the FOUNDATION for PERIPHERAL NEUROPATHY®

Welcome!

FPN Webinar:

Hereditary Neuropathies & Genetic Testing

featuring **Florian Thomas, MD, PhD**

Wednesday, October 30, 2024

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.

If you are having trouble with the audio using your computer, you can dial in by phone (check your email for dial-in instructions).

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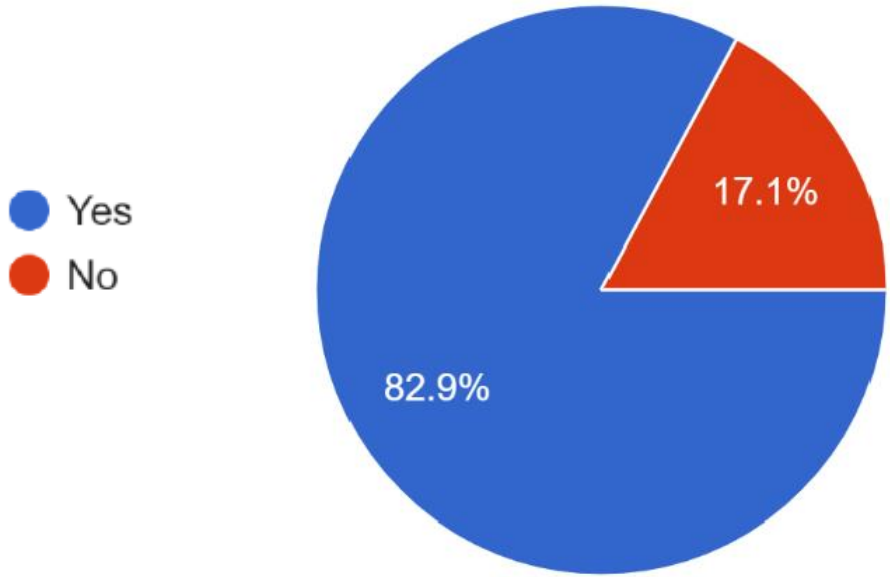
Pre-Webinar Survey Responses

Are you, or members of your family, interested in getting genetically tested?

432 responses



If "no," why not interested?

- Don't see how it would be beneficial
- I don't have children
- I'm too old
- Cost
- Don't like needles
- Want to keep my information private
- Family members deceased
- Already been tested
- No one else in my family has it
- Already did 23&Me

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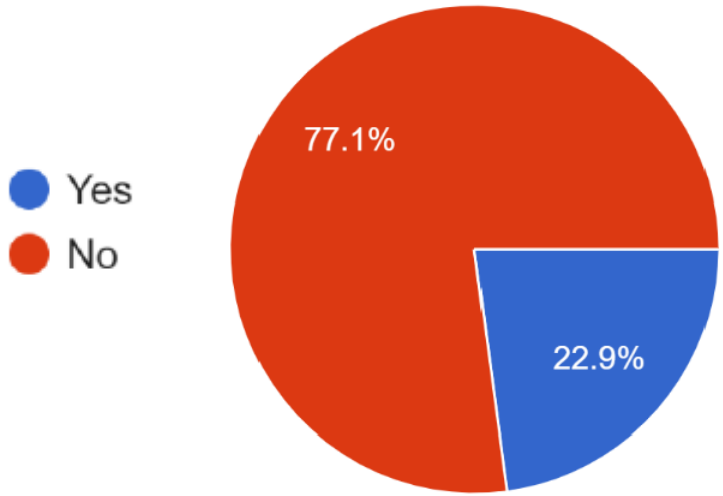
Pre-Webinar Survey Responses

Did you encounter any barriers when trying to speak to a genetic counselor or getting genetically tested?

179 responses



If "yes," what barriers did you encounter?

- Test wasn't available
- Patient didn't present with symptoms
- Finding a genetic counselor
- Cost (not covered by insurance)
- Lack of connection to proper labs
- Doctors say it won't make a difference
- No availability of testing outside the US
- Long waitlist
- Too many tests to choose from

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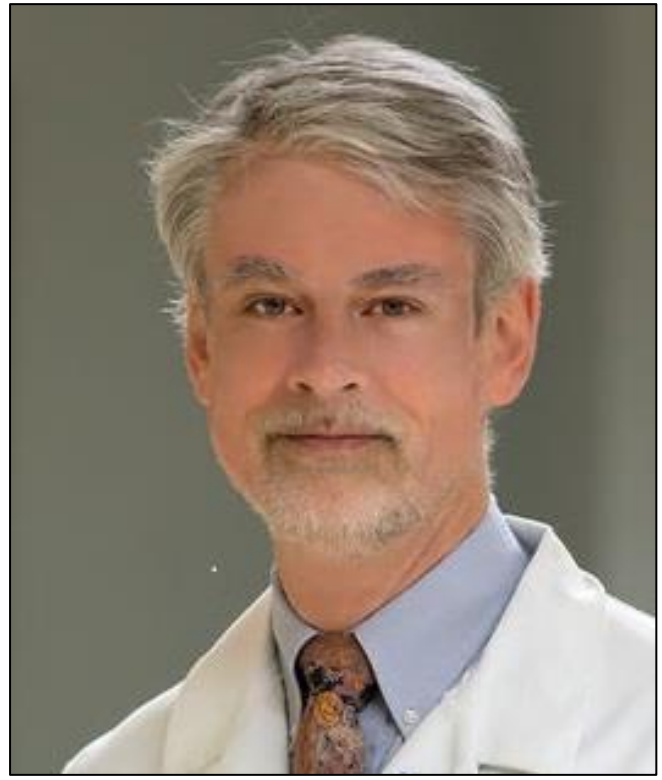
Today's Expert:



Florian Thomas, MD, MA, PhD, MSc
Director, Hereditary Neuropathy Center,
Hackensack University Medical Center,
Founding Chair & Professor, Department of Neurology,
Hackensack Meridian School of Medicine

Hereditary Neuropathies

Presented at the 10/30/24 TFFPN Webinar

Florian P. Thomas, MD, PhD
Director, Hereditary Neuropathy Foundation & CMTA Center of Excellence
Founding Chair & Professor, Department of Neurology
Associate Dean for Faculty Advancement
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Hackensack Meridian School of Medicine

Disclosures

Dr. Thomas has no relevant disclosures

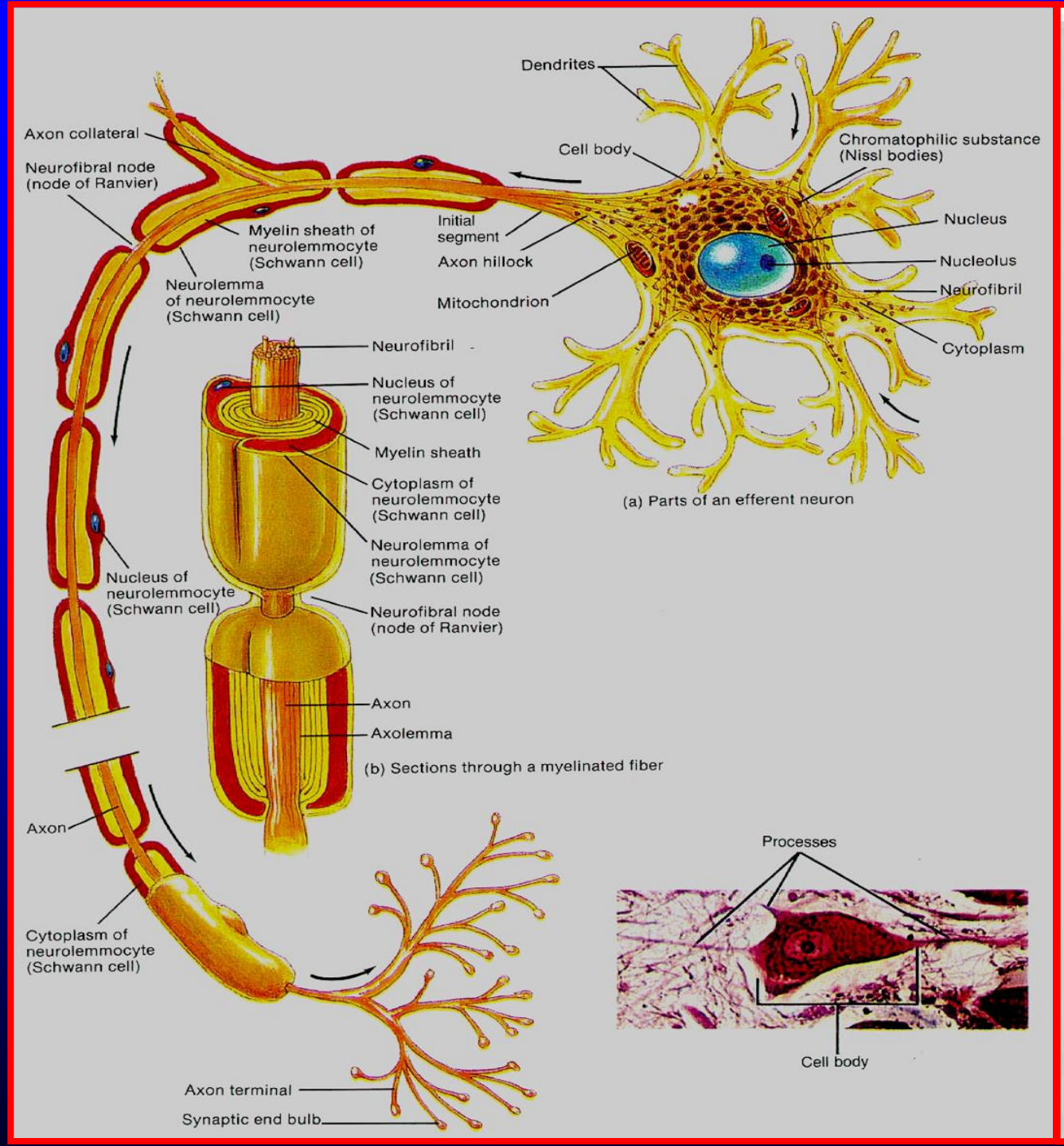
Courtesy of CMTA

Proto-typical Neuron

Sensory: vibration, temperature, joint position, pin prick, light touch

