

ALL IN THE FAMILY:
**Update on hereditary neuropathies
and treatments**

featuring
Dr. Amanda Peltier & Sean R.

Thursday, February 5, 2026



Today's moderator:



Amanda Homscheid
Program Manager
the Foundation for Peripheral Neuropathy



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FoundationForPN.org/past-webinars



Questions?

Submit questions anytime in the

questions box.

We will answer as many as we can.



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Today's experts:



Amanda Peltier

MD, MS

Associate Professor
Vanderbilt University
Medical Center

Sean R.

Neuropathy patient,
Speaker, and Advocate



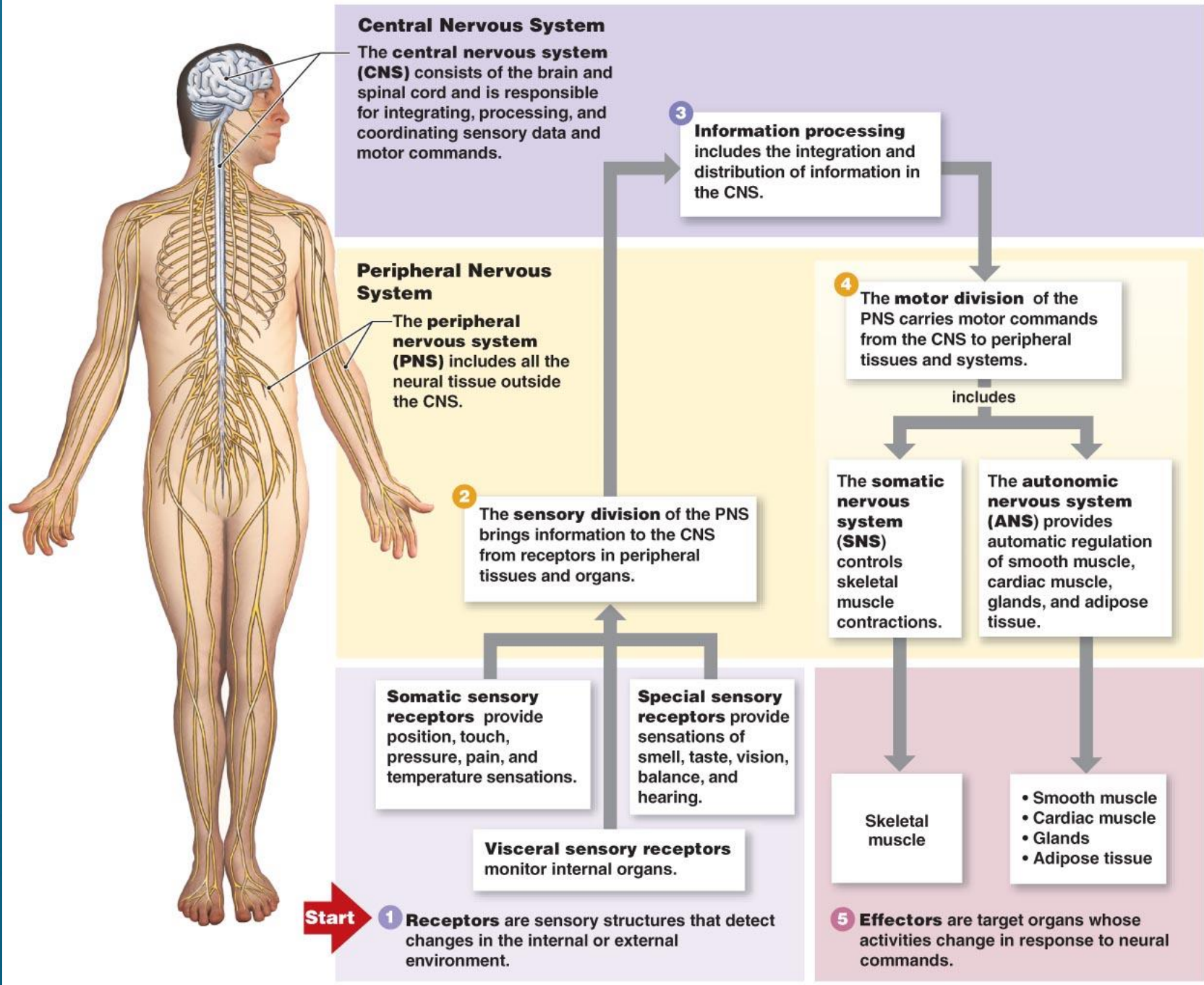
Hereditary Neuropathies, Hereditary Amyloidosis and Genetics

Amanda Peltier, MD MS
Professor of Neurology

VANDERBILT  UNIVERSITY
MEDICAL CENTER

Types of Nerve Fibers and their Function

- Motor: large myelinated nerves which go to muscle. Cause weakness, atrophy (shrinkage) of muscles.
- Sensory fibers
 - Large myelinated sensory fibers convey vibration, light touch, proprioception (ability to know where your limb is in space)
 - Small non-myelinated sensory fibers found in the skin convey pain, temperature, also some light touch
- Autonomic fibers
 - Small non-myelinated sensory fibers go to different organs to control automatic functions like heart rate, blood pressure, ability to urinate, sexual function, gastrointestinal function.



What are Inherited Neuropathies?

- Neuropathies caused by a single gene mutation or gene deletion, duplication.
- Account for about 7% of all neuropathy (125,000 patients of approximately 1.86 million people in the United States)
- Can be only motor, only sensory, sensory and motor (most common) sensory and autonomic (most rare), or sensory, motor and autonomic nerves involved.
- Originally described by Charcot, Marie, Tooth, 3 different neurologists in the 1800s.
- Hereditary amyloidosis first described in 1952 by Andrade in Portugal, affects about 50,000 worldwide.

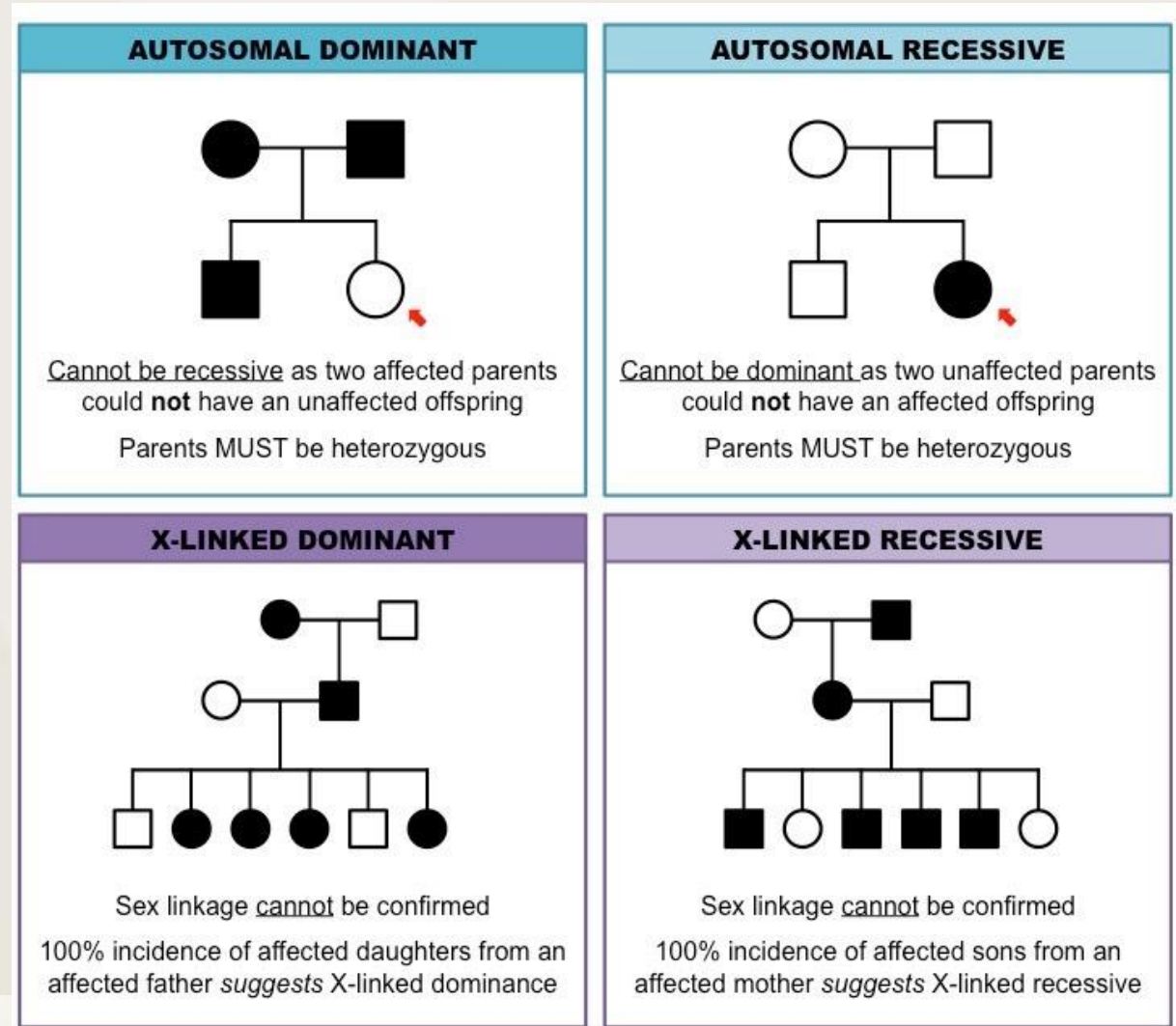
Charcot Marie Tooth or Hereditary Sensory Motor Neuropathy

