the FOUNDATION for PERIPHERAL NEUROPATHY®

Welcome!

FPN Webinar:

Hereditary Neuropathies & Genetic Testing

Monday, March 3, 2025

Webinar generously sponsored by: Alnylam

We will begin our presentation shortly.

the FOUNDATION for PERIPHERAL NEUROPATHY®

Today's moderator:

Lindsay Colbert
Executive Director
the Foundation *for* Peripheral Neuropathy

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Before We Begin

This presentation is being recorded. The recording link will be emailed to you so you can view it again later.

Submit your questions anytime via the Questions Box. We will try to answer them during this webinar.

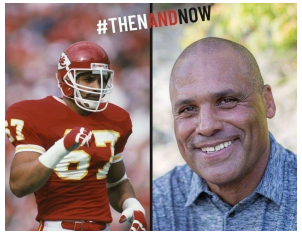
We are now pleased to offer closed captioning. Check your dashboard to activate the tool.

the FOUNDATION for PERIPHERAL NEUROPATHY®

Today's Experts:

Amanda Peltier, MD, MS
Professor of Neurology
Vanderbilt University Medical Center

Shawna Feely, MS, LGC
Certified Genetic Counselor
Seattle Children's Hospital



Art Still
Former NFL Player
hATTR Amyloidosis Patient

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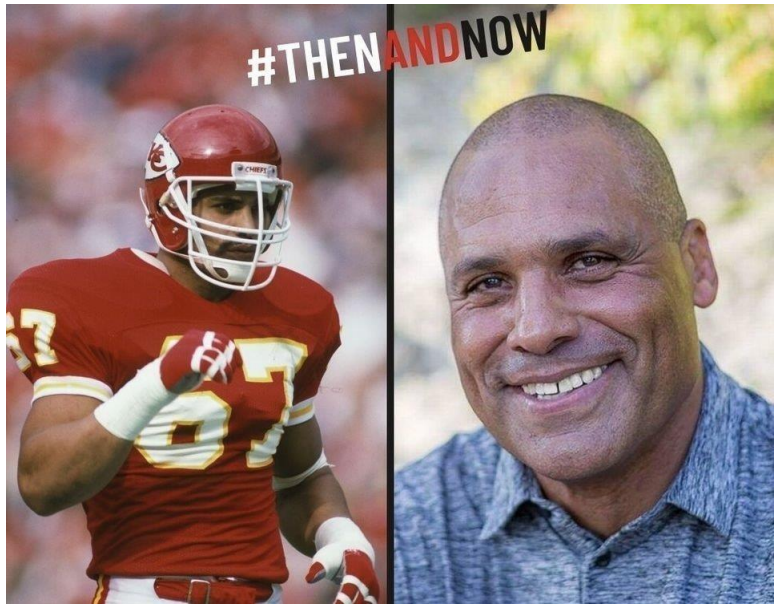
Patient Ambassador:



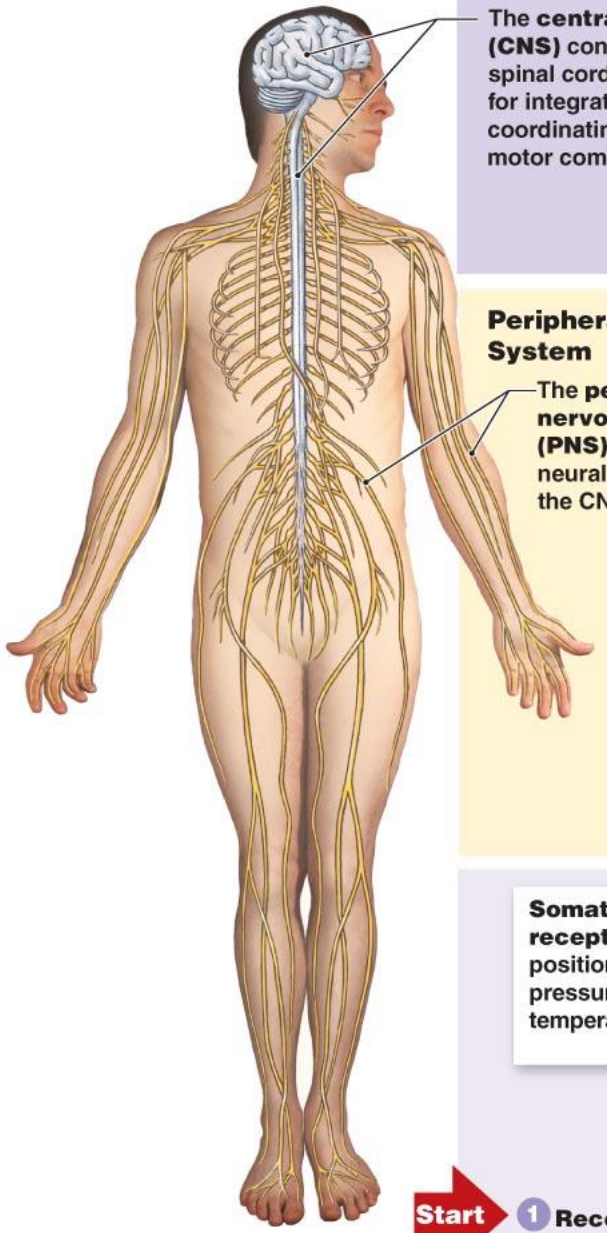
Art Still's journey with hTTR Amyloidosis

Hereditary Neuropathies, Hereditary Amyloidosis and Genetics

Amanda Peltier, MD MS
Professor of Neurology

VANDERBILT UNIVERSITY
MEDICAL CENTER

The major components and functions of the nervous system



Central Nervous System

The **central nervous system (CNS)** consists of the brain and spinal cord and is responsible for integrating, processing, and coordinating sensory data and motor commands.

3 **Information processing** includes the integration and distribution of information in the CNS.

Peripheral Nervous System

The **peripheral nervous system (PNS)** includes all the neural tissue outside the CNS.

4 The **motor division** of the PNS carries motor commands from the CNS to peripheral tissues and systems.

includes

The **somatic nervous system (SNS)** controls skeletal muscle contractions.

The **autonomic nervous system (ANS)** provides automatic regulation of smooth muscle, cardiac muscle, glands, and adipose tissue.

2 The **sensory division** of the PNS brings information to the CNS from receptors in peripheral tissues and organs.

Somatic sensory receptors provide position, touch, pressure, pain, and temperature sensations.

Special sensory receptors provide sensations of smell, taste, vision, balance, and hearing.

Visceral sensory receptors monitor internal organs.

Skeletal muscle

- Smooth muscle
- Cardiac muscle
- Glands
- Adipose tissue

Start

1 **Receptors** are sensory structures that detect changes in the internal or external environment.

5 **Effectors** are target organs whose activities change in response to neural commands.

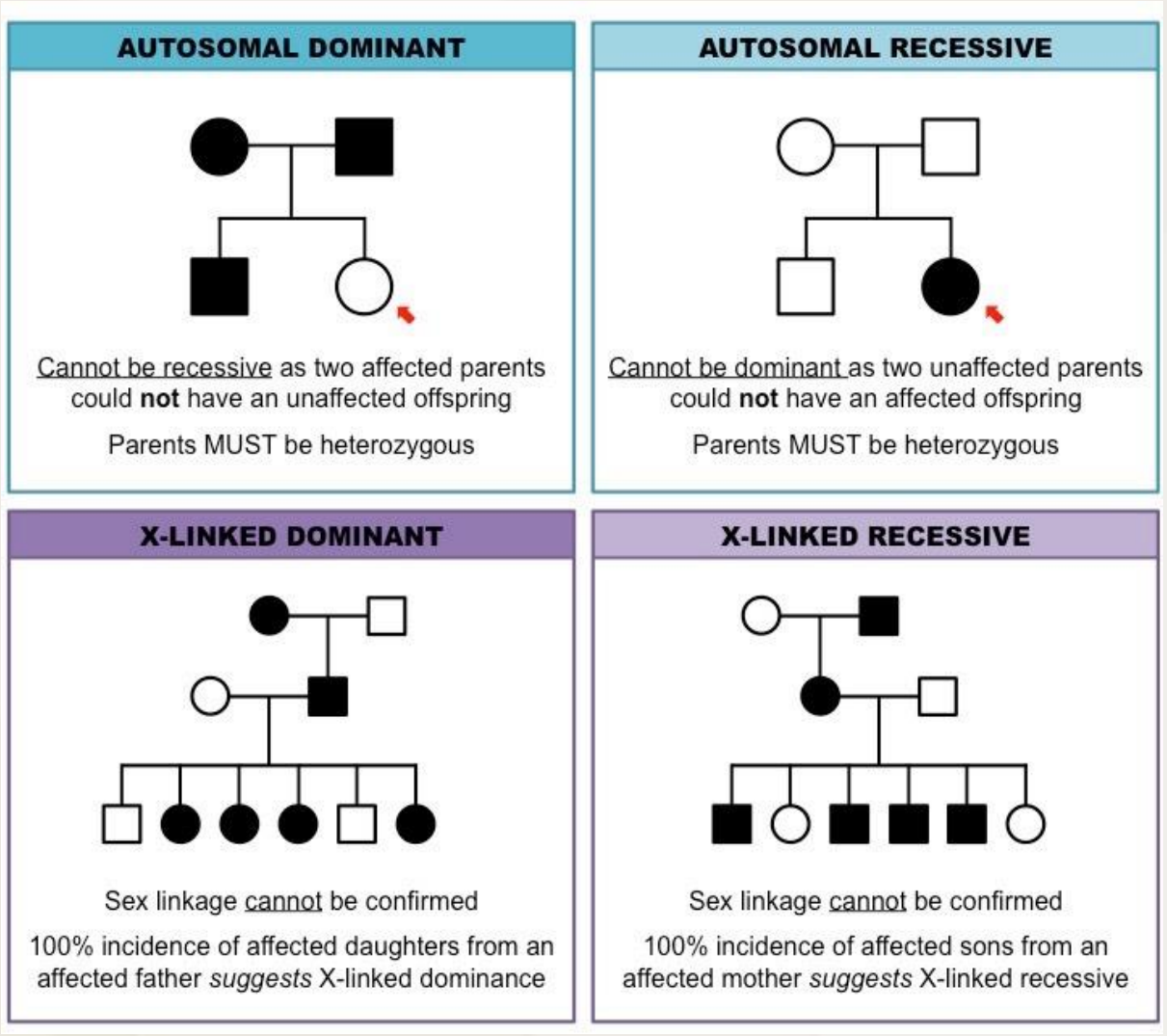
What are Inherited Neuropathies?