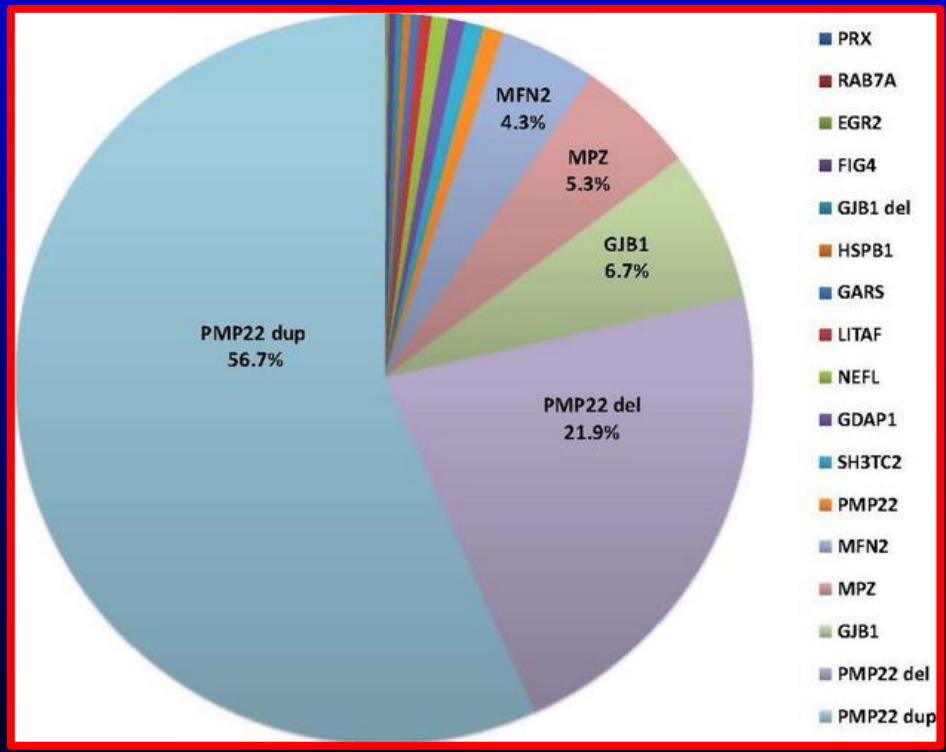
Motor: strength, bulk

Autonomic: bladder, bowel, blood pressure, sexual function



Background: History of CMT

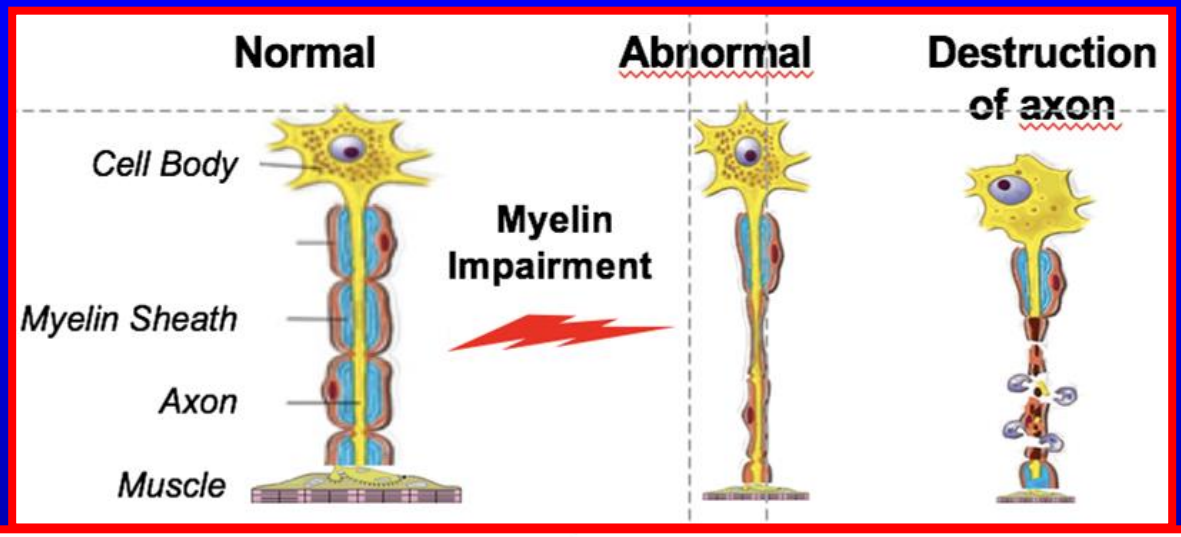
1856,1873, 1878, 1885, 1886, 1889, 1895 Early descriptions
1939 Correlation of severity & inheritance
1952 Hereditary Amyloidosis characterized
1960s Classification as axonal CMT2 vs demyelinating CMT1
1980s Gene linkages to chromosomes (1, 17, X)
1990s 5 Genes identified
2006 25
2011 50
2017 60
2018 80
2024 >120 easily testable genes

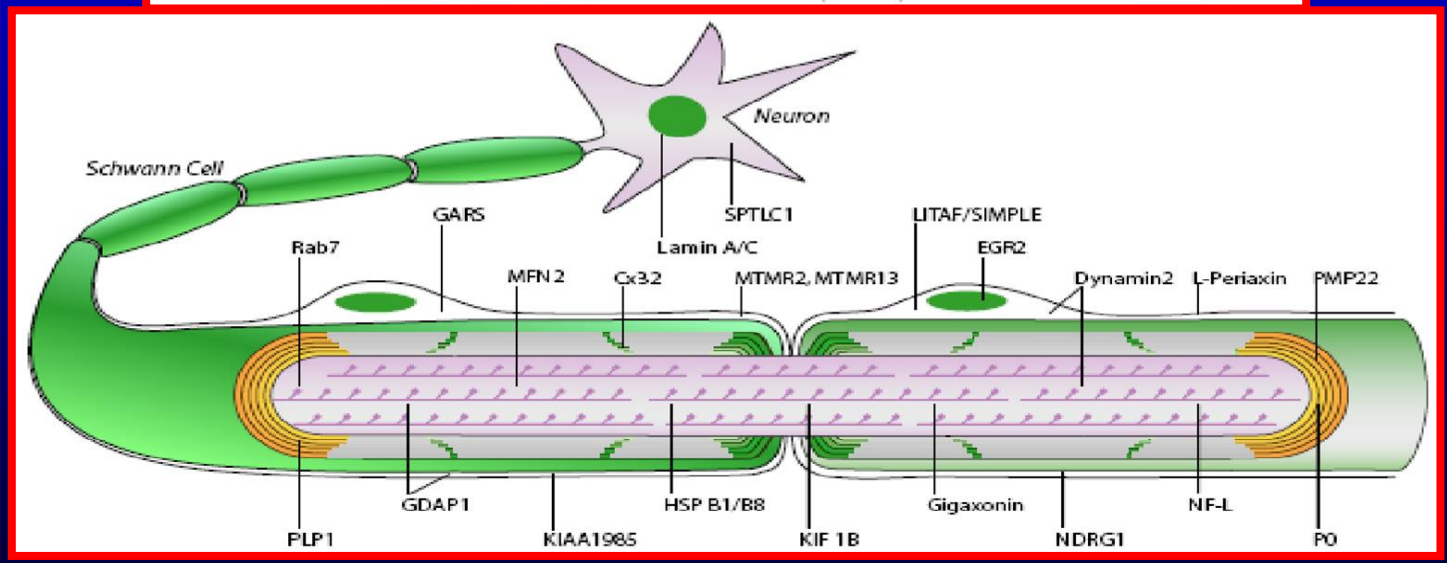


Classification

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
DI CMT	Sensory and motor myelinated fibers	Autosomal dominant	Childhood Teens	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

