingling, numbness, or burning in the hands, legs, or feet.
- **Autonomic neuropathy** (damage to the nerves that help control the internal organs), characterized by symptoms including constipation, diarrhea, sexual dysfunction, and dizziness.

Other factors that influence risk

- Age
- Sex

What do we test?

- Tests for three variants in the TTR gene linked to TTR-related hereditary amyloidosis.
- Genetic testing for TTR-related hereditary amyloidosis in the general population is not currently recommended by any healthcare professional organizations.

Relevant ethnicities

- **V122I:** Most common and best studied in African Americans and people of West African descent.
- **V30M:** Most common and best studied in people of Portuguese, Northern Swedish, and Japanese descent.
- **T60A:** Most common and best studied in people of Irish descent and also found in people of British descent.

Test performance summary

Accuracy was determined by comparing results from the test with results from sequencing. Greater than 99% of test results were correct. While unlikely, this test may provide false positive or false negative results. For more details on the analytical performance of this test, refer to the [package insert](#).

UNANSWERED QUESTION #1

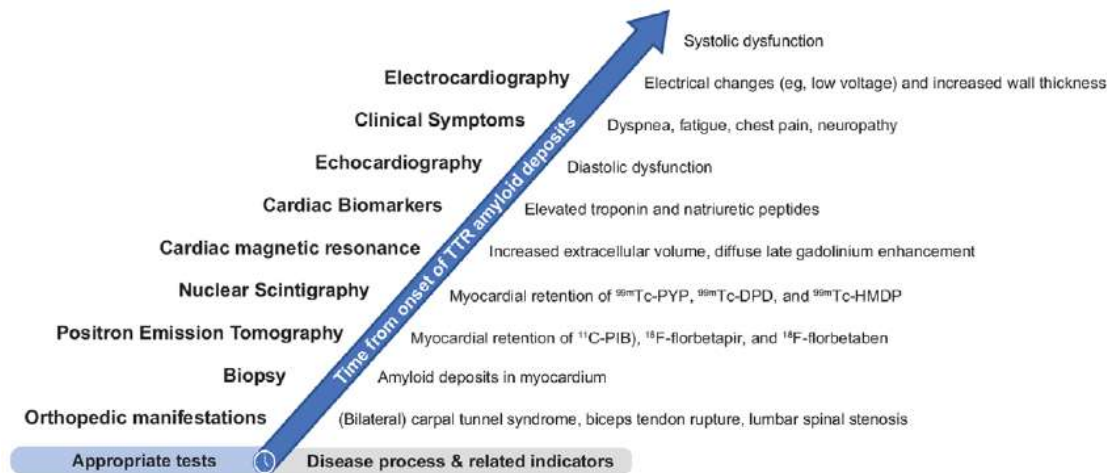
- Genotype carriers (phenotype negative)
 - When to initiate therapy?
 - Prior to development of symptoms
 - What to prescribe?

UNANSWERED QUESTION #2

- When to recommend testing of offspring or siblings of affected patients?
 - Above an age threshold?
 - At the predicted age of disease onset (PADO) or some defined time prior?
 - Mutation, sex, and family dependent

ADVANCES IN HEART FAILURE

Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis



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Frederick L. Ruberg, MD
Ronald Witteles, MD
Giampaolo Merlini, MD

Also to consider – prealbumin (TTR) concentration

THE FIRST GUIDELINES IN AMYLOIDOSIS!



EXPERT CONSENSUS RECOMMENDATIONS

ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI EXPERT CONSENSUS RECOMMENDATIONS FOR MULTIMODALITY IMAGING IN CARDIAC AMYLOIDOSIS: PART 1 OF 2—EVIDENCE BASE AND STANDARDIZED METHODS OF IMAGING

Abbreviations	
AL	Amyloid immunoglobulin light chain
ATTR	Amyloid transthyretin
DPD	^{99m} Tc-3,3-Diphosphono-1,2-propano-dicarboxylic acid
ECV	Extracellular volume
EF	Ejection fraction
HMDP	Hydroxymethylenediphosphonate
LGE	Late gadolinium enhancement
LV	Left ventricular
PYP	Pyrophosphate
Tc	^{99m} Tc-Technetium

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EXPERT CONSENSUS RECOMMENDATIONS

