the Foundation *for* Peripheral Neuropathy

Welcome!

Hereditary Neuropathy and Genetic Testing

Thursday, September 30, 2021

We will begin our presentation shortly.

Webinar sponsored by: Alnylam® PHARMACEUTICALS

the Foundation *for* Peripheral Neuropathy

Moderator:

Nancy Frohman
Director of Development & Marketing

the Foundation *for* Peripheral Neuropathy

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).

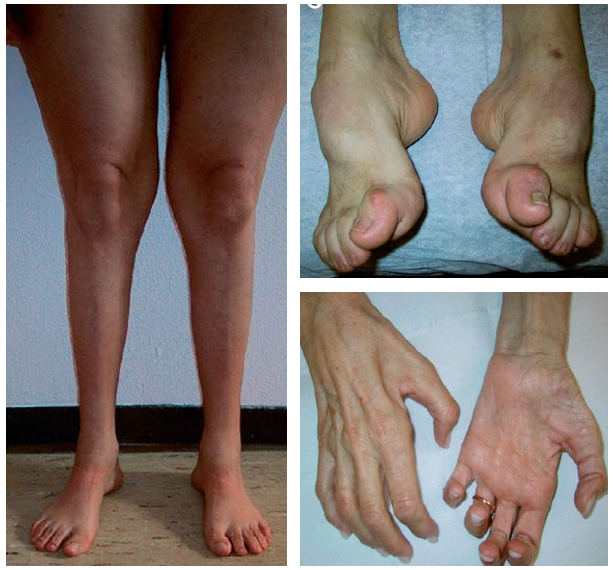
the Foundation *for* Peripheral Neuropathy

Presenters:

Brett McCray, MD, PhD
Assistant Professor, Neurology
Johns Hopkins Medical Center

Christy Smith, ScM, CGC
Certified Genetic Counselor
Johns Hopkins Department of Genetic Medicine

Inherited Neuropathy: Basics and Beyond

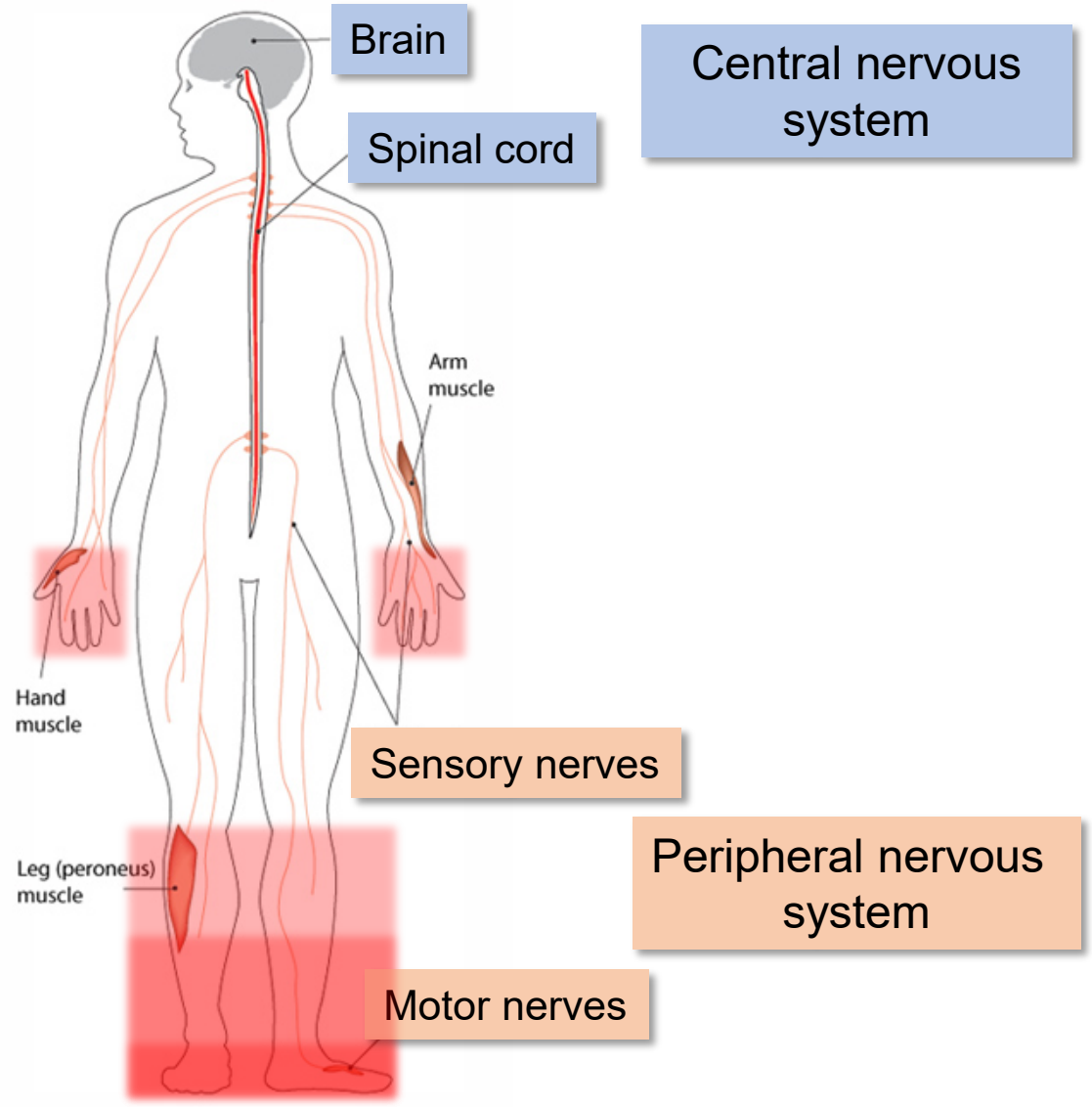


Brett McCray, MD, PhD
Assistant Professor of Neurology, Neuromuscular Division
Johns Hopkins School of Medicine
9/30/2021

What is peripheral neuropathy?