Pathophysiology: Dying back Mechanism

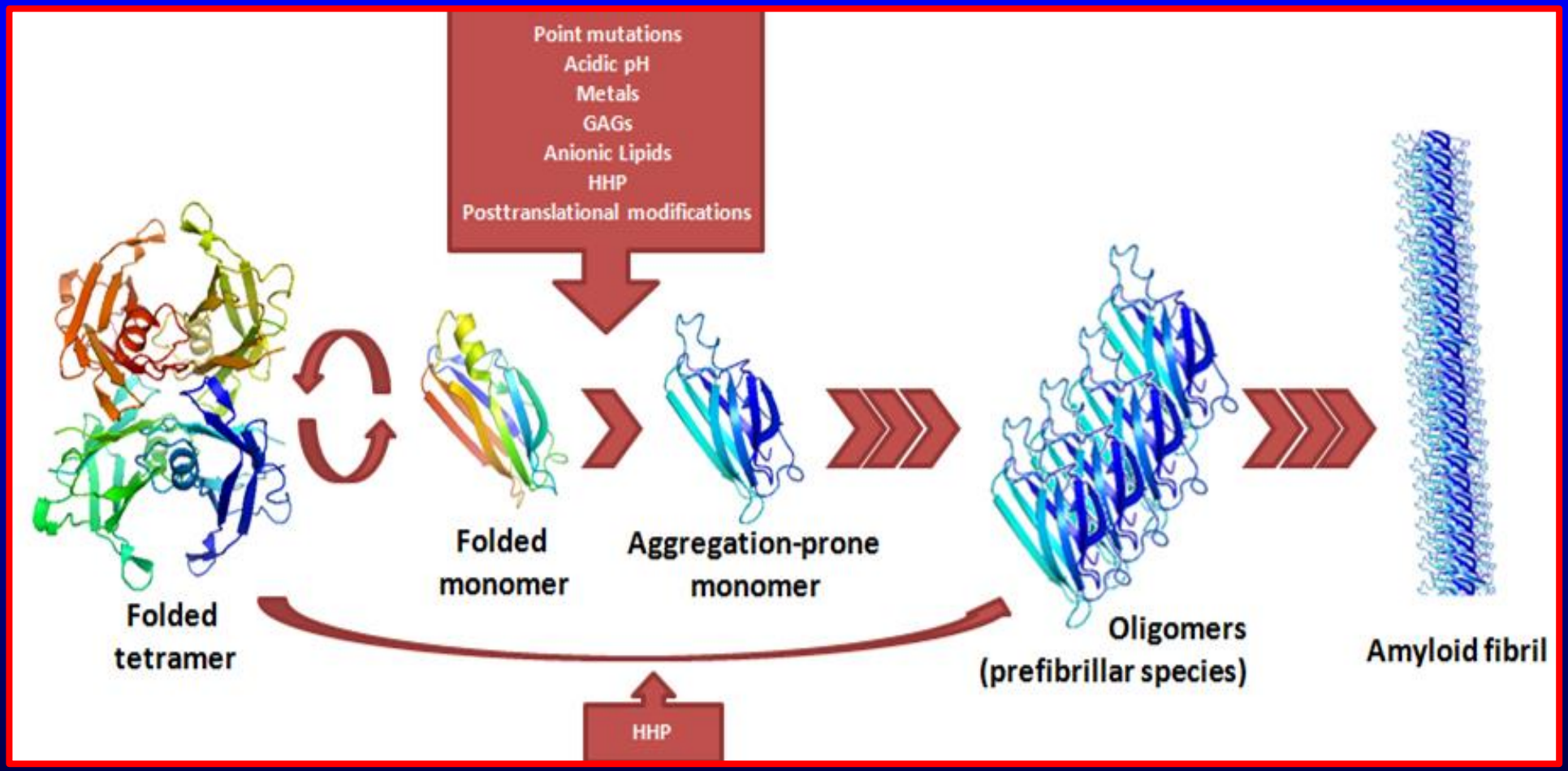




N Engl J Med 1992;326:386

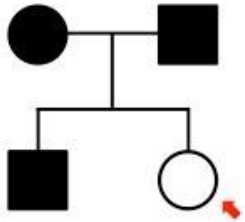
Niemann, Berger, Suter, Neuromolecular Med 2007

Pathophysiology: Amyloid fibrils



Prevalence & Inheritance

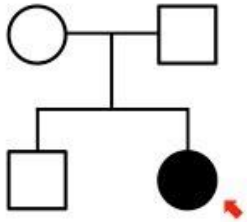
AUTOSOMAL DOMINANT



Cannot be recessive as two affected parents could **not** have an unaffected offspring

Parents MUST be heterozygous

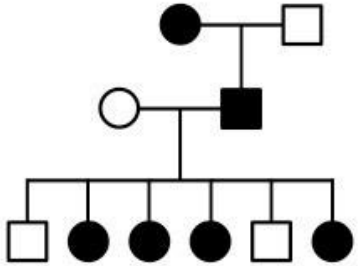
AUTOSOMAL RECESSIVE



Cannot be dominant as two unaffected parents could **not** have an affected offspring