- Often there is a family history (but not always)
- Distal to proximal gradient
- Slow progression over years
- Associated with pes cavus, champagne bottle legs, etc.
- Often associated with essential tremor, scoliosis.
- May have slightly elevated CSF protein, but not over 100 mg/dL.



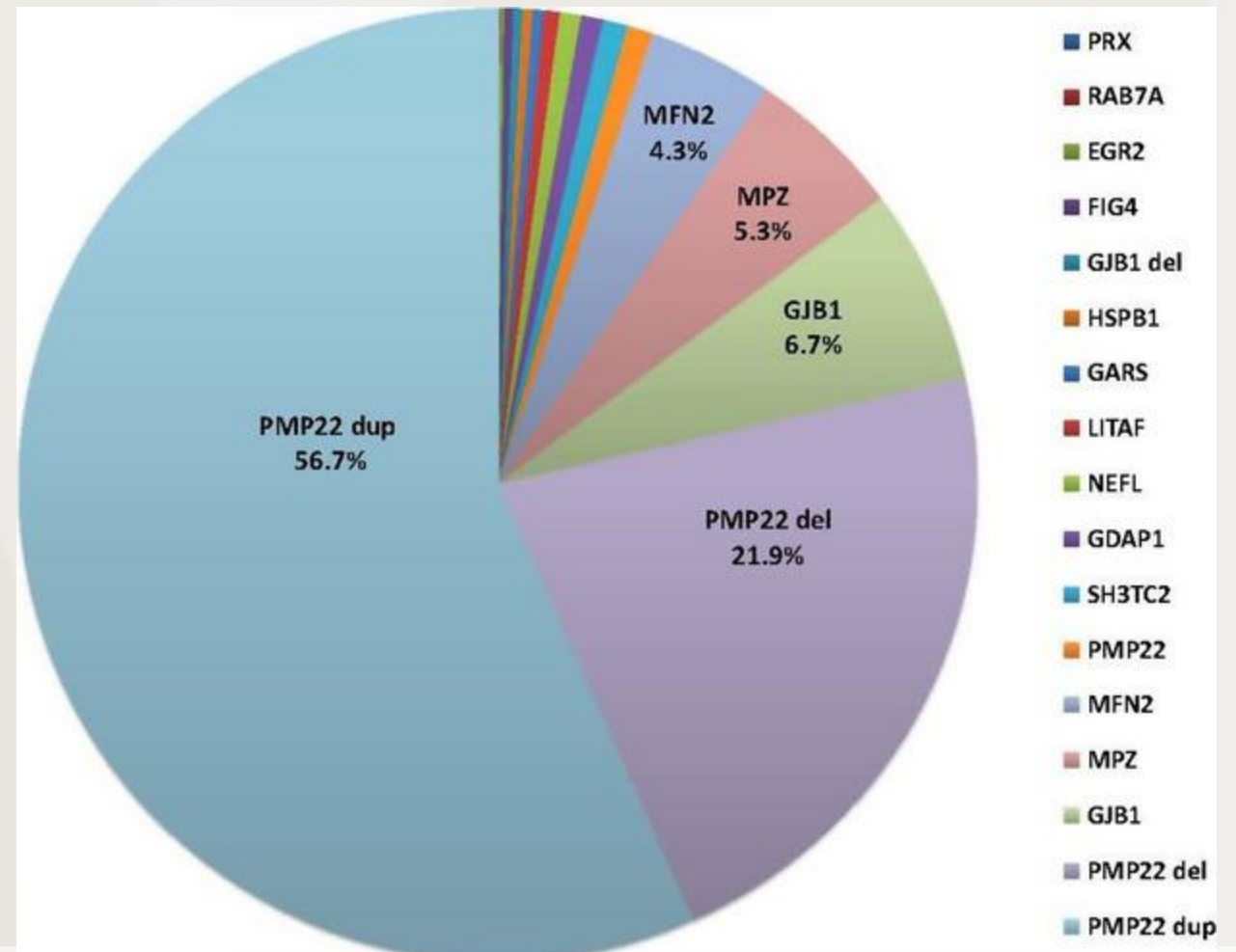
Inherited Disorders

- Can be inherited as dominant, Recessive, X-linked depending on how many gene copies needed to have a disorder.



Distribution of Common Mutations

- The most common mutation causing neuropathy is a duplication of the PMP gene, accounting for over half of all inherited neuropathies.

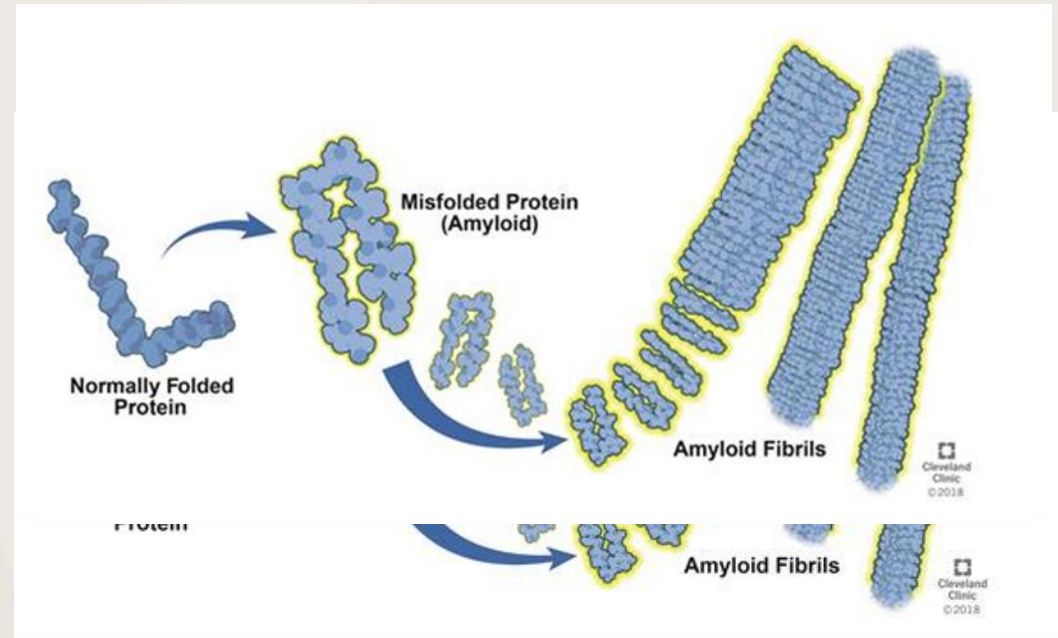


Classification of Hereditary Neuropathies

Class	Types of Fibers Involved	Inheritance Pattern	Typical age of presentation	Typical Symptoms	Nerve conduction findings
CMT1	Sensory and motor myelinated fibers	Autosomal dominant	Teens (rarely early childhood)	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Slowing of nerves to 10-20 m/s
CMT2	Sensory and motor myelinated fibers	Autosomal dominant	Childhood, Teens	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Normal to mildly slowed nerve fiber velocity (above 40 m/s), loss of nerve fiber responses
CMT 4	Sensory and motor myelinated fibers	Autosomal recessive	Childhood, Teens	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Normal to mildly slowed nerve fiber velocity (above 40 m/s), loss of nerve fiber responses
CMTX	Sensory and motor myelinated fibers	X-linked recessive	Teens, young adulthood	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Intermediate slowing 25-35 m/s
Hereditary Sensory and Autonomic Neuropathies	Sensory and autonomic non-myelinated fibers	Mostly autosomal recessive	Childhood	Pain or loss of pain, amputations, autonomic symptoms	Normal nerves (EMG only tests large fibers)
Hereditary Amyloidosis	Motor, Sensory, Autonomic myelinated and non-myelinated fibers	Autosomal dominant	Adulthood to 80s	Carpal tunnel syndrome, numbness, pain, weakness, autonomic symptoms	Can be normal (small fiber at first), can have mild to moderate slowing, loss of nerve responses

