CHARCOT-MARIE-TOOTH DISEASE

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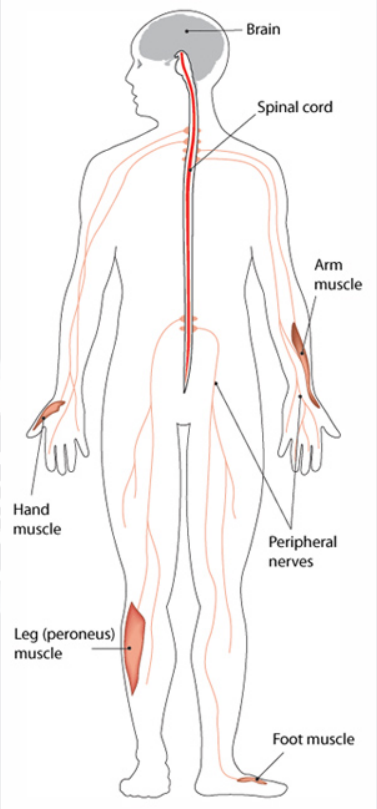
INTRODUCTION

- Charcot-Marie-Tooth disease, also called hereditary motor and sensory neuropathy is one of a group of inherited disorders that cause damage to the peripheral nerves.
- It is also called hereditary motor and sensory neuropathy (HMSN) or perineal muscular atrophy.
- Gradually progressive disease
- Occurs in adolescence and early childhood

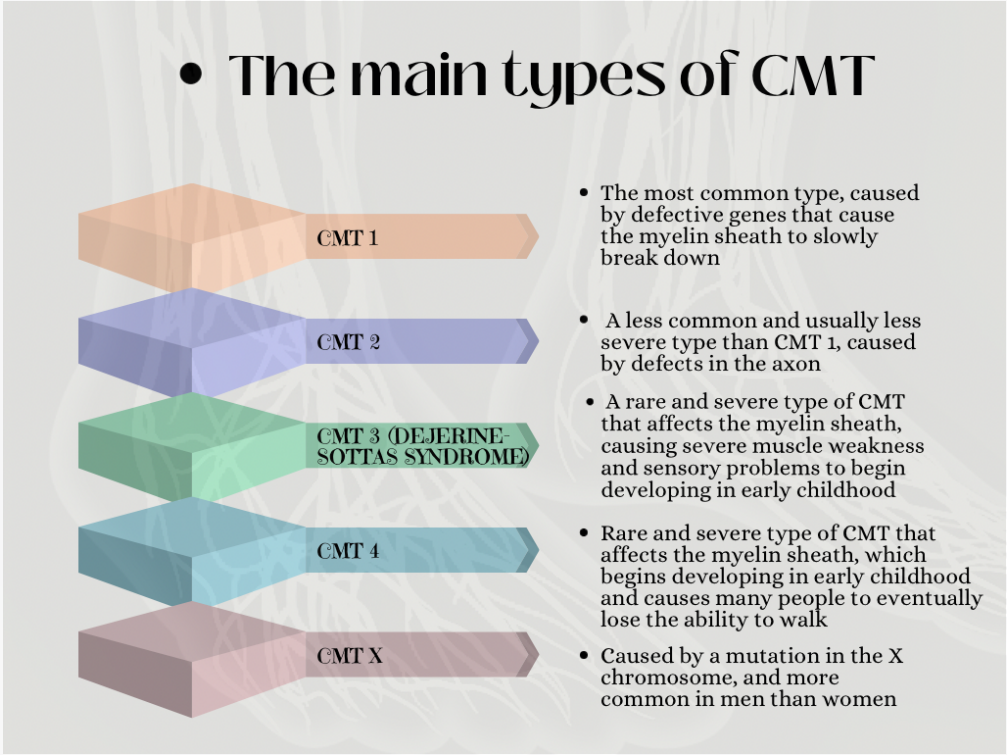
What is CMT?

1. CMT is a group of disorders that **damage peripheral nerves**, affecting transmission of signals from the brain and spinal cord to and from the rest of the body, as well as sensory information back to the spinal cord and brain
2. It can also **affect the nerves that control muscles**, resulting in progressive muscle weakness that becomes noticeable in adolescence or early adulthood
3. Symptoms **usually begin in the feet and lower legs** and can eventually affect the fingers, hands, and arms
4. CMT is one of the **most common inherited neurological disorders**, affecting an estimated 126,000 individuals in the U.S. and 2.6 million people worldwide
5. Nearly all cases are inherited, with some individuals having mutations in multiple genes causing different types of CMT
6. CMT is named after the three physicians who first described it in 1886: Jean-Martin Charcot, Pierre Marie, and Howard Henry Tooth



