Overview of Hereditary Transthyretin Amyloidosis (hATTR)

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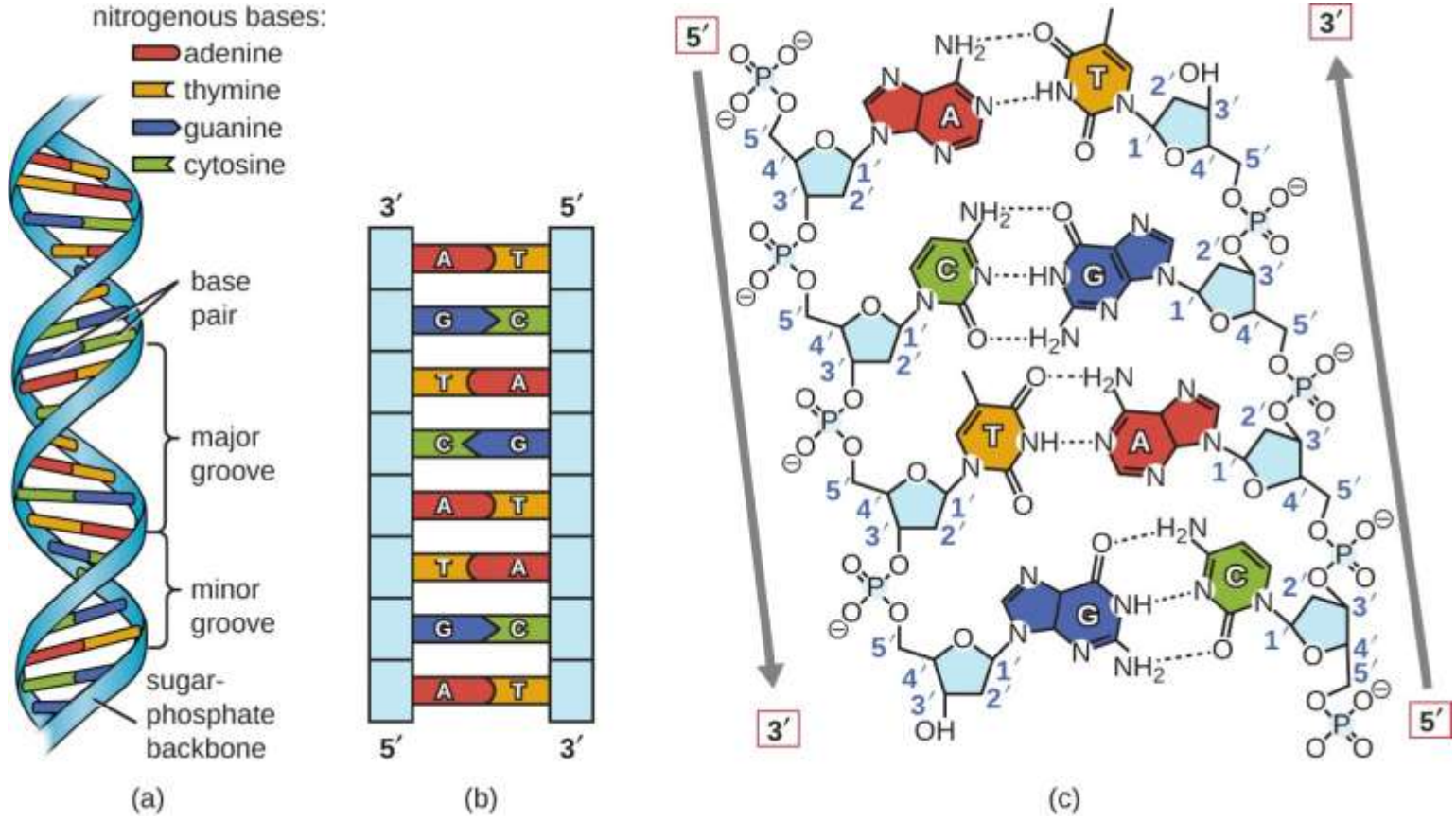
Boston Medical Center is the primary teaching affiliate of the Boston University School of Medicine.

DISCLOSURES

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

GENETICS: BASIC BIOLOGY – DNA STRUCTURE



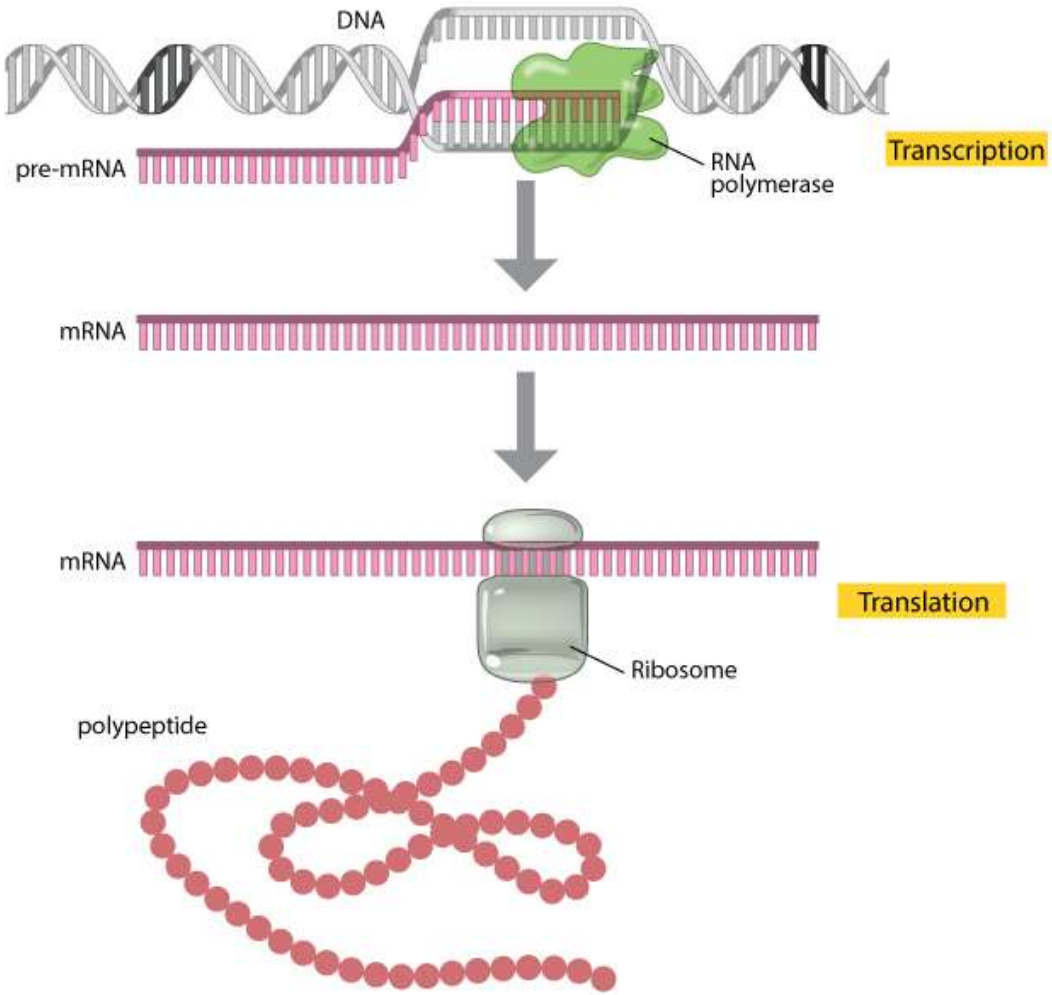
https://microbenotes.com/dna-structure-properties-types-and-functions/