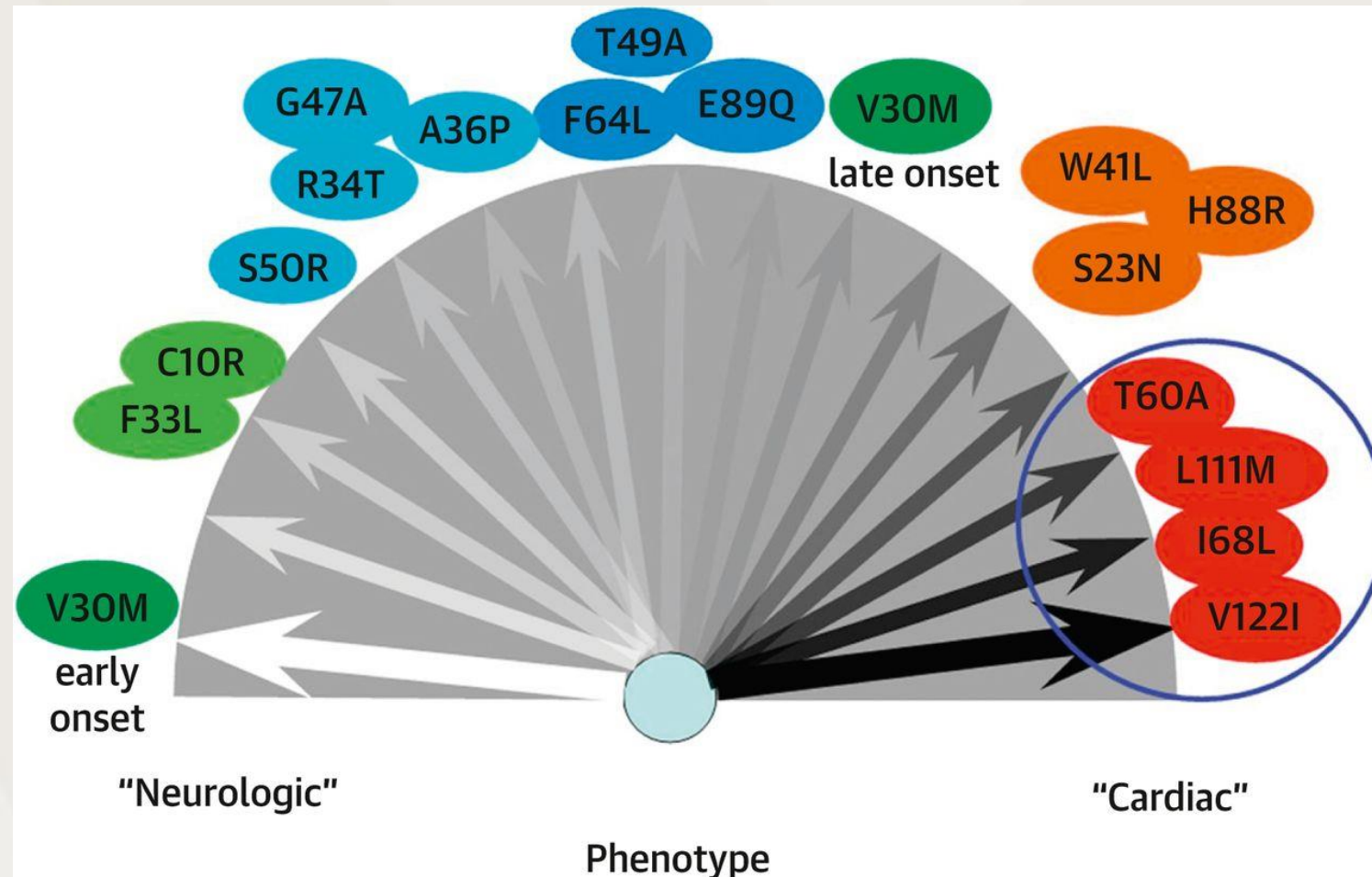
Amyloid

- Homogenous, amorphous “gunk”
- Looks pink on hematoxylin and eosin stains
- Apple-green birefringence when viewed under polarized light
- In electron micrographs, linear fibrils in a mat in β pleated sheet formation

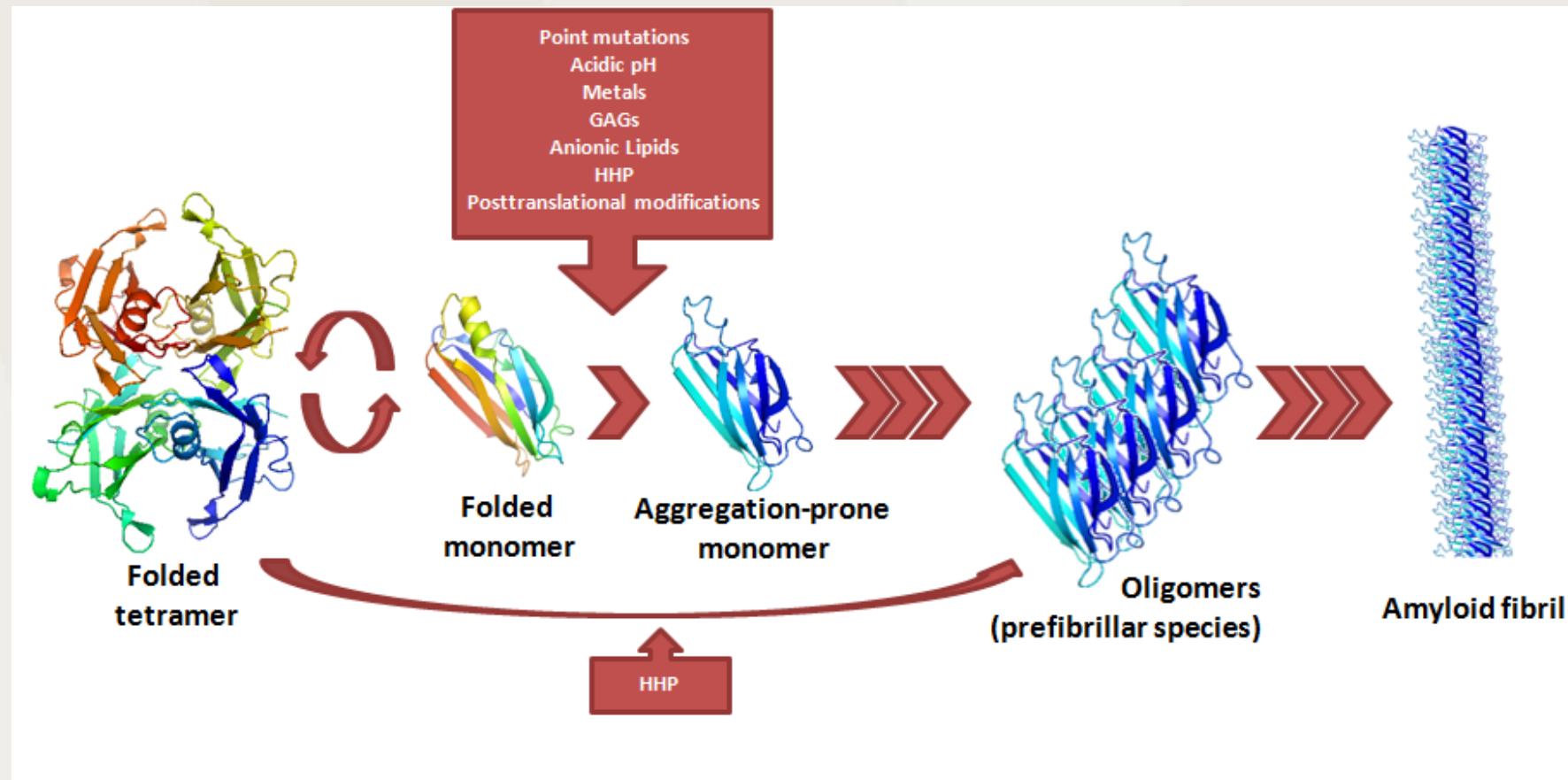


<https://my.clevelandclinic.org/health/diseases/15718-amyloidosis-al-amyloid-light-chain>