Parents MUST be heterozygous

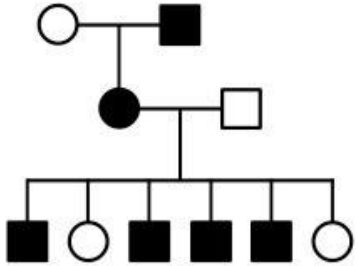
X-LINKED DOMINANT



Sex linkage cannot be confirmed

100% incidence of affected daughters from an affected father *suggests* X-linked dominance

X-LINKED RECESSIVE



Sex linkage cannot be confirmed

100% incidence of affected sons from an affected mother *suggests* X-linked recessive

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

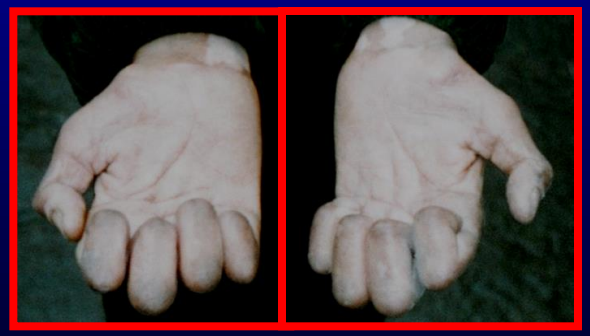
Prevalence & Inheritance

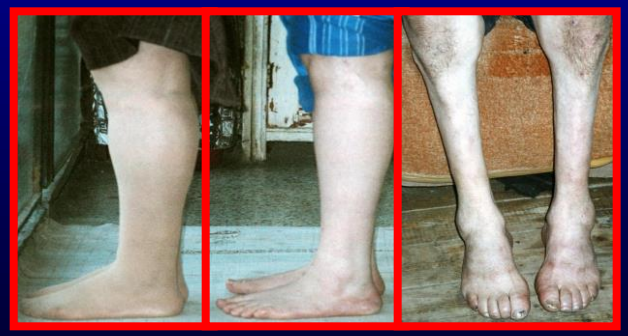
World	1 : 2,500	7% of all neuropathies are inherited
US	140,000	
CMT1	2/3	
CMT2	1/3	

		Autosomal dominant	X Linked recessive	Autosmal recessive
CMT1A	~1/5000	X		
CMTX1	~1/50,000		X	
CMT2A	~1/50,000	X		
CMT1B	~1/50,000	X		
CMT4	Rare			X
DI CMT	Rare	X		
SORD	1/100,000			X
TTR	1/1000,000	X		

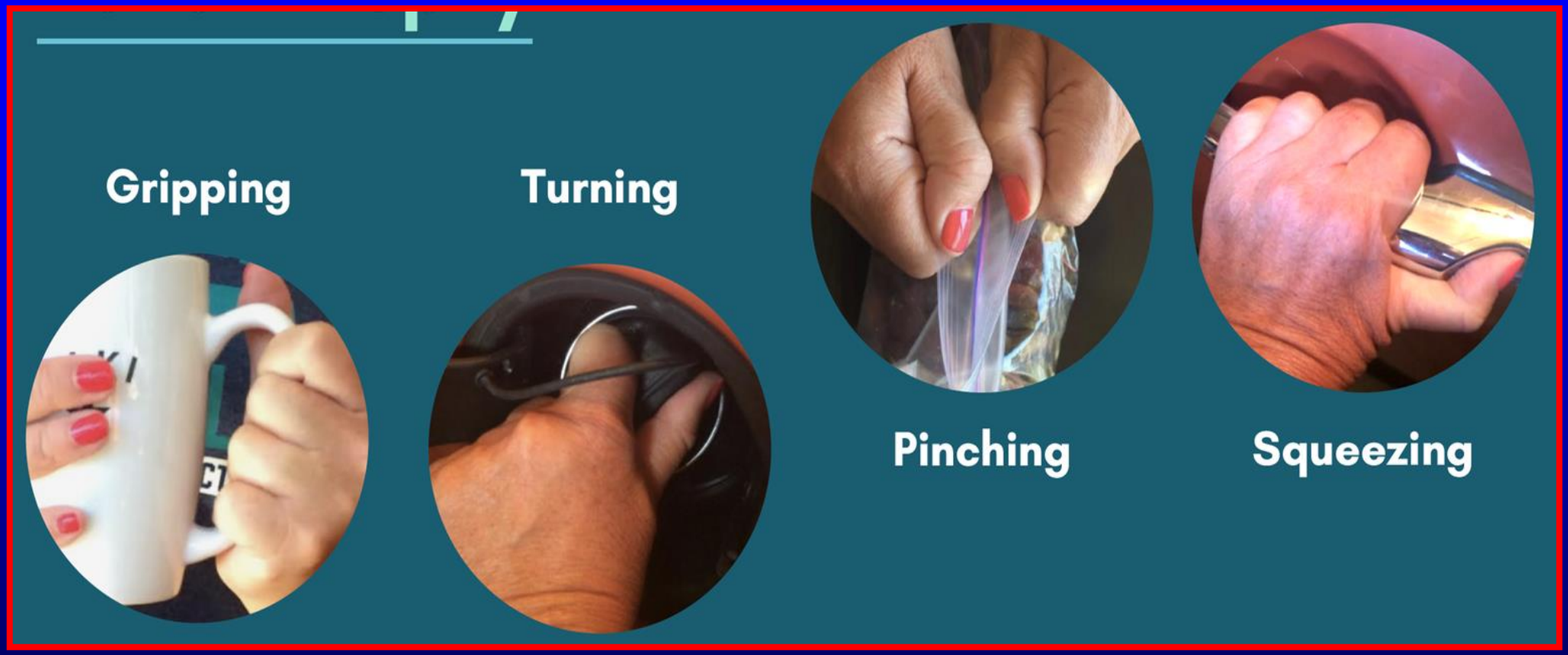
Symptoms & Signs

- Nerve dysfunction causes distal weakness, atrophy, sensory loss & hyporeflexia
- Strength — Imbalance of weak muscles causes high arches, flat feet, hammertoes
  Difficulty pinching, turning keys, gripping, squeezing
- Balance — Increased risk for ankle sprains, falls & fractures
- Pain — Neuropathic & nociceptive
- 44% — Significant disability
- Age >50 — Faster progression, Retirement 10 years earlier
- 18% — Depression
- 50% — CMT interferes with professional life
- Disability — Some women opt against childbearing
  CMT may progress during pregnancy