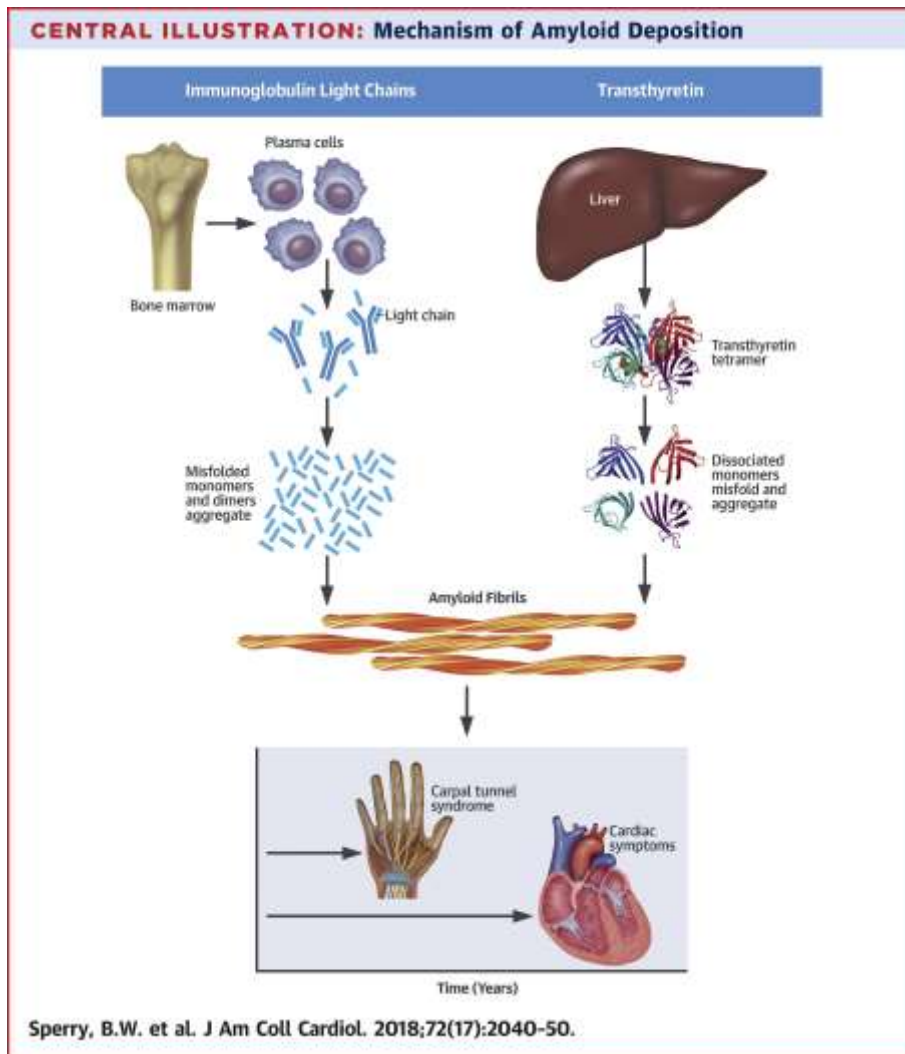
ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI EXPERT CONSENSUS RECOMMENDATIONS FOR MULTIMODALITY IMAGING IN CARDIAC AMYLOIDOSIS: PART 2 OF 2—DIAGNOSTIC CRITERIA AND APPROPRIATE UTILIZATION

Cardiac amyloidosis is emerging as an underdiagnosed cause of heart failure and mortality. Growing literature suggests that a noninvasive diagnosis of cardiac amyloidosis is now feasible. However, the diagnostic criteria and utilization of imaging in cardiac amyloidosis are not standardized. In this paper, Part 2 of a series, a panel of international experts from multiple societies define the diagnostic criteria for cardiac amyloidosis and appropriate utilization of echocardiography, cardiovascular magnetic resonance imaging, and radionuclide imaging in the evaluation of patients with known or suspected cardiac amyloidosis.

Key Words: Cardiac amyloidosis • Diagnosis • Appropriate use • Expert consensus • Multimodality

Abbreviations	
AL	Amyloid immunoglobulin light chains
ATTR	Amyloid transthyretin
DPD	^{99m} Tc-3,3-diphosphono-1,2-propano-dicarboxylic acid
EF	Ejection fraction
HMDP	Hydroxymethylenediphosphonate
LV	Left ventricular
PYP	Pyrophosphate
Tc	^{99m} Tc-Technetium

ORTHOPEDIC MANIFESTATIONS – EARLIEST CLUES?



98 patients → 10 new cases and 2 with hATTR

Other clinical clues:

- **Bilateral carpal tunnel**
- **Spinal Stenosis**
- **Spontaneous biceps tendon rupture**

CONCLUSIONS

- hATTR results from a single base pair change in the *TTR* gene, that causes a change in the TTR protein resulting in misfolding and amyloid fibril formation
- hATTR is passed down to children in an autosomal dominant manner (50% chance of passage)
- The type of mutation determines the predicted symptoms and organ systems that are affected
- Determination of genotype is critical to selecting treatment
- We must move toward early identification to give treatments the best chance to work

AMYLOIDOSIS CENTER BOSTON UNIVERSITY/ BOSTON MEDICAL CENTER



<http://www.bu.edu/amyloid/>
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