Familial Amyloidosis



Transthyretin



Azevedo et al. 2013.

Differences and Similarities:
Amyloid neuropathy from light chain malformations (most common) and inherited transthyretin amyloid neuropathy.

Shared pathology in ATTRv and AL

Impaired autonomic nerves cause orthostatic hypotension and arrhythmias

Impaired sudomotor nerves cause loss of sweat

Amyloid deposited in the heart causes cardiac autonomic neuropathy

Amyloid deposited in kidney pericapsular vessels, medulla and cortex interstitium, and tubular membrane basement causes nephrotic syndrome

Amyloid deposited in the gastrointestinal tract causes enteric autonomic plexus impairment

Amyloid deposited in muscle causes weakness

Amyloid deposited in myelinated and unmyelinated axons causes polyneuropathy

Differential pathology in ATTRv and AL

Amyloid deposited in meninges only in ATTRv

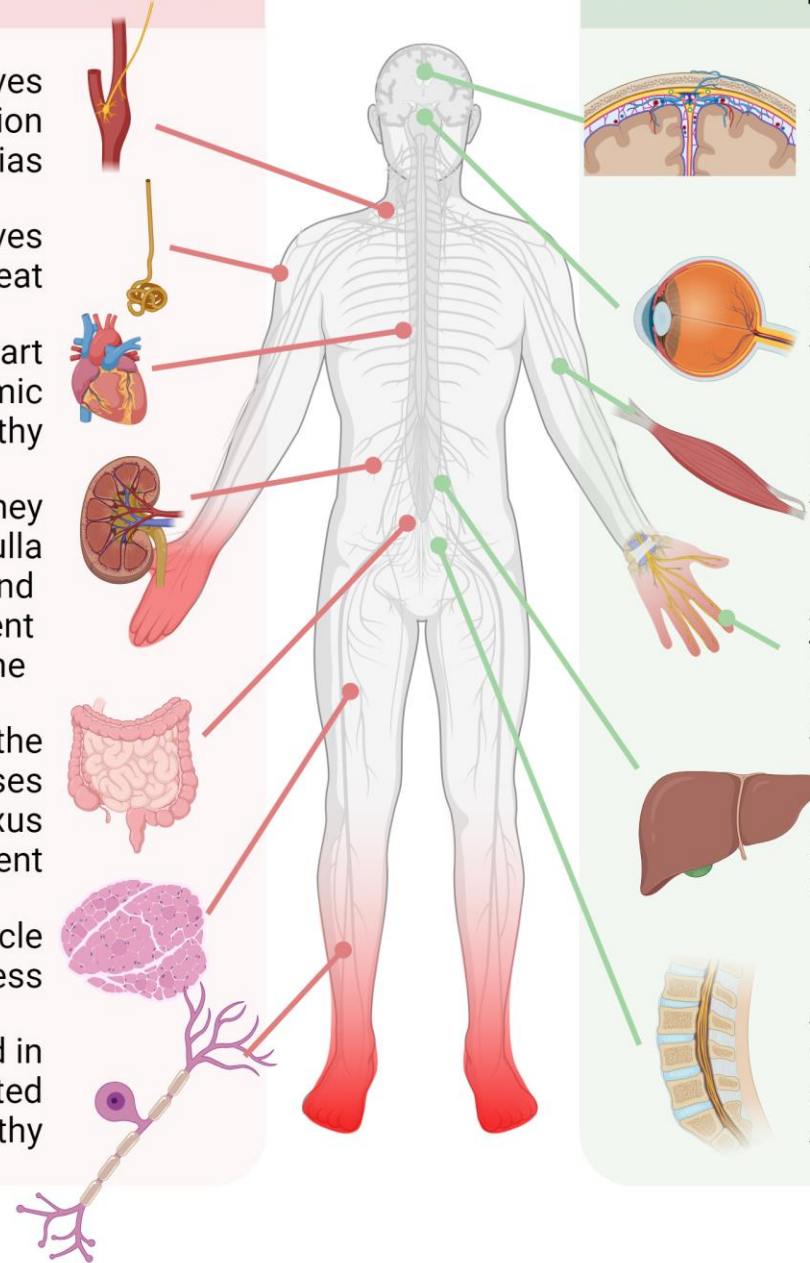
Amyloid deposited in ocular cornea and vitreous humor in ATTRv more than AL

Bicep tendon rupture only in ATTRv

Amyloid deposited in the transverse ligament causes carpal tunnel syndrome in ATTRv more than AL

Hepatomegaly and elevated alkaline phosphatase in AL

Amyloid deposited in lamina of cervical and lumbar spine causes spinal stenosis in ATTRv more than AL



Carpal tunnel syndrome and neuropathy can predate cardiac manifestations for years (ATTR-V122I)