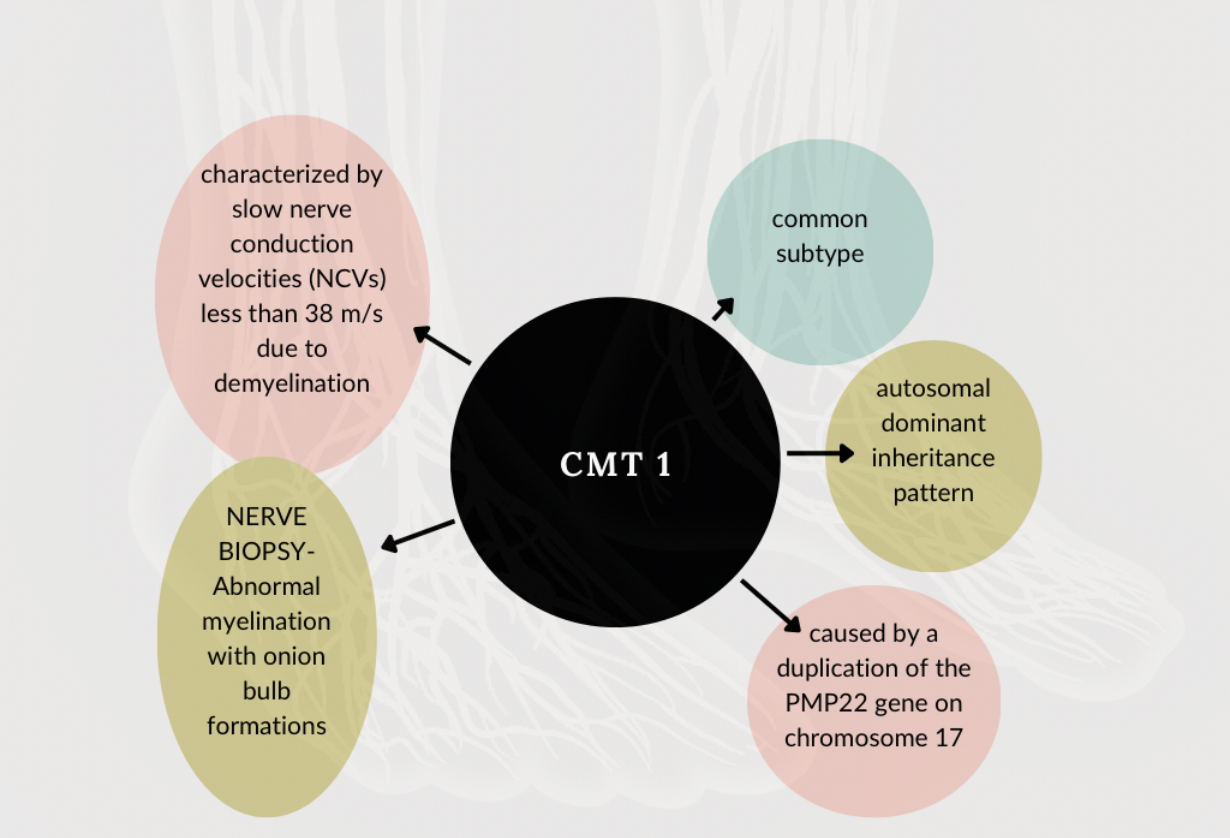
ETIOLOGY

-CMT is caused by **mutations in genes** that affect the production of proteins involved in nerve function and maintenance
-CMT can be **inherited** in an autosomal dominant, autosomal recessive, or X-linked pattern
-In **autosomal dominant inheritance**, a person with one copy of the mutated gene has a 50% chance of passing it on to each of their children
-In **autosomal recessive inheritance**, both parents must carry a copy of the mutated gene for their child to be affected
-In **X-linked inheritance**, the mutated gene is located on the X chromosome, and males are typically more severely affected than females
-In some cases, CMT may occur **spontaneously** without any family history
CMT is a **genetically heterogeneous disorder**, meaning that mutations in many different genes can cause the condition
-Over 100 genes have been identified as being associated with CMT, with each gene playing a slightly different role in nerve function and maintenance.

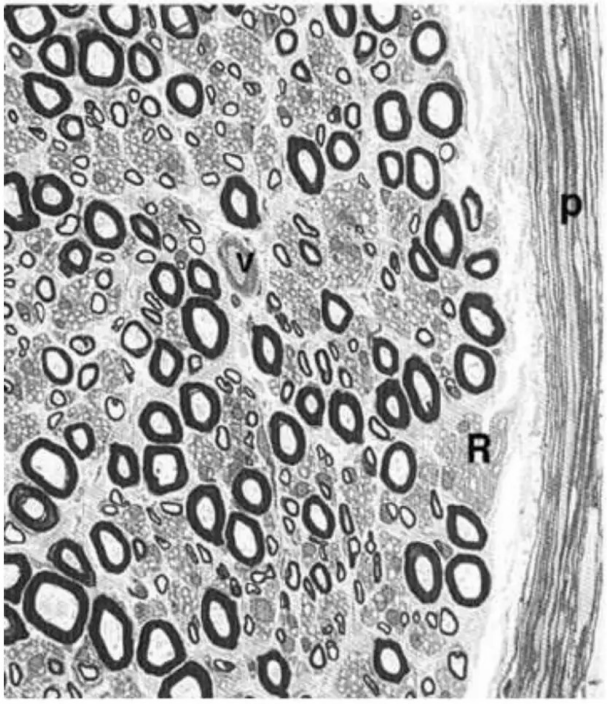


Demyelinating forms
Reduced nerve conduction velocity (<38 m/sec) in upper limb nerves and myelin abnormalities on biopsy (e.g. onion bulb formation).
-CMT type 1
-CMT type 4

