Charcot Marie Tooth Disease

Prof Vandana Rai

Charcot- Marie –Tooth Disease (Hereditary Neuropathy)

- In 1886, French neurologists J. M. Charcot (1825–1893) and P. Marie (1853–1940) and, independently, H. H. Tooth (1856–1925), a British physician, published detailed descriptions of a disease characterized by atrophy of the muscles on the outer side (peroneal) and distal portion of the legs, progressing over time to the feet, hands, and forearms.
- Charcot-Marie-Tooth (CMT) hereditary neuropathy refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy.
- The affected individual typically has distal muscle weakness and atrophy often associated with mild to moderate sensory loss, depressed tendon reflexes, and high-arched feet.

Charcot- Marie –Tooth Disease

- **CMT is both genetically and clinically heterogeneous**. Because both motor and sensory nerves are primarily affected in CMT, a more specific designation—**hereditary motor and sensory neuropathy (HMSN)—**has been suggested as an alternative name for CMT.
- CMT affects peripheral nerves.
- The peripheral nerves lie outside the brain and spinal cord and supply the muscles and sensory organs in the limbs.
- Disorders that affect the peripheral nerves are called peripheral neuropathies.

Symptoms

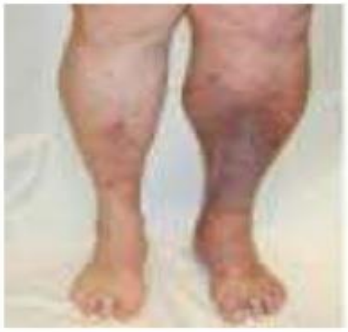
- Onset of the disease usually occurs in the second or third decade of life.
- CMT is not fatal and people with most forms of CMT have a normal life expectancy and **it almost never affects the brain.**.
- Typically,affected individuals suffer from a peripheral neuropathy manifested as progressive wasting of the distal muscles of the limbs.
- The wasting can cause characteristic deformities and decreased sensation in the hands and feet.
- The initial signs of CMT are a stumbling gait, awkwardness while running, and ankle weakness in childhood.
- Later, in many adult patients, sensory responses to touch, pain, temperature, and vibration in the feet and hands decrease and often are lost.
- In some instances, learning or breathing may be adversely affected.

Foot deformities

Foot deformities such as high arches and hammertoes (a condition in which the middle joint of a toe bends upwards) are also characteristic due to weakness of the small muscles in the feet.

In addition, the lowest legs may take an 'inverted champagne bottle' appearance due to loss of muscle bulk.

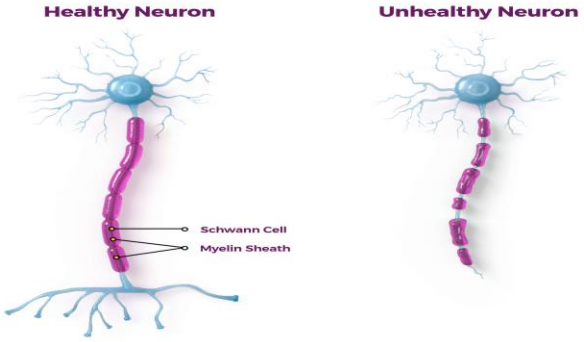
Atypical feature include weakness of the foot and lower leg muscles, which may result in foot drop and a high –stepped gait with frequent



https://pt.slideshare.net/ArunK29/charcot-marietooth-disease/9

Sensory Loss and Associated Symptoms

- Because CMT causes damage to **sensory axons**, most people with CMT have a *decreased sensitivity* to heat, touch and pain in the feet and lower legs.
- Combined with the regular abrasions caused by foot deformities, the lack of pain sensitivity makes people with CMT at risk for developing *ulcerations* - wounds that have gone unnoticed and become severely infected.
- Paradoxically, some people with CMT experience *more* pain - a combination of painful muscle cramps and *neuropathic pain*. This pain isn't caused by an external trigger, but by defective signals in sensory axons. Both types of pain can usually be alleviated with medication.
- In many people with CMT, sensory loss is associated with dry skin and hair loss in the affected area.
- In rare cases, sensory loss can include **gradual hearing impairment and sometimes deafness.**



Prevalence

- It occurs in populations worldwide with a prevalence of about 1 in 3,300 individuals.