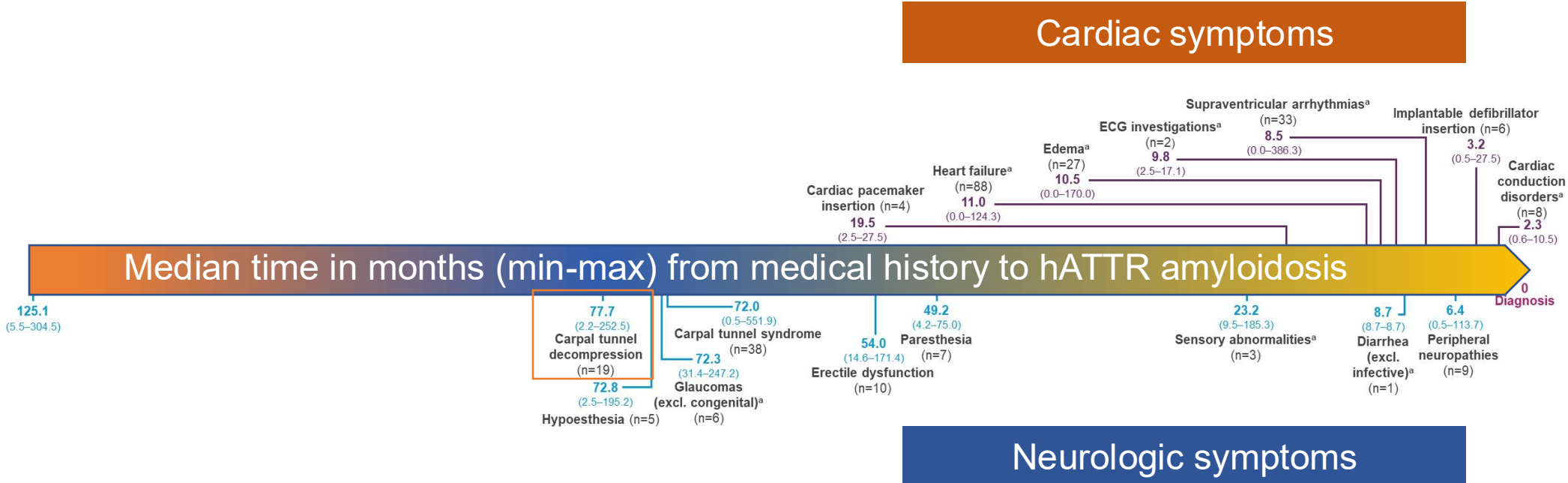
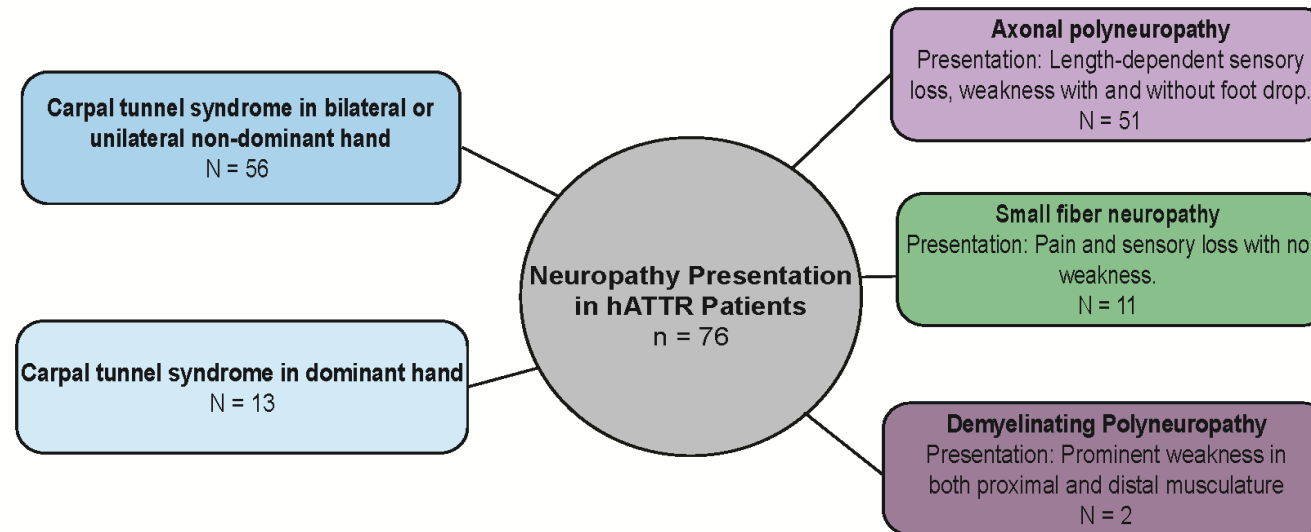


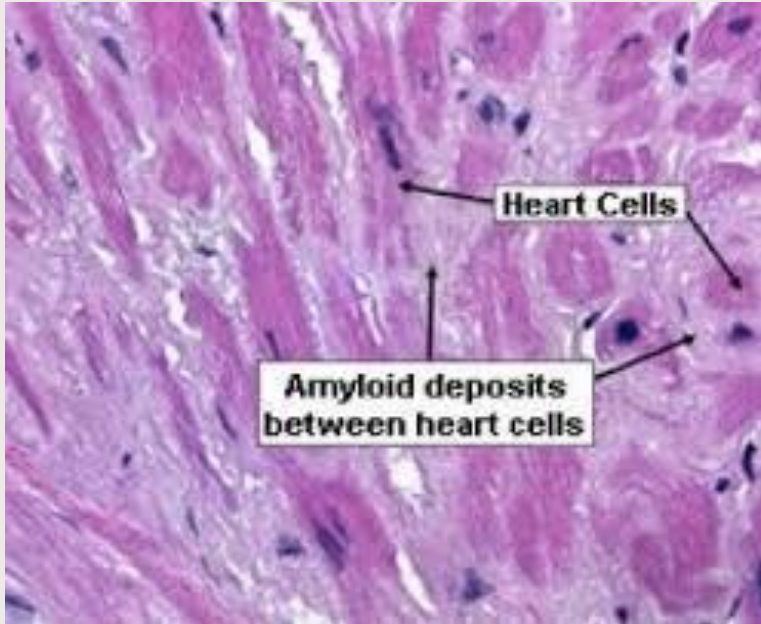
Figure adapted from Grogan M et al. 2019 ¹

hATTR, hereditary transthyretin amyloidosis; CTS, carpal tunnel syndrome

1. Grogan M et al. Poster presentation at 23rd Annual Scientific Meeting of Heart Failure Society of America (HFSA); Philadelphia PA, USA; September 13-16, 2019.

Types of ATTRv Amyloid Neuropathy Presentations



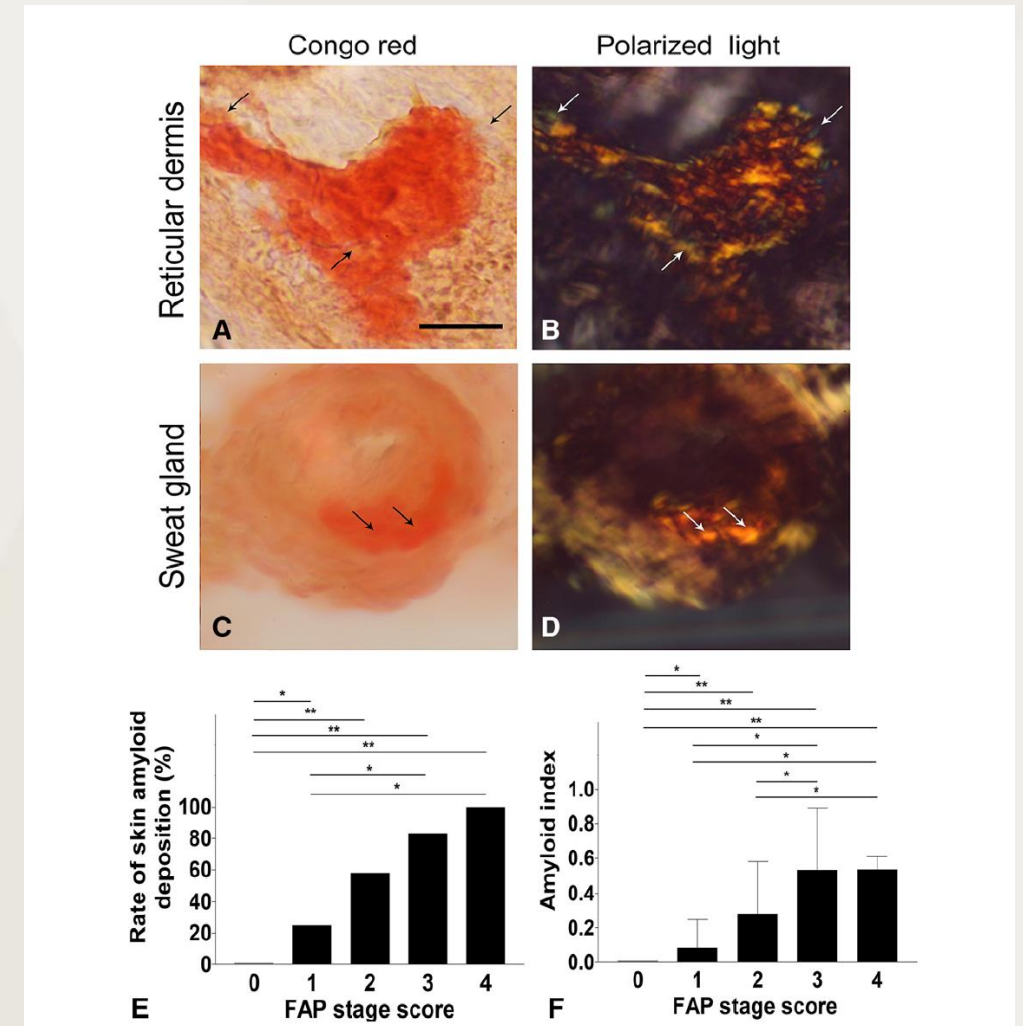


<https://www.acc.org/latest-in-cardiology/articles/2016/07/07/14/59/cardioidosis>

- Amyloid deposits with congo red staining and green birefringence can be seen in the heart, GI tract, kidneys, skin, nerves.
- In peripheral nerves often found in spinal roots and ganglia-sural nerve biopsy sensitivity <50%