Symptoms & Signs



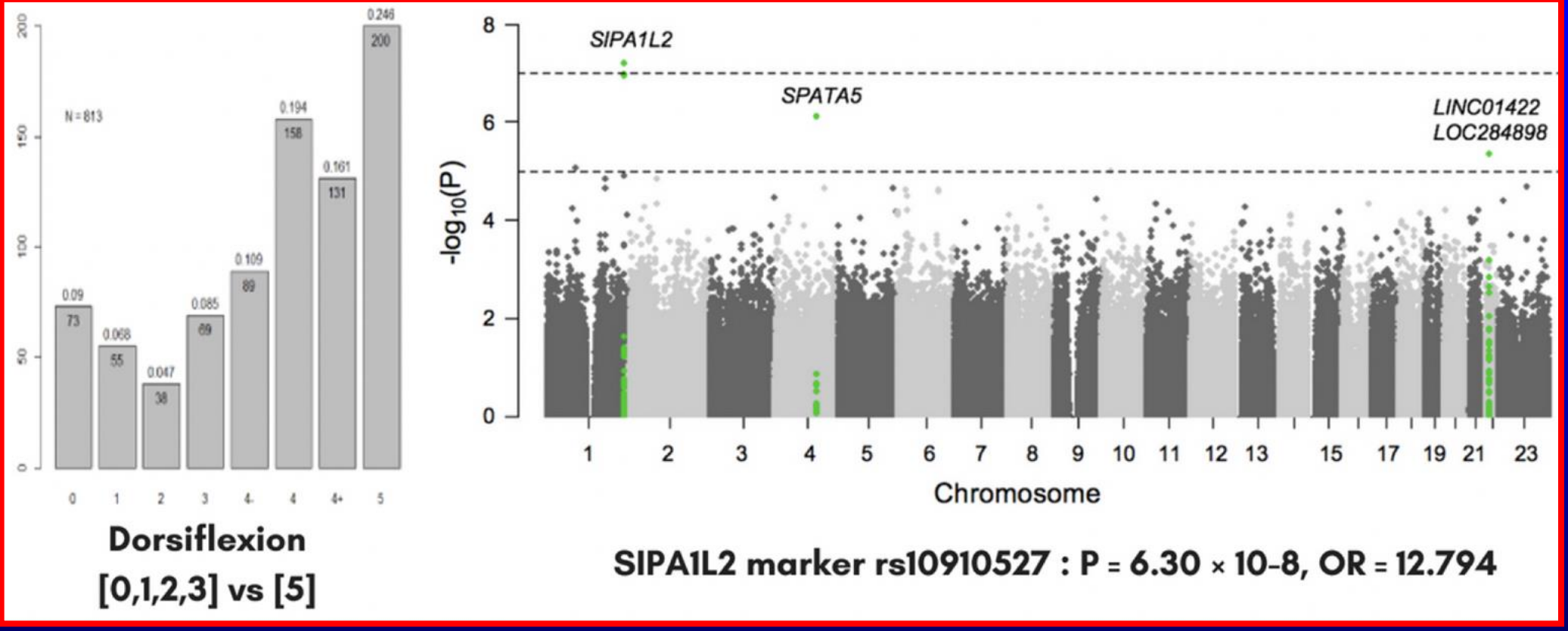
Courtesy of M Shy

Age of Onset & Severity

- Highly subjective & dependent on family's knowledge of CMT

- Dejerine Sottas Old term for severe CMT
- Autosomal recessive CMT is often but not always more severe
- X-linked CMT is often but not always less severe in females
- Few become wheelchair users in childhood or adulthood
- Some develop scoliosis & hip dysplasia
- Rare respiratory compromise, vocal cord & phrenic nerve paralysis,
  upper motor neuron signs, problems with vision, hearing, joints, cognition, heart, bladder, bowel

CMT is not just a monogenetic Condition



Tao F, et al. Variation in SIPA1L2 is correlated with phenotype modification in CMT1A. Ann Neurol 2019;85:316–30

Work-Up for suspected CMT

- Quantitate exam longitudinally (ONLS, CMTNS)
- Consider CNS–PNS overlap, eg hyperreflexia
- Rare non-neurological signs, eg cardiac, in ATTR (heart, kidneys, eyes, joints, GI tract, bladder)
- Think outside the box if presentation is unusual
- 1 genotype vs 1 phenotype quandary
- Check or asymmetry, eg, HNPP, IBPN
- Examine skin, shoes
- Assess gait safety (some patients avoid AFOs)
- Assess distal-most bulk, weakness
- Routine labs for neuropathy
- Genetic testing
- EDX to separate inherited vs acquired vs both
- Sural nerve bx (rare)
- Evaluate depression, anxiety