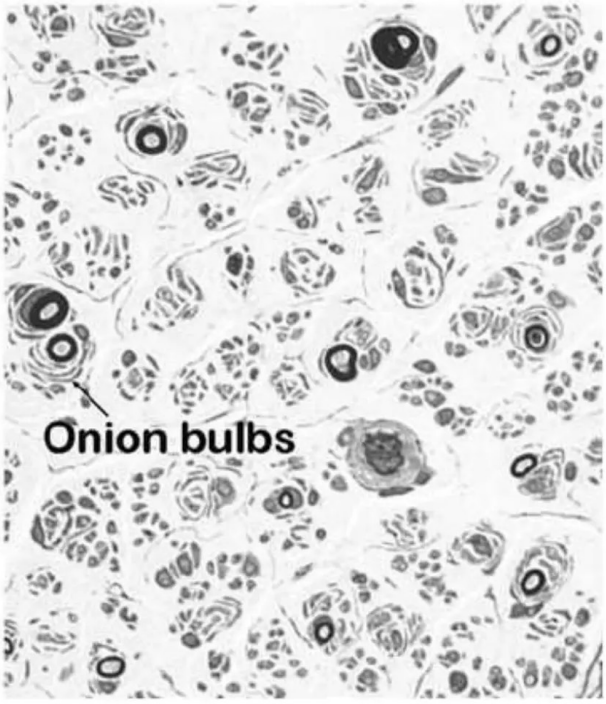
Axonal forms
Preserved or mildly affected nerve conduction velocity (>38 m/s) and nerve biopsy evidence of degeneration and regeneration
- CMT type 2

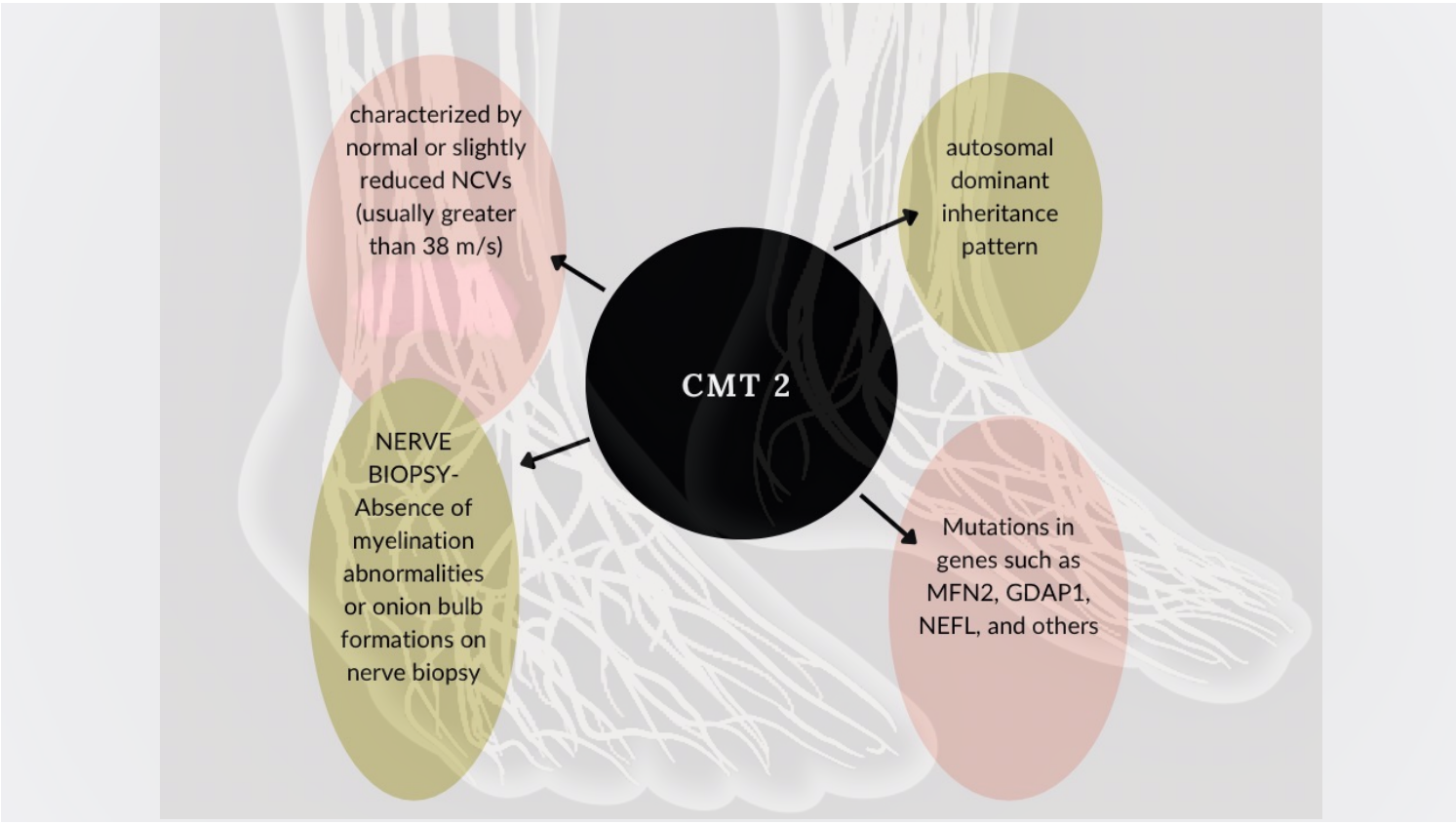

CMT 1
characterized by slow nerve conduction velocities (NCVs) less than 38 m/s due to demyelination
common subtype
autosomal dominant inheritance pattern
NERVE BIOPSY- Abnormal myelination with onion bulb formations
caused by a duplication of the PMP22 gene on chromosome 17