GENETICS: BASIC BIOLOGY – AMINO ACID CODES

1st letter	Second Letter: U	Second Letter: C	Second Letter: A	Second Letter: G	3rd letter
U	UUU Phe UUC UUA Leu UUG	UCU UCC Ser UCA UCG	UAU Tyr UAC UAA Stop UAG Stop	UGU Cys UGC UGA Stop UGG Trp	U C A G
C	CUU CUC Leu CUA CUG	CCU CCC Pro CCA CCG	CAU His CAC CAA Gln CAG	CGU CGC Arg CGA CGG	U C A G
A	AUU AUC Ile AUA AUG Met	ACU ACC Thr ACA ACG	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG	U C A G
G	GUU GUC Val GUA GUG	GCU GCC Ala GCA GCG	GAU Asp GAC GAA Glu GAG	GGU GGC Gly GGA GGG	U C A G

http://biology.kenyon.edu/courses/biol114/Chap05/Chapter05.html

GENETICS: BASIC BIOLOGY – DNA, RNA, AND PROTEINS



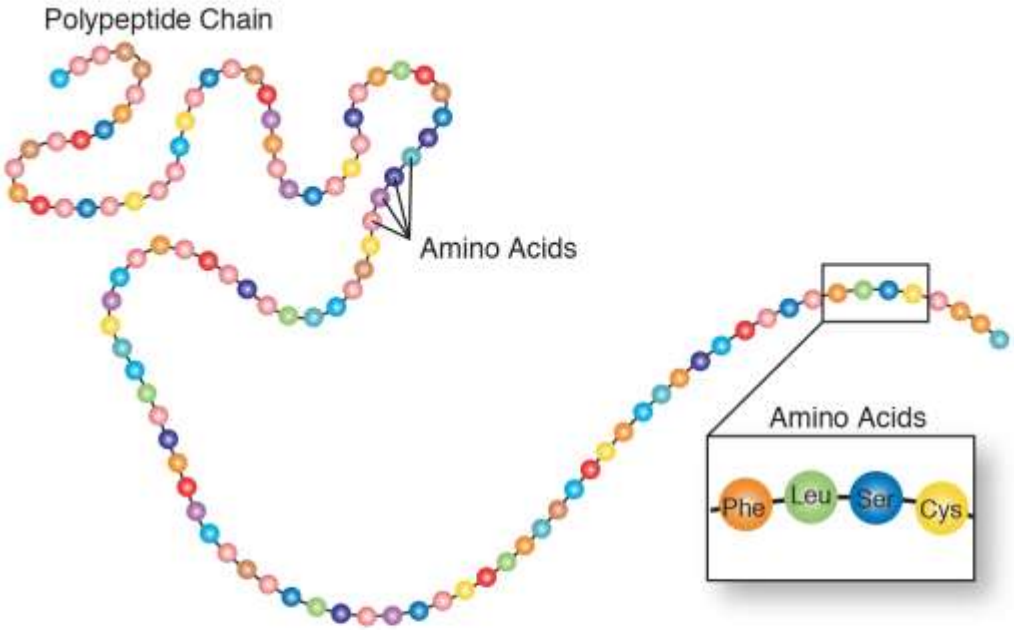
DNA

mRNA

Protein

Clancy and Brown, *Nature Education* 2008

GENETICS: BASIC BIOLOGY – PROTEIN STRUCTURE

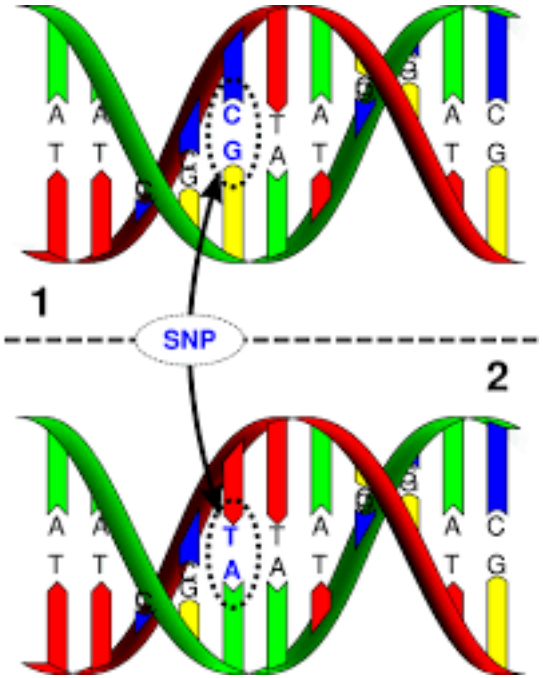


Amino Acids

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: Tyrosisne
Cys:Cysteine	Ile: Isoleucine	Pro: Proline	Val: Valine

https://www.genome.gov/sites/default/files/tg/en/illustration/amino_acids.jpg

GENETICS: BASIC BIOLOGY – SINGLE NUCLEOTIDE POLYMORPHISMS (SNP)