Skin Biopsy in hATTR Neuropathy

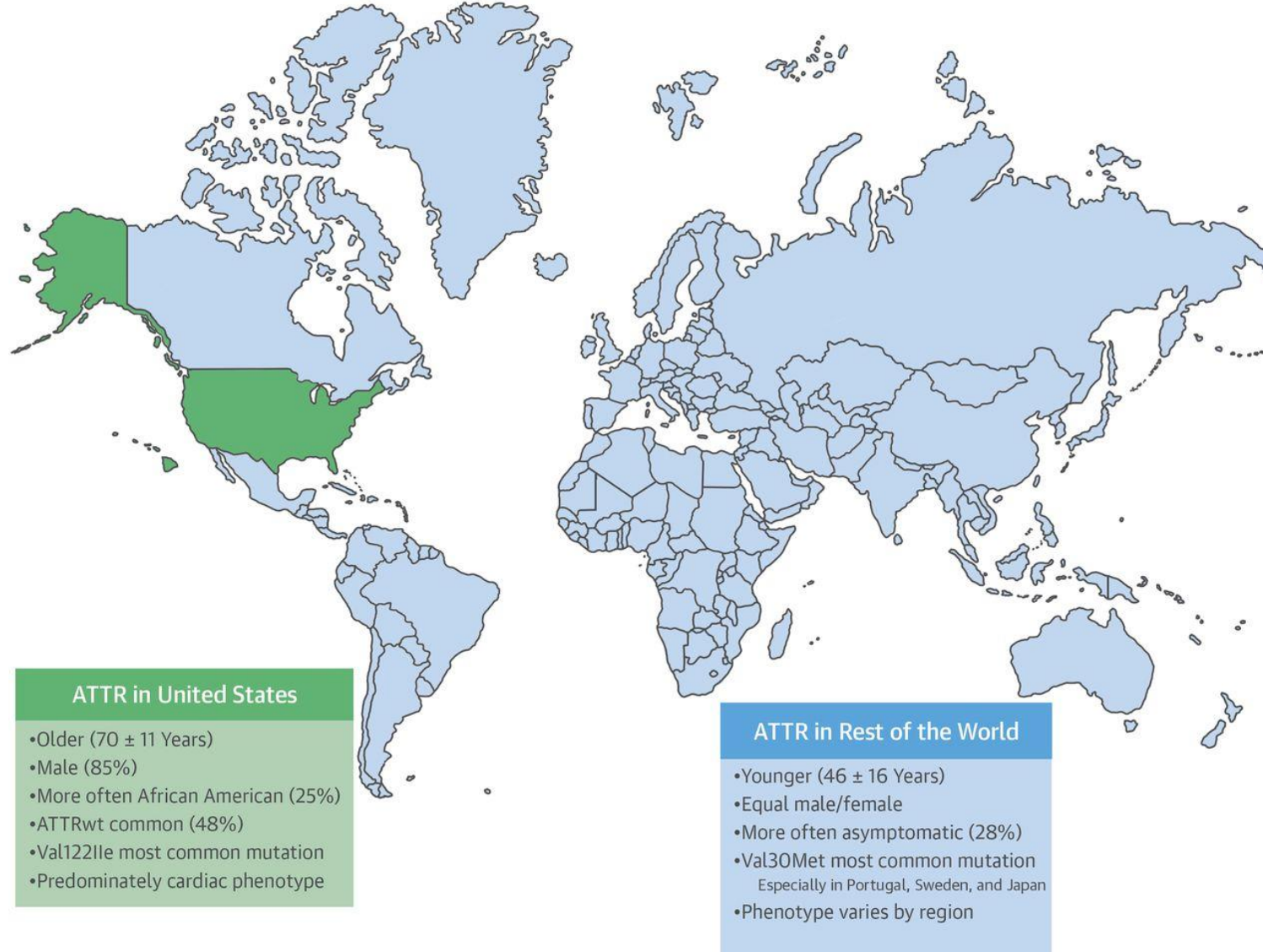
- In a study of 70 TTR patients
 - 48 with neuropathy
 - 22 genetic carriers without symptoms/signs of disease
 - Increasing amyloid deposition correlates with increasing disease severity



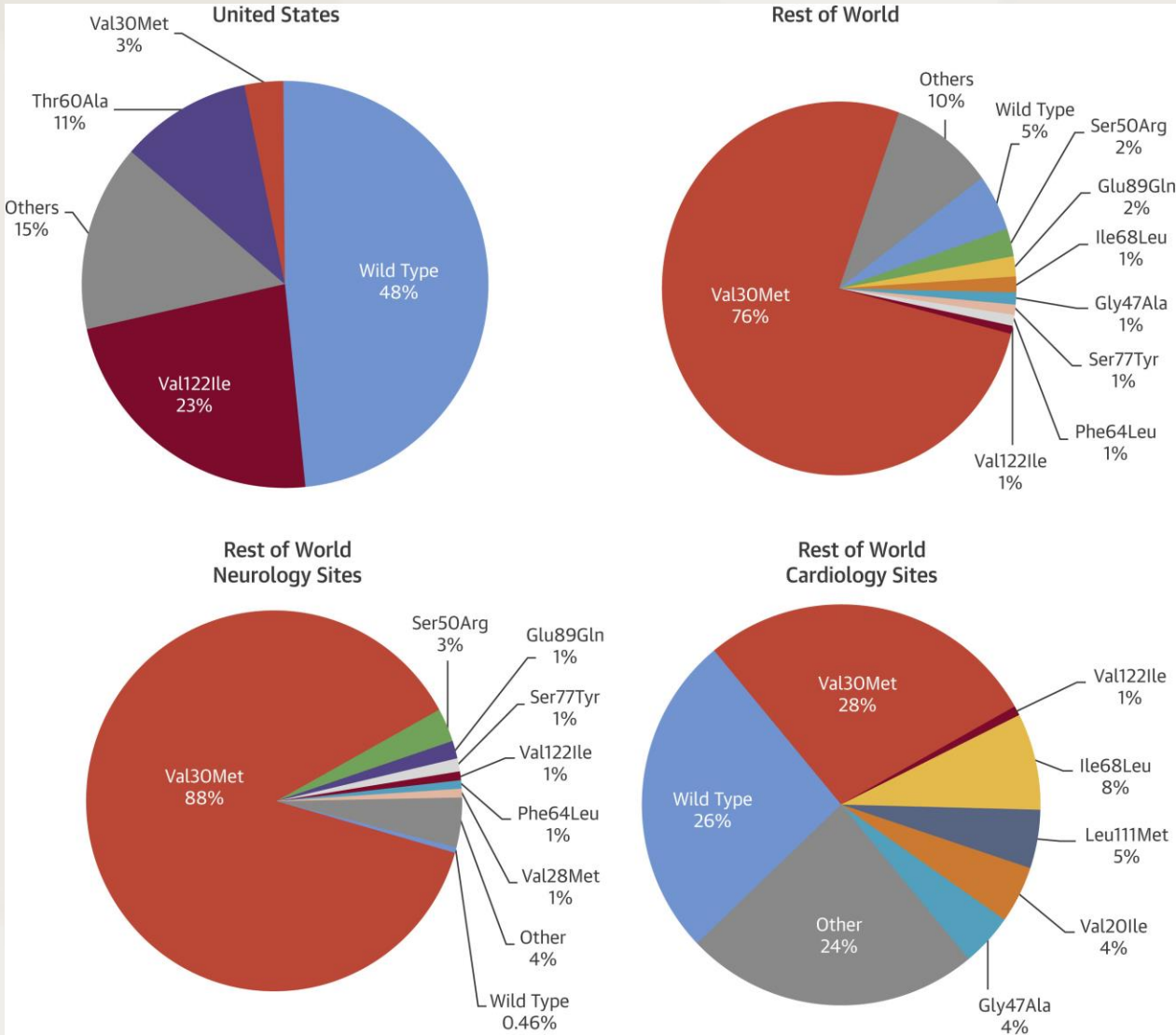
Chao CC, Hsueh HW, Kan HW, Liao CH, Jiang HH, Chiang H, Lin WM, Yeh TY, Lin YH, Cheng YY, Hsieh ST. Skin nerve pathology: Biomarkers of premanifest and manifest amyloid neuropathy. Ann Neurol. 2019