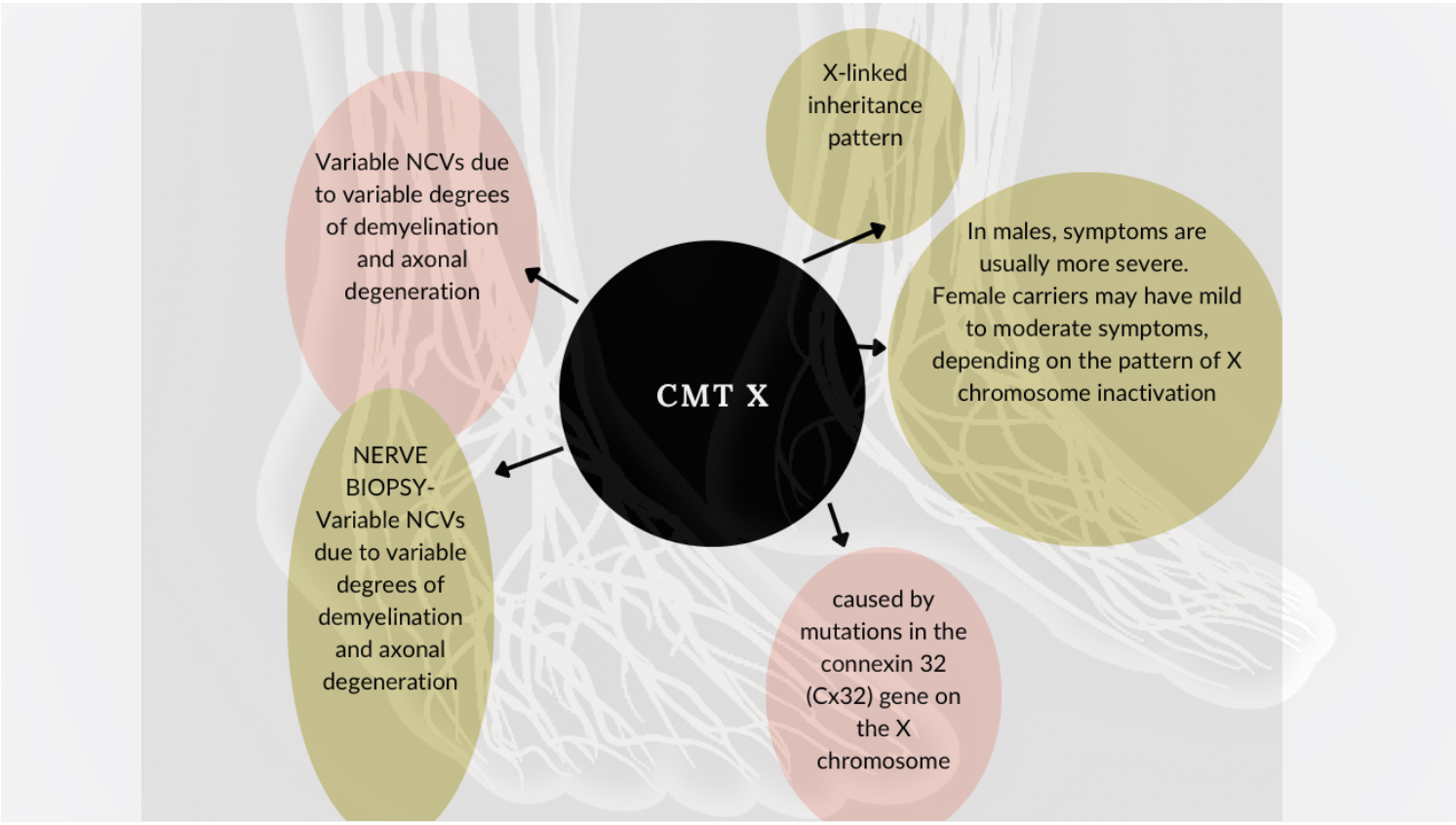
Healthy

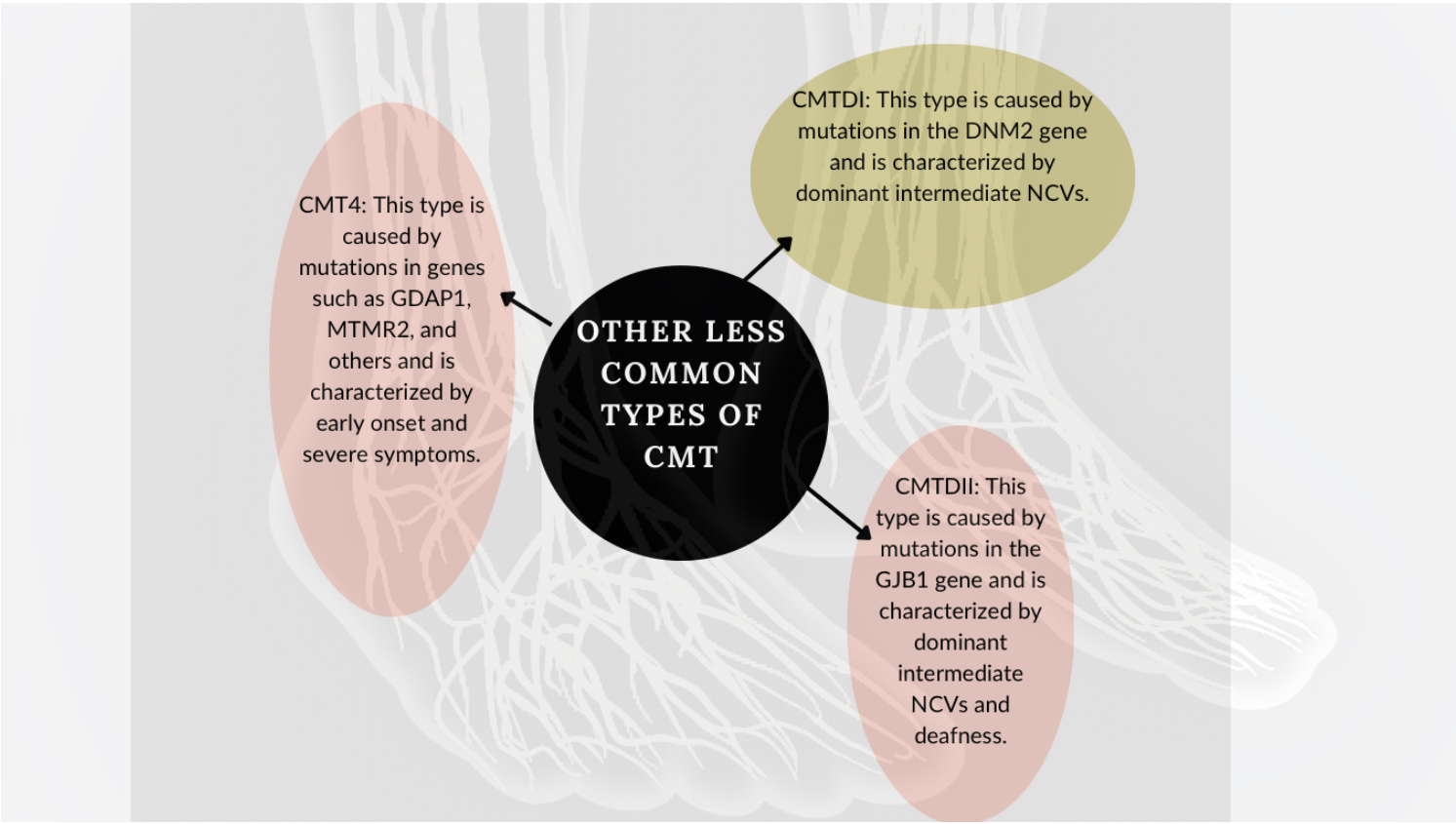


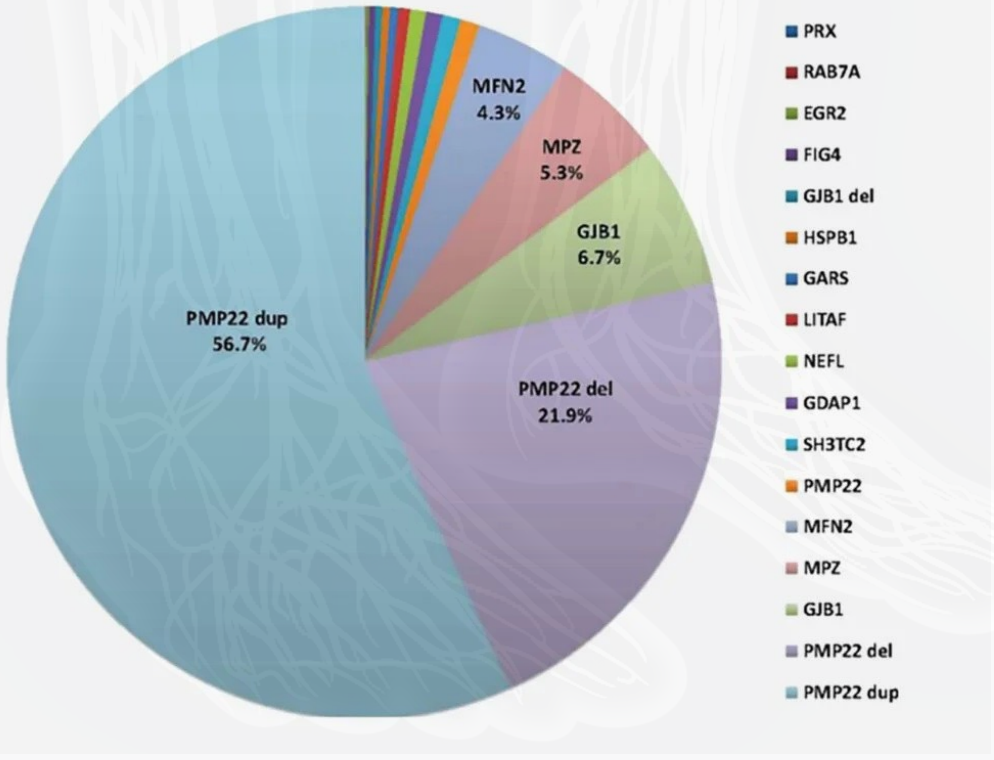
Neuropathy

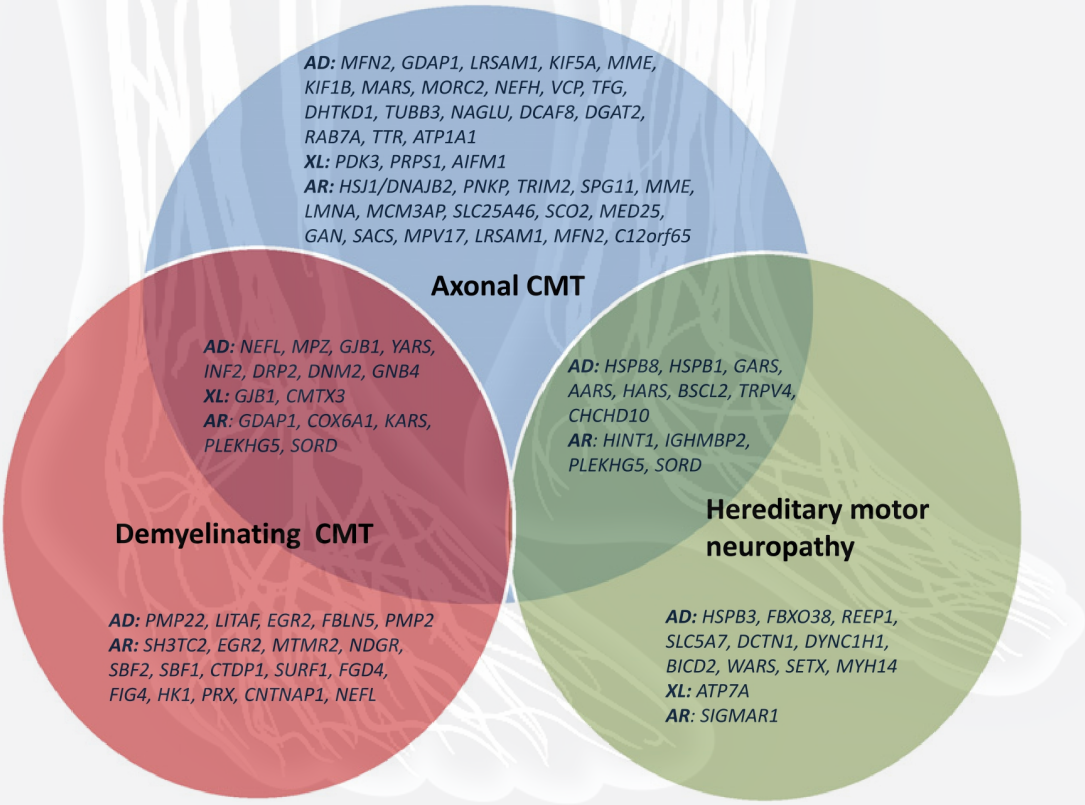



characterized by normal or slightly reduced NCVs (usually greater than 38 m/s)
autosomal dominant inheritance pattern
CMT 2
NERVE BIOPSY- Absence of myelination abnormalities or onion bulb formations on nerve biopsy
Mutations in genes such as MFN2, GDAP1, NEFL, and others


X-linked inheritance pattern
Variable NCVs due to variable degrees of demyelination and axonal degeneration
In males, symptoms are usually more severe. Female carriers may have mild to moderate symptoms, depending on the pattern of X chromosome inactivation
CMT X