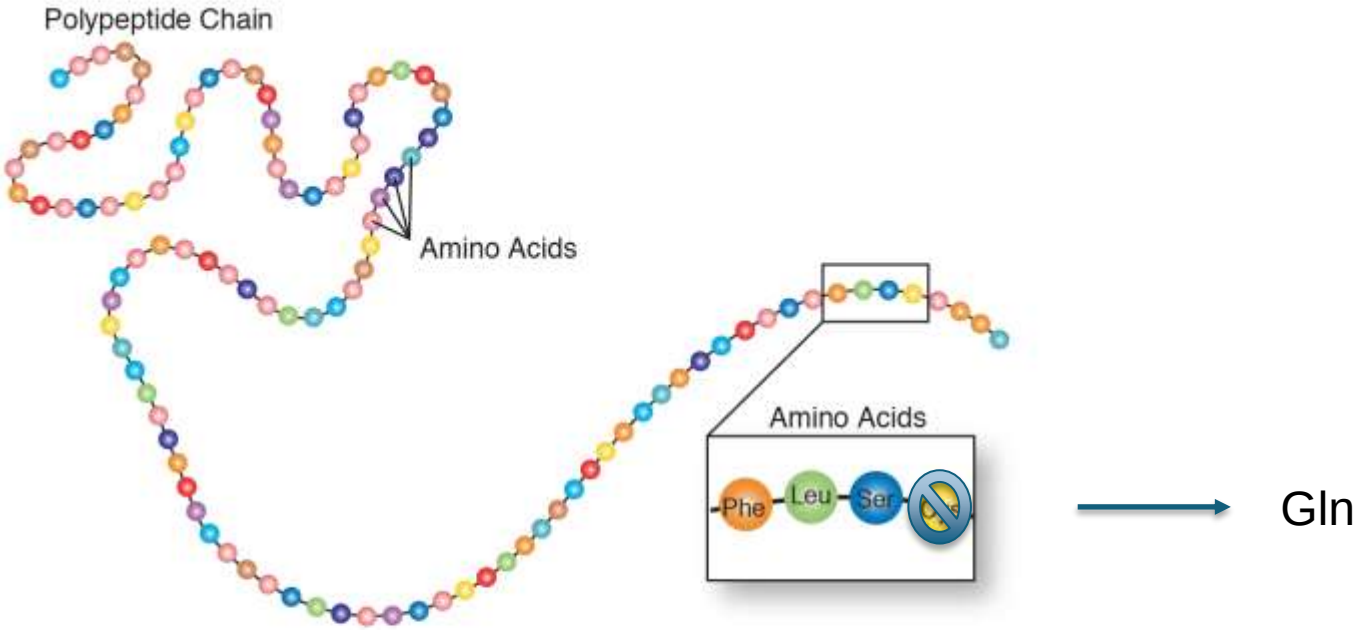
Normal Protein

Missense mutation

Abnormal Protein

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

GENETICS: BASIC BIOLOGY – PROTEIN STRUCTURE WITH SNP

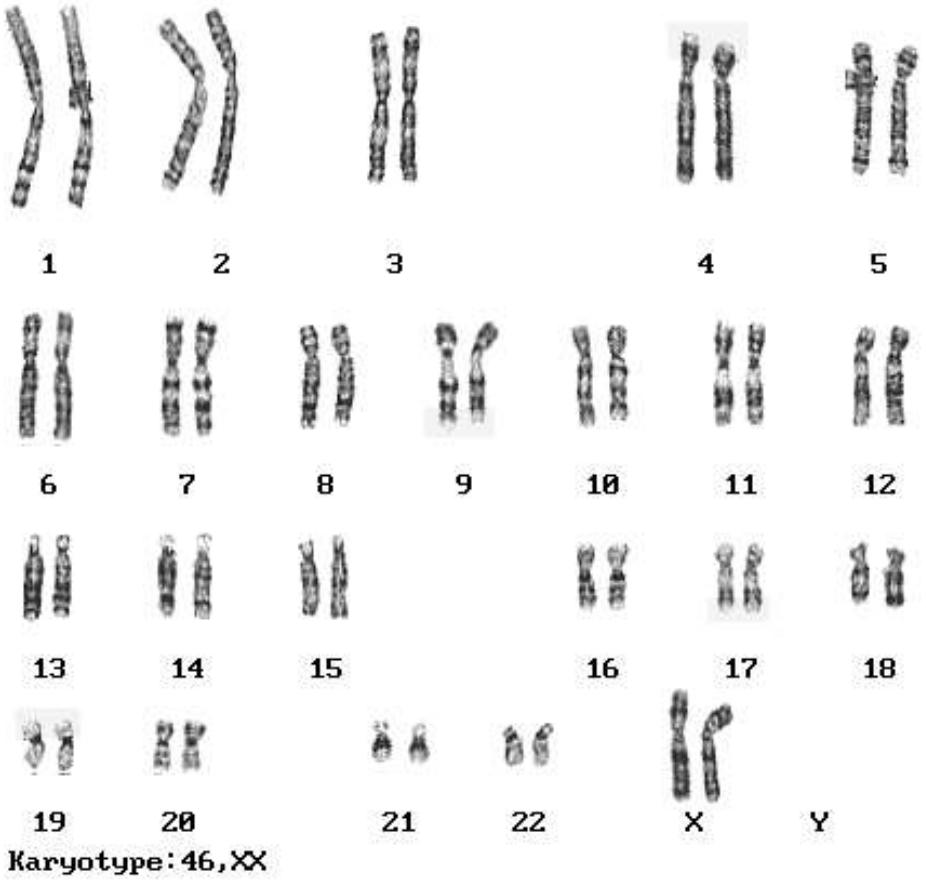


Amino Acids

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: Tyrosisne
Cys:Cysteine	Ile: Isoleucine	Pro: Proline	Val: Valine