- 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.

Inherited Disorders

- Can be inherited as dominant,

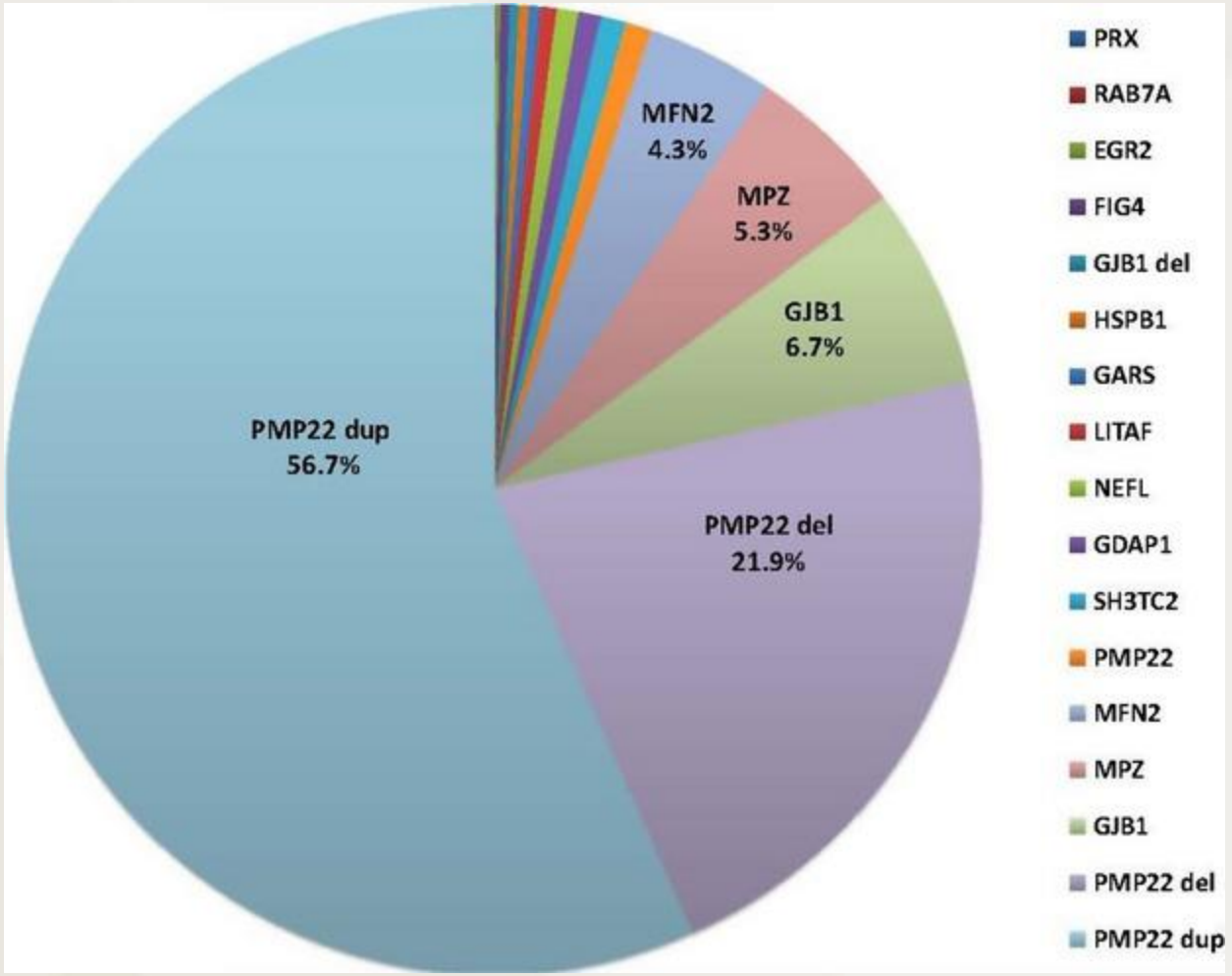
Recessive, X-linked depending on how many gene copies needed to have a disorder.



Pedigree Charts/Bioninja https://ib.bioninja.com.au/_Media/pedigree-charts_med.jpeg

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.



https://onlinelibrary.wiley.com/cms/asset/9f290b2b-64b0-4813-ade4-bf3c18506674/mgg3106-fig-0001-m.jpg

Types of Nerve Fibers and their Function

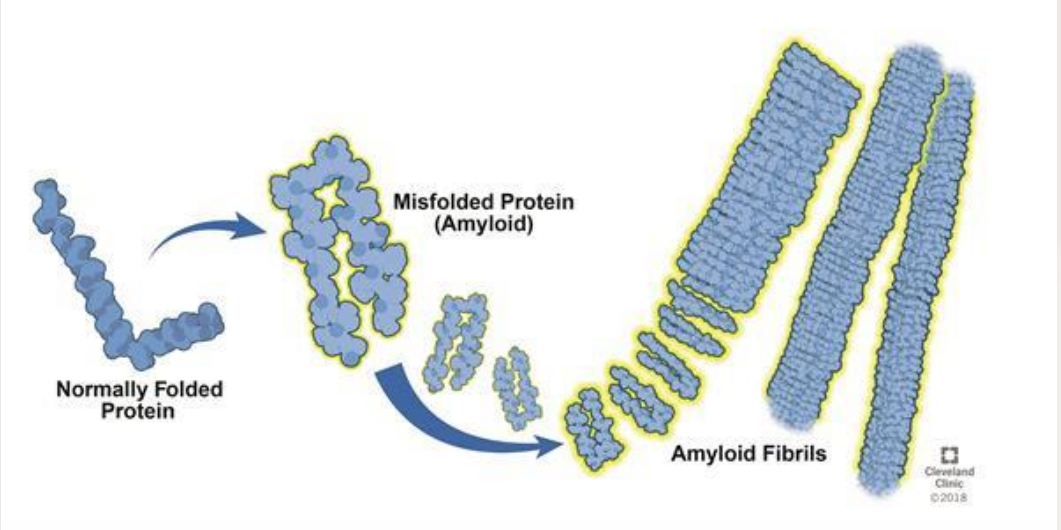
- Motor: large myelinated nerves which go to muscle. Cause weakness, atrophy (shrinkage) of muscles.
- Sensory fibers
  - Large myelinated sensory fibers convey vibration, light touch, proprioception (ability to know where your limb is in space)
  - Small non-myelinated sensory fibers found in the skin 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.