NERVE BIOPSY- Variable NCVs due to variable degrees of demyelination and axonal degeneration
caused by mutations in the connexin 32 (Cx32) gene on the X chromosome

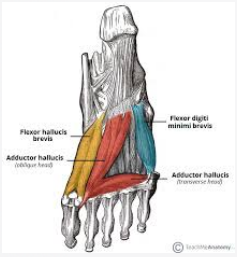

OTHER LESS COMMON TYPES OF CMT
CMTDI: This type is caused by mutations in the DNM2 gene and is characterized by dominant intermediate NCVs.
CMT4: This type is caused by mutations in genes such as GDAP1, MTMR2, and others and is characterized by early onset and severe symptoms.
CMTDII: This type is caused by mutations in the GJB1 gene and is characterized by dominant intermediate NCVs and deafness.


MFN2
4.3%
MPZ
5.3%
GJB1
6.7%
PMP22 del
21.9%
PMP22 dup
56.7%
PRX
RAB7A
EGR2
FIG4
GJB1 del
HSPB1
GARS
LITAF
NEFL
GDAP1
SH3TC2
PMP22
MFN2
MPZ
GJB1
PMP22 del
PMP22 dup


AD: MFN2, GDAP1, LRSAM1, KIF5A, MME, KIF1B, MARS, MORC2, NEFH, VCP, TFG, DHTKD1, TUBB3, NAGLU, DCAF8, DGAT2, RAB7A, TTR, ATP1A1
XL: PDK3, PRPS1, AIFM1
AR: HSJ1/DNAJB2, PNKP, TRIM2, SPG11, MME, LMNA, MCM3AP, SLC25A46, SCO2, MED25, GAN, SACS, MPV17, LRSAM1, MFN2, C12orf65
Axonal CMT
AD: NEFL, MPZ, GJB1, YARS, INF2, DRP2, DNM2, GNB4
XL: GJB1, CMTX3
AR: GDAP1, COX6A1, KARS, PLEKHG5, SORD
AD: HSPB8, HSPB1, GARS, AARS, HARS, BSCL2, TRPV4, CHCHD10
AR: HINT1, IGHMBP2, PLEKHG5, SORD
Demyelinating CMT
Hereditary motor neuropathy
AD: PMP22, LITAF, EGR2, FBLN5, PMP2
AR: SH3TC2, EGR2, MTMR2, NDGR, SBF2, SBF1, CTDP1, SURF1, FGD4, FIG4, HK1, PRX, CNTNAP1, NEFL
AD: HSPB3, FBXO38, REEP1, SLC5A7, DCTN1, DYNC1H1, BICD2, WARS, SETX, MYH14
XL: ATP7A
AR: SIGMAR1