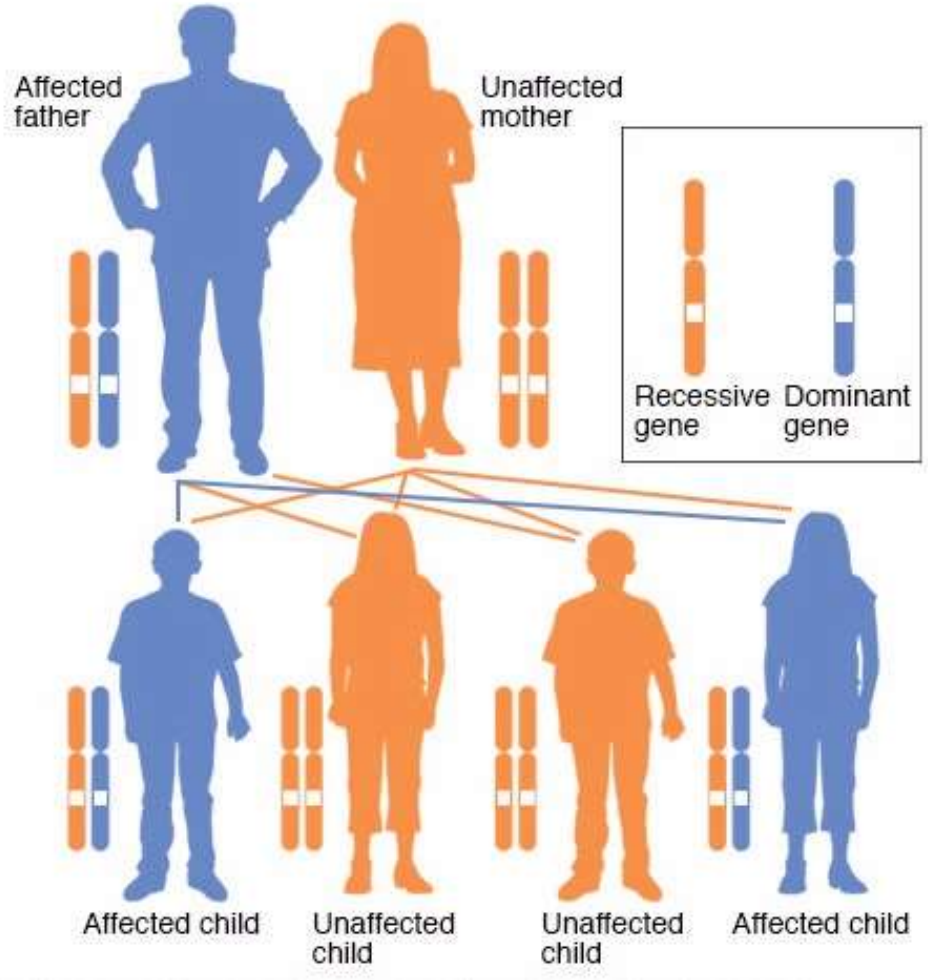
https://www.genome.gov/sites/default/files/tg/en/illustration/amino_acids.jpg

GENETICS: BASIC BIOLOGY – DNA ORGANIZED INTO CHROMOSOMES



https://www.biology.iupui.edu/biocourses/N100/2k2humancsomaldisorders.html

GENETICS: BASIC BIOLOGY – AUTOSOMAL DOMINANCE



https://baguioejournal.wordpress.com

HEREDITARY ATTR (hATTR) AMYLOIDOSIS

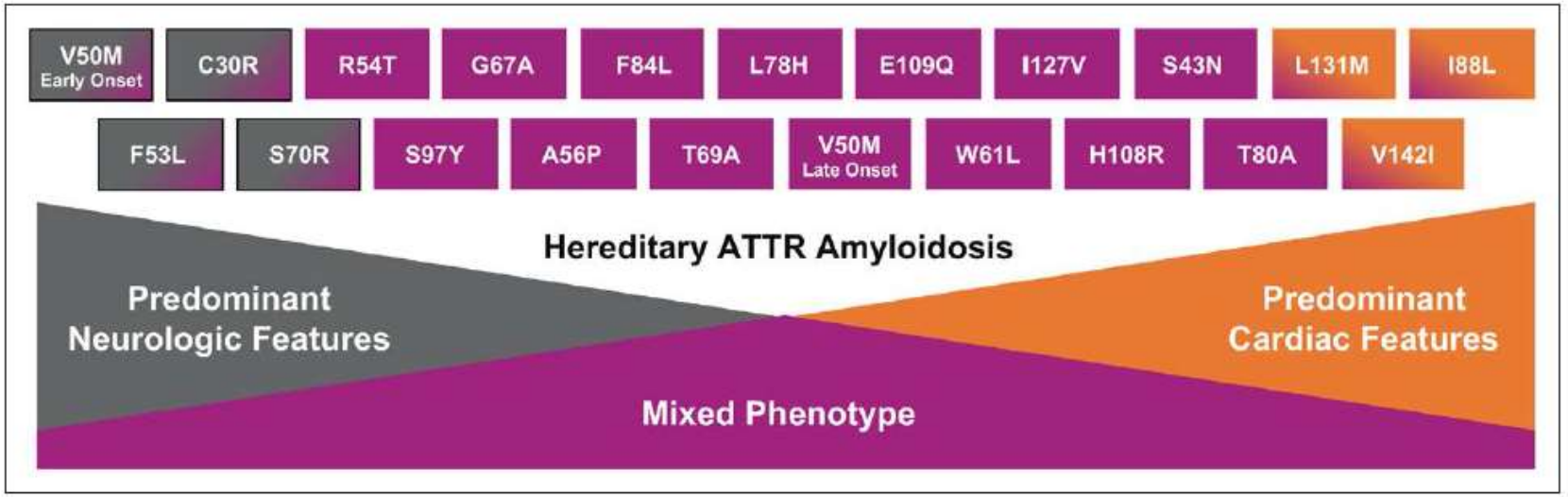
- Autosomal dominant (50% chance of passage to offspring)
  - AKA ATTRv (variant) or ATTm (mutant)
- Missense SNP – change in amino acid of TTR protein causing misfolding of the protein and amyloid deposits
- Present since birth, amyloidosis develops with age
- Naming – Normal amino acid-position in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