Thaos Study of hATTR Amyloidosis: US vs. the World

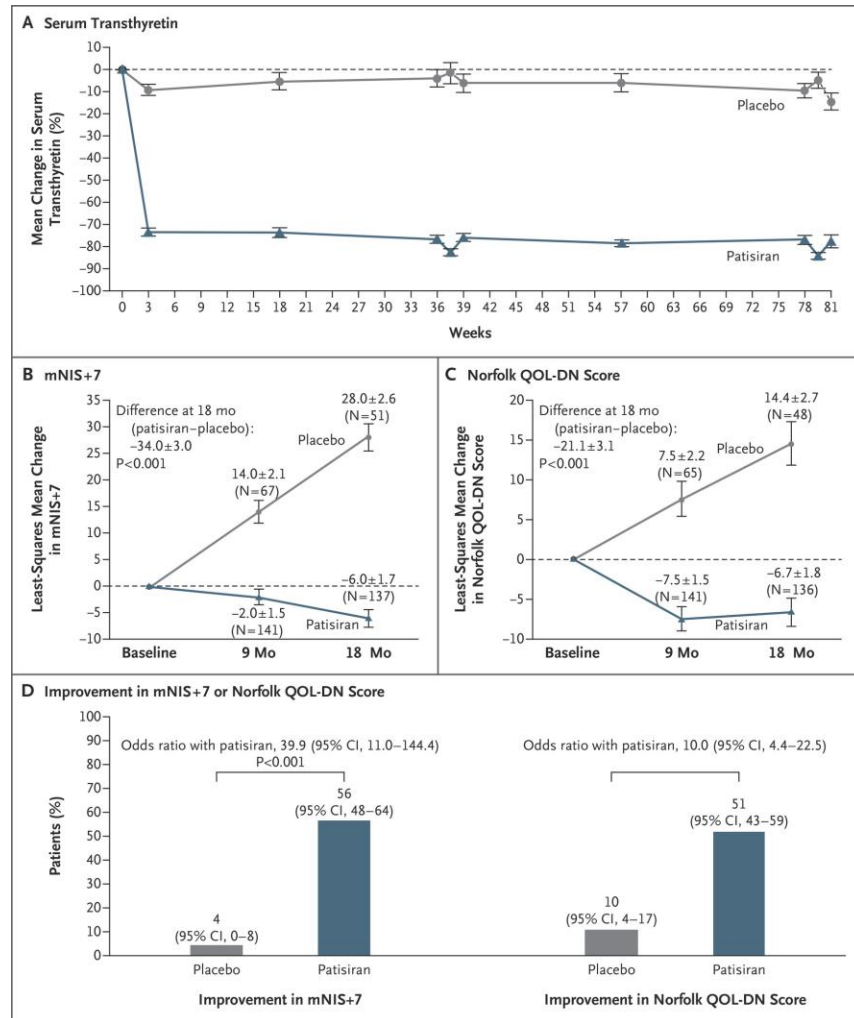
Transthyretin Amyloid Outcomes Survey (THAOS)



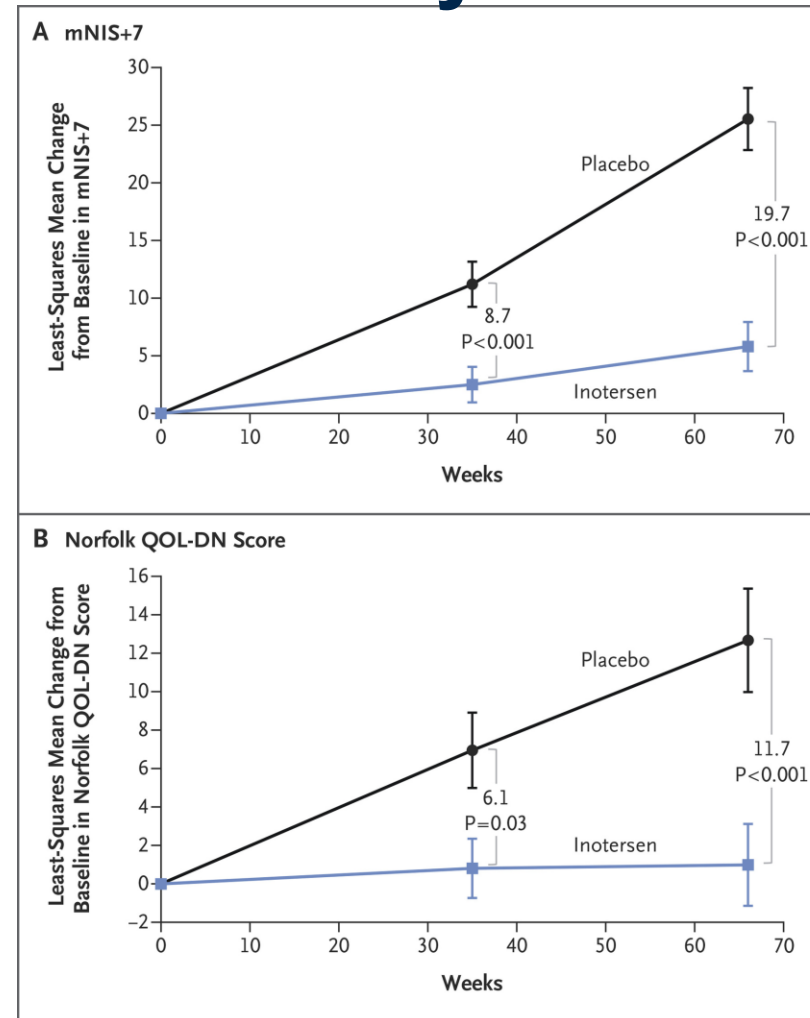
Predominant TTR Manifestations in US and Worldwide



Effects of Gene Silencers in hATTR Amyloid Neuropathy



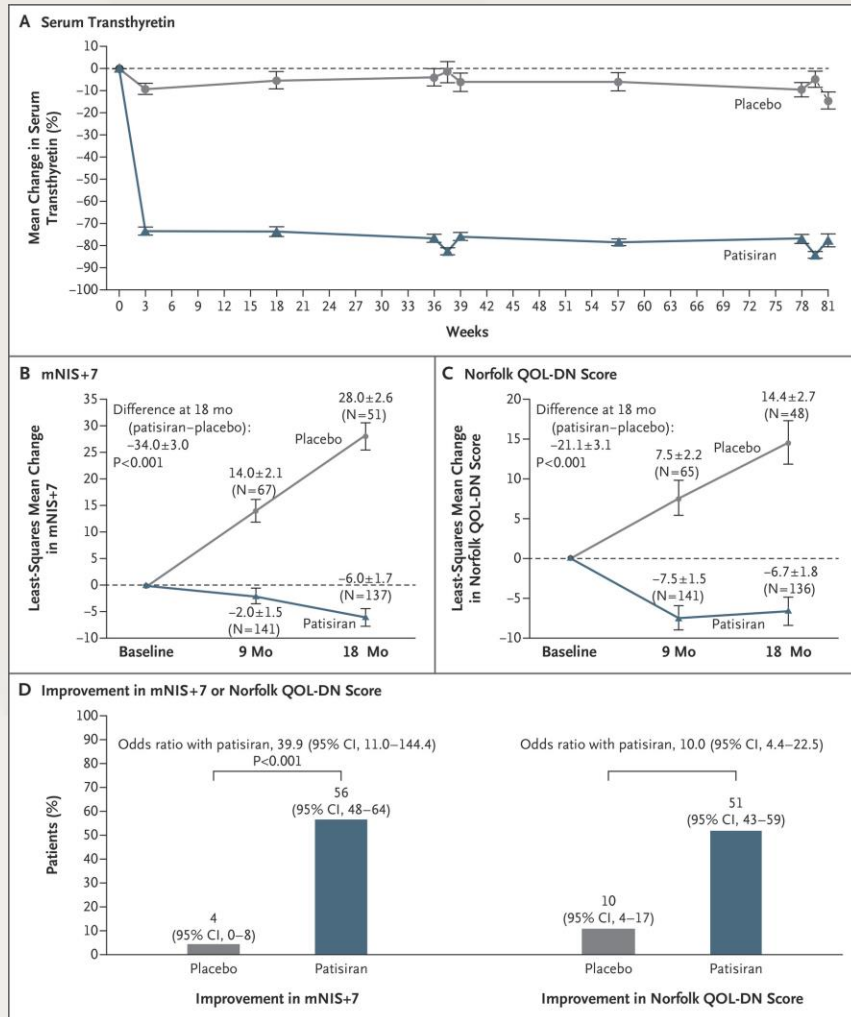
From Adams et al. NEJM 2018.