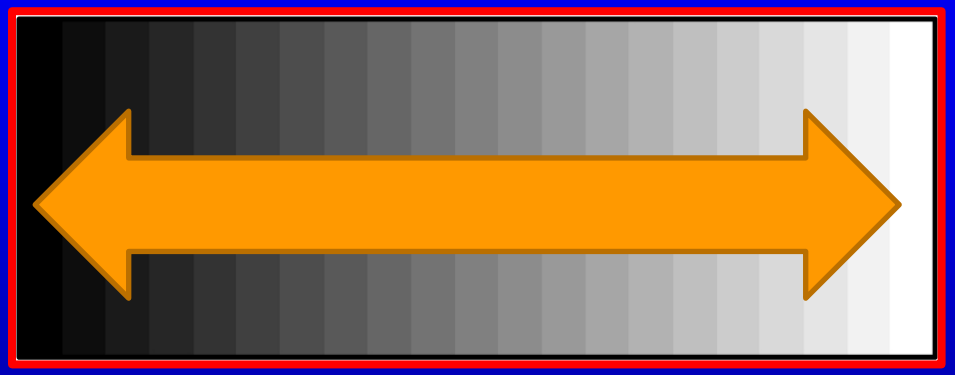
Genetic Counseling

Pre-test Counseling	Post-test Counseling	Pre-conception
• Exploratory • Know you want to proceed	• Review results and medical management implications • Family screening	• Considering having a baby • Prenatal genetic testing options • IV

Genetic Testing: How does it work?

- Test samples: blood, saliva, buccal swab
- Can be done at home
- 2–4 week turn-around time

Genetic Testing:
It's a spectrum, not black and white



- Positive
- Negative
- Variant of uncertain Significance (VUS)
- VUS are more common with larger # of genes tested
- Can be difficult to interpret
- VUS can be reclassified as further information is learned

Care of the Patient with CMT

Genetic Counseling

- IVF after selection of unaffected embryo
- IVF with donated egg/sperm. Surrogacy?
- Adoption

Interprofessional Care Team

- Pediatrician, PCP, Geriatrician
- Orthopedist, Podiatrist
- School Nurse & Coach
- (Child) Neurologist & Neurophysiologist
- PT, OT, Orthotist, Physiatrist
- Counseling Psychologist

Care of the Patient with CMT

General Health & Health Behavior

- Risk of sedentary lifestyle
- Home evaluation, especially in the elderly
- Risk of frailty, falls, osteoporosis, polypharmacy
- Depression, Anxiety, Pain, Body Image
- Worries about employment, ADLs, childcare
- Respiratory Insufficiency
- Intercurrent Illnesses, e.g. DM, RA
- Conditions requiring neurotoxic drugs
- Vocational Rehab (e.g. tool & die maker, optician)

Foot & ankle surgery evaluation

- Choice of MD, timing, procedure

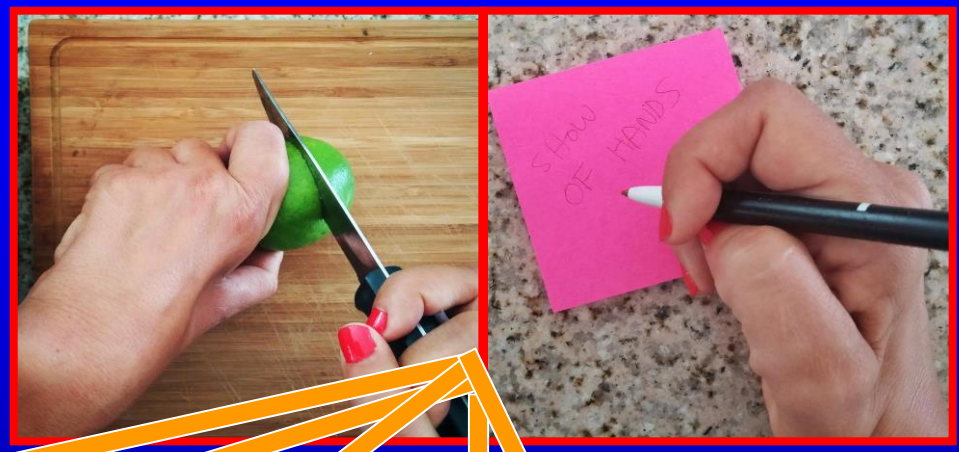
Care of the Patient with CMT

Pain & Cramps

- Stretching
- Standard Medications

Hand/Wrist Weakness

- Orthotic Devices



Care of the Patient with CMT

Ankle & Ankle Weakness

- Orthotic Devices
- Wheelchair systems (5% power)
- Vehicle Modification




Care of the Patient with CMT

Indications for Surgery

- Pain not relieved by shoe modification/bracing
- Inability to ambulate adequately
- Ulceration and impending skin breakdown

Surgical Planning

- Strength of each muscle affecting the foot & ankle?
- Deformities present? Fixed or Flexible?
- Sensory status, especially on plantar surface?

Berberian W. with permission

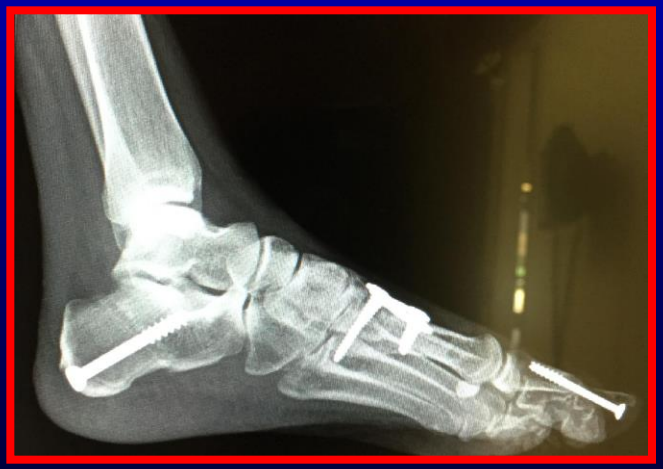
Care of the Patient with CMT

Presentation

- Severely weak dorsiflexors
- Contracted Achilles tendon & plantar fascia
- Flexible cavovarus deformity
- Intact protective sensation
- Pain