- It has a prevalence of around 1 in 2500 people in the US.

Classification of CMT

CMT is clinically divided into subgroups according to the combination of the inheritance pattern and NCV, which helps to estimate the underlying pathology (demyelination or axonopathy).

Four clinical types of CMT have been delineated CMT1, 2, 3 and 4 (CMT1, CMT2, CMT3, CMT4).

- Generally, demyelination is the primary defect with CMT Types 1, 3, and 4.
- Axonal loss highlights CMT Type 2.

MNCV myelinated nerve conduction velocity)=25m/sec.(Normal range of MNCV=40-50m/sec)

Demyelination of motor nerves

Schwann cells around the axons do not produce myelin sheaths but form bulbous outcroppin called onion bulbs

These classifications appear to reflect primary pathological involvment of myelin (CMT1) or axon(CMT2)of the peripheral nerve

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Types of CMT

CMT Type 1: Type 1 (CMT1) is characterized by abnormalities in myelin, the fatty substance that covers nerve cells, protecting them and helping to transmit nerve impulses. These abnormalities slow the transmission of nerve impulses and can affect the health of the nerve fiber.

CMT Type 2: Type 2 (CMT2) is characterized by abnormalities in the fiber, or axon that extends from a nerve cell body to muscles or to sense organs. These abnormalities reduce the strength of the nerve impulse.

CMT Type 3:In forms of Charcot-Marie-Tooth disease classified as intermediate type, the nerve impulses are both slowed and reduced in strength, probably due to abnormalities in both myelin and axons.

CMT Type 4:Type 4 (CMT4) is distinguished from the other types by its pattern of inheritance; it can affect either the axons or the myelin.

CMT Type X:Type X Charcot-Marie-Tooth disease (CMTX) is caused by mutations in

CMT1

CMT1 is further classified into seven subgroups, from CMT1A to 1G (CMT1A, CMT1B, CMT1C, CMT1D, CMT1E, CMT1F and CMT1G).

CMT1A disease:

- Type 1A CMT disease is the most common inherited neuropathy,it involves
- Degeneration of the myelin sheathes that surround peripheral nerves,
- Decreased nerve conduction velocities,
- Slow degeneration of the distal muscles,
- Absence of nervous reflexes and
- Flat feet

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Type 1B CMT disease

- In the rare type 1B CMT disease, the same clinical symptoms are induced by a point mutation in a gene for a different protein $P_{0,}$the structural component of myelin sheaths.
- Subsequent linkage studies indicated that CMT1B families were relatively rare compared to CMT1A families.
- Type 1BCMT disease maps to chromosome 1q22-23.
- Protein zero (P0)is a 28 kDa glycoprotein which is the major structural protein of peripheral myelin ;the gene(MPZ) that encode myelin protein zero is located at chromosome 1 in the regionq22-23.
- Analysis of the coding region of MPZ in several patients has revealed six different mutations.
- All six mutations are within the extracellular domain,which is the sole immunoglobulin-related domain in P0 and is important for the adhesion

CMT2

- CMT2, which accounts for 20% of genetically diagnosed CMT patients, and is autosomal dominant neuropathy with its main affect on the axon. The average nerve conduction velocity is slightly below normal, but generally above 38m/s
- **CMT type 2A** - **CMT2A** (OMIM 118210) - The cause is likely located on chromosome 1 for the mitofusion 2 (MFN2) protein (locus 1p36). Some research has also linked this form of CMT to the protein kinesin 1B (KIF1B) (1p36.2). Does not show up on nerve condution velocity tests, because it is caused by axonopathy.
- **CMT type 2B** - **CMT2B** (OMIM 600882) - RAB7 gene (3q21).
- **CMT type 2C** - **CMT2C** - (12q23-q24) - May cause vocal cord, diaphragm, and distal weaknesses.
- **CMT type 2D** - **CMT2D** (OMIM 601472) - GARS gene (7p15). Patients with mutations in the GARS gene tend to have more severe symptoms in the upper extremities (hands), which is atypical for CMT in general.
- **CMT type 2E** - **CMT2E** - NEFL gene (8p21).