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

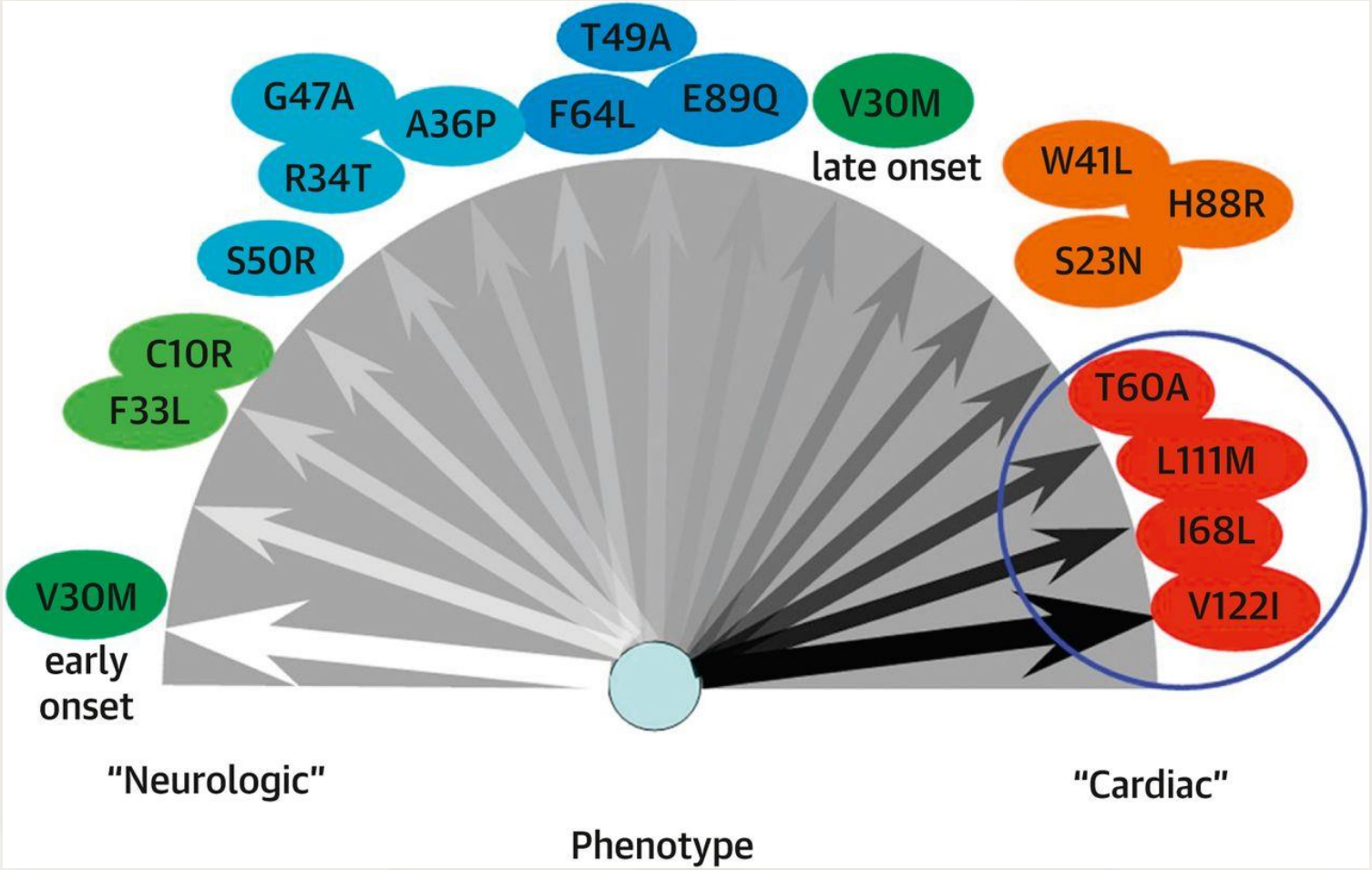
Amyloid

- Homgenous, 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



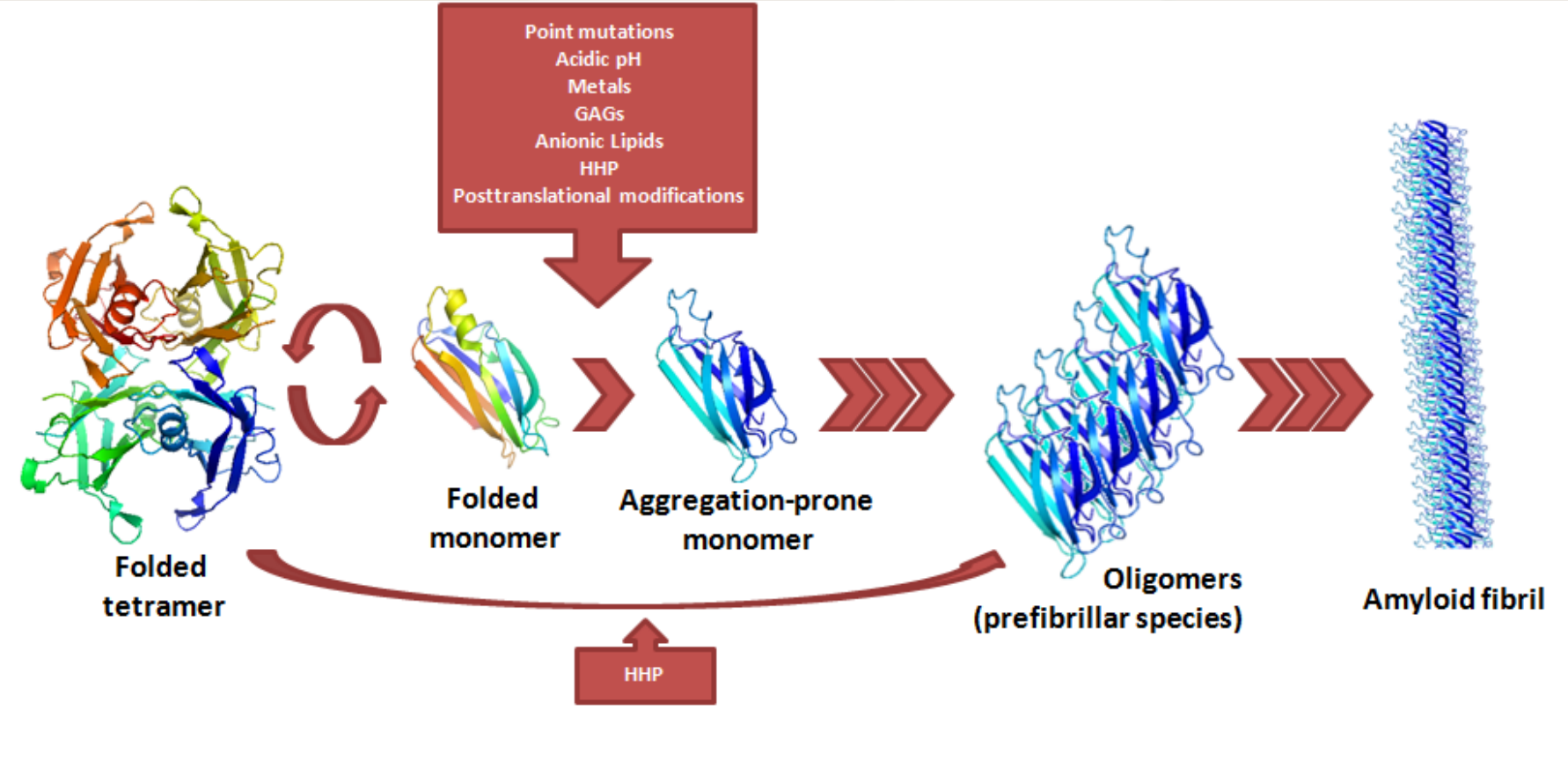
https://my.clevelandclinic.org/health/diseases/15718-amyloidosis-al-amyloid-light-chain

Familial Amyloidosis

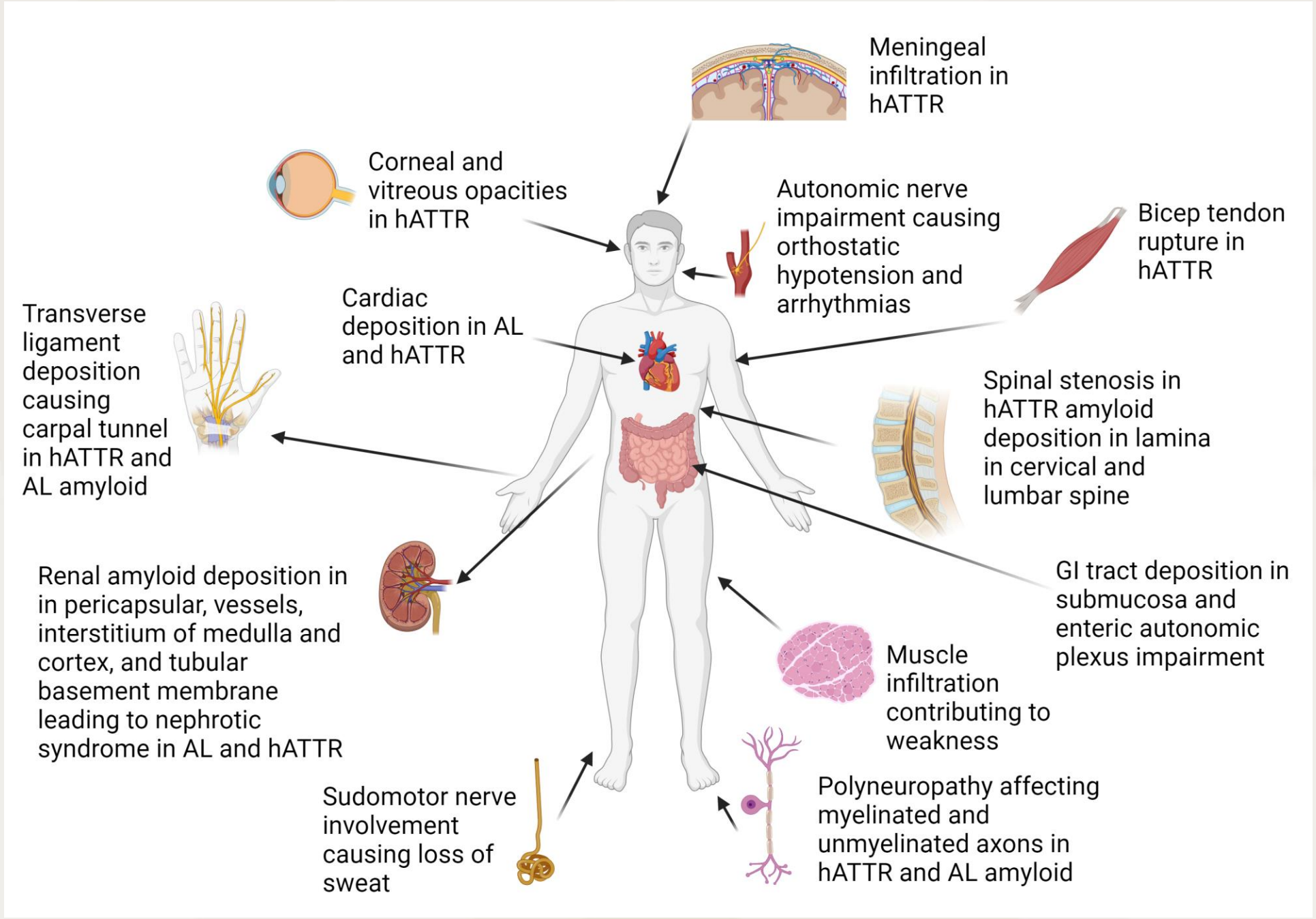


From: Semigran MJ. JACC 2016.

Transthyretin



Azevedo et al. 2013.


Meningeal infiltration in hATTR
Corneal and vitreous opacities in hATTR
Autonomic nerve impairment causing orthostatic hypotension and arrhythmias
Bicep tendon rupture in hATTR
Transverse ligament deposition causing carpal tunnel in hATTR and AL amyloid
Cardiac deposition in AL and hATTR
Spinal stenosis in hATTR amyloid deposition in lamina in cervical and lumbar spine
Renal amyloid deposition in in pericapsular, vessels, interstitium of medulla and cortex, and tubular basement membrane leading to nephrotic syndrome in AL and hATTR
GI tract deposition in submucosa and enteric autonomic plexus impairment
Muscle infiltration contributing to weakness
Sudomotor nerve involvement causing loss of sweat
Polyneuropathy affecting myelinated and unmyelinated axons in hATTR and AL amyloid