Procedures

- Lengthening of Achilles tendon & plantar fascia
- Calcaneal osteotomy
- Metatarsal osteotomies
- Fusion of hallux IP joint
- Multiple tendon transfers



Berberian W. with permission

Care of the Patient with CMT

Outcome

Ambulates without pain or braces

Pre–Op

Post–Op

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Pipeline Drugs for Patients with CMT

Gene Silencing

- shRNA gene silencing in a mouse model of CMT1A

Gene Replacement

- Gene Replacement for CMT1X

NMD670

- Chloride channel inhibition to improve neuromuscular transmission & muscle function

FDA approved Drugs for aTTR Neuropathy

Table 2. Disease-Modifying Therapies for Transthyretin Amyloidosis (ATTR) Approved by the FDA

Drug	Indication	Effect on transthyretin
Tafamidis	Wild-type or hereditary ATTR cardiomyopathy	Stabilizer
Vutrisiran	Hereditary ATTR with neuropathy	Silencer
Patisiran	Hereditary ATTR with neuropathy	Silencer
Inotersen	Hereditary ATTR with neuropathy	Silencer

Validated Assessments Tools

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? Yes ☐ No ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their bands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0=Normal
1=Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE=____**
2=Disability in one or both arms affecting but not preventing any of the functions listed
3=Disability in one or both arms preventing at least one but not all functions listed
4=Disability in both arms preventing all functions listed but purposeful movement still possible
5=Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐	**If yes:** (please circle) **right/left**

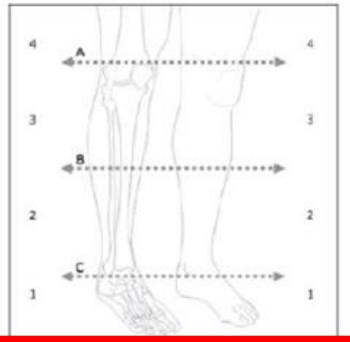
Leg grade
0=Walking/climbing stairs/running not affected
1=Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE=____**
2=Walks independently but gait looks abnormal
3=Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4=Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)
5=Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6=Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7=Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale=arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) **TOTAL SCORE=____**
Is there any disorder, other than peripheral neuropathy, which affects the above functions Yes ☐ No ☐
If **yes** please describe:

Graham RC, et al. A modified peripheral neuro-
pathy scale: The ONLS. JNNP 2006;77:973–6

Parameter	0	1	2	3	4
Sensory symptoms*	None	Symptoms below or at ankle bones	Symptoms up to the distal half of the calf	Symptoms up to the proximal half of the calf, including knee	Symptoms above knee (above the top of the patella)
Motor symptoms (legs)†	None	Trips, catches toes, slaps feet Shoe inserts	Ankle support or stabilization (AFOs) Foot surgery‡	Walking aids (cane, walker)	Wheelchair
Motor symptoms (arms)	None	Mild difficulty with buttons	Severe difficulty or unable to do buttons	Unable to cut most foods	Proximal weakness (affect movements involving the elbow and above)
Pinprick sensibility*,§	Normal	Decreased below or at ankle bones	Decreased up to the distal half of the calf	Decreased up to the proximal half of the calf, including knee	Decreased above knee (above the top of the patella)
Vibration‖	Normal	Reduced at great toe	Reduced at ankle	Reduced at knee (tibial tuberosity)	Absent at knee and ankle
Strength (legs)¶	Normal	4+, 4, or 4− on foot dorsiflexion or plantar flexion	≤3 on foot dorsiflexion or ≤3 on foot plantar flexion	≤3 on foot dorsiflexion and ≤3 on plantar flexion	Proximal weakness
Strength (arms)¶	Normal	4+, 4, or 4− on intrinsic hand muscles**	≤3 on intrinsic hand muscles**	≤5 on wrist extensors	Weak above elbow
Ulnar CMAP (median) Radial SAP amplitude, antidromic testing	≥6 mV (≥4 mV) ≥15 μV	4–5.9 mV (2.8–3.9) 10–14.9 μV	2–3.9 mV (1.2–2.7) 5–9.9 μV	0.1–1.9 mV (0.1–1.1) 1–4.9 μV	Absent (absent) <1 μV

AFO, ankle-foot orthoses; CMAP, compound muscle action potential; SAP, sensory action potential.
*Use the picture below to discriminate the level of the symptoms.
†Uses aid *most of the time*. The patient was prescribed to wear/use or should be wearing/using the aid in the examiner's opinion (see written instructions, Table S2).
‡See written instructions for details of eligible foot surgery.
§Abnormal if patient says it is definitely decreased compared to a normal reference point.
‖Use Rydel-Seiffer tuning fork. Definition of normal: ≥5.
¶Limb strength scores refer to MRC grade.
**Intrinsic hand muscles strength assessment: test only abductor pollicis brevis (APB) and first dorsal interosseus (FDI), then choose the stronger to give the score.



Shy ME, et al. Reliability & validity of the CMT neuropathy score as a measure of disability. Neurology 2005;64:1209–14

the FOUNDATION for PERIPHERAL NEUROPATHY®

Questions?

the FOUNDATION for PERIPHERAL NEUROPATHY®

Alnylam® PHARMACEUTICALS

Thank You for Watching!

Did you like this webinar? Please take our survey at the end of this webinar. A recording will be uploaded on our website at www.foundationforpn.org shortly. Stay tuned.

Do you like us? Please consider supporting us so that we can continue to fulfill our mission of improving the lives of people living with Peripheral Neuropathy. You can give securely online, via mail or via phone. Every dollar matters!

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 485 E. Half Day Road, Suite 350, Buffalo Grove, Illinois 60089.