CMT3

- The term CMT3 was previously used for infant-onset and the severe CMT subtype.
- However, CMT3 is no longer used because it proved to be a severe form of early-onset CMT1 or CMT4 by genetic analysis.
- CMT3, which was historically termed Dejerine–Sottas neuropathy.
- Type 3 affects a very few CMT patients.
- **CMT3** - Rarely found. Autosomal recessive. Average NCV: Normal (50-60m/s)
- Dejerine-Sottas disease (HMSN III) hypertrophic neuropathy of infancy, congenital hypomyelinated neuropathy)-Autosomal recessive inheritance.

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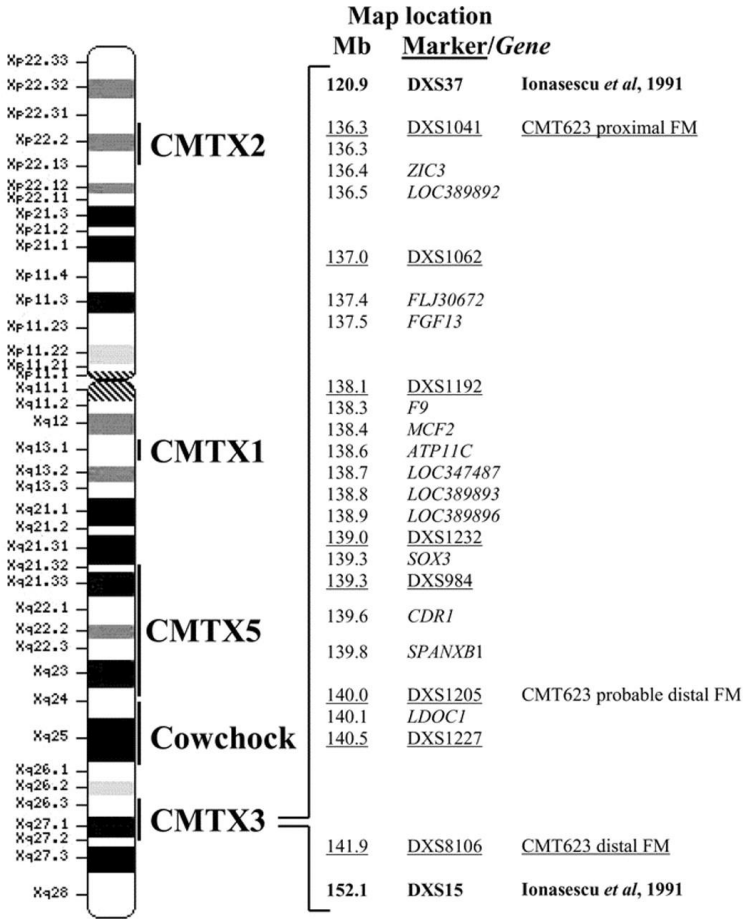
CMT Type 4 (CMT4)

- CMT4 is a rare subtype of CMT that is inherited in an autosomal recessive pattern. Generally, cases of CMT4 present with more severe symptoms compared to CMT1 or CMT2. In general, CMT4 is caused by defects in the myelin sheath which insulates the axon. However, other variations include:
- CMT4A is caused by defects in the GDAP1 gene.
- CMT4B is caused by defects in the genes MTMR2 (CMT4B1), or MTMR13 (CMT4B2).
- CMT4C is caused by defects in the SH3TC2 gene.
- CMT4D is caused by defects in the NDRG1 gene.
- CMT4E is caused by defects in the EGR2 gene.
- CMT4F is caused by defects in the PRX gene.
- CMT4H is caused by defects in the FDG4 gene.
- CMT4J is caused by defects in the FIG4 gene.

https://hnppwellbeing.com/2017/08/17/the-difference-between-hnpp-cmt-and-cidp/

X-linked Charcot-Marie-Tooth disease(CMTX)