Pathoanatomy

Affected muscles become weak

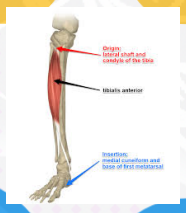


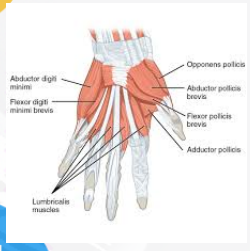
Peroneus brevis

Tibialis anterior

Intrinsic muscles of hand and foot

Peroneal involvement is typically first and most profound



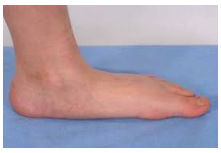


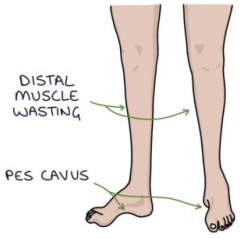
Results in muscle imbalance and varus deformity

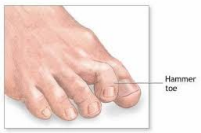
Weakness results in dropfoot

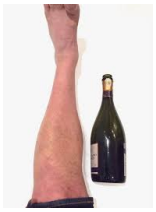
Wasting of 1st dorsal interosseous in hand

SYMPTOMS









Early Signs

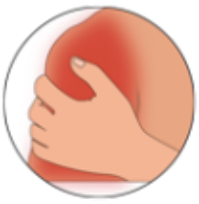
1. Difficulty walking or an awkward walking pattern
2. Clumsiness at a young age
3. Lack of agility
4. Pes-Cavus (highly arched feet)
5. Pes planus (Flat feet)
6. Curled or hammertoes
7. Inverted champagne bottle (thin lower legs, normal thigh muscles)

Common Symptoms

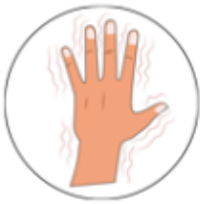
1. Sensory loss and numbness in both arms and legs
2. Cold hands and feet due to poor circulation

Later Symptoms

1. Loss of fine motor control
2. Loss of dexterity and overall hand strength
3. Pain
4. Tremors
5. Upper limbs including both the hands and forearms may be affected as the disease progresses



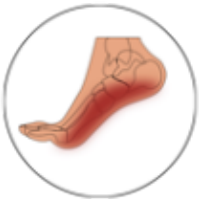
Muscle Pain



Hand Tremors

Cold Hands and feet

Drop Foot

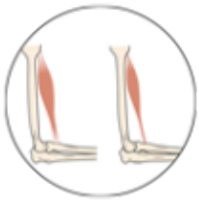


Nerve Pain (Burning, Shooting, Stabbing, Stinging)

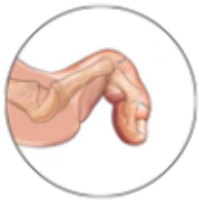
Chronic Fatigue

Numbness

Curled Fingers



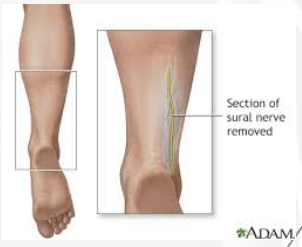
Muscle Atrophy in Legs & Arms



Curled Toes

High Arches (or Flat Feet)

Breathing Difficulties



DIAGNOSIS

Initial Diagnosis:

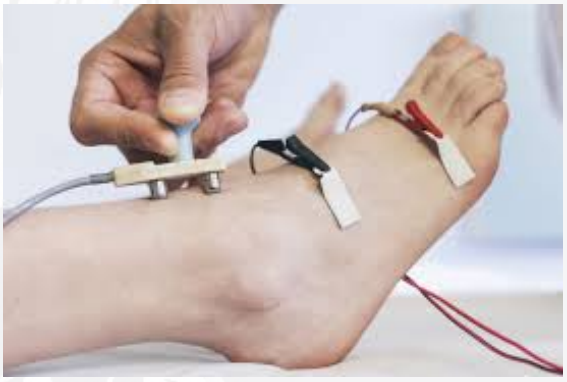
- Patients history
- Family history
- Symptoms
- Neurological findings