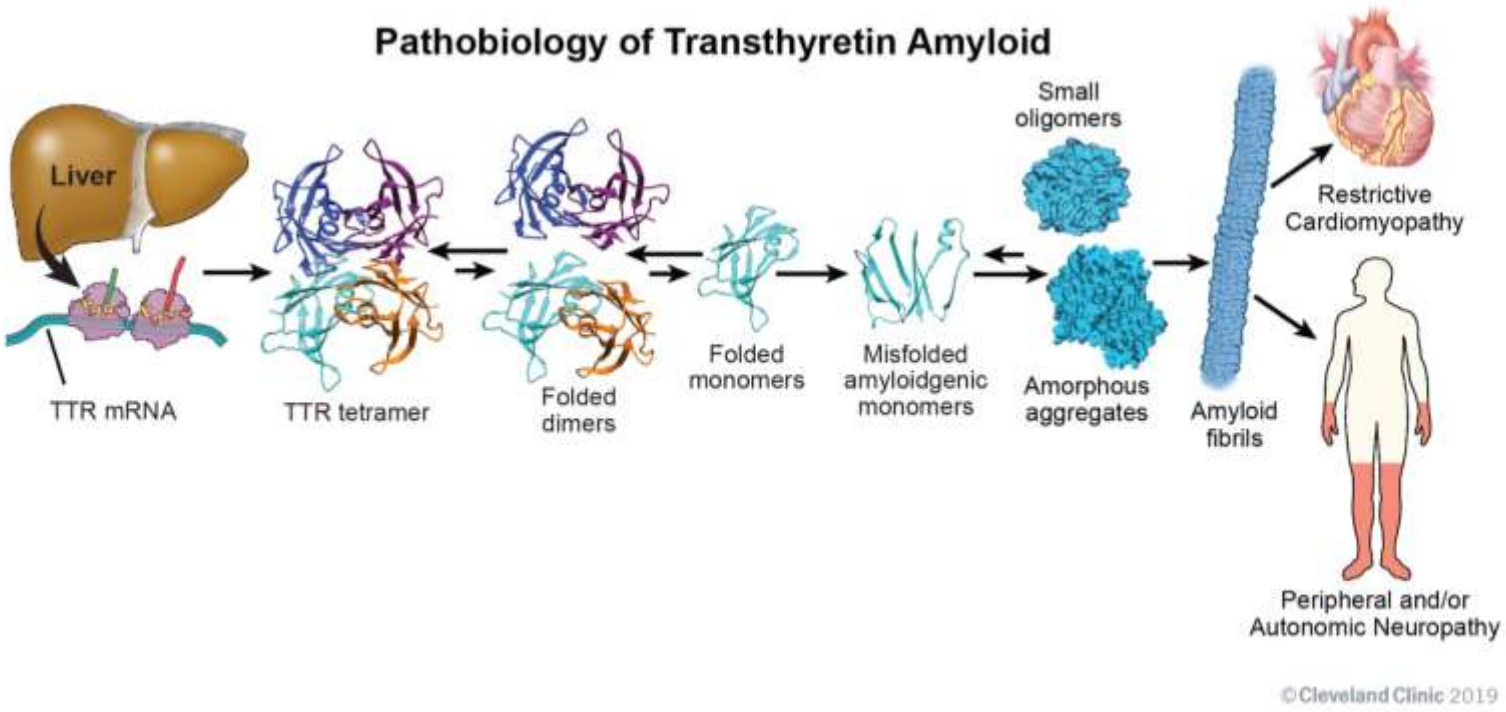
hTTR IS CAUSED BY SNP RESULTING IN AMYLOIDOSIS OF DIFFERENT ORGAN SYSTEMS

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



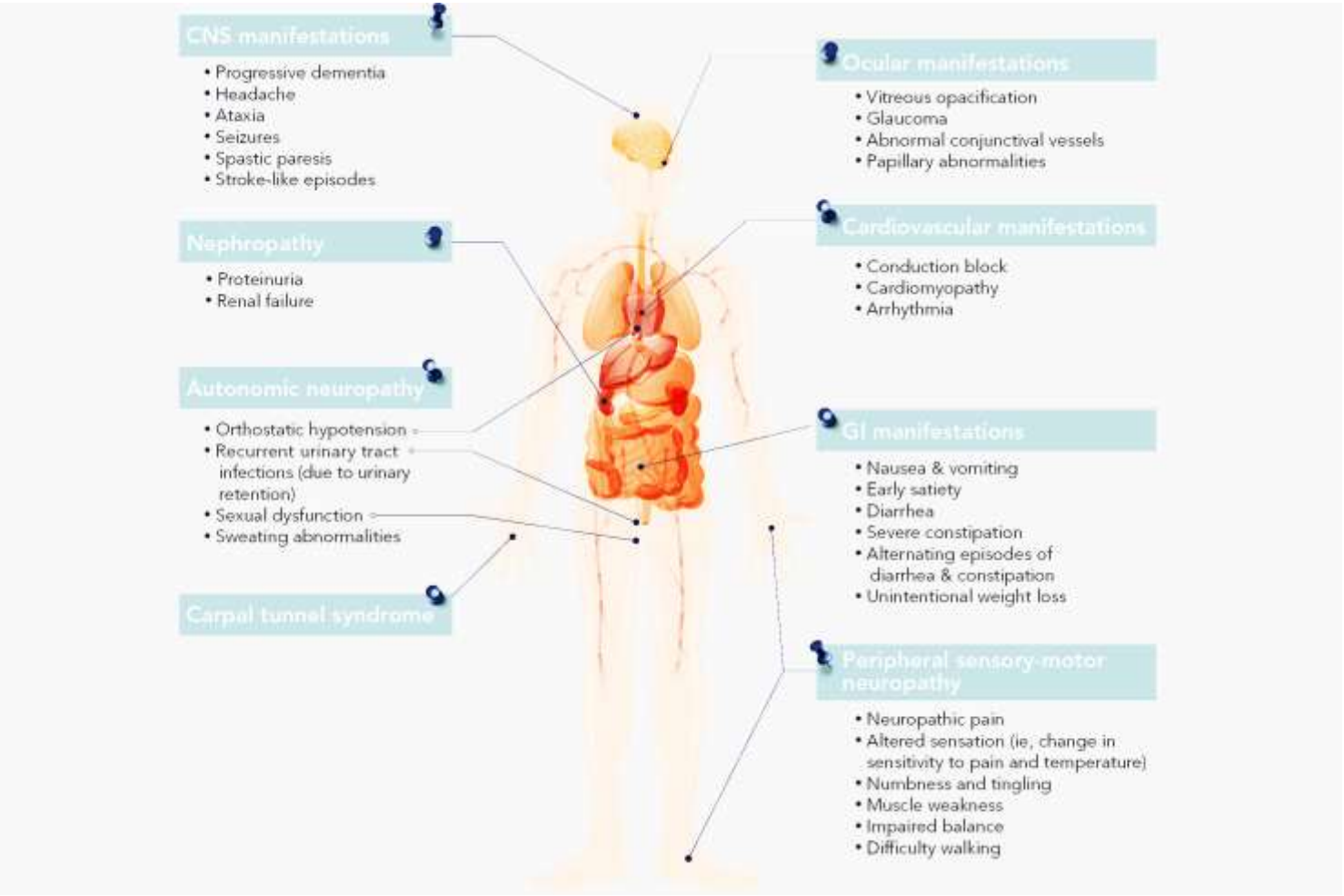
Maurer, *Circulation: Heart Failure* 2019

