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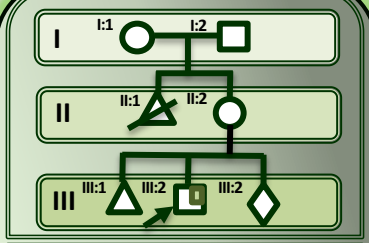
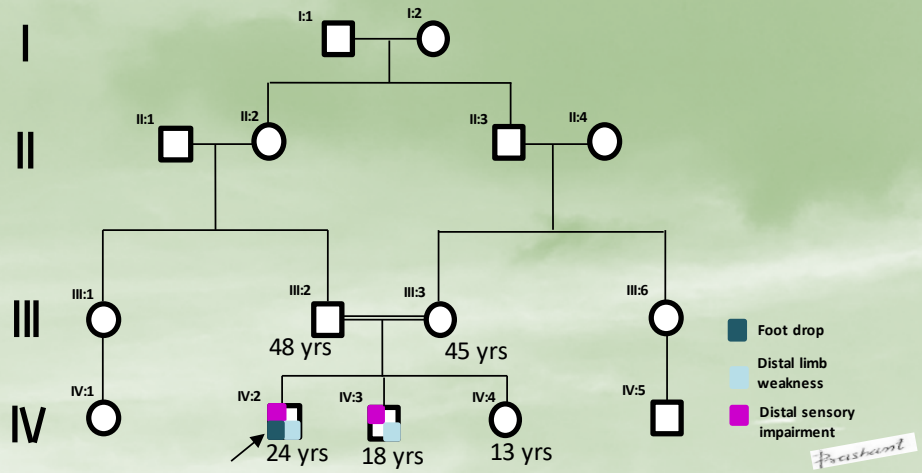
Progeroid Syndromes Like (PSL)-IV / LAMIN A/C related disorders / Charcot-Marie-Tooth type 2B1 (CMT2B1)



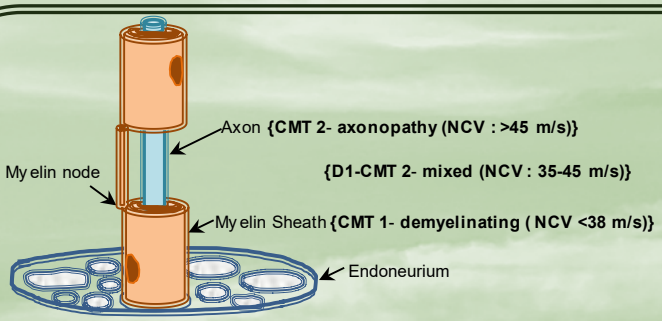
From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals.

The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.



Charcot-Marie-Tooth Hereditary Neuropathy(CMTHN) or Hereditary Motor and Sensory Neuropathy (HMSN)



- **CMTHN** or **HMSN** or Distal hereditary motor neuropathy **(dHMN)** and distal spinal muscular atrophy **(DSMA)**: chronic, symmetrical, usually painless, monogenic motor and sensory polyneuropathy usually without any primarily complex neurological features.
- **CMTHN** is classified 1 & 2 on the basis of nerve conduction velocities (**NCVs**) (delayed versus normal >45 m/s), but both have reduced the total action potentials in the muscle by motor unit [Compound Muscle Action Potential (**CMAP**)].
- Because of quite overlapping NCV/EMG phenotypes, **present classification is based on genetic aetiology**.
- Majority peripheral neuropathy is not counted as CMT with **complex neurogenetic disorders** or **the presence of additional neurological signs or symptoms**.

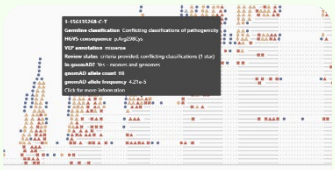
Insight:

1. What is the difference between CMTHN, and HSMN?
2. What are the online variant browser databases for inherited neuropathy?
3. How would you counsel family for molecular testing of case IV:4?
4. What are the key characteristic presentations of CMT?
5. How would you localize the mutation variant in gnomAD , pathogenicity Heatmap and structure viewer?