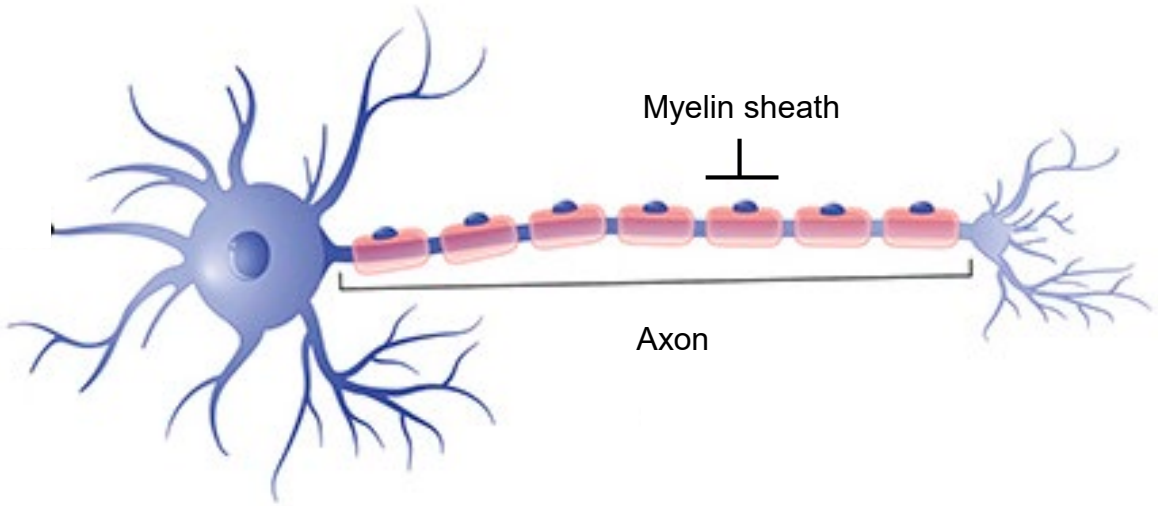
- Peripheral neuropathy is a general term for any problems with the nerves after they have left the brain and spinal cord
  - Can affect sensory nerves causing numbness, tingling, pain, or other unusual sensations
  - Can affect motor nerves causing weakness and muscle atrophy

- Symptoms follow a typical pattern
  - Symmetrical: affecting both sides of the body equally
  - Length-dependent: affecting toes and feet before upper legs and hands

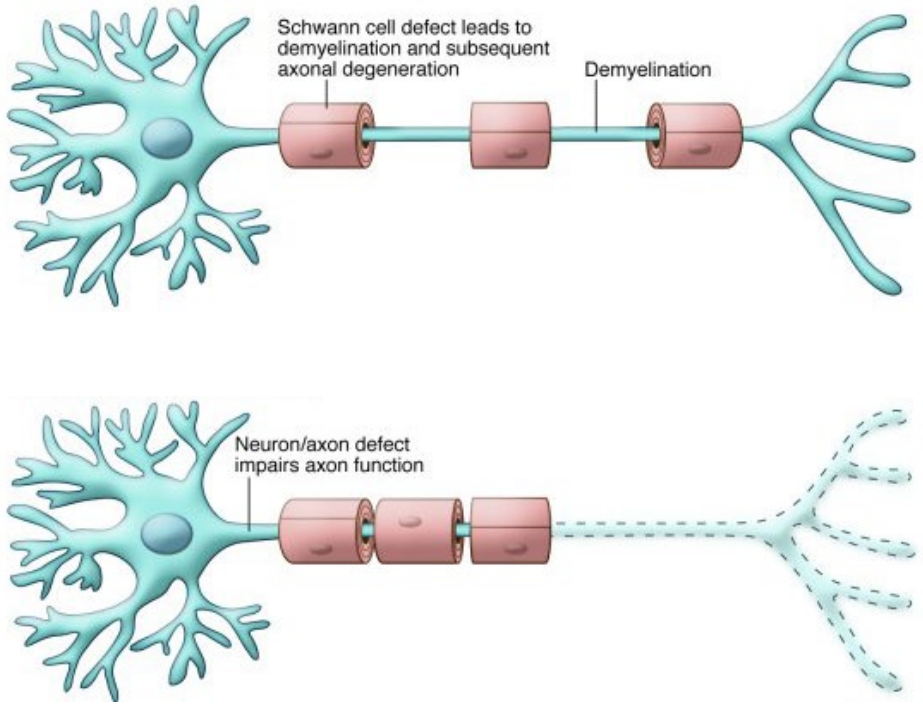


What is peripheral neuropathy?

- Basics of nerves
  - Conduit for electrical signals
  - The “wire” is the axon
  - The “insulation” is the myelin sheath

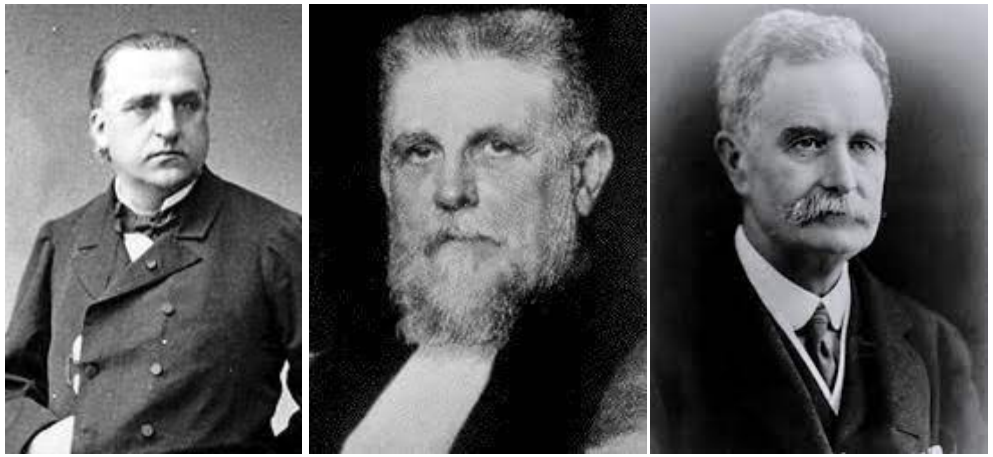


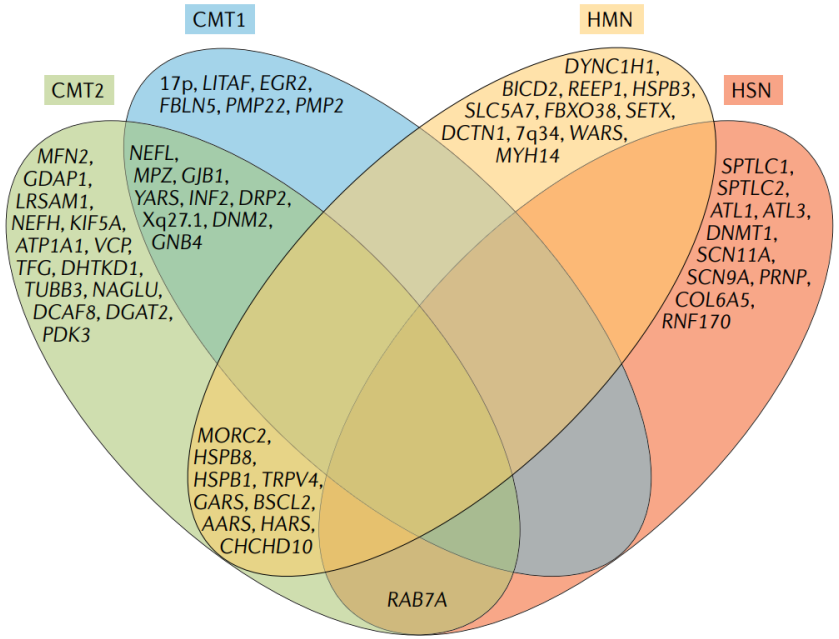
- Peripheral neuropathy can affect either or both
  - “Demyelinating neuropathy”
  - “Axonal neuropathy”



