Live Case #3

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Clinical Presentation

- This patient is an 18-year-old right-handed male with a history of high arched feet, curled toes, and toe walking.
- The family noted toe walking and slower running than his peers starting at 5 years of age.
- At age 13, he started tripping more and developed pain in his feet on ambulation. He underwent bilateral Achilles tendon lengthening surgeries.
- Persistent walking difficulties prompted a new referral to orthopedic surgery.
- During the initial visit, he reported his toes catch frequently, resulting in near falls, and uses railing for assistance when climbing stairs. He also reported muscle cramps in both hands.
- He denied tingling-like sensations, but did report numbness and pain in his feet in cold weather.
- He denied swallowing issues, shortness of breath, orthopnea, or double vision

Review of Systems
Family History
Social History

Additional History
Physical and Neurological Examination

Electrodiagnostic Findings

Sensory NCSs

Site	Onset (ms)	Peak (ms)	O-P Amp (µV)	Site	Dist (cm)	Vel (m/s)
Right Median Anti Sensory (2nd Digit)						
Wrist	2.6	3.6	36.9	2nd Digit	13.0	50
Right Ulnar Anti Sensory (5th Digit)						
Wrist	2.1	3.0	29.0	5th Digit	11.0	52

Motor NCSs

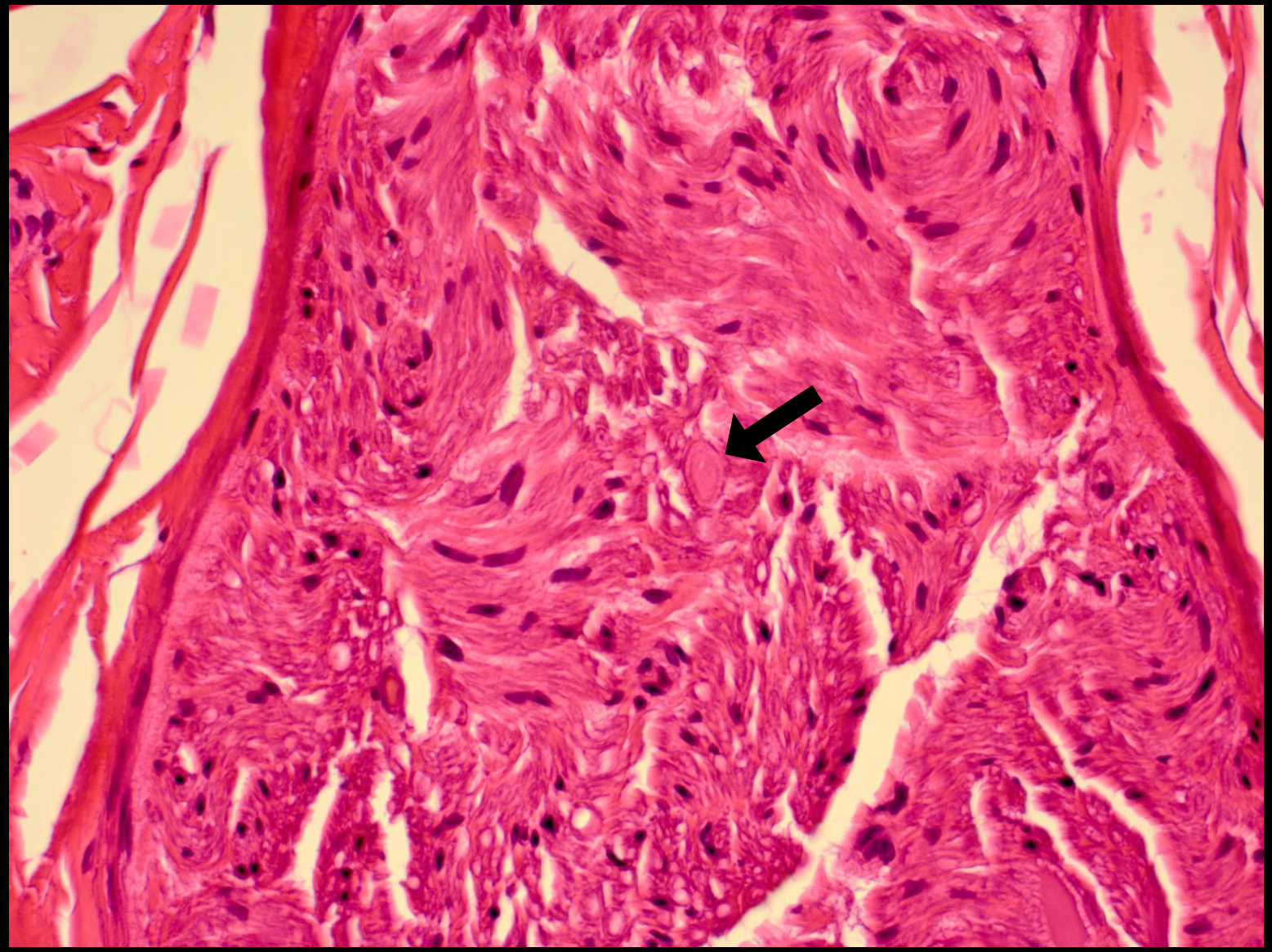
Site	Onset (ms)	O-P Amp (mV)	Site1	Site2	Dist (cm)	Vel (m/s)
Right Median Motor (Abd Poll Brev)						
Wrist	4.9	8.5	Elbow	Wrist	23.0	51
Elbow	9.4	8.2				
Right Peroneal Motor (Ext Dig Brev)						
Ankle	NR	NR				
Right Tibial Motor (Abd Hall Brev)						
Ankle	9.1	1.0	Knee	Ankle		
Right Ulnar Motor (Abductor Digit Minimi)						
Wrist	3.0	7.7	B Elbow	Wrist	22.5	52
B Elbow	7.3	7.6	A Elbow	B Elbow	9.0	50
A Elbow	9.1	7.6				

EMG

Side	Muscle	Nerve	Root	Ins Act	Fibs/PSW	Fasc	Other	Amp	Dur	Poly	Recrt
Right	AntTibialis	Dp Br Peron	L4-5	Incr	2+	None	None	Nml	Nml	Nml	Nml