TTR STRUCTURE AND AMYLOID FIBRIL FORMATION



Ruberg, *J Am Coll Cardiol*, 2019

SIGNS AND SYMPTOMS OF hATTR



https://hattramyloidosis.co.uk/en-gb/symptoms

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)

Gertz, *Am J Managed Care* 2017

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

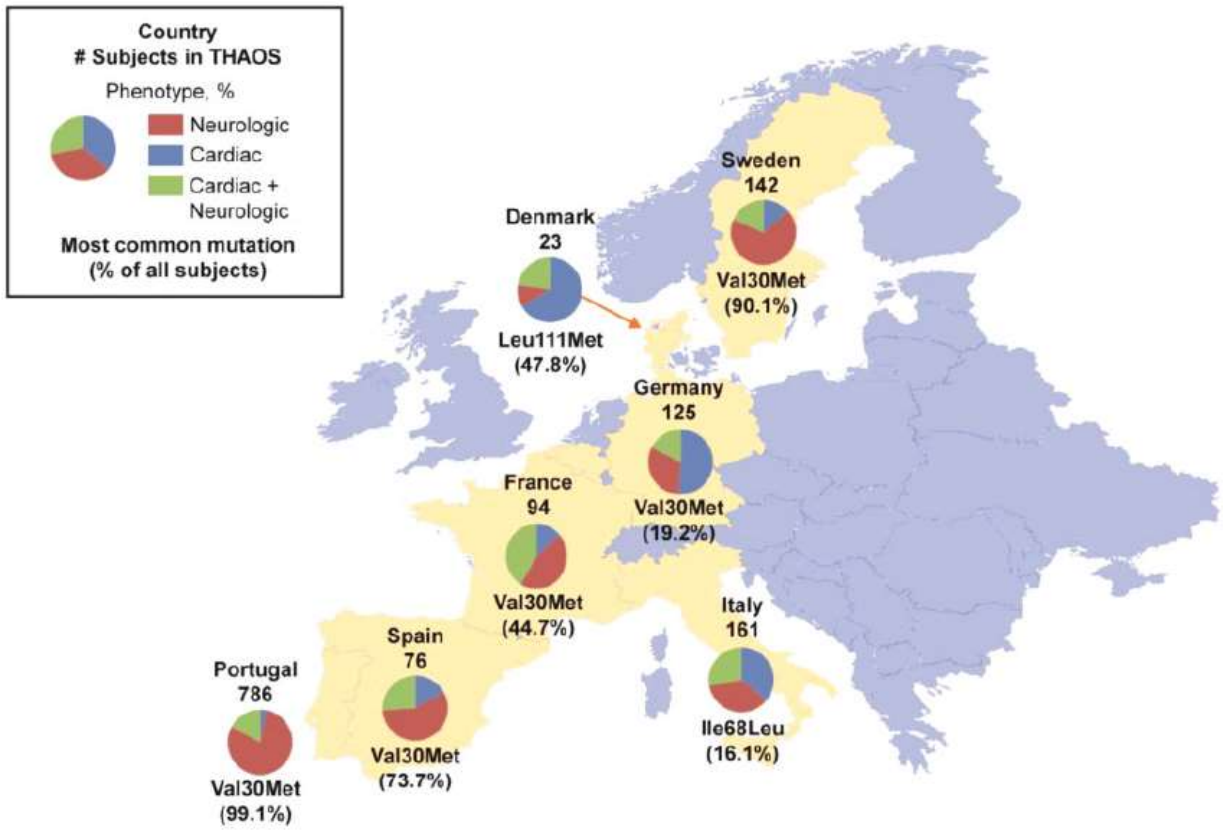
101 African Americans with HF, age > 60y, and wall thickness >/= 12 mm