Physical Examination

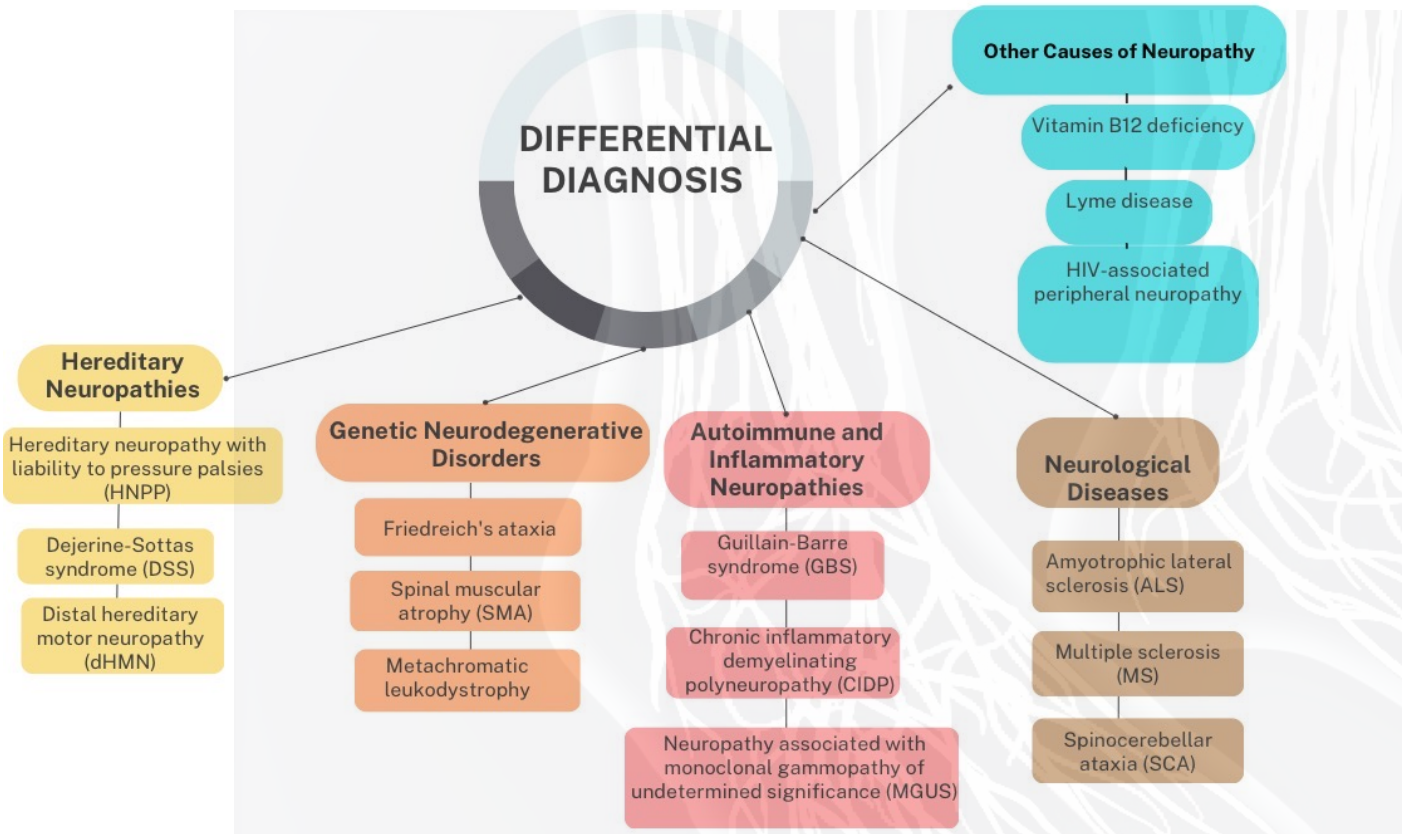
- Muscle weakness
- Decreased muscle bulk
- Reduced tendon reflexes
- Sensory loss
- Nerve enlargement

Additional tests

- Nerve conduction studies
- Electromyography (EMG)
- Genetic testing
- Nerve biopsy



- **DNA analysis** - PCR analysis used to detect peripheral myelin protein 22 (PMP22) gene mutations
- **Chromosomal analysis**-duplication on chromosome 17 seen in autosomal dominant (most common) form


DIFFERENTIAL DIAGNOSIS
Other Causes of Neuropathy
Vitamin B12 deficiency
Lyme disease
HIV-associated peripheral neuropathy
Hereditary Neuropathies
Hereditary neuropathy with liability to pressure palsies (HNPP)
Dejerine-Sottas syndrome (DSS)
Distal hereditary motor neuropathy (dHMN)
Genetic Neurodegenerative Disorders
Friedreich's ataxia
Spinal muscular atrophy (SMA)
Metachromatic leukodystrophy
Autoimmune and Inflammatory Neuropathies
Guillain-Barre syndrome (GBS)
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Neuropathy associated with monoclonal gammopathy of undetermined significance (MGUS)
Neurological Diseases
Amyotrophic lateral sclerosis (ALS)
Multiple sclerosis (MS)
Spinocerebellar ataxia (SCA)

TREATMENT

Physical and Occupational Therapies:

- Physical and occupational therapies are often recommended for individuals with CMT to help manage symptoms and improve mobility.

Orthopaedic Devices:

- Orthopedic devices, such as braces, can help with disabling symptoms and provide support for weak ankles. High-top shoes or boots can also be helpful.

Pain-Relief Drugs:

- Pain-relief drugs can be prescribed for severe nerve pain associated with CMT.

Maintaining Mobility and Muscle Strength:

- Maintaining mobility, flexibility, and muscle strength is important for individuals with CMT. Assistive devices should be used before disability sets in to prevent muscle strain and reduce muscle weakening.

Surgical Options:

- Surgeries, such as deformity correction, plantar fascia release, metatarsal osteotomy, calcaneal osteotomy, and triple arthrodesis, may be recommended to improve mobility and correct deformities associated with CMT.
- Rebalancing of deforming muscle forces can be achieved through EDL transfer, posterior tibial tendon transfer, Achilles tension lengthening, and peroneus longus to peroneus brevis tendon transfer.

COMPLICATIONS

-CMT is not fatal and most people with it live to a normal age and remain active.
-Rarely, CMT may affect the muscles needed for **breathing**, requiring a nighttime breathing assistive device.
-More common complications include **injuries from falls.**
-Certain medicines may worsen the disease.
-People with CMT may be at risk for **injuries or infections of the feet** that go unnoticed due to lack of pain and temperature sensation.

PROGNOSIS

- The prognosis for CMT varies depending on the type and severity of the disease. Most people with CMT have a normal lifespan and are able to lead relatively normal lives, but some may experience more severe disability.

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