Types and classifications of inherited neuropathy

- Naming of inherited neuropathy is a bit of a mess
- Sensory and motor neuropathy: Charcot-Marie-Tooth (CMT) disease
  - CMT Type 1: Demyelinating neuropathy
  - CMT Type 2: Axonal neuropathy
- Sensory only: Hereditary sensory and autonomic neuropathy (HSAN)
- Motor only: Hereditary motor neuropathy (HMN)
- Inherited neuropathy associated with other problems in the body
  - Giant axonal neuropathy
  - Familial amyloid polyneuropathy (hereditary amyloidosis)

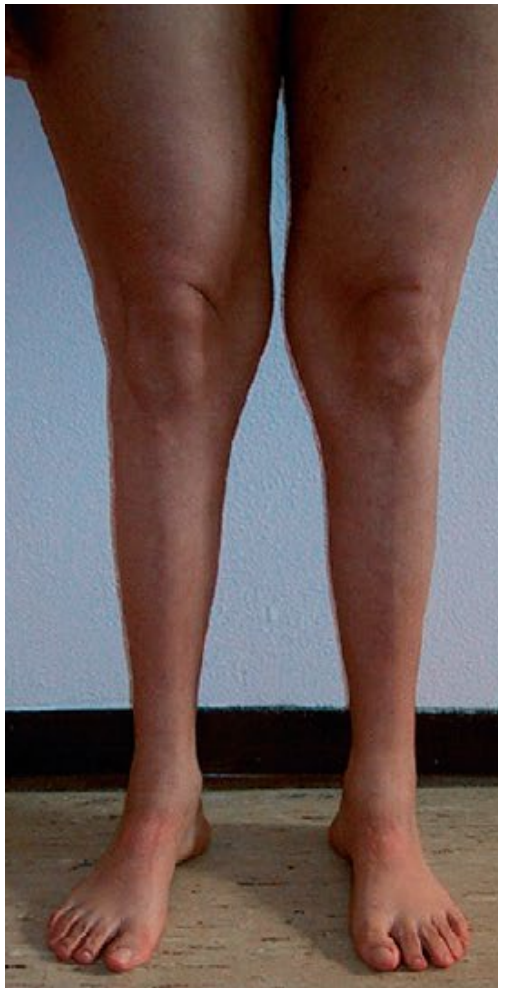


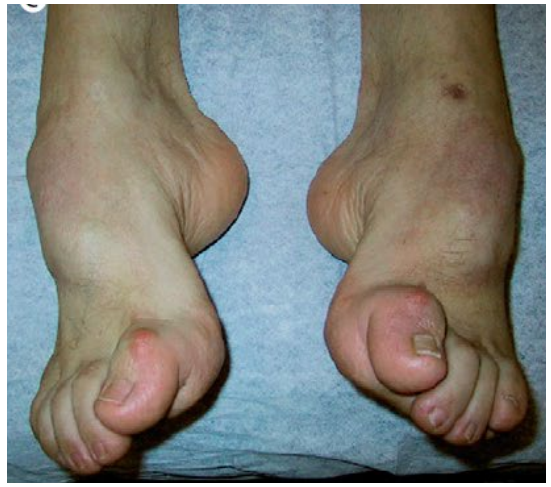


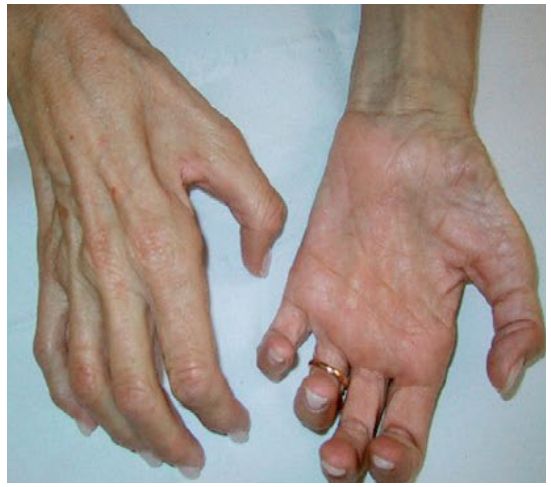
Pipis et al., Nat Rev Neuro 2019

Inherited neuropathy: Signs and symptoms

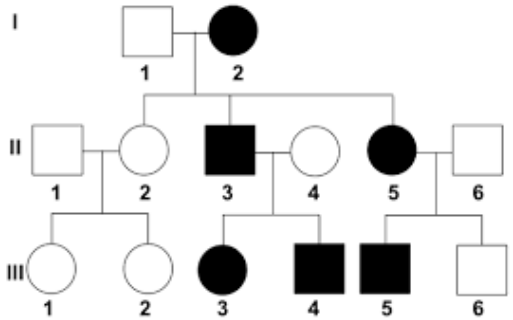
- Numbness more than tingling or pain
- Weakness in the toes, feet, and ankles
- Foot changes: high arches (or flat arches), curled toes (hammertoes)
- Skinny legs
- Difficulty with running, jumping, or balance
- Hand problems later in life
- Others in the family have neuropathy







Inherited neuropathy: Patterns in families



- Most forms are dominant
  - One copy of the disease gene (from either parent)
- Some forms are recessive
  - Need two copies of the disease gene (1 from each parent)
- Some forms are X-linked
  - Males are more affected
  - Females can be asymptomatic, but can pass the gene to children
  - Males can only pass on to females
- Genetic change can occur spontaneously

When to suspect inherited neuropathy

In favor of inherited neuropathy

Family history

- Affected parents, siblings, or children

Age of onset

- Symptoms before the age of 40
- Long-standing foot deformities
- Difficulty with athletics as a child

Neurological exam

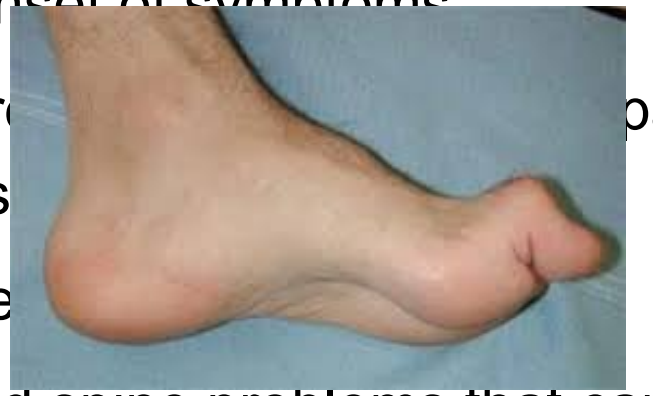
- Significant leg atrophy
- Sensory loss, difficulty with balance
- Foot changes