6.7% males were V122I gene positive

60% penetrance

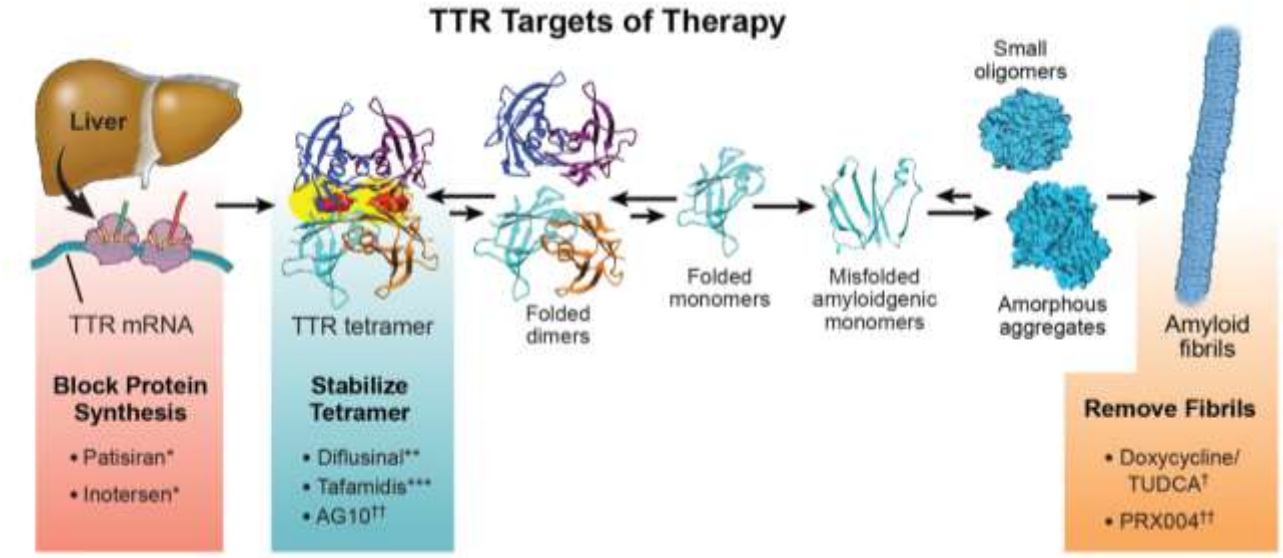
Arvanitis, Amyloid 2017

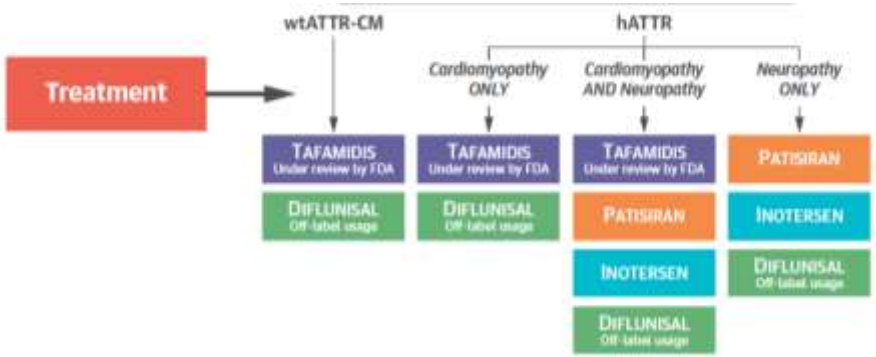
hATTR ACROSS CONTINENTAL EUROPE – COUNTRY OF ORIGIN



Damy, *EHJ* 2019

DETERMINATION OF GENOTYPE IS CRITICAL TO TREATMENT





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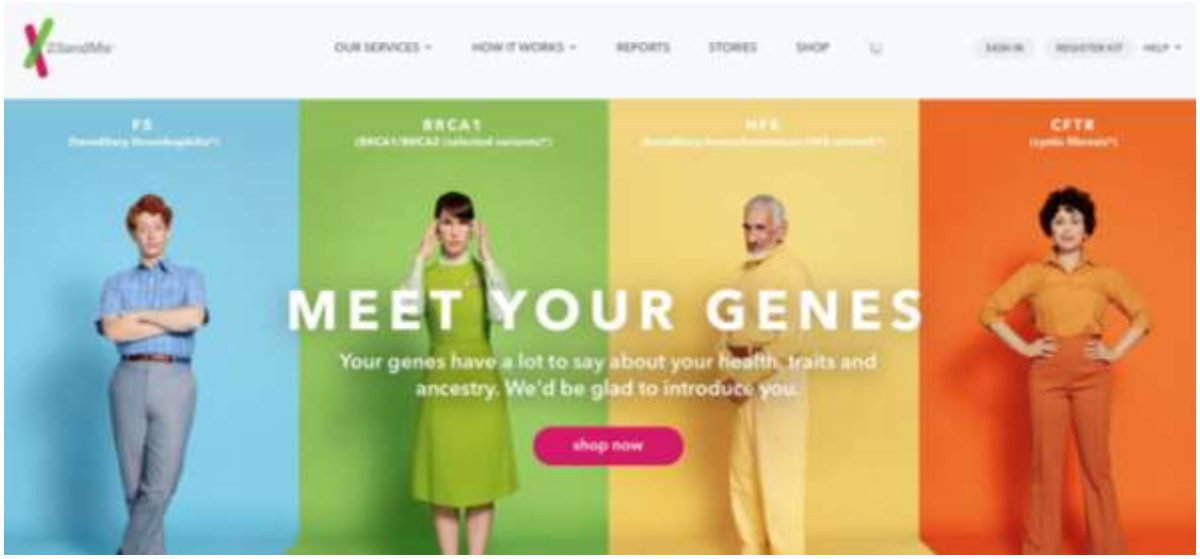
ANYONE CAN KNOW THEIR TTR GENOTYPE



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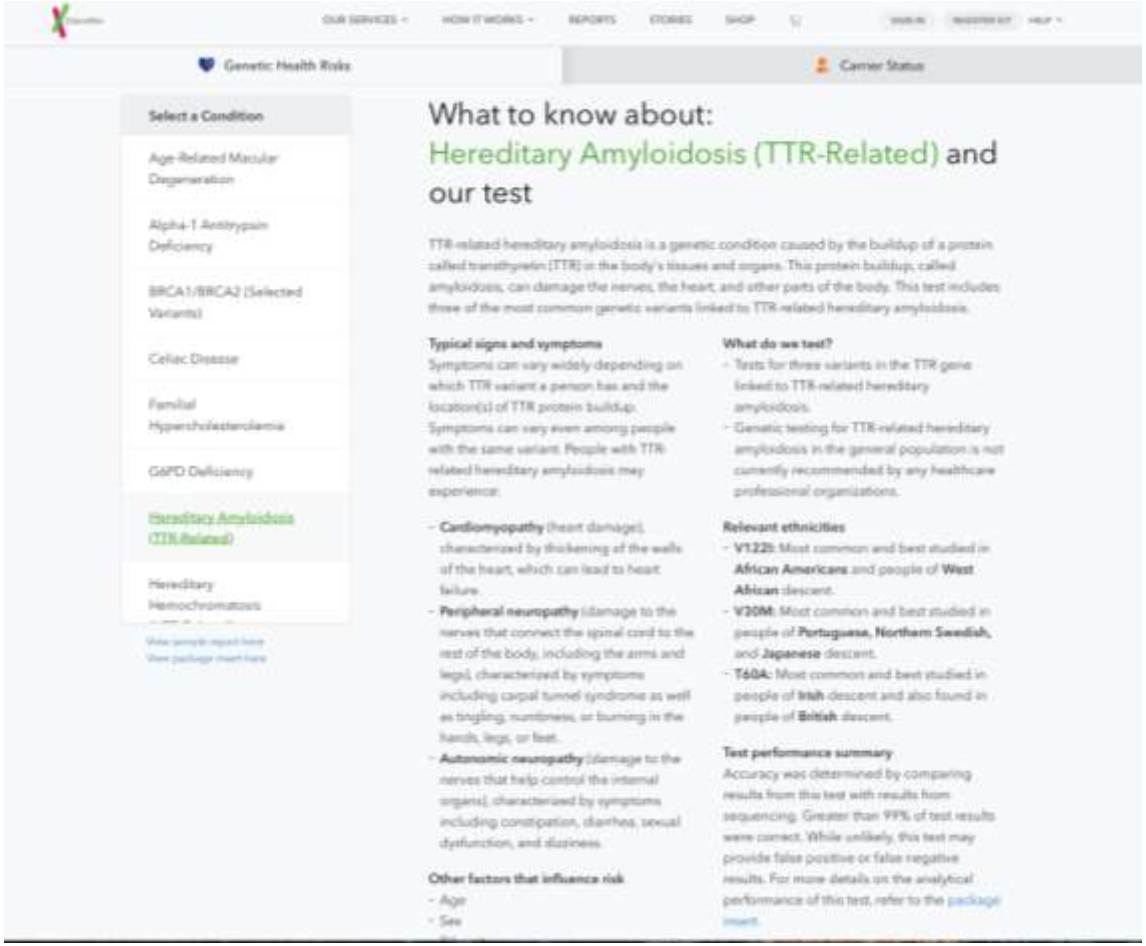
ANYONE CAN KNOW THEIR TTR GENOTYPE – 23&ME