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

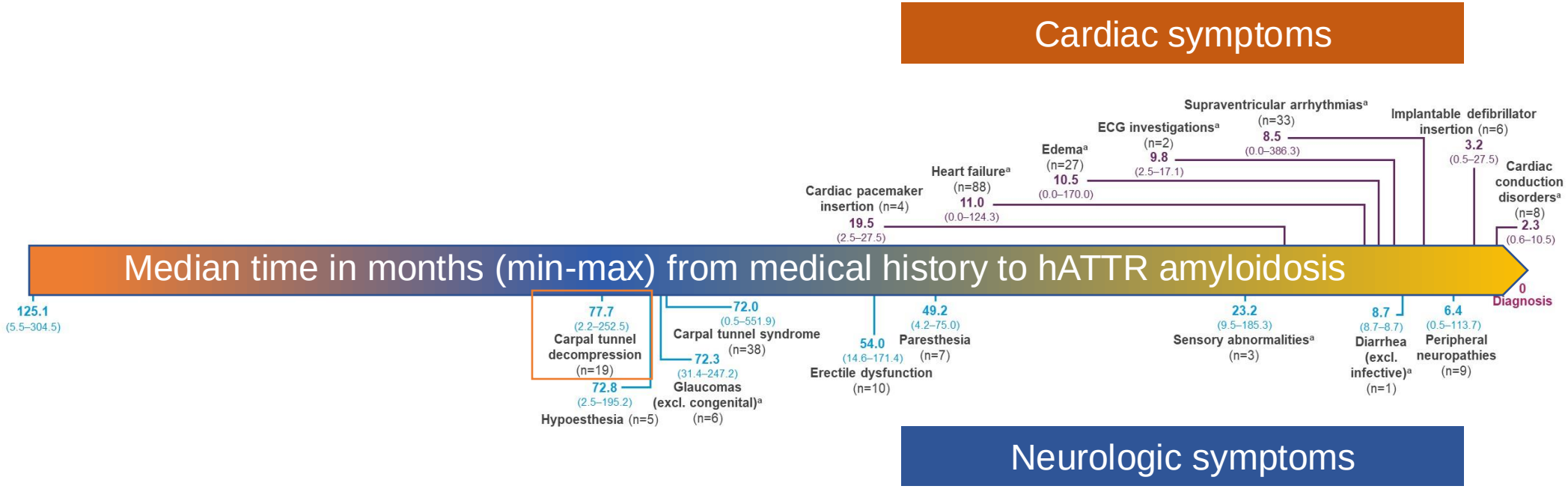
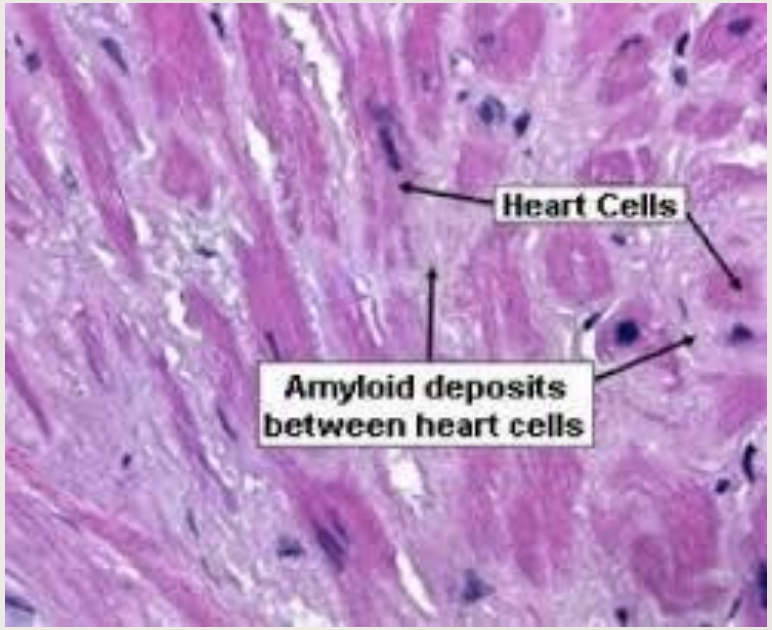


Figure adapted from Grogan M et al. 2019 [1]

hATTR, hereditary transthyretin amyloidosis; CTS, carpal tunnel syndrome

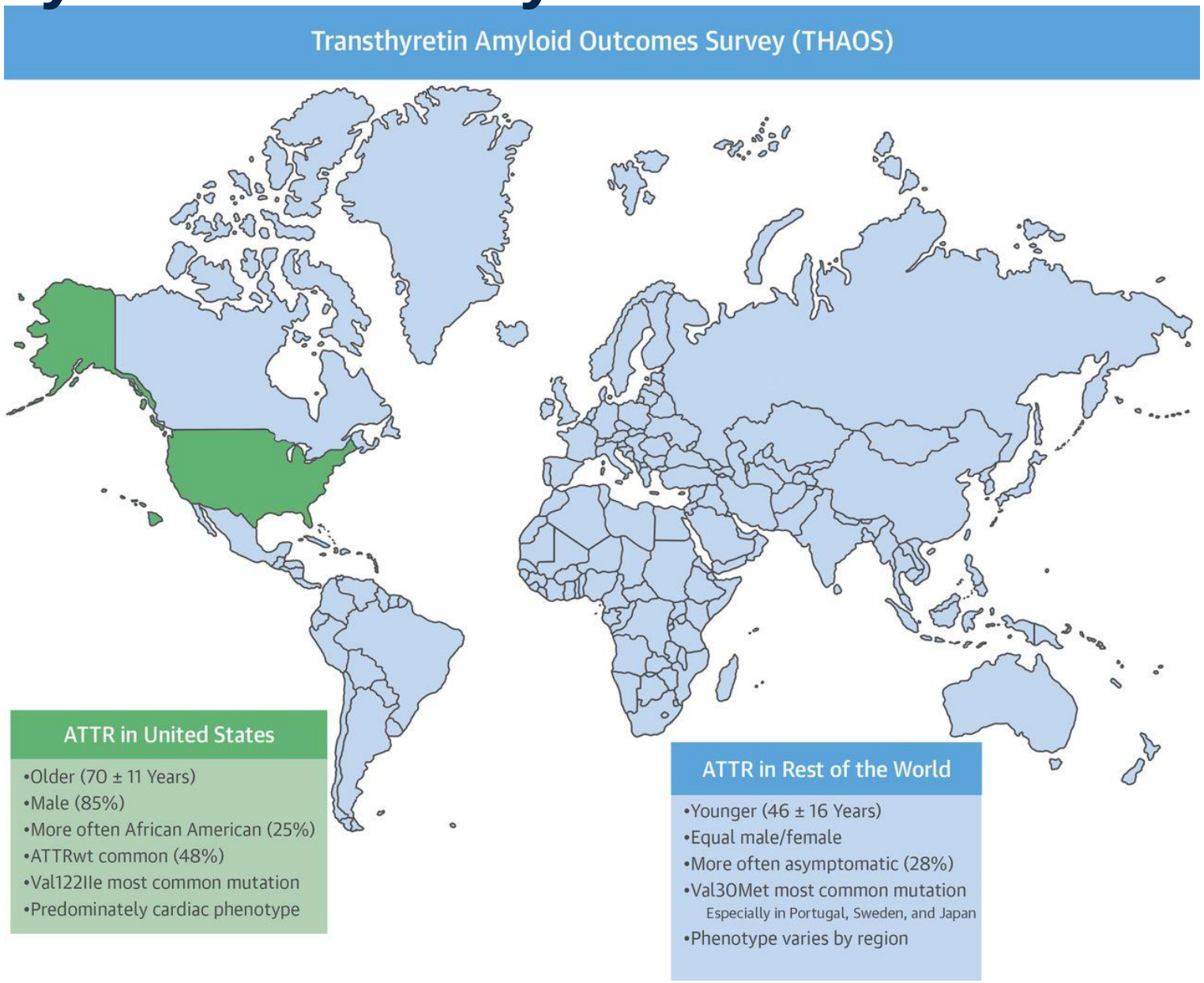
1. Grogan M et al. Poster presentation at 23rd Annual Scientific Meeting of Heart Failure Society of America (HFSA); Philadelphia PA, USA; September 13–16, 2019.



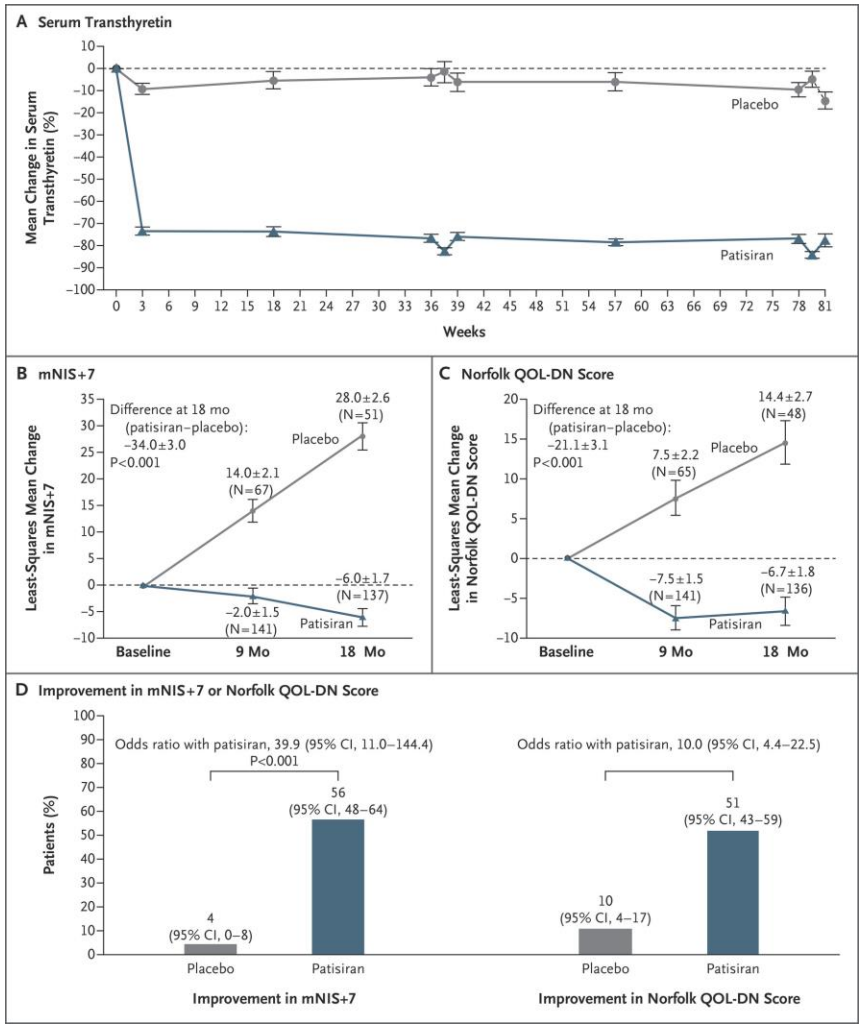
https://www.acc.org/latest-in-cardiology/articles/2016/07/07/14/59/cardiac-amyloidosis