Specific features of EMG/NCS

- “Uniform” slowing of nerve impulses

Argues against inherited neuropathy

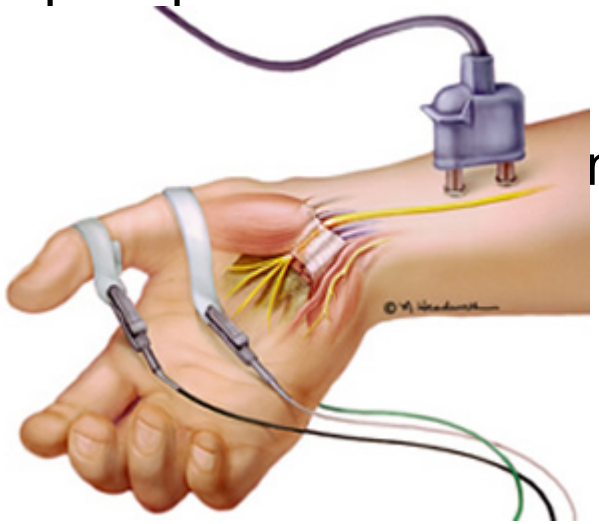
Rapid onset of symptoms



Known r pathy (e.g. diabetes

Asymme

Back and spine problems that can explain symptom



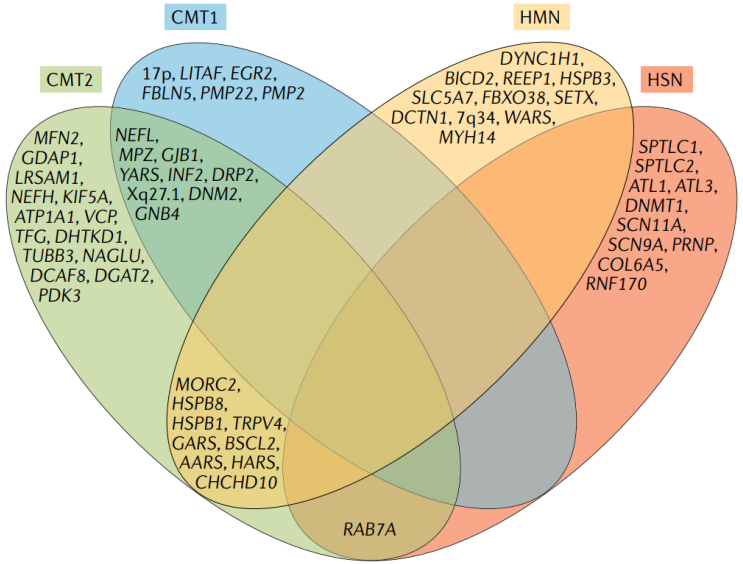
“Non-unif mpulses

Diagnosis of inherited neuropathy

- Genetic testing of you or an affected family member
  - More details in the next talk

- Diagnosis of CMT or other form of inherited neuropathy
  - >100 different causative genes
  - CMT1A ~50% of all cases
  - CMT2A and CMT1X
  - Most types of CMT are more similar than different
  - Exceptions
    - CMT2C: vocal cord weakness
    - CMTDIE: kidney problems
    - CMT2A: eye problems

- What does negative genetic testing mean?
  - Makes it less likely that you have inherited neuropathy
  - BUT, can't rule it out completely
  - Constant discover of new genes
    - SORD mutations in recessive axonal CMT (AR-CMT2)
    - RFC1 mutations in CANVAS and sensory neuropathy



Pipis et al., Nat Rev Neuro 2019

nature genetics
ARTICLES
https://doi.org/10.1038/s41588-020-0615-4
Check for updates

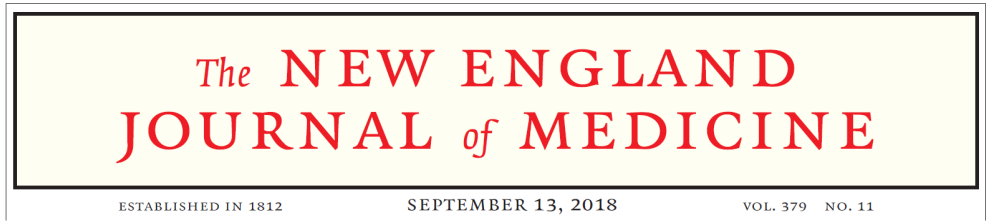
Biallelic mutations in *SORD* cause a common and potentially treatable hereditary neuropathy with implications for diabetes

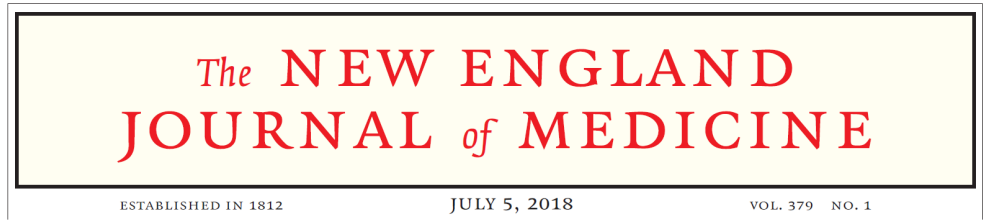
Andrea Cortese[1,2,3,37], Yi Zhu[4,5,37], Adriana P. Rebelo[1,37], Sara Negri[6], Steve Courel[1], Lisa Abreu[1], Chelsea J. Bacon[7], Yunhong Bai[7], Dana M. Bis-Brewer[1], Enrico Bugiardini[2], Elena Buglo[1], Matt C. Danzi[1], Shawna M. E. Feely[7], Alkyoni Athanasiou-Fragkouli[2], Nourelhoda A. Haridy[2,8], Inherited Neuropathy Consortium*, Rosario Isasi[1], Alaa Khan[2,9], Matilde Laurà[2], Stefania Magri[10], Menelaos Pipis[2], Chiara Pisciotta[11], Eric Powell[1], Alexander M. Rossor[2], Paola Saveri[11], Janet E. Sowden[12], Stefano Tozza[13], Jana Vandrovcova[2], Julia Dallman[14], Elena Grignani[6], Enrico Marchioni[15], Steven S. Scherer[16], Beisha Tang[17], Zhiqiang Lin[18], Abdullah Al-Ajmi[19], Rebecca Schüle[20,21], Matthis Synofzik[20,21], Thierry Maisonobe[22], Tanya Stojkovic[23], Michaela Auer-Grumbach[24], Mohamed A. Abdelhamed[8], Sherifa A. Hamed[8], Ruxu Zhang[18], Fiore Manganelli[13], Lucio Santoro[13], Franco Taroni[10], Davide Pareyson[11], Henry Houlden[2], David N. Herrmann[12], Mary M. Reilly[2], Michael E. Shy[7], R. Grace Zhai[4,5] and Stephan Zuchner[1]

Cortese et al., Nat Gen 2020

Why is it useful to know?