https://www.23andme.com/test-info/

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

Obici, Cur Opin Neurol 2016

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

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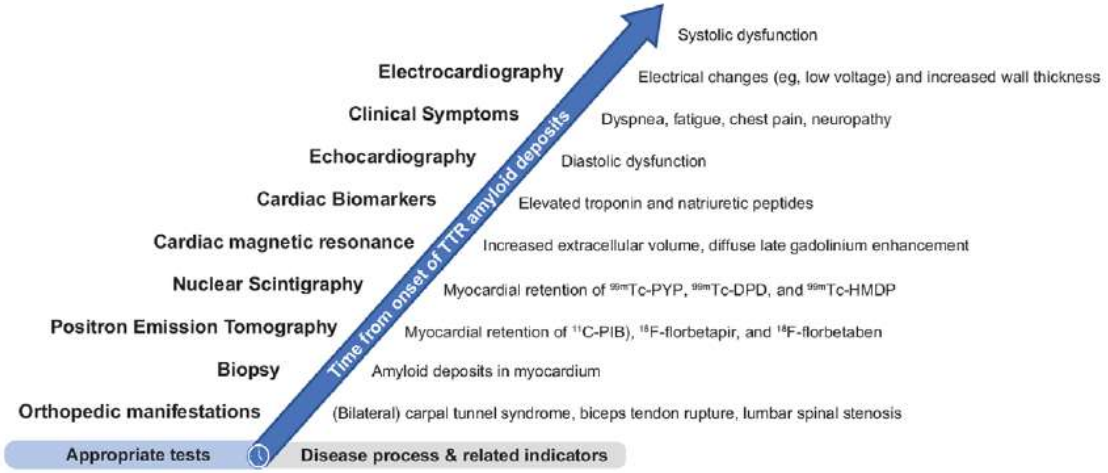

Also to consider – prealbumin (TTR) concentration

Maurer, *Circulation: Heart Failure* 2019

THE FIRST GUIDELINES IN AMYLOIDOSIS!

ASNC

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}Technetium

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ASNC

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-propanodi-carboxylic acid
EF	Ejection fraction
HMDP	Hydroxymethylenediphosphonate
LV	Left ventricular
PYP	Pyrophosphate
Tc	^{99m}Technetium

Dorbala, *J Nuc Med* and *J Card Fail*, 2019

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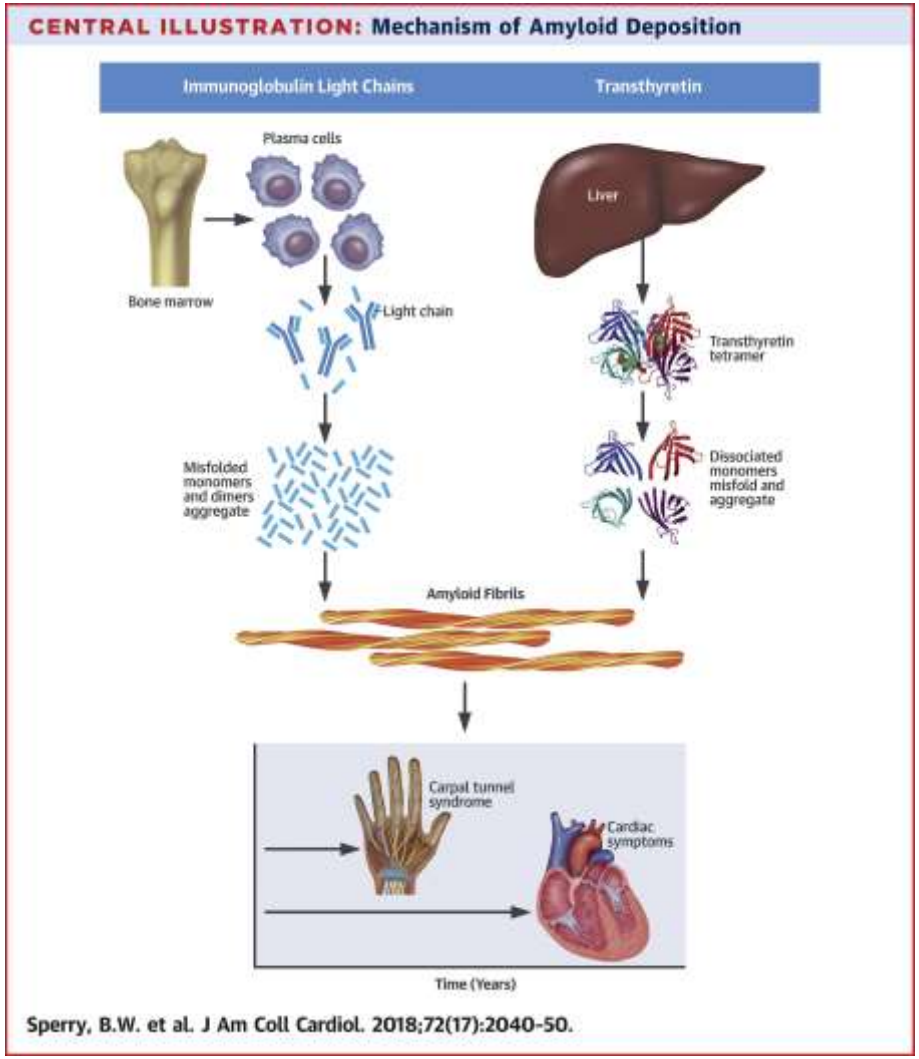
ORTHOPEDIC MANIFESTATIONS – EARLIEST CLUES?



98 patients → 10 new cases and 2 with hATTR

Other clinical clues:

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

Sperry, Hanna *JACC* 2018

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

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