- 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%

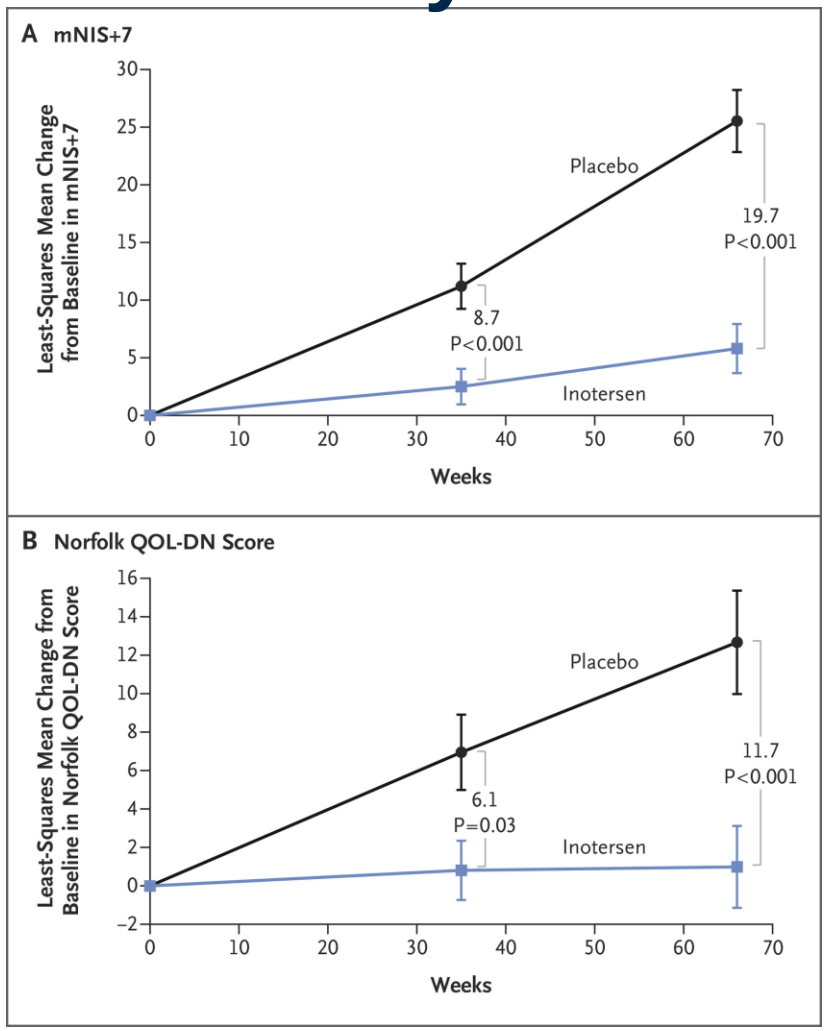
Thaos Study of hATTR Amyloidosis: US vs. the World



Effects of Gene Silencers in hATTR Amyloid Neuropathy



From Adams et al. NEJM 2018.



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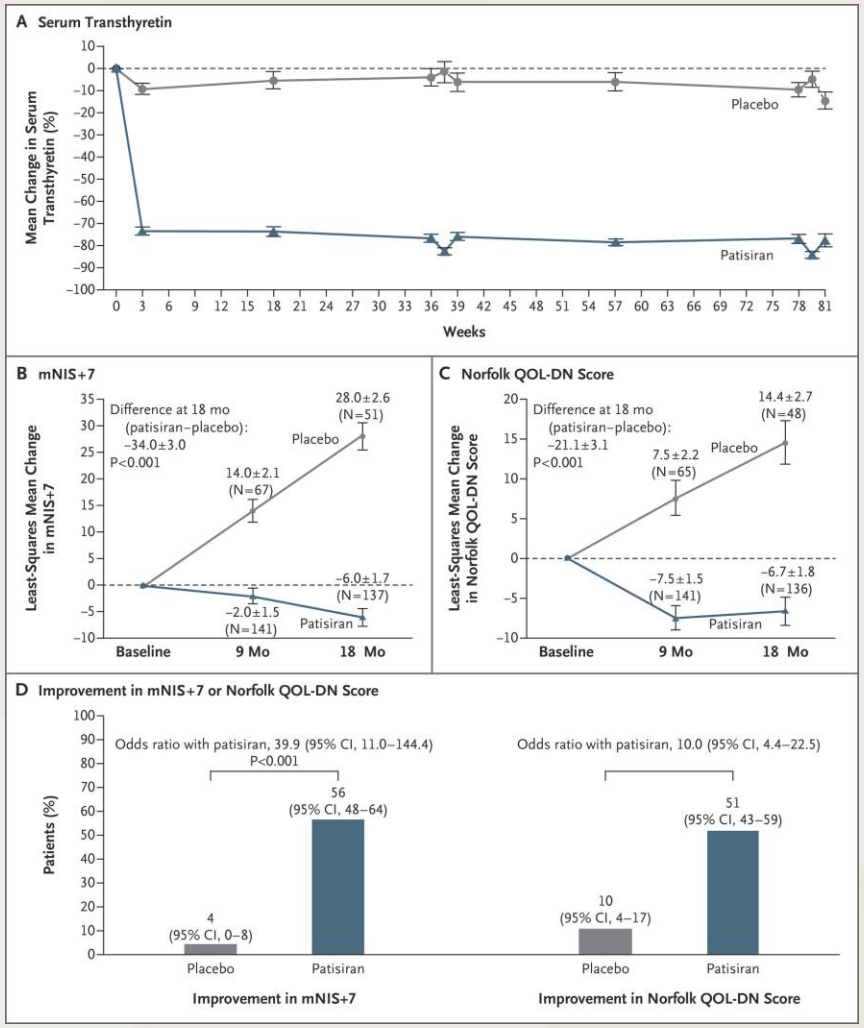

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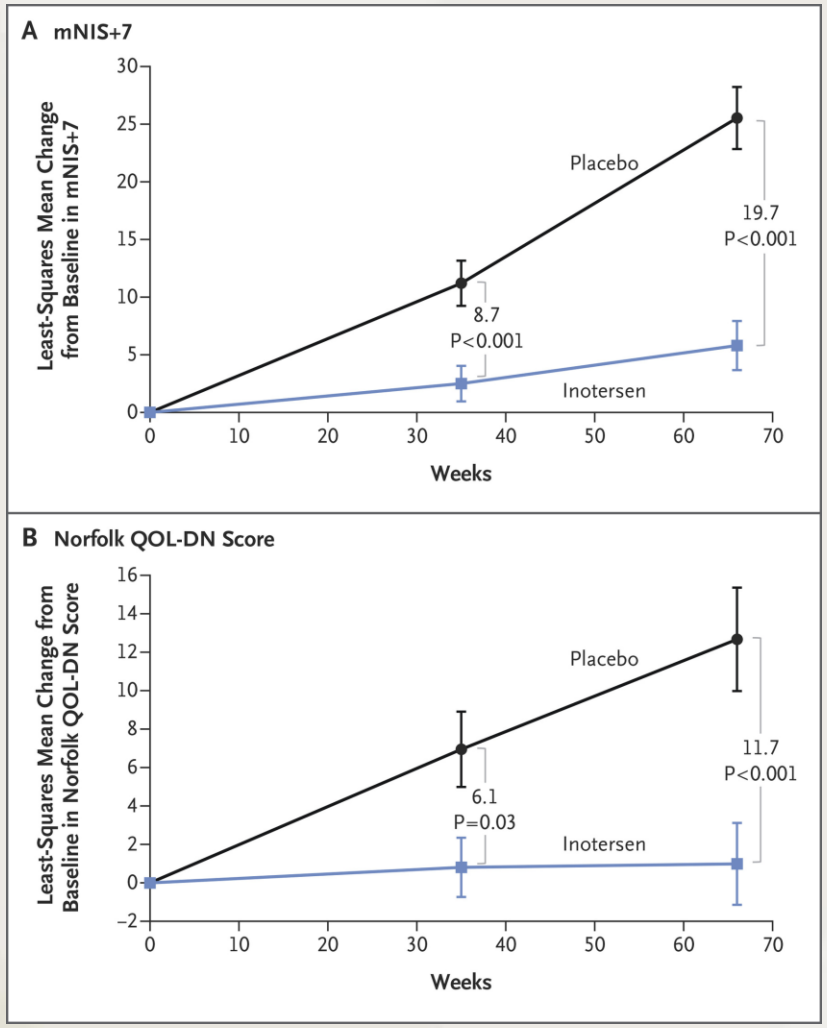

From Benson et al. NEJM 2018.

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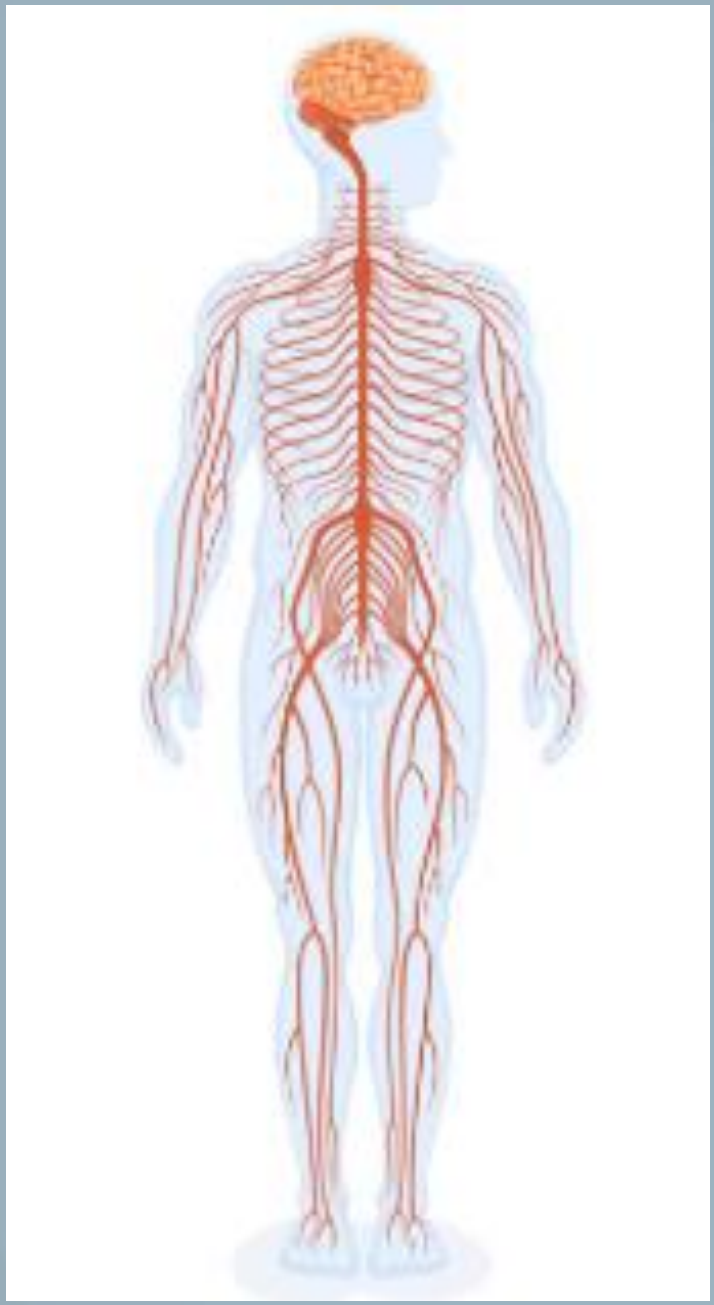
Genetic Testing & Genetic Counseling for People with Peripheral Neuropathy