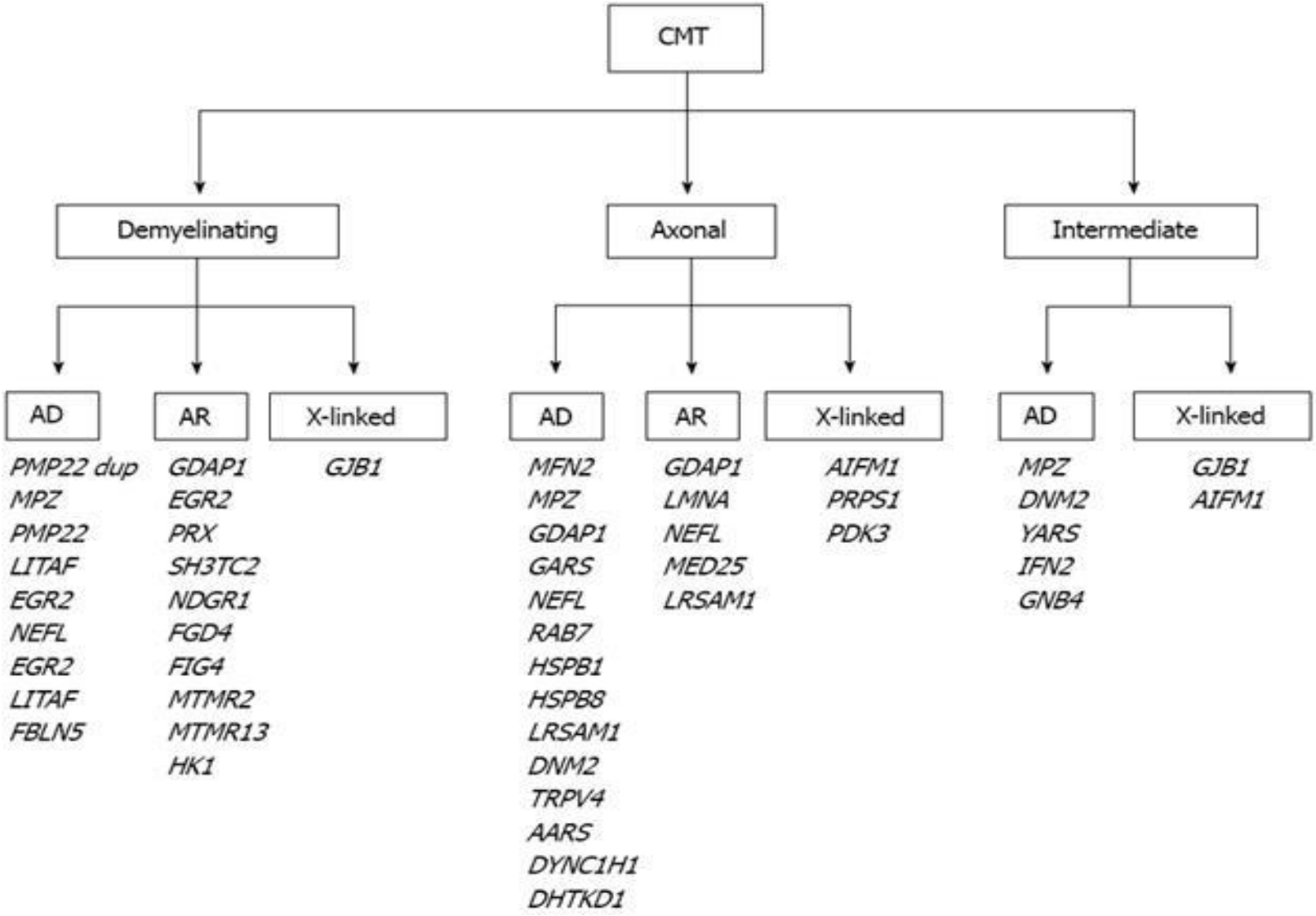
- An x-linked form of CMT is mapped to the band Xq13,which encode connexin 32 (Cx32),one of many well-characterized gap –junction proteins.
- Analysis of connexin 32 gene in several patients has revealed six single-base changes that results in non-conservative amino acid substitutions and one base insertion that causes frame-shift.
- Immunohistochemical studies have demonstrated the presence of Cx32 protein in myelinated peripheral nerve tissue at the node of Ranvier and at Schmidt-Lanterman incisures.
- Cx32 is present in many tissues ,including the brain and liver; thus the phenotype of CMTX suggests that Cx32 function is particularly crucial in the peripheral nerves. An alternative possibility is that other connexins can substitute for Cx32 in various tissues, but not in the peripheral nerves.



https://doi.org/10.1212/01.wnl.0000247271.40782.b7

Heterogenous disease

- CMT is a heterogenous genetic disease and inherited as an
- autosomal dominant trait,
- autosomal recessive,
- X-linked recessive, and
- X-linked dominant forms.