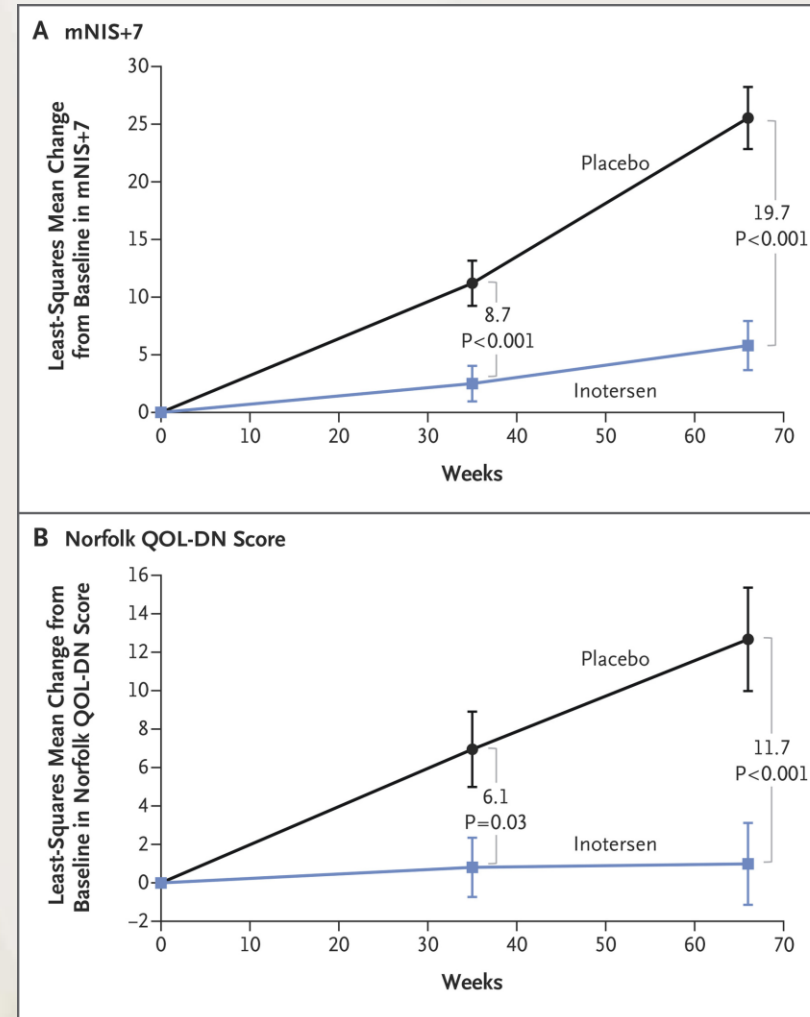
From Benson et al. NEJM 2018.

Treatment of Hereditary Transthyretin Amyloidosis

- Protein Stabilizers
 - Tafamidis
 - Acoramidis
 - Diflusinal
- Gene Silencers
 - Patisiran
 - Inotersen
 - Vutrusiran
 - Eplontersen
- CRISPR Gene Therapy

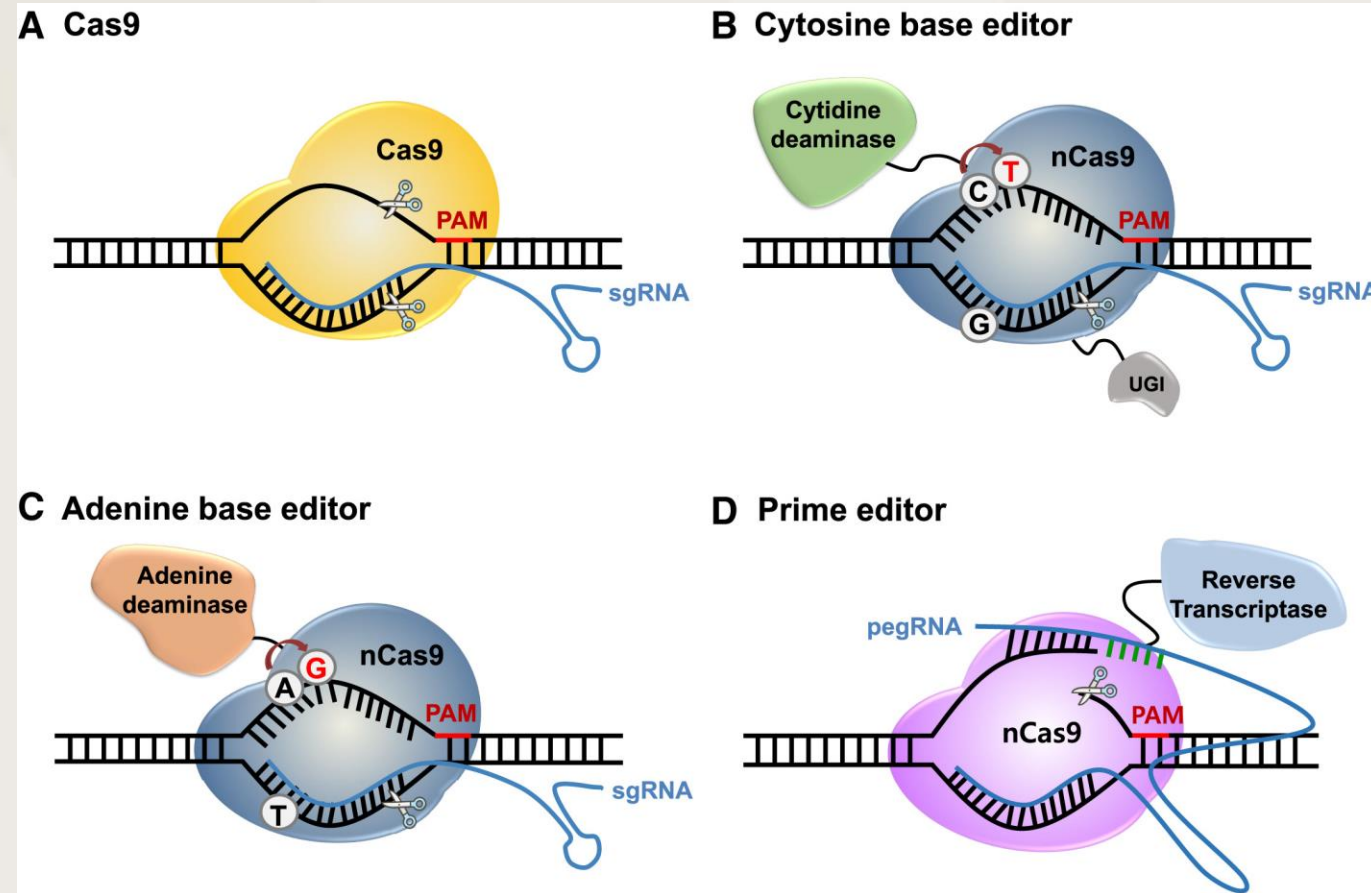


From Adams et al. NEJM 2018.



From Benson et al. NEJM 2018.

CRISPR: Gene Editing in Hereditary Transthyretin Amyloidosis



Thank you!

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A patient's perspective



Sean R.

Neuropathy patient, Speaker, and Advocate



Thanks for joining us!

ANY QUESTIONS?!



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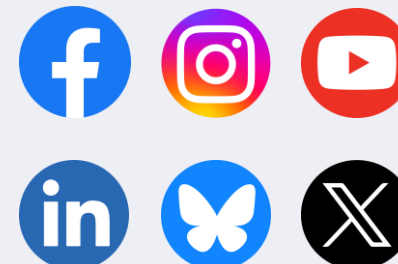


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