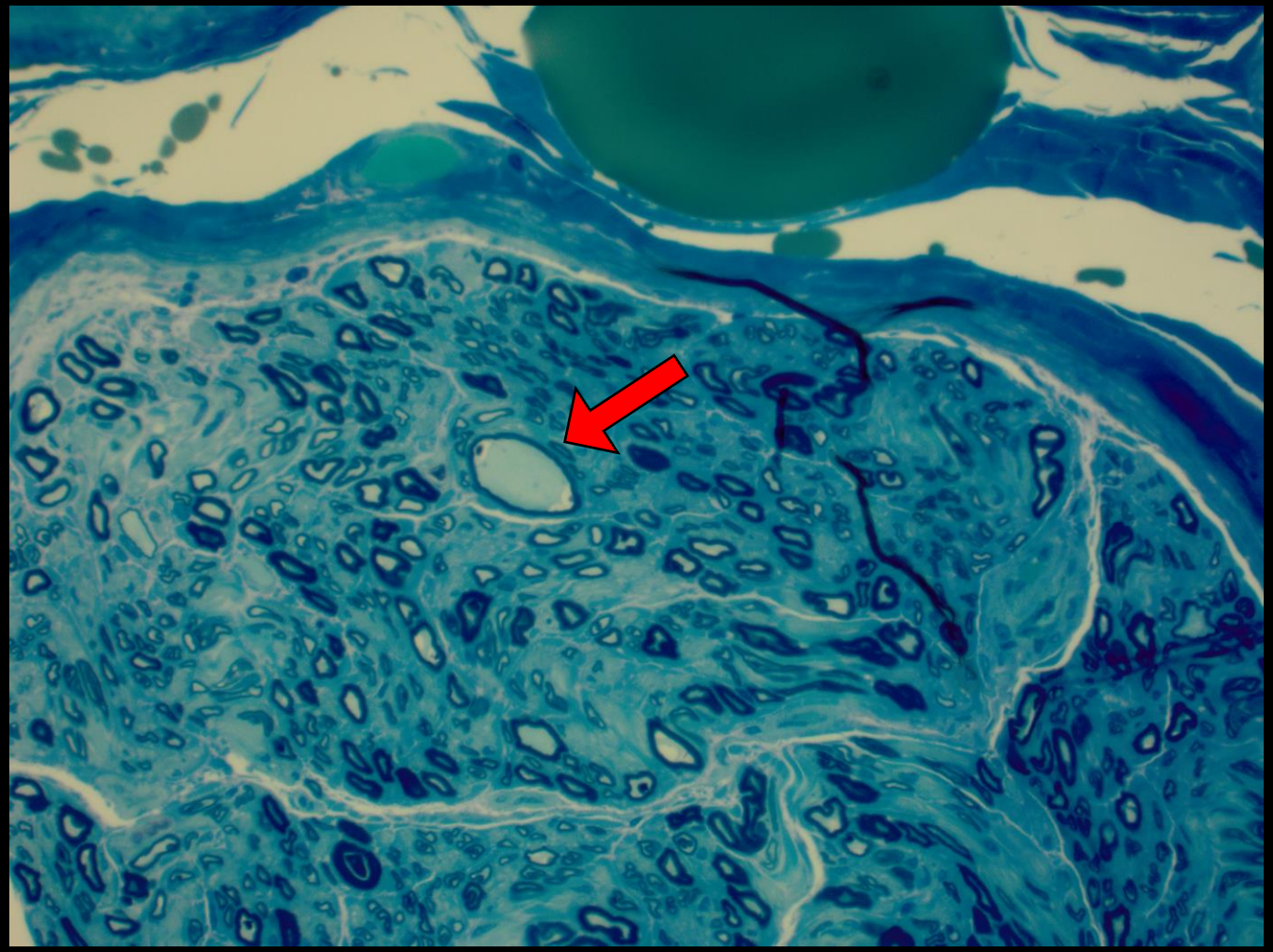
A diagnostic test was performed.

Sural Nerve Biopsy

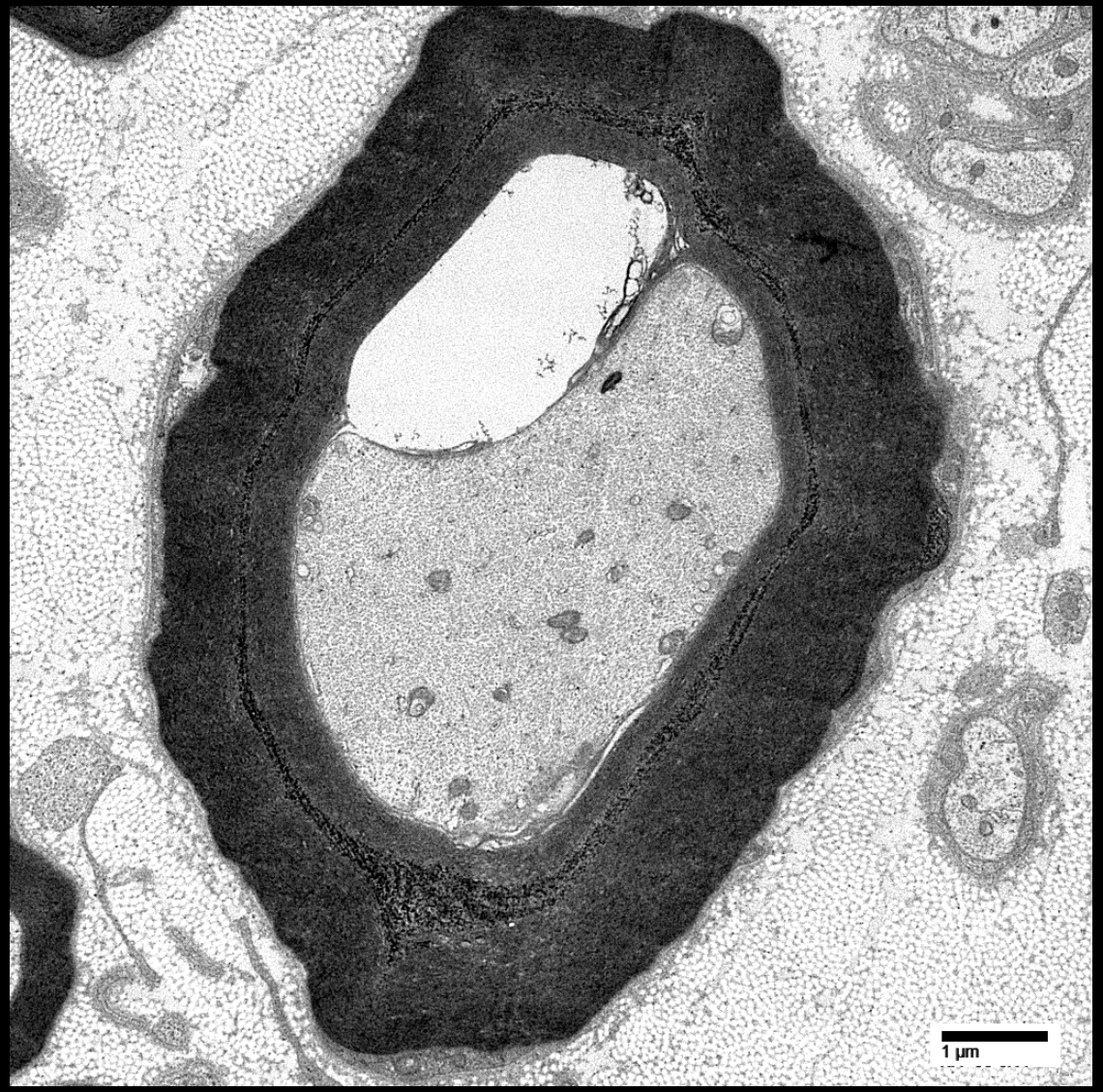


H&E

Sural Nerve Biopsy: Electron Microscopy (EM)

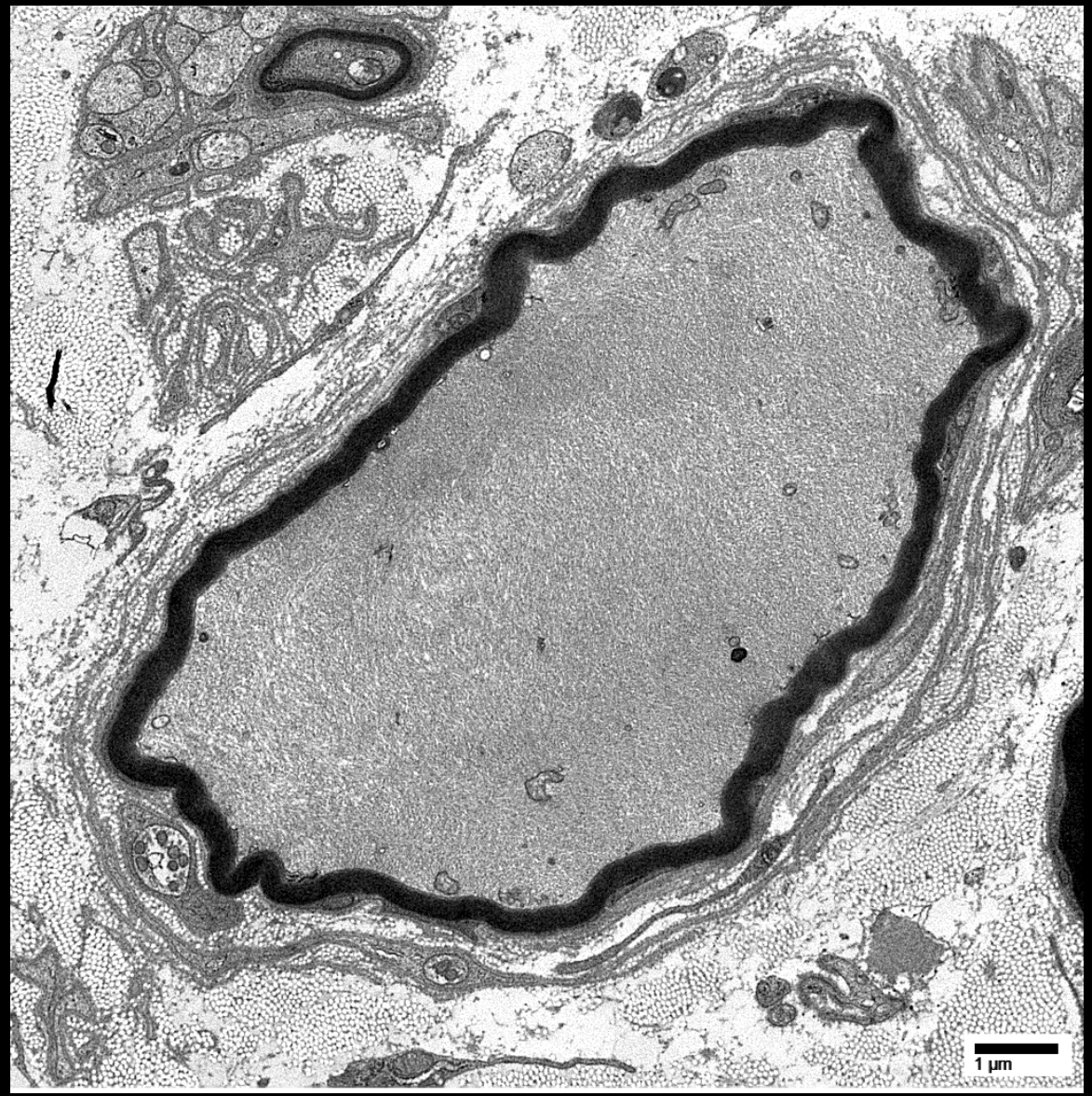


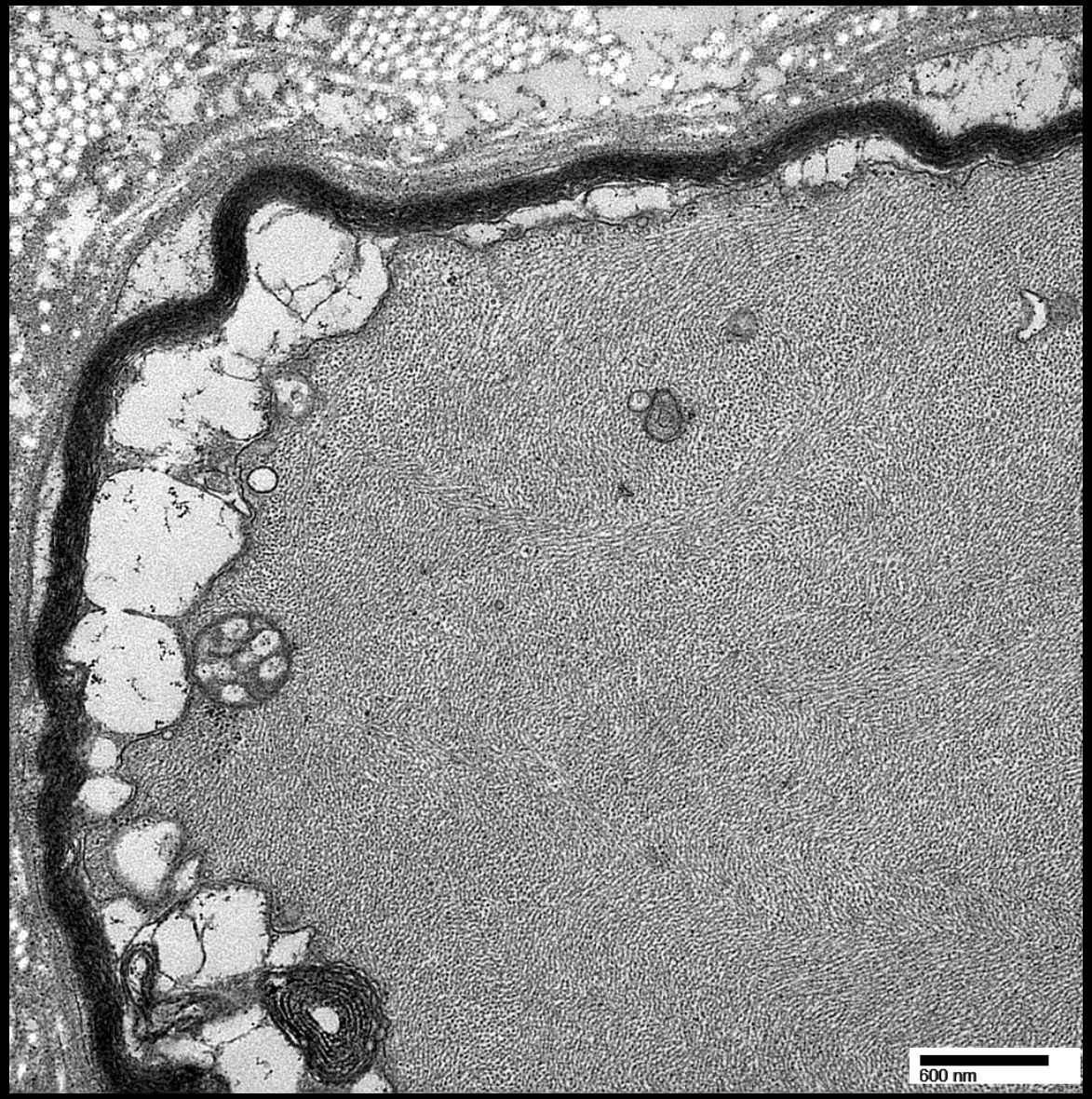
Methylene Blue



EM

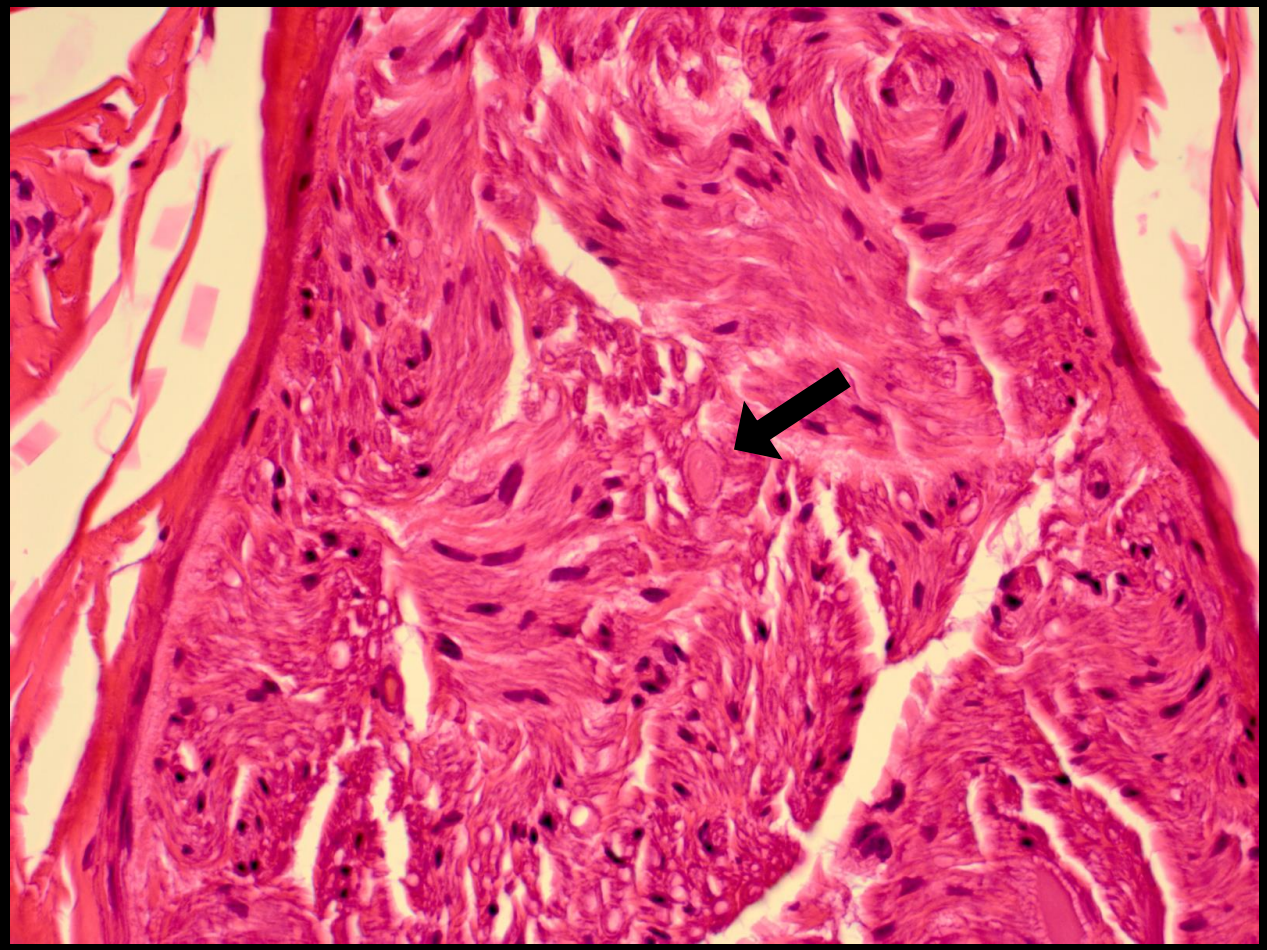
Sural Nerve Biopsy: Electron Microscopy



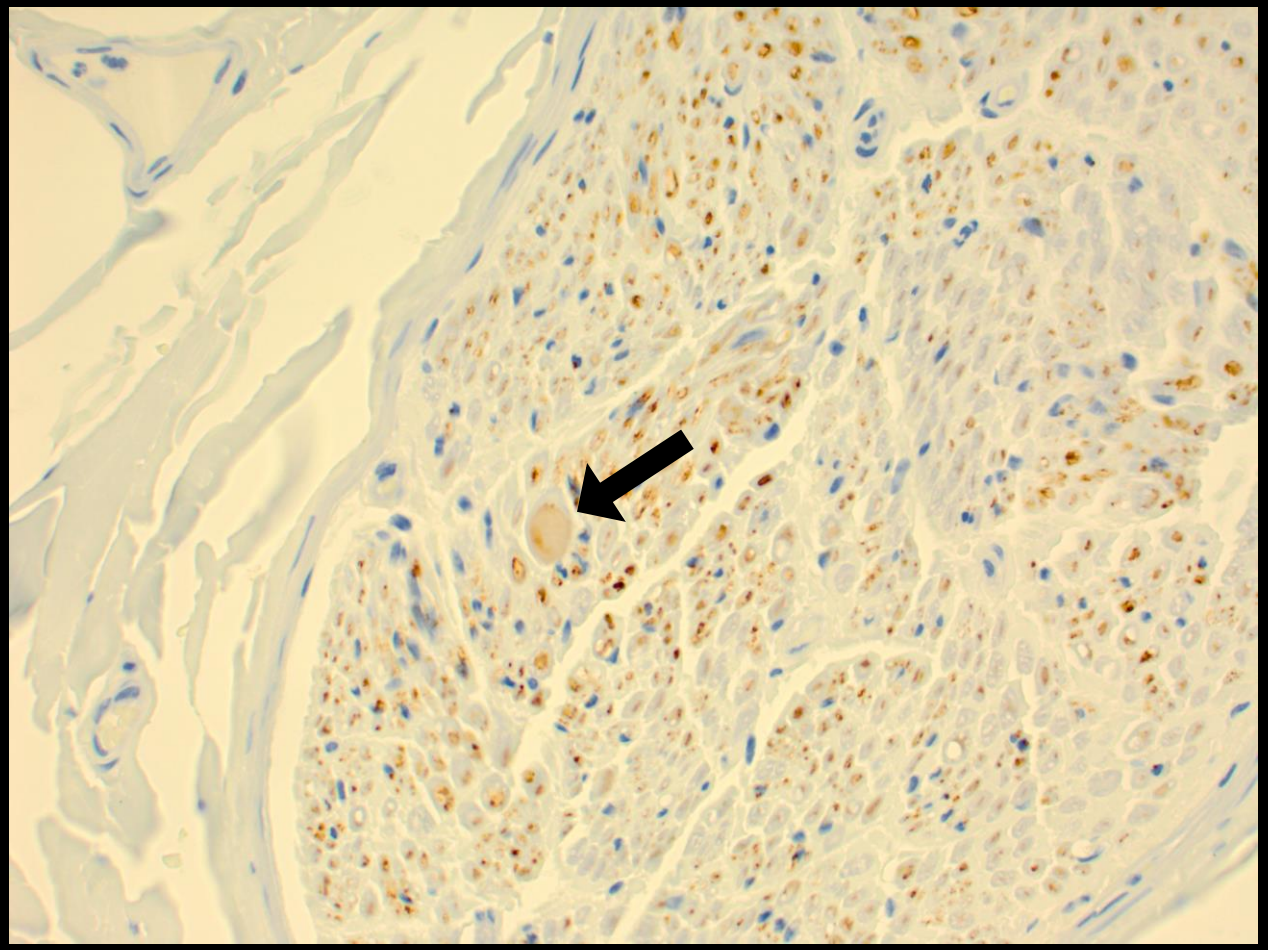


Sural Nerve Biopsy

H&E



Neurofilament



Genetic Testing

- Two VUS in the *GAN* (gigaxonin) gene:
  - c.1506G>T (p.Trp502Cys) (maternal)
  - c.944C>T (p.Pro315Leu) (paternal)

- c.944C>T has been previously reported by Bruno et. al. 2004 and Houlden et. al. 2007

- c.1506G>T has not been reported.

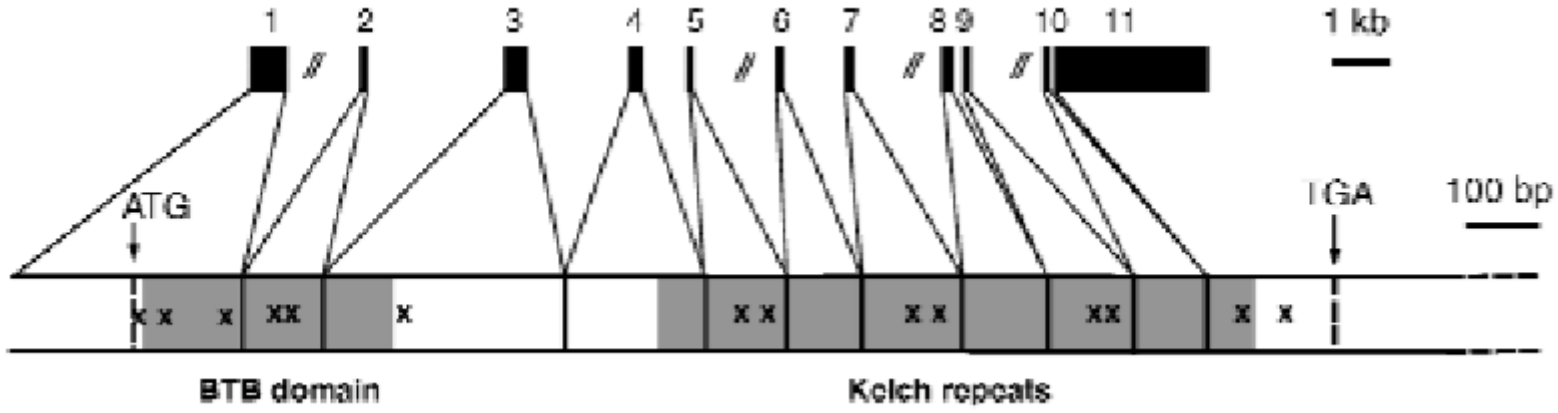
Giant Axonal Neuropathy (GAN)

- In its classic form, it is a severe autosomal recessive disease that affects both the peripheral and central nervous system
- First Described in 1972
- Very rare
- Only about 50 families have been described in the medical literature
- Likely underdiagnosed

Giant Axonal Neuropathy (GAN)

- The gigaxonin gene *GAN* was identified as the mutated gene in giant axonal neuropathy in 2000 (Bomont et. al. Nat Genet). Located in chromosome 16q24

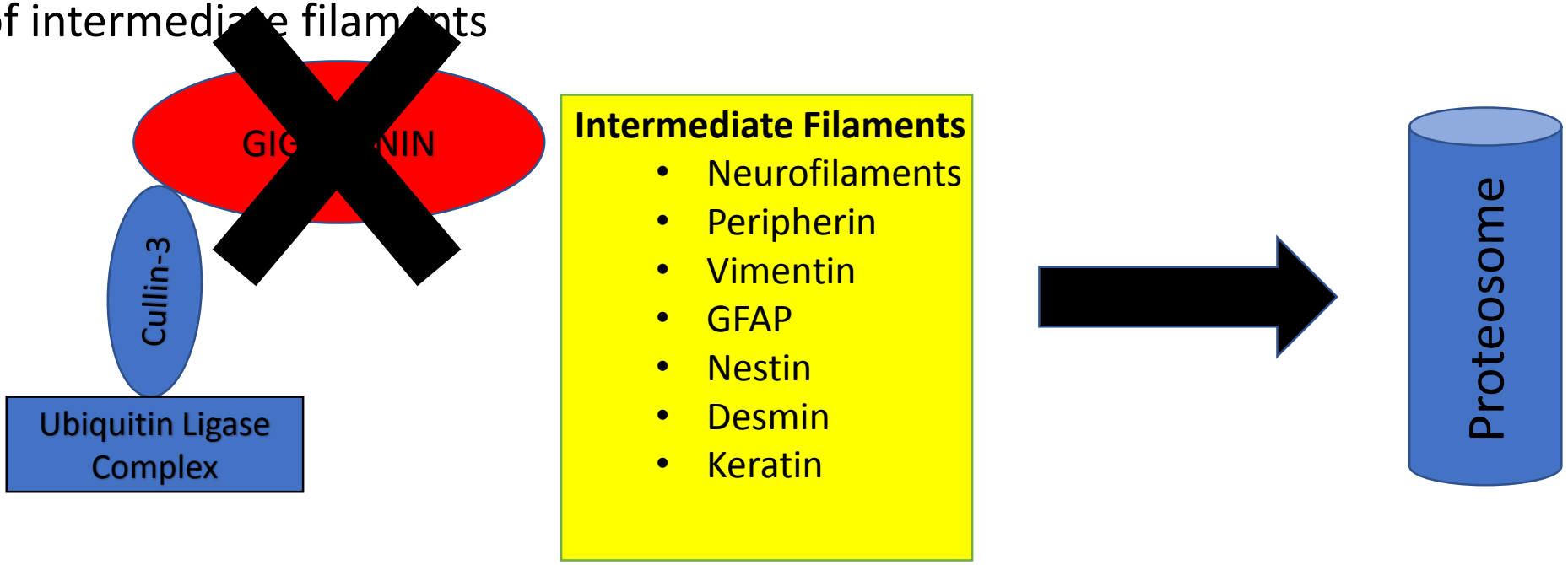
- Composed of an amino-terminal BTB (for Broad-Complex, Tramtrack and Bric a brac) domain followed by six Kelch repeats



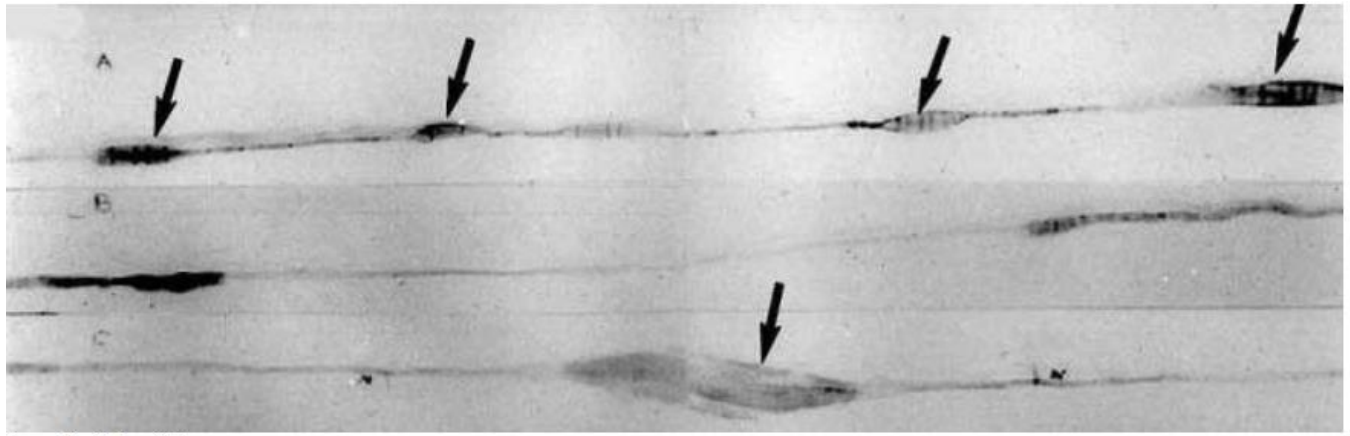
- More than 40 different mutations have been reported.

Giant Axonal Neuropathy (GAN)

- E3-ligase adaptor that works as part of the ubiquitin-proteasome system and plays a role in the breakdown of intermediate filaments



- Loss of GAN causes accumulation of intermediate filaments-> axonal accumulation and axonal swelling



From Pr P Landrieu

Teased axons with focal swellings (Arrows).

Source. https://neuromuscular.wustl.edu

Giant Axonal Neuropathy (GAN)

nature

Vol 438|10 November 2005|doi:10.1038/nature04256

LETTERS

Gigaxonin-controlled degradation of MAP1B light chain is critical to neuronal survival

Elizabeth Allen[1]*, Jianqing Ding[1]*, Wei Wang[1], Suneet Pramanik[1], Jonathan Chou[1], Vincent Yau[1] & Yanmin Yang[1]

Giant Axonal Neuropathy (GAN)

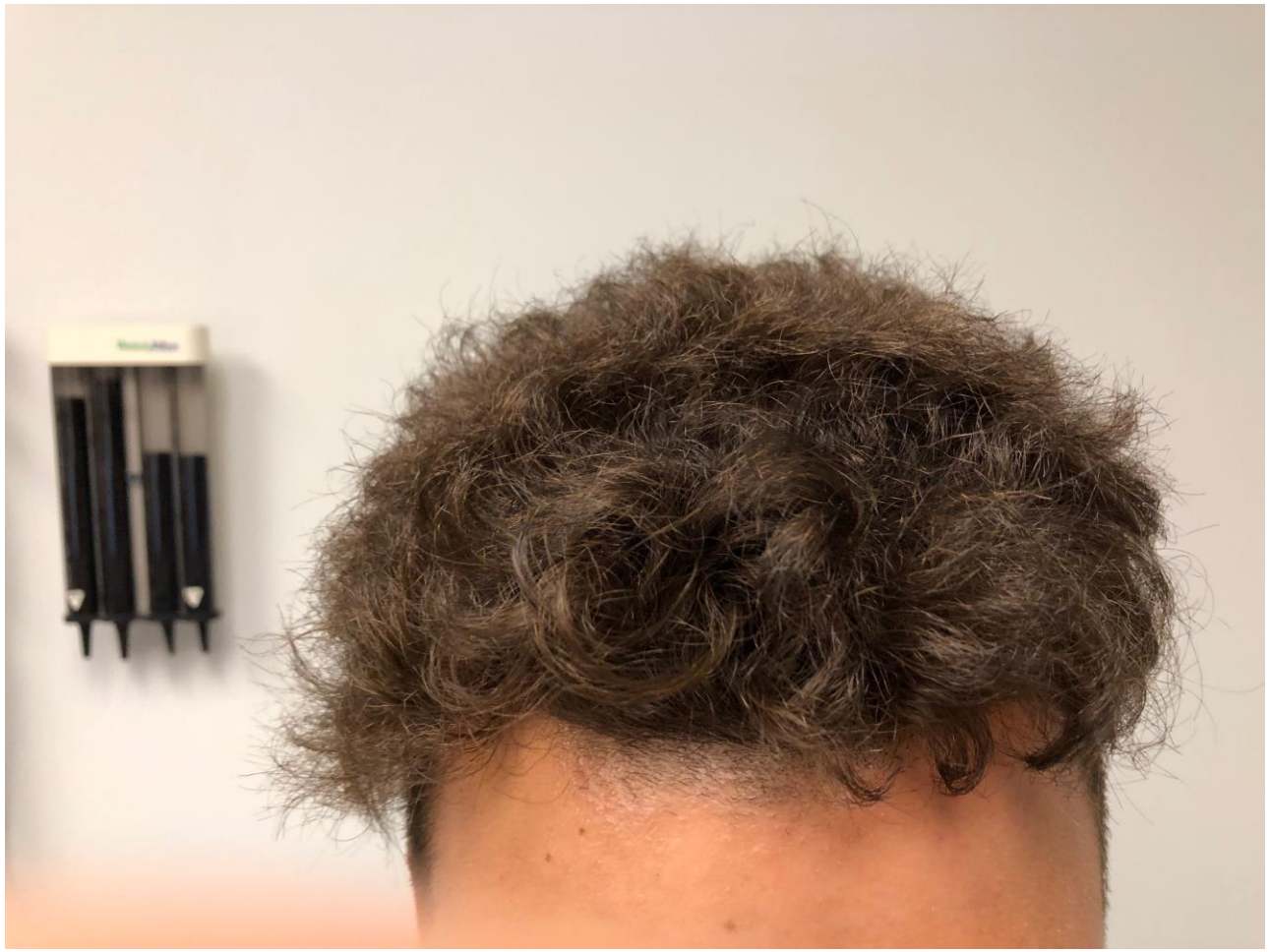
- **Physical appearance:** kinky hair, high forehead, pale complexion, and long eyelashes

Source. https://blog.timesunion.com

Source. https://irp.nih.gov

Source. https://globalgenes.org

Giant Axonal Neuropathy (GAN): Kinky hair



Our patient’s family

Giant Axonal Neuropathy (GAN)

- **Physical appearance:** red and kinky hair, high forehead, pale complexion, and long eyelashes

- **Symptoms:** usually begin before age 5 with gait disturbances and frequent falls due to both weakness and ataxia; numbness is present as well

- **CNS involvement**: cerebellar dysfunction, spasticity, and **optic atrophy**; hearing can be affected; intellectual disability, seizures, and dementia can occur

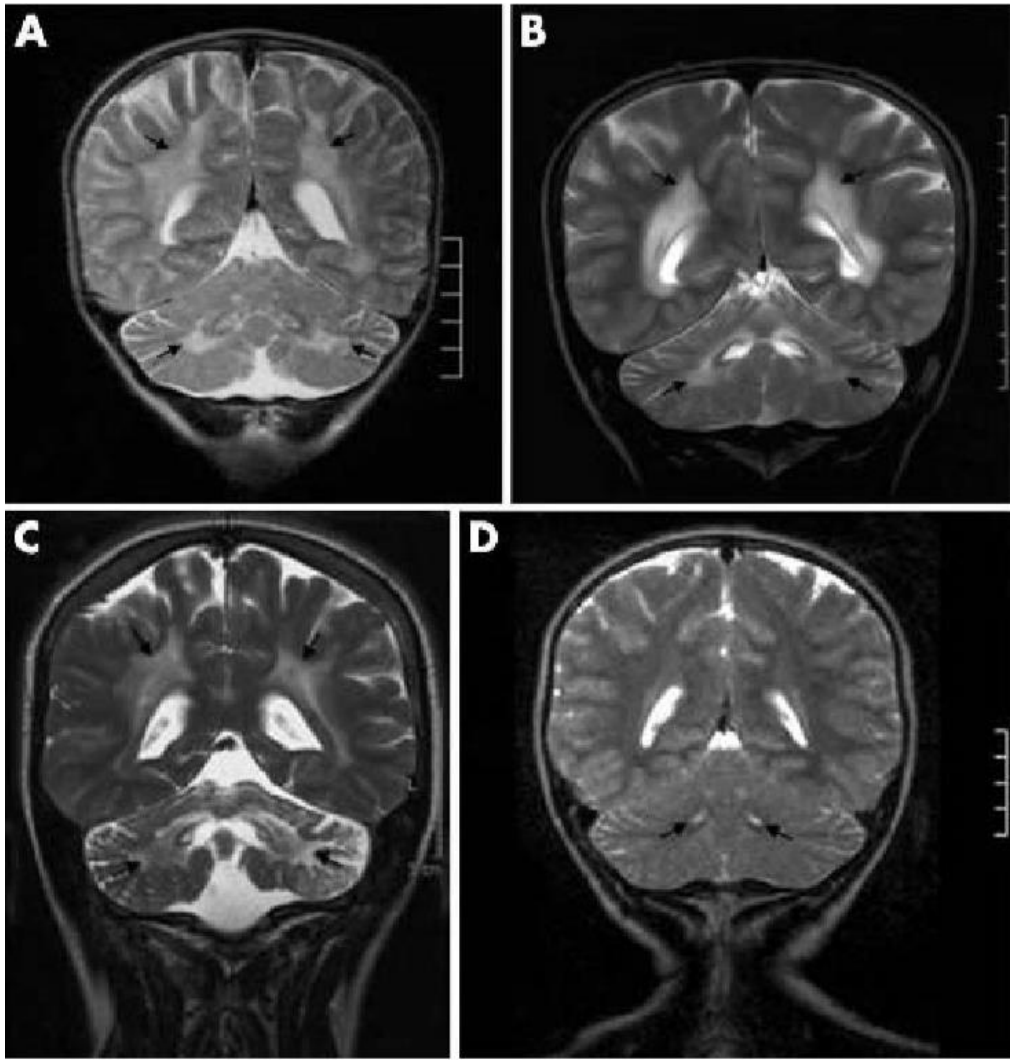
- **Autonomic nervous system involvement:** neurogenic bladder, constipation, heat intolerance, hypohidrosis or anhidrosis

- Most children become wheelchair dependent in the 2nd decade. Death usually occurs in the 3rd decade most often due to respiratory failure.

Giant Axonal Neuropathy (GAN): Findings

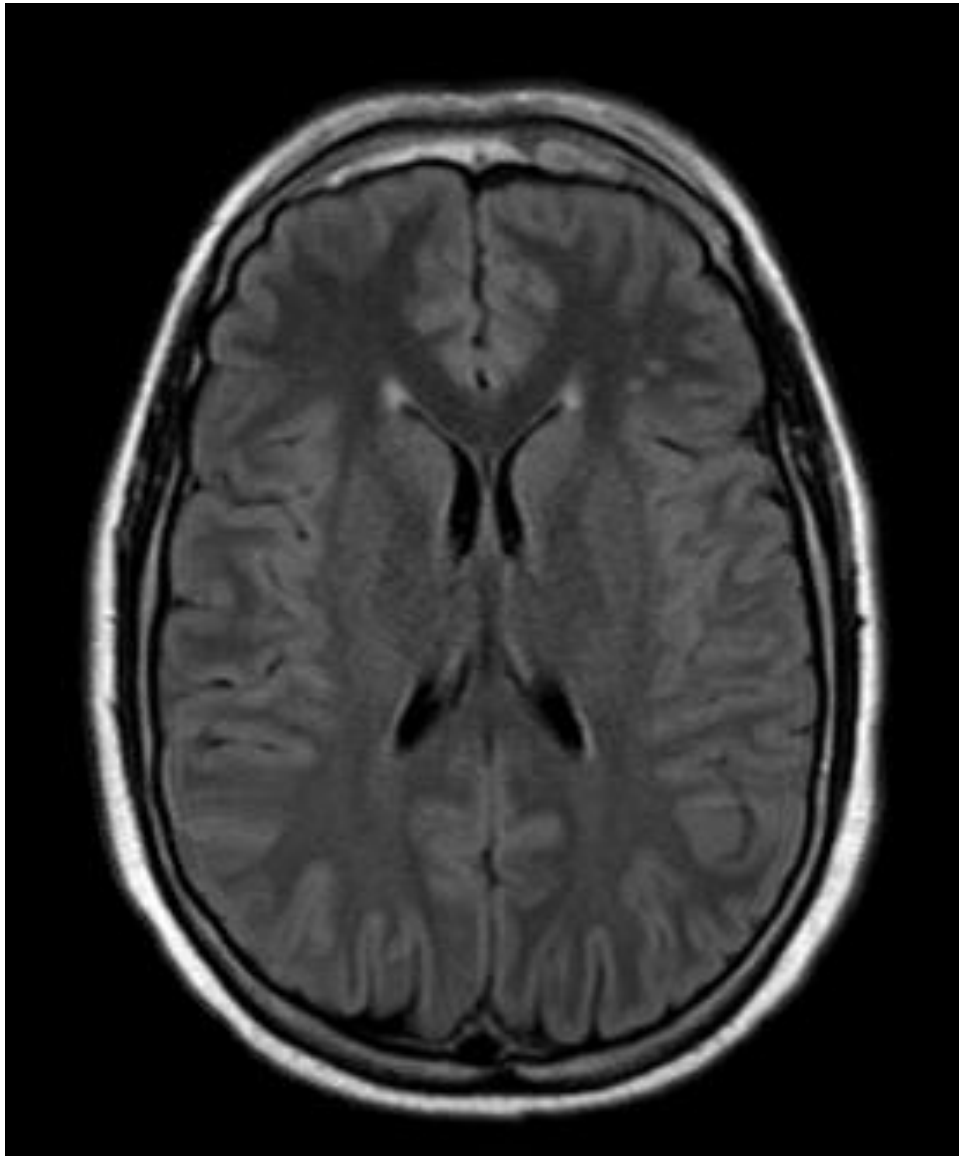
- NCS/EMG: SNAPs are typically absent; motor NCSs can be normal or with amplitude reductions

- Imaging Findings:
  - White matter changes, atrophy of the cerebellum, and optic tracts



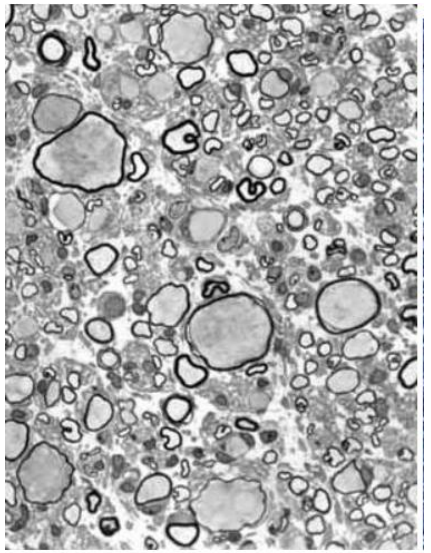
Demir et. al. J Neurol Neurosurg Psychiatry 2005

Giant Axonal Neuropathy (GAN): Our Patient



Giant Axonal Neuropathy (GAN): Diagnosis

- Diagnosis: Nerve biopsy and genetic testing
- Nerve Biopsy: Classic findings include axonal loss, giant axon swelling, densely packed bundles of neurofilaments



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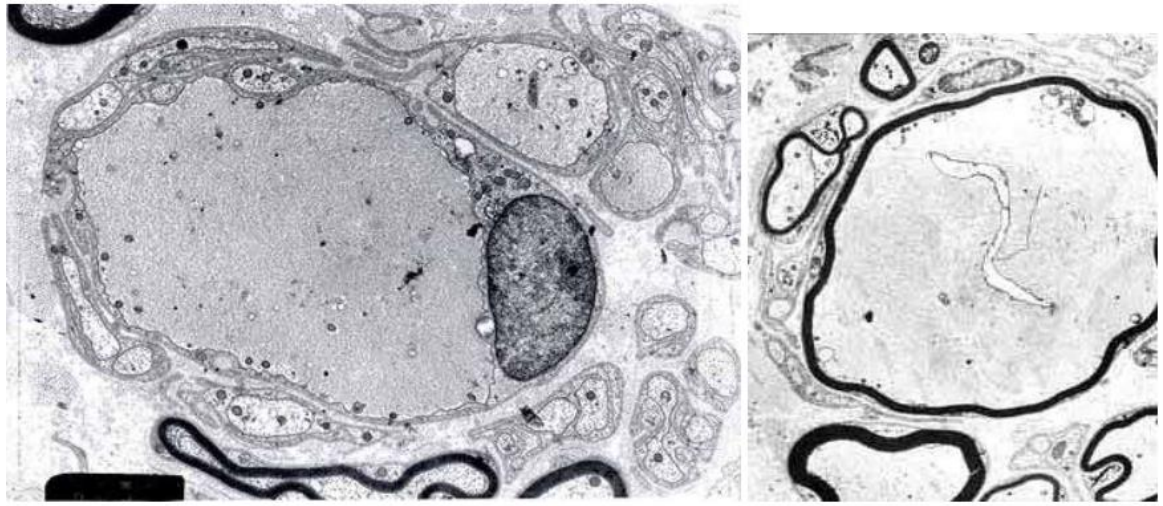
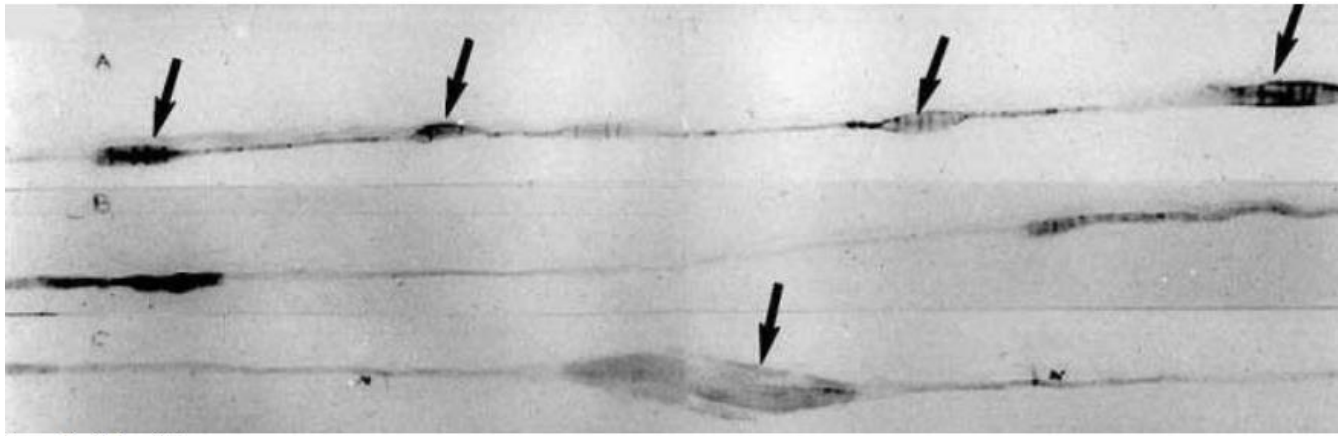


From Pr P Landrieu

Enlarged unmyelinated, or thinly myelinated, axons.



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Giant Axonal Neuropathy (GAN)

What about Treatment?

A Phase I Study of Intrathecal Administration of scAAV9/JeT-GAN for the Treatment of Giant Axonal Neuropathy

- ClinicalTrials.gov Identifier: NCT02362438
- PI: Dr. Carsten Bonnemann
- NIH Clinical Center in Bethesda, MD
- Utilizes an AAV9 vector

Bailey et. al. Mol Ther Methods Clin Dev 2018

- Delivered intrathecally
- Purpose is to primarily target the spinal cord and brainstem motor neurons, as well as the dorsal root ganglion

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