- Treatment?
  - There are no treatments for any forms of CMT (yet!)
  - Treatments exist for rare forms of neuropathy
    - Familial amyloid polyneuropathy
    - Metabolic neuropathies
- Participate in research to move things forward
- Prognosis
  - Most forms of CMT cause slow progression over years
  - Minimize exposure to treatments that won't help
    - Medications: steroids, IVIG, etc
    - Surgeries: nerve release surgeries, tendon transfers
- Peace of mind
- Family testing and family planning





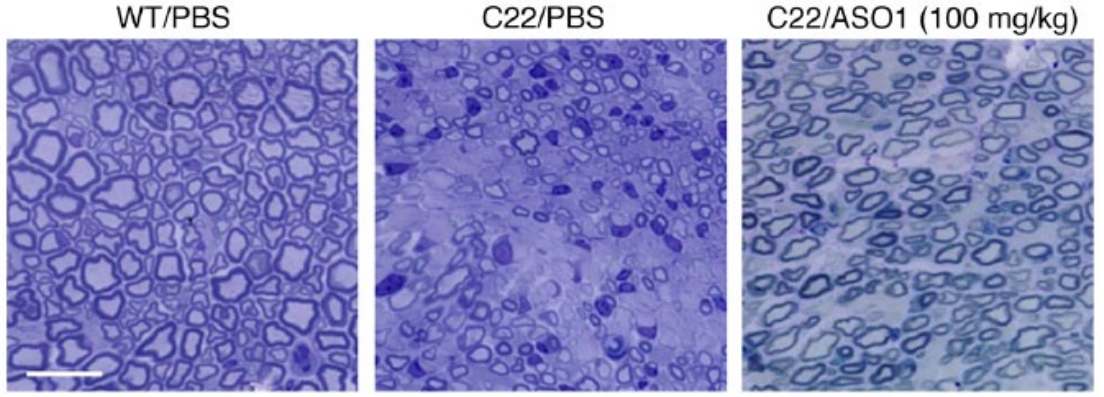
What happens next?

- Management of symptoms
  - PT, OT, orthotics
  - Neuropathic pain medications
- Connection with patient advocacy groups
- Testing of other family members
- Participation in clinical research
  - Natural history studies
  - Clinical trials?

CMT1A, CMT1X, CMT2A, CMT2D, TRPV4, SORD neuropathy, Giant axonal neuropathy

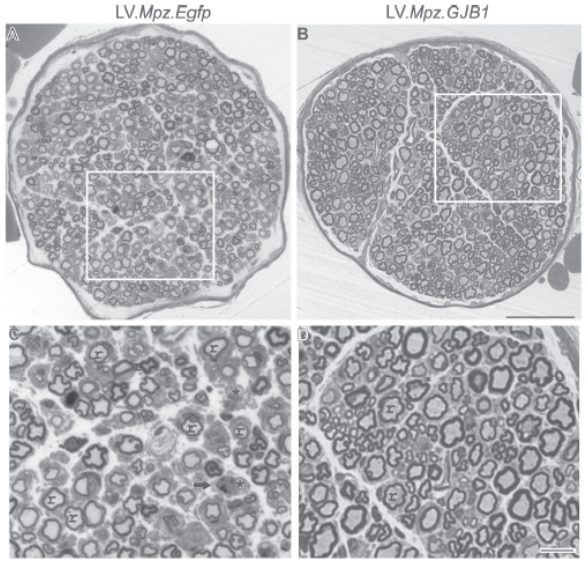
Treatments possibly on the horizon

- CMT1A
  - Accounts for almost half of all CMT
  - Caused by an extra copy of the *PMP22* gene
  - Reducing the amount of PMP22 with ASOs is beneficial in mice



Zhao et al., JCI 2017

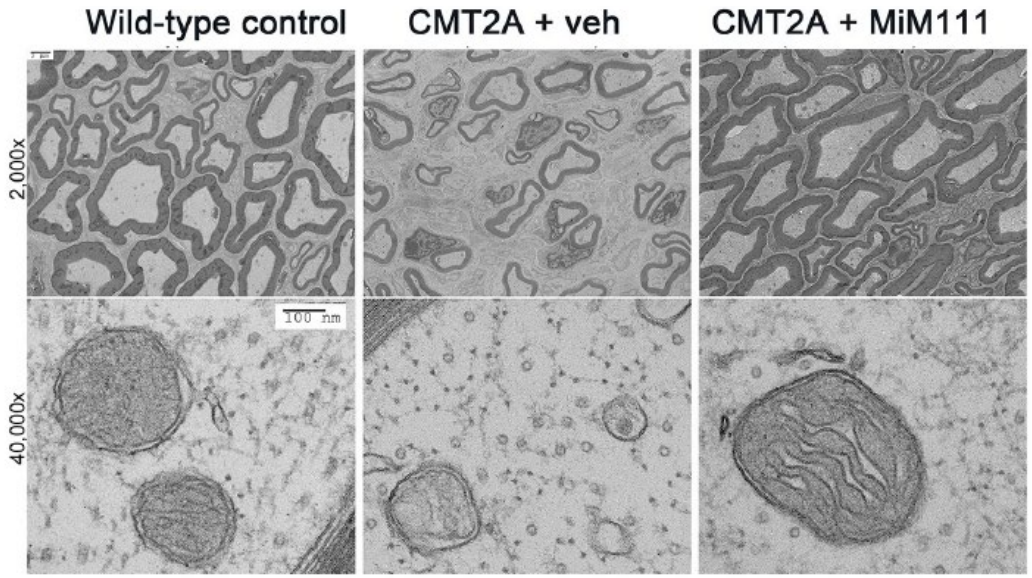
- CMT1X
  - X-linked intermediate form
  - Mutations in *GJB1*
  - Gene therapy approach using a lentivirus improved function in mice



Kagiava et al., Hum Mol Gen 2019

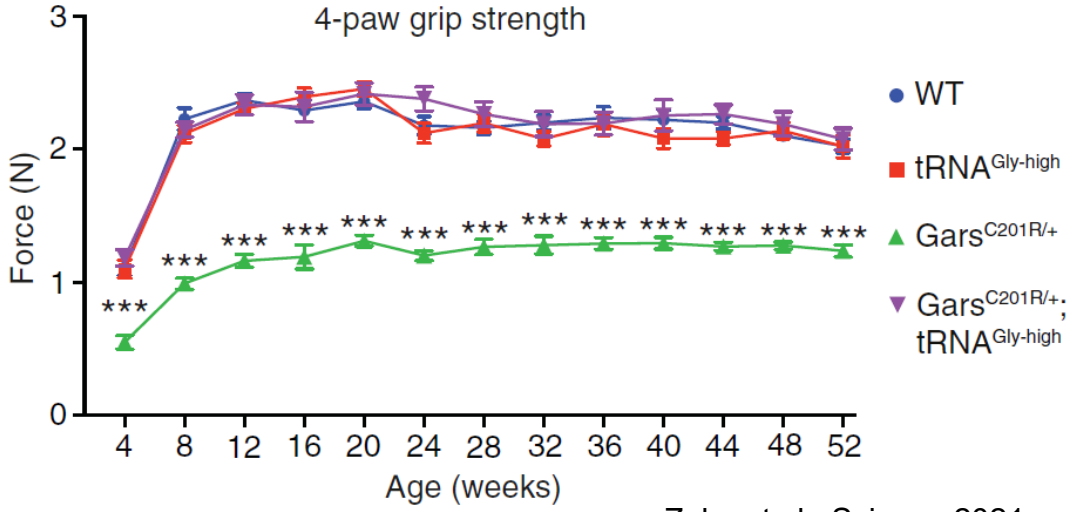
Treatments possibly on the horizon

- CMT2A
  - Most common cause of CMT2
  - Mutations in *MFN2*
  - Boosting MFN1, which is similar to MFN2, with a drug improved function in mice



Franco et al., eLife 2020

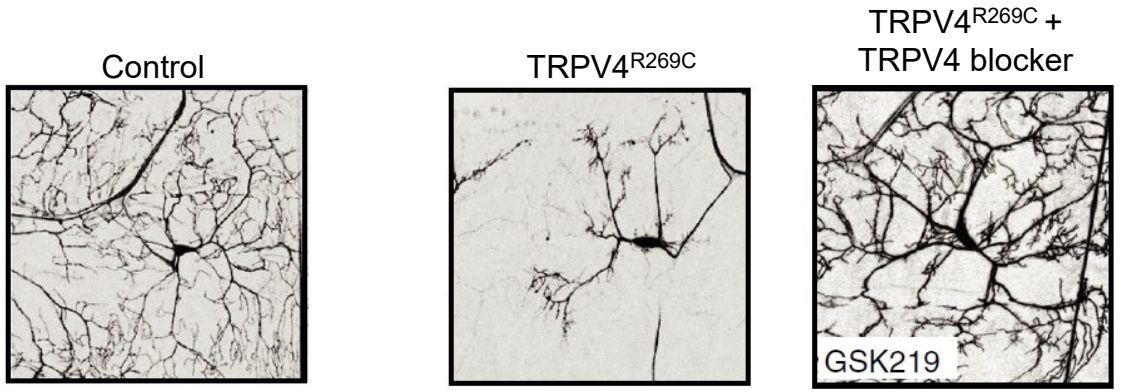
- CMT2D
  - Mutations in *GARS,* a tRNA synthetase
  - Similar to CMT2N, CMT2W, CMTDIC, CMTRIB, HMN9
  - Expressing extra tRNA-^{Gly} can improve strength and nerve function in mice



Zuko et al., Science 2021

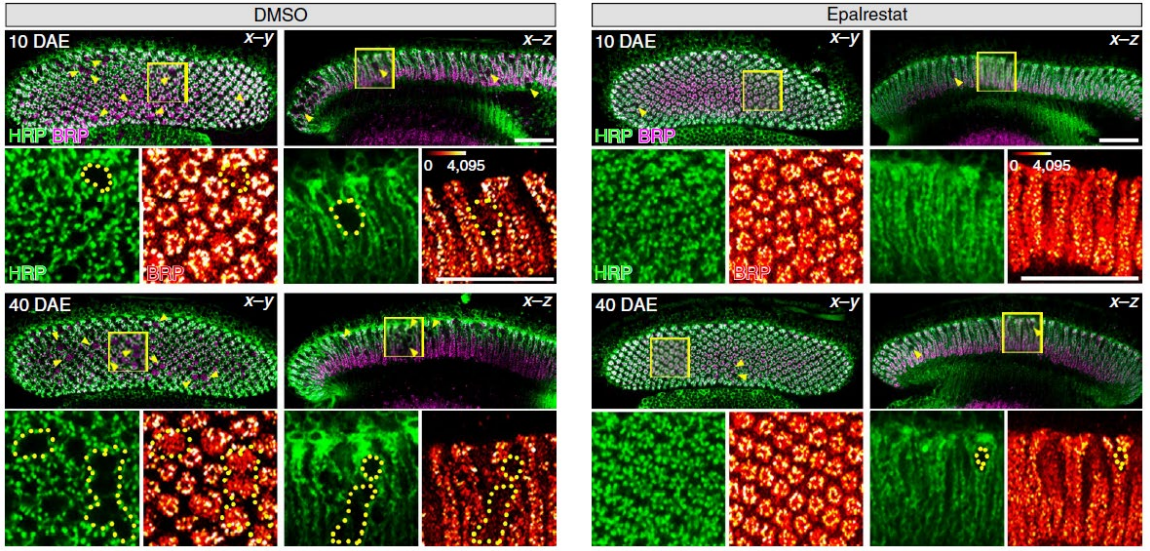
Treatments possibly on the horizon

- TRPV4
  - Codes for an ion channel
  - Causes CMT2C and forms of spinal muscular atrophy
  - TRPV4-blocking drugs rescue fly and mouse models of the disease



Woolums et al., Nat Commun 2020

- SORD neuropathy
  - Perhaps the most common cause of recessive CMT
  - Mutations in the enzyme SORD cause accumulation of sorbitol
  - Drugs that block production of sorbitol are already approved for other purposes



Cortese et al., Nat Gen 2020

Genetic Counseling and Testing for Hereditary Neuropathies

Christy H. Smith, ScM, CGC
Johns Hopkins University
MDA Genetic Counselor
September 30, 2021

JOHNS HOPKINS
MEDICINE

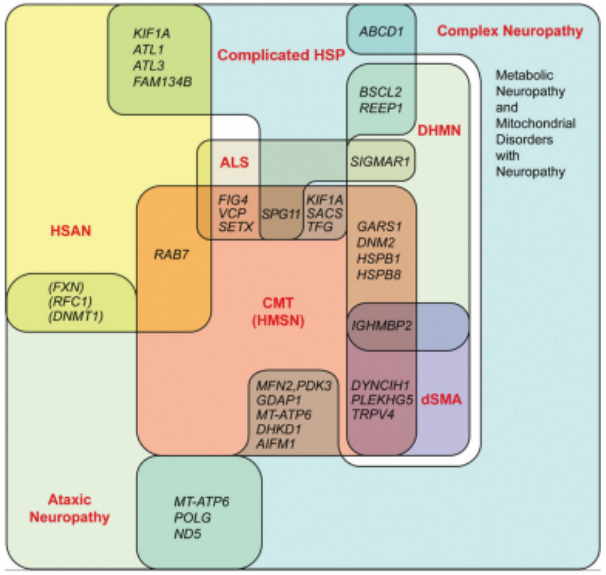
Hereditary Neuropathies

- Charcot-Marie-Tooth disease (CMT)
  - Aka hereditary motor and sensory neuropathy
- Distal hereditary motor neuropathies (dHMN)
- Hereditary sensory and autonomic neuropathy (HSAN)
- Episodic attack forms (e.g. HNPP)
- Complex hereditary neuropathies (**familial transthyretin amyloidosis**, mitochondrial disorders, HSP, SCA, Friedreich ataxia, metabolic disorders such as LSDs [Fabry disease, metachromatic leukodystrophy, Krabbe disease])

Challenges to Diagnosing Hereditary Neuropathies

- High genetic heterogeneity (lots of genes!)
- Non-specific and overlap of symptoms
  - Mildly symptomatic to severe disability, even within the same family
- Often no family history to indicate an inheritance pattern
- Limitations to non-genetic tests

(e.g. EMG/NCV, nerve biopsies)



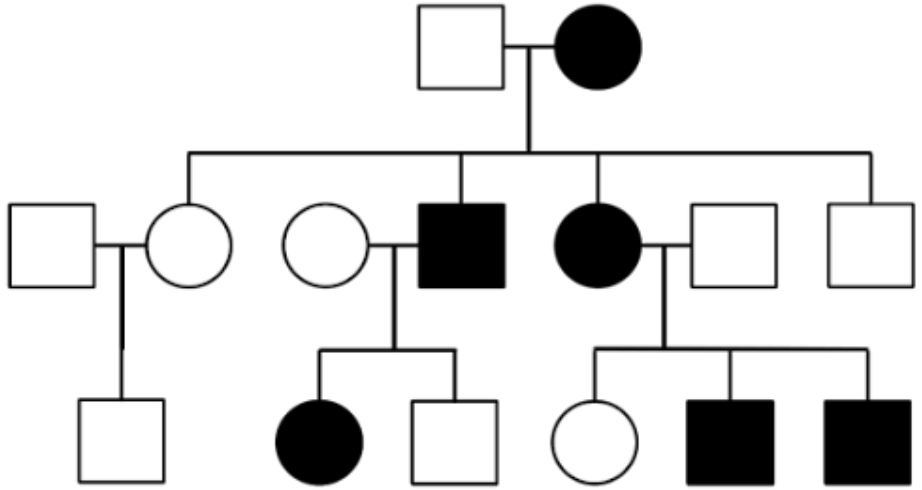
Importance of a Genetic Diagnosis

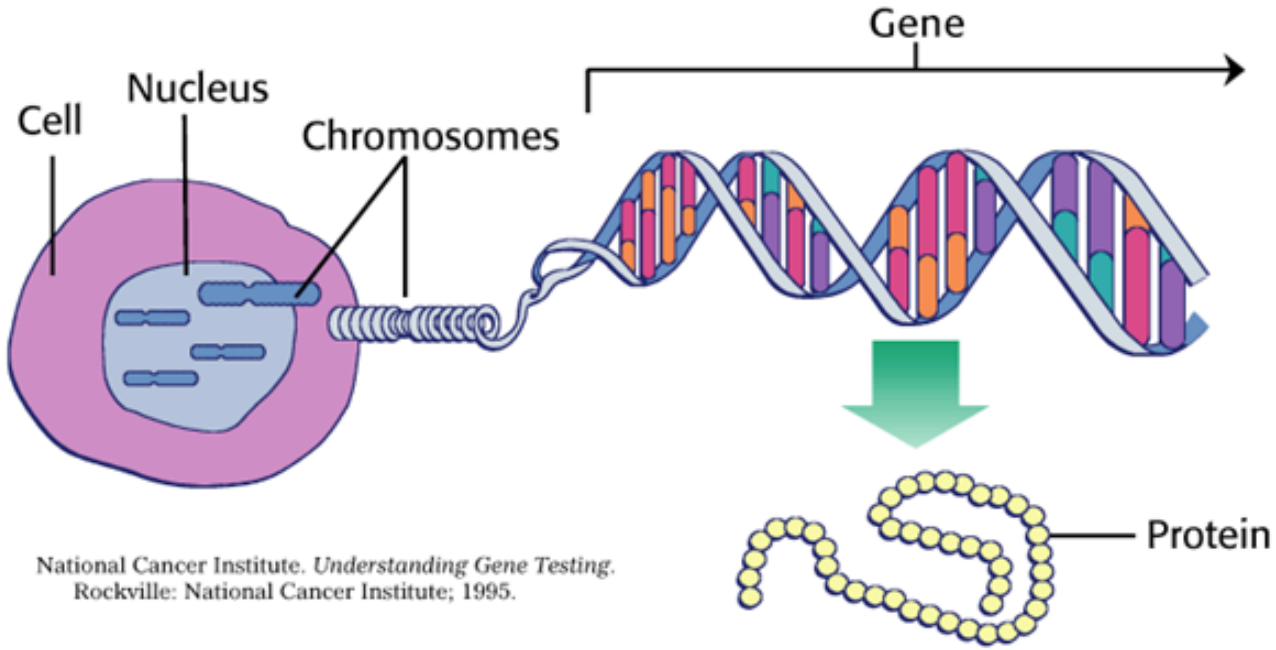
- Identify cause and prognosis
- Medical management – supportive therapies; r/o non-genetic causes (CIDP, Lyme, diabetes, vitamin B12 deficiency, etc)
- Treatment – gene-specific therapeutics:
  - RNA interference (e.g. patisiran and inotersen for TTR amyloidosis); ERT and/or oral chaperone therapy (Migalastat) for Fabry disease; PMP22 clinical trials
- Identification of at-risk relatives
- Recurrence risk, reproductive options
- Psychosocial benefits

Genetic Counseling

- Review of medical/family history to inform:
  - Possible inheritance pattern in family and genetics education
  - Appropriate test (targeted testing, gene panel, exome)
    - Obtain a copy of prior testing done in patient or relatives
  - Reproductive risks/options; risks to other relatives

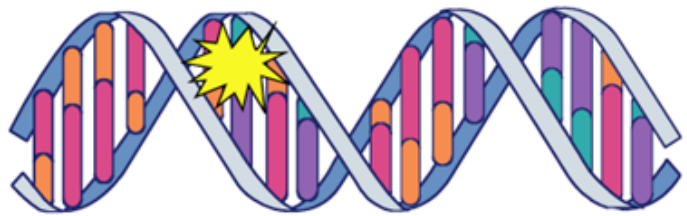
Pedigree →





National Cancer Institute. *Understanding Gene Testing*. Rockville: National Cancer Institute; 1995.

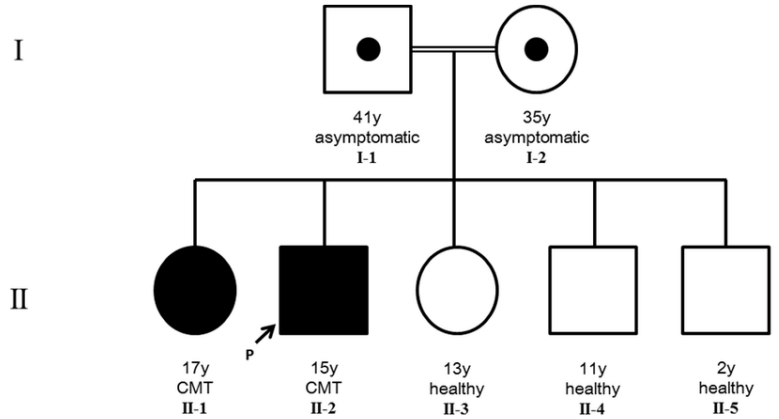
A mutation is a change in the normal base pair sequence



Commonly used to define DNA sequence changes that alter protein function

Inheritance

- Autosomal dominant
  - Most forms of hereditary neuropathy
- Autosomal recessive
- X-linked
  - No male to male transmission
  - Males and females affected differently
- Mitochondrial
- Multi-factorial



Types of Genetic Tests

- Targeted testing → known variant in the family
- Large gene panels
  - Cover many hereditary neuropathy genes
  - Negative results do not rule out hereditary neuropathy
    - Gene not included on the panel or discovered yet
    - Phenotypic overlap with distal myopathies and distal motor neuron diseases, which may be missed on a neuropathy panel
- Mitochondrial DNA analysis
  - Blood vs. buccal vs. biopsy sample
- Whole exome sequencing…

Whole exome sequencing

- Analyzes all 20,000 genes (1-2% of all DNA)
  - Only ~5,000 are known in relation to human disease
  - Negative result; re-analysis
  - Importance of trios
  - Secondary Findings
- Cannot detect all genetic disorders
  - Repeat expansions (Friedreich ataxia, SCA's, and CANVAS)
  - Non-coding variants
  - Certain deletions/duplications

Reproductive Risks

- Prenatal diagnosis
  - CVS at 10-13 weeks gestational age
  - Amniocentesis 16-20 weeks
- Pre-implantation genetic testing (PGT)
- Adoption, embryo adoption, egg or sperm donation
- Usually meet with a prenatal GC and/or fertility center

Genetic Counseling

- Discuss genetic testing options and results
  - Positive, negative, uncertain
  - Nuances of testing other family members (VUS's, importance of neuro exam)

- Psychosocial aspects
  - Coping with diagnosed or undiagnosed disease
  - Relationships with other family members
  - Guilt at passing onto children
  - Connecting with support groups

How is genetic testing done?

- Blood, saliva, buccal, or biopsy tissue
- Kit can often be sent to home
- Results can take anywhere from a few weeks to a few months
- 23andMe versus clinical testing

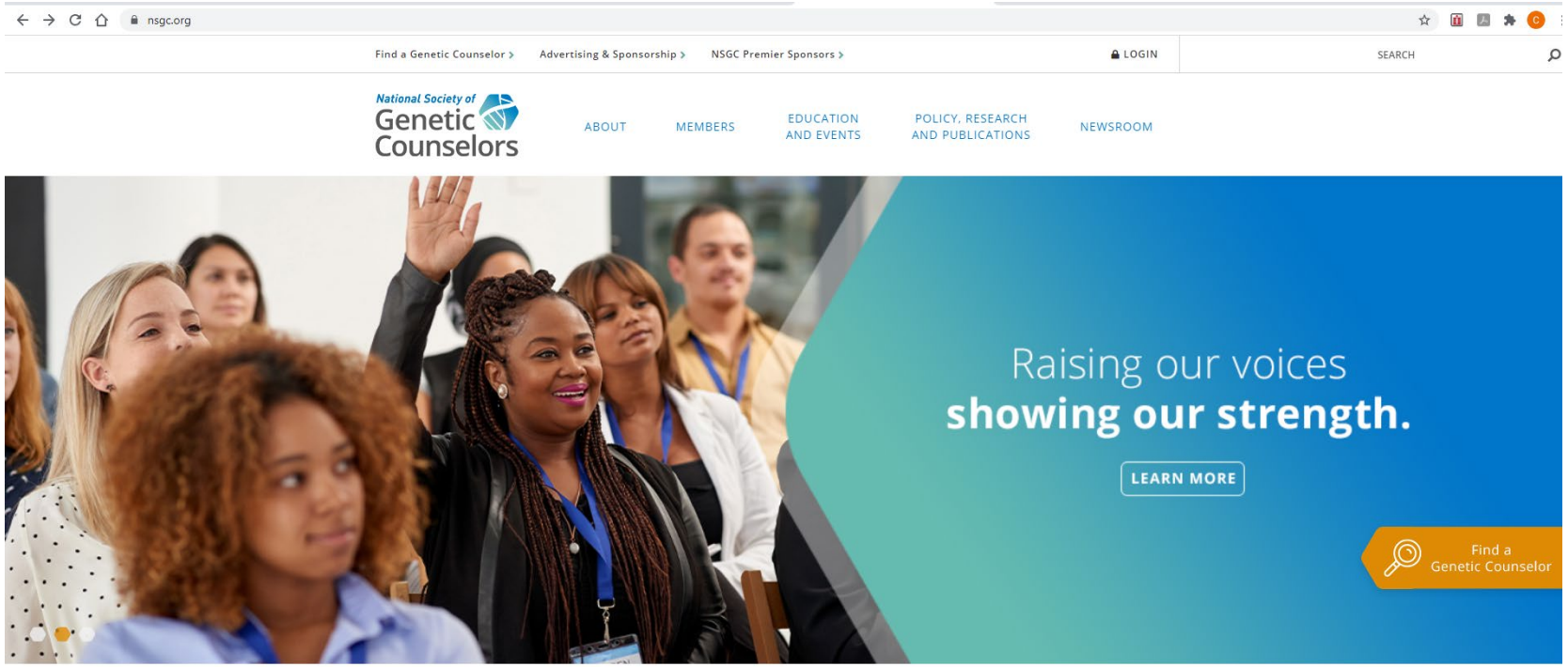
GINA

- Genetic Information Non-Discrimination Act (GINA)
  - Enacted in 2008
  - Applies primarily to *unaffected* individuals
  - Protects against discrimination from health insurance and employer
  - Does not protect potential discrimination in: life insurance, disability insurance, long-term insurance

- Genetic counseling can be helpful even if you've had a prior negative, positive, or inconclusive test
  - New testing options
  - Understanding implications
  - Variant interpretation/updates
- Genetic testing ideal for an affected person
  - Test unaffected relatives once gene alteration identified
  - Importance of neurological exam

How do I find a genetic counselor?

- Ask your PCP or neurologist for referral
- Visit www.nsgc.org → Find a Genetic Counselor



Thank you

Christy H. Smith, ScM, CGC
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Questions?

the Foundation *for* Peripheral Neuropathy

Upcoming Webinar…

hATTR Amyloidosis

Tuesday, October 26

2:30 p.m. ET

Sponsored by:

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