Plausible tenets:

Gene: LMNA (1q22) Genomic coordinates (GRCh38) 1:156,082,573-156,140,081 (from NCBI)

- **LMNA (Lamin A, included Lamin C),** a complex protein network beneath the nuclear membrane responsible for nucleus resilience, **having 42 splice variants, which might have cell lineage-specific regulatory functions**
- **Recognize as the FIRST gene that can cause AR CMT2**
- p.Arg298Cys (**c.892C>T**) is **the most common reported variant** with the CMT2B phenotype.



https://gnomad.broadinstitute.org/gene/ENSG00000160789?dataset=gnomad_r4

https://alphafold.ebi.ac.uk/entry/P02545, AlphaMissense Pathogenicity Heatmap, AF-P02545-F1-v4

Clinical phenotypes: Variable Age of onset: 6 to 27 years**;** the proximal lower limb muscles could be involved

Management: Clinical practice guideline for the management of paediatric Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry. 2022 May;93(5):530-538. doi: 10.1136/jnnp-2021-328483. Epub 2022 Feb 9. PMID: 35140138

Graphical representation of phenotype/gene relationship(s): PS118220 https://omim.org/graph/linear/PS118220

Inherited peripheral neuropathies (1 in 2500 persons), often known as Charcot-Marie-Tooth (CMT) disorders, were described by Charcot and Marie in France and, independently, by Tooth in England in the late 1800s. Inherited Neuropathy Variants Browser: https://neuropathybrowser.zuchnerlab.net/#/ , and individual variant in a particular gene can be browse: https://gnomad.broadinstitute.org/ https://www.ebi.ac.uk/eva/?Variant%20Browser , https://genome.ucsc.edu/

Peripheral nerve fiber classification on the basis of their caliber & myelination

Group I- large (12–22 µm)—primary sensory fibers of muscle spindles (Group Ia) & smaller fibers of Golgi tendon organs (Group Ib)

Group II - the secondary sensory terminals of muscle spindles, with diameters of **6–12 µm**

Group III – (1–6 µm), free sensory endings in the connective tissue sheaths around and within muscles, and are nociceptive and, in skin, also thermosensitive

Group IV - unmyelinated, with diameters below **1.5 µm;** included free endings in skin and muscle, and are primarily nociceptive.

Investigations for CMT

EMG/NCV can direct laboratory testing by determining if it is axonal or demyelinating.

Molecular tests are available for PMP22, connexin 32, P0, EGR2, MFN2, and a few other rarer forms.

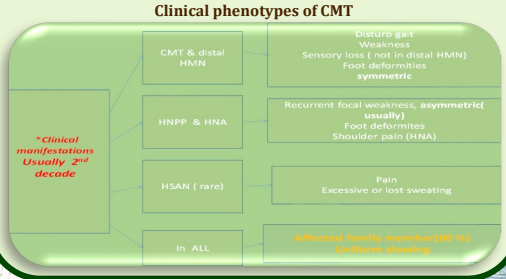
Nerve biopsy—occasionally can be useful in excluding other causes of neuropathy (i.e., Refsum disease, vasculitis).

CSF protein may be mildly elevated, which can make it difficult to distinguish from CIDP in certain clinical situations.

Genetic test: panel test/ Whole exome sequencing

Test	Applicability
CMT panels	broad range of genetic tests, expensive
CMT 1–like phenotype	1st – FISH for PMP22 duplication, if negative 2nd - PMP22, Cx32, MPZ sequencing
CMT 2–like phenotype	1st -Cx32 (unless M to M transmission +) 2nd -MPZ, 3rd -MFN2, esp. if childhood onset, 4th –NFL
Severe/early-onset CMT 1/CMT3	1st -PMP22 sequencing, 2nd -MPZ, 3rd -Consider EGR2, GDAP1 (both rare)

Clinical phenotypes of CMT



Approach to the case of the hereditary polyneuropathy

1st – detail family history

2nd - PNS, PNS + CNS, PNS + systemic signs

3rd - Spot diagnostic features – present or not,

4th – Additional clinical finding/supporting,

5th – Genetic phenotype variability in a few cases.

Counsel the family for Case IV: 4- Genotyping for phenotypically normal individuals is indicated in the following situation:

1. A medically actionable genetic condition
2. Preconception molecular testing
3. Further classification of doubtful variant
4. Specific case scenario as legal or psychological

Thought Riveting:

- ***What would be the surveillance criteria for the CMT2B1 case? Would you like to search for other hypomorphic phenotypes in each case of CMT2B1?***
- ***Why are there no obvious progeria features with CMTD due to LMNA gene mutation?***
- ***What are the molecular functional differences between the genes of CMDT and HSAN?***
- ***Could the peripheral neuropathy be recognised as a common progeroid feature in humans?***
- ***What are the disease modifier genes for the CMDT Laminopathies especially for p.Arg298Cys (c.892C>T) variant ?***