Shawna Feely, MS, LGC

Certified Genetic Counselor



Shawna Feely, MS, LGC

No Disclaimers or Conflicts of Interest

General subtypes of Hereditary Neuropathies

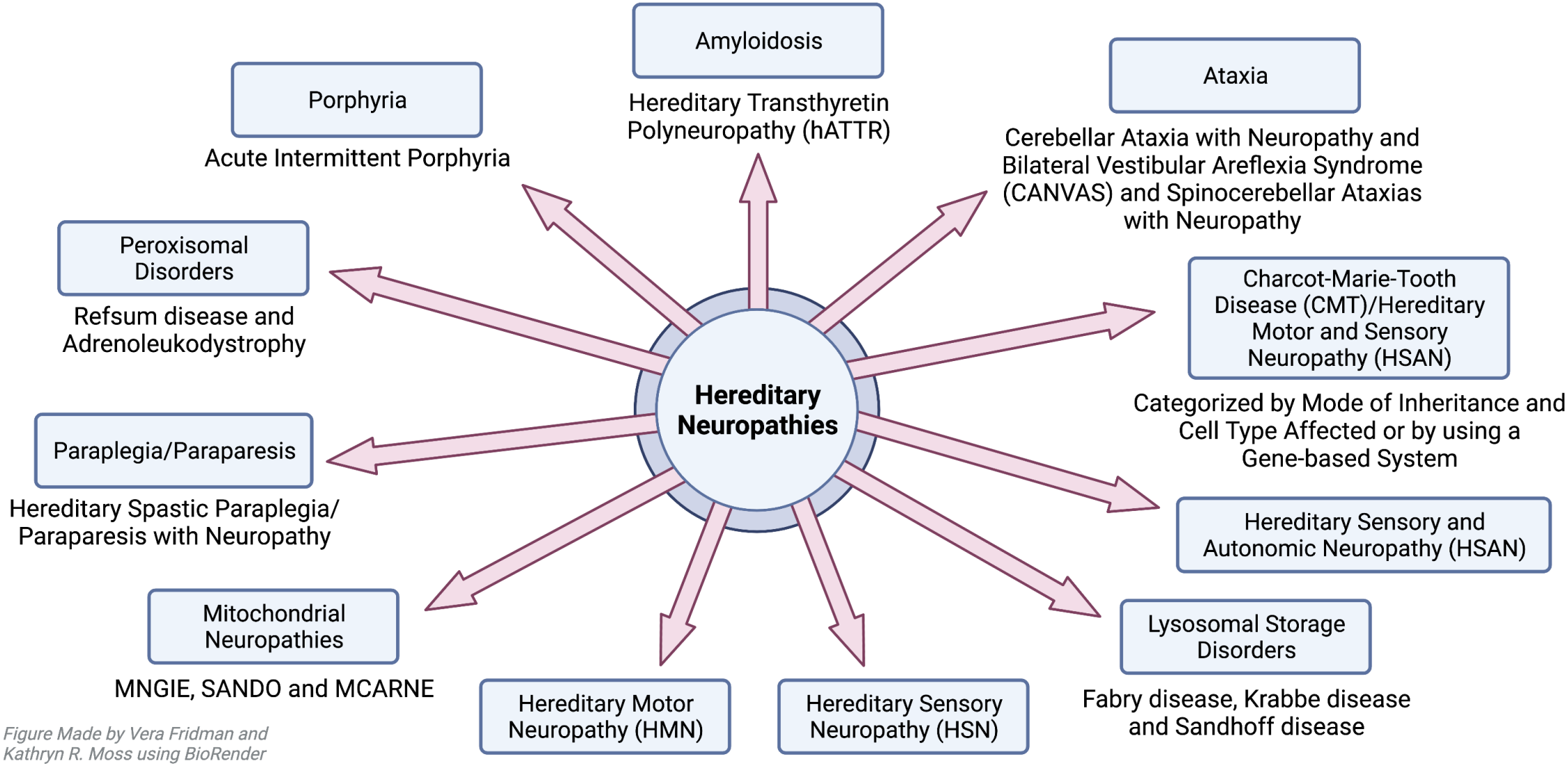
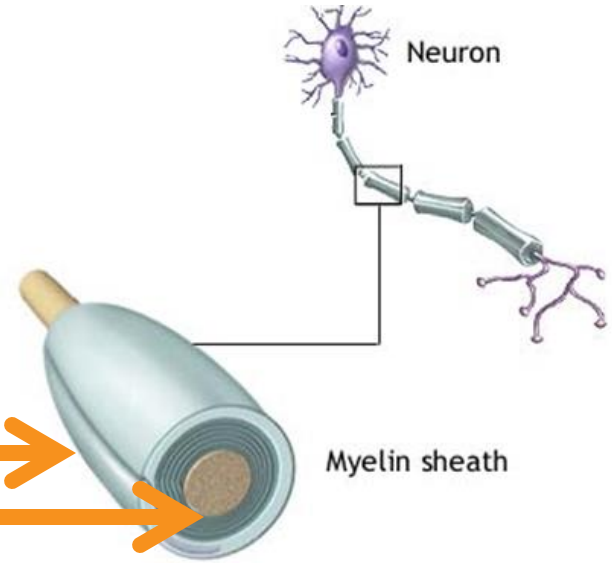


Figure Made by Vera Fridman and Kathryn R. Moss using BioRender

What is Peripheral Neuropathy?

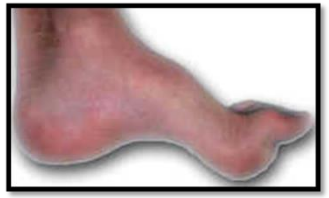
- Neuropathies: Primary diseases of nerve

- Peripheral Nerves
  - Demyelinating Neuropathy
  - Axonal Neuropathy

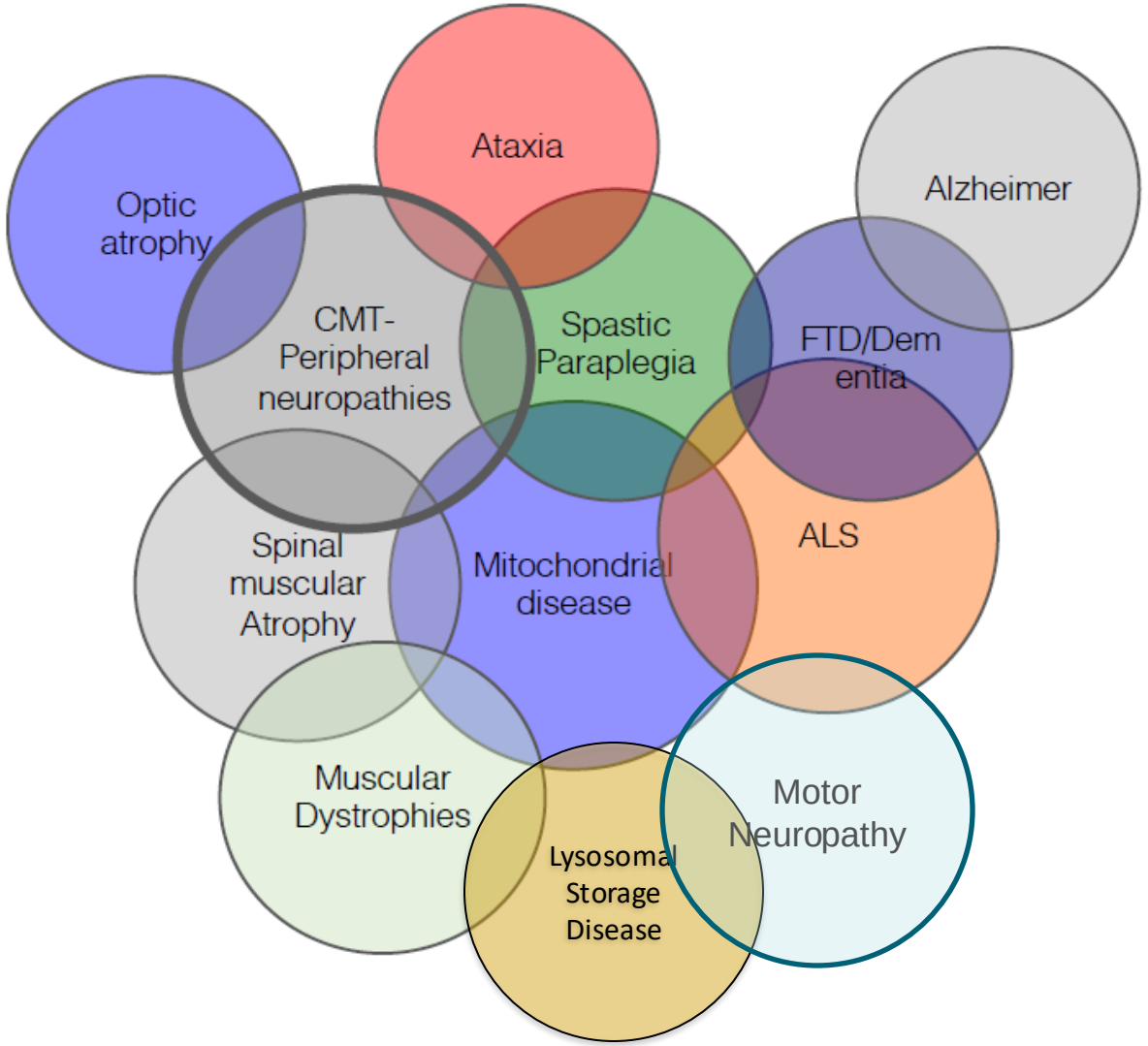


- Clinical Hallmarks
  - Distal muscle weakness and atrophy
  - Loss of proprioception and sensation
  - Classical steppage gait, pes plannus or pes cavus
  - Fatigue and depression can often accompany disease

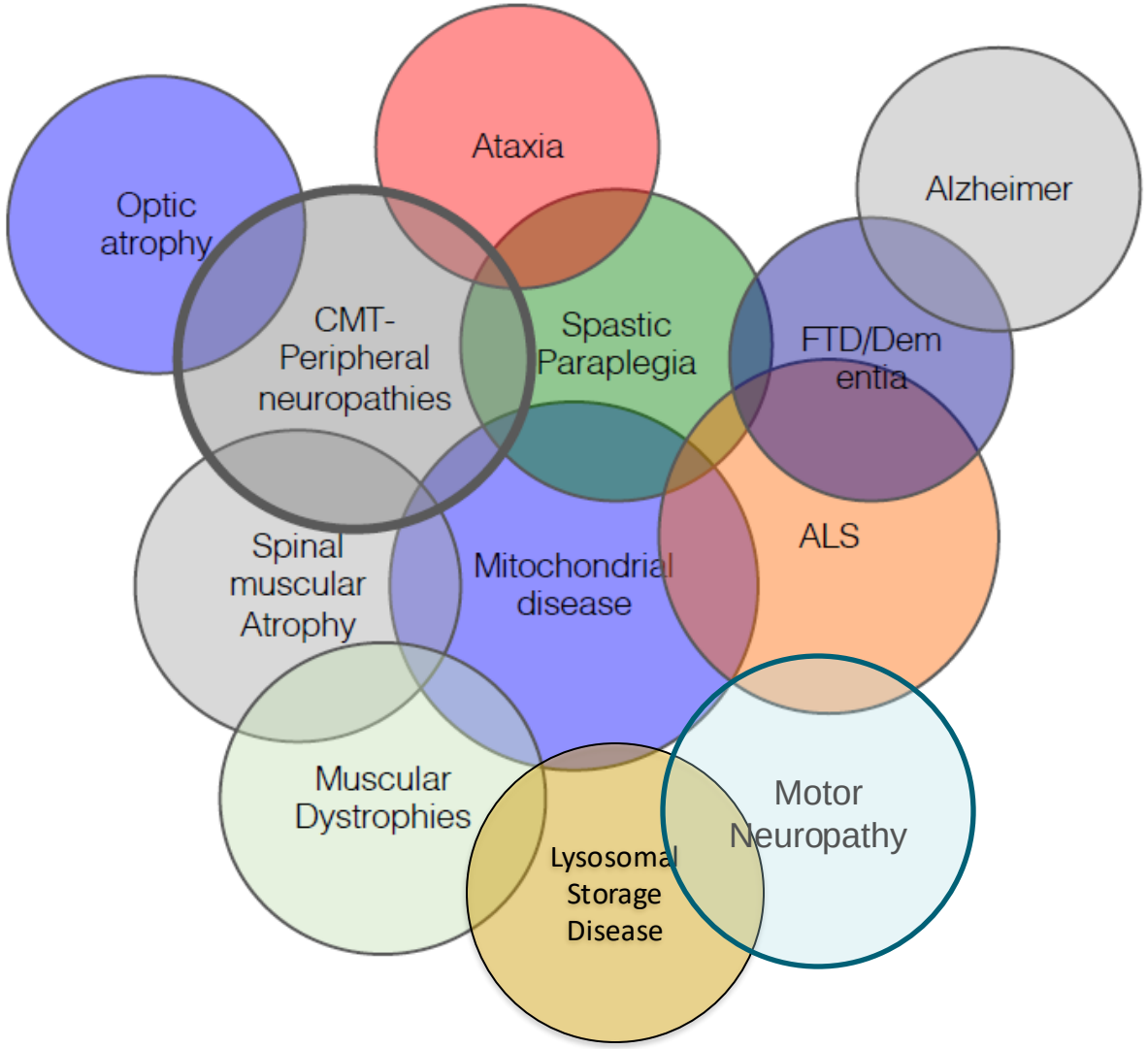
- Genetic heterogeneity
  - Over 100 known genetic causes

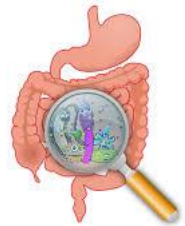


Overlap between neurologic disease

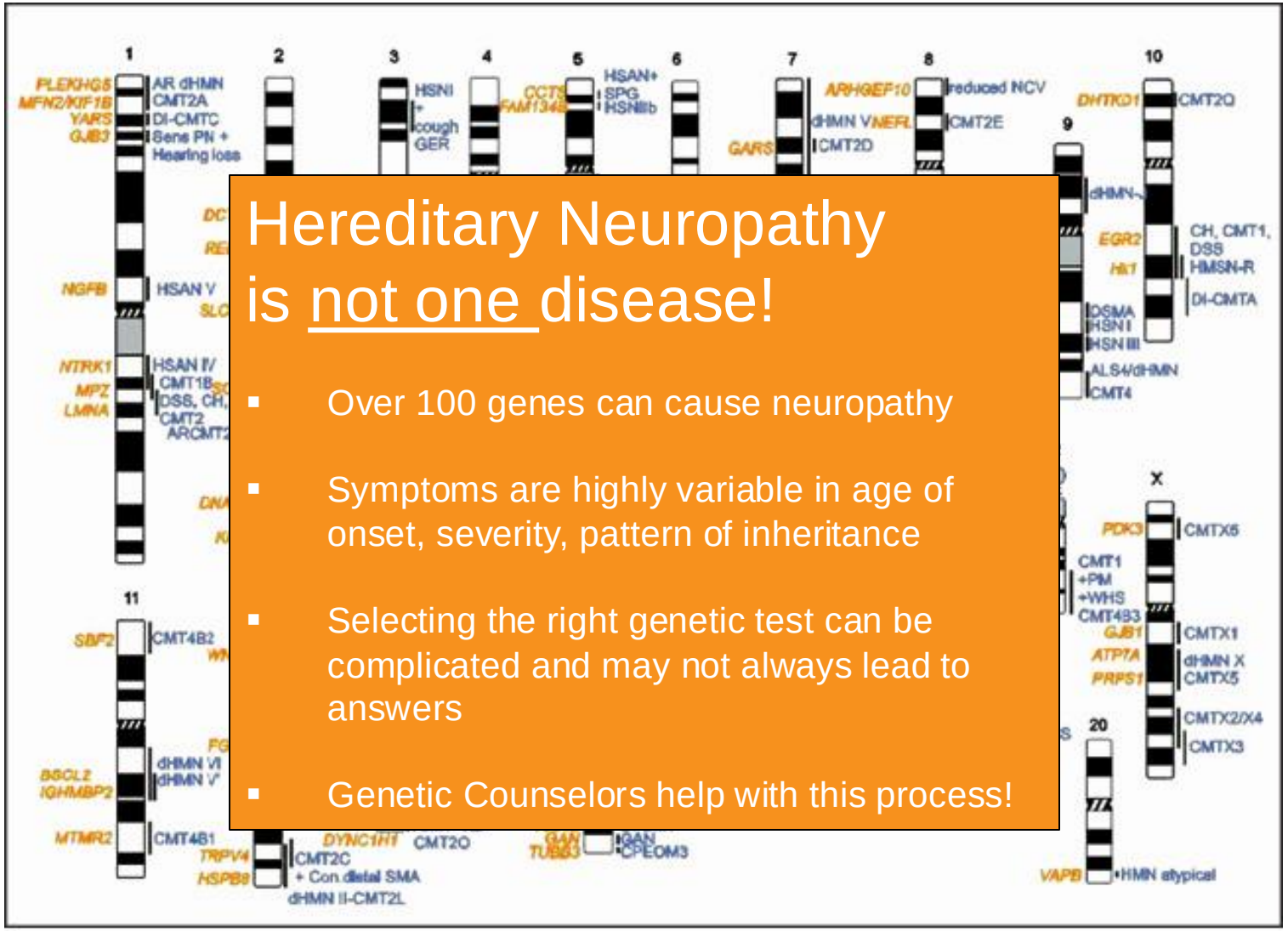


Overlap between neurologic disease





Vision



Hereditary Neuropathy is not one disease!

- Over 100 genes can cause neuropathy
- Symptoms are highly variable in age of onset, severity, pattern of inheritance
- Selecting the right genetic test can be complicated and may not always lead to answers
- Genetic Counselors help with this process!

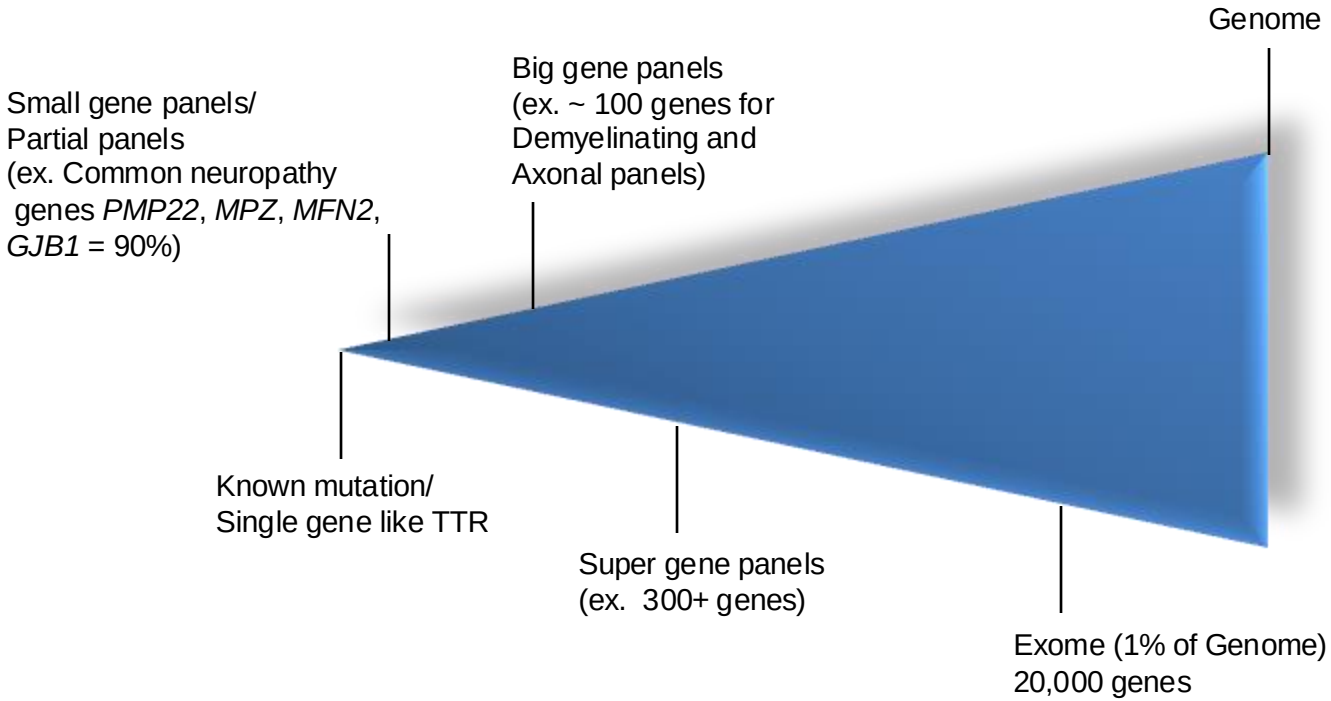
Figure-2: Genes and loci for Charcot-Marie-Tooth (CMT) and related inheritedperipheral neuropathies.

Perveen et al 2015, JPMA

Genetic Testing: Types of Testing

- Single Gene
- Multigene: Next Generation Sequencing panels or CGH
- Exome Sequencing
- Genome Sequencing
- Non-Genetic Genetic Testing

Types Genetic Testing



Labs that do peripheral neuropathy testing

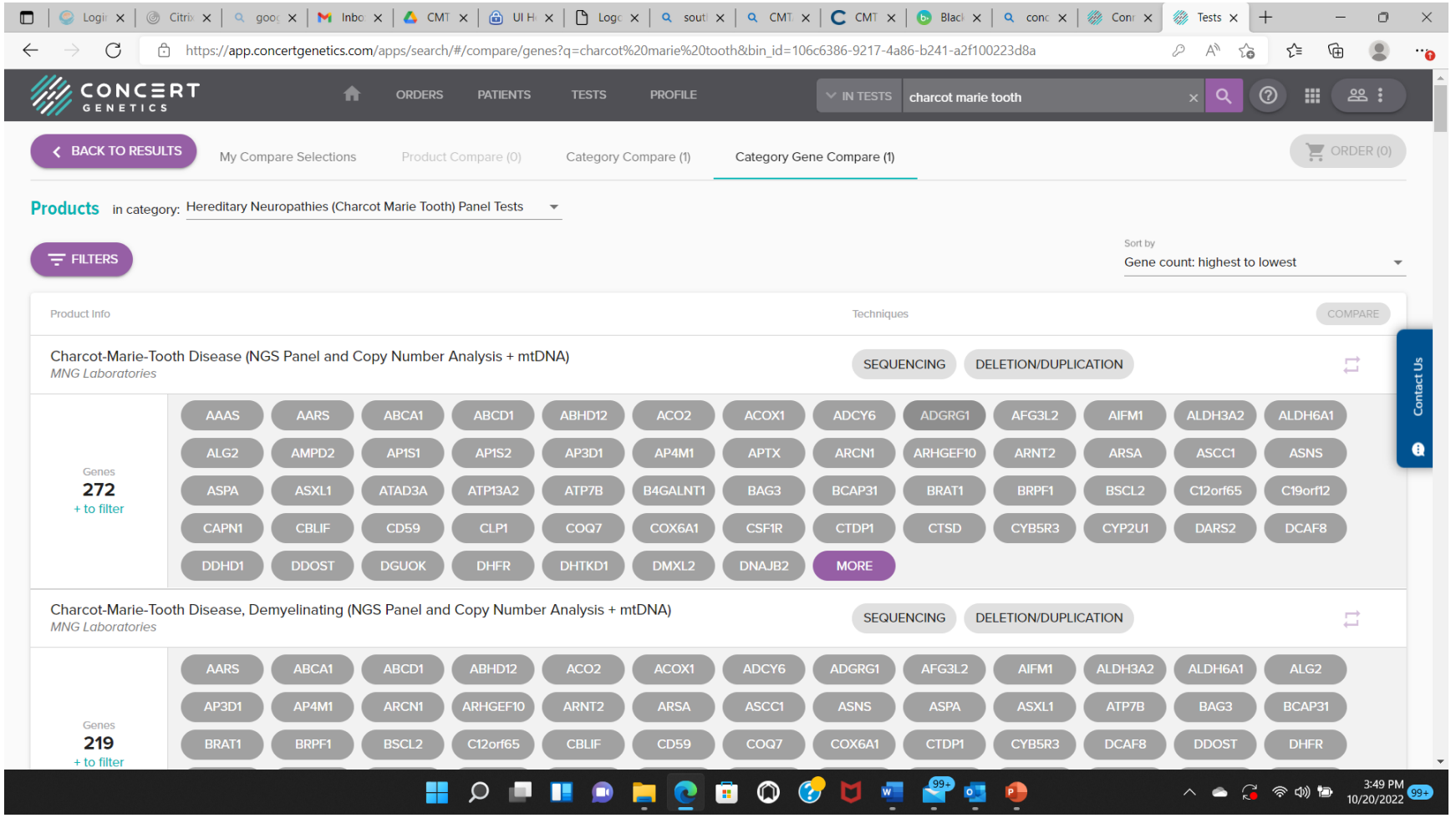
Not all genetic testing is the same!

- Labs differ in cost, what insurance is accepted for coverage, genes that are included in their testing, and the number of genes that are tested
- Panels change from year to year for all of these things
- Genetic Counselors help people living with genetic disease to navigate this process!

Genetic Testing Panels

- Not all panels are the same
  - Vary in cost, number of genes, specific genes incl.

Genetic Testing Panels



[Connecting the Genetic Health Information Network | Concert Genetics : Concert Genetics]
www.concertgenetics.com

Genetic Testing Panels

- Not all panels are the same
  - Vary in cost, number of genes, specific genes incl.
- Existence on a panel does not mean that gene has a definitive role in the disease

Gene Clinical Validity Classification

Definitive	Repeatedly demonstrated in research and clinical settings
Strong	Excess of pathogenic variants in cases vs. controls & supporting experimental data
Moderate	≥3 unrelated probands with pathogenic variants & supporting experimental data
Limited	<3 proband with pathogenic variants
No Evidence Reported	Candidate genes based on animal models or disease pathways, but no pathogenic variants reported
Disputed	Significant evidence refuting a role for gene in this disease
Refuted	Evidence refuting the role of the gene significantly outweighs any supportive evidence

ClinGen Clinical Genome Resource

https://www.clinicalgenome.org/working-groups/gene-curation/projects-initiatives/clinical-validity-classifications/

Genetic Testing Panels

- Not all panels are the same
  - Vary in cost, number of genes, specific genes incl.
- Existence on a panel does not mean that gene has a definitive role in the disease
- As number of genes tested increase, so does the possibility of Variants of Uncertain Significance (VUS)

Genetic Testing Results

- Positive
  - A *mutation* was found in a gene that is known to be disease causing for the specific phenotype of the patient, and the variant is a known disease causing change.

- Negative
  - No mutation was found in the gene that causes the phenotype. Variants that are found in people who do not have the condition may or may not be listed on the report.

- Variant of uncertain significance (VUS)
  - A change was found in the gene that is not known if it is or is not disease causing. Additional studies may be necessary.
  - Just because something is rare and there, doesn’t mean it is disease causing

What is Genetic Counseling?

- Process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease (NSGC.org)
- Help to guide through the testing process
- Facilitate the most cost-effective approach to testing
- Identify the most likely way to get a positive result
- Review the pros and cons of testing for patients to make an informed choice
- Interpret genetic information and inform / educate patients

What happens during Genetic Counseling?

- Typically start by asking about family history
- GC Reviews the basics of genetic inheritance
- GC Reviews information about the genetic condition
- GC Reviews genetic testing options
  - What est?
  - Pros and cons?
  - Ordering method?
  - Plan and cost?
  - Interpretation and implications of results
- Genetic Testing is not a required step when seeing a genetic counselor

Genetic Testing Pros and Cons

- Pros:
  - Tailoring prognoses and recommendations
  - Access to clinical trials
  - Having a definitive answer
  - Relief of uncertainty and anxiety
  - Facilitating reproduction decisions
  - Determine if other family members are at risk

- Cons:
  - Testing may not be informative
  - Genetic test may not be available
  - Impact on family dynamics
  - Psychological distress for positive or negative results
  - Non-paternity
  - Genetic discrimination
  - Overall cost of testing

Decreasing with advancing technology and sometimes free!

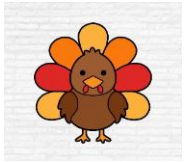
Know your genetic checklist!

How to get a genetic test

- Identify a provider
- Ask what testing is right for you
- Ask to see a genetic counselor or locate one near you

How to prepare for your GC visit

- Know your symptoms along with the timeline



- Know your family history as much as possible

What to do with your results

- Understand what your results mean
- Know your mutation and the implications
- Communicate this with at-risk family members (ask your GC for help with this!!)
- If testing is non-diagnostic, ask for reanalysis/testing every 2-5 years

Useful Websites

- GeneReviews : www.ncbi.nlm.nih.gov/books/
  - Great source for disease overview, help with differential, inheritance and genetic information, some information may be outdated.
- OMIM: www.ncbi.nlm.nih.gov/omim
  - Online Mendelian Inheritance in Man database. Up to date and validated info.
- ClinVar: www.ncbi.nlm.nih.gov/clinvar/
  - Information about genomic variation and impact on human health.
- CDC: www.cdc.gov/genetics/
  - CDC genetics web site
- ConcertGenetics:www.concertgenetics.com/
  - Compare tests, laboratories, prices, and methods.
- NSGC – find a GC near you: www.nsgc.org
  - National Society of Genetic Counselors website

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Questions?

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Can we help with anything else? Call 847-883-9942 or email info@tffpn.org. You may also mail inquiries and donations to *the* Foundation *for* Peripheral Neuropathy at 2700 Patriot Blvd, Suite 250, Glenview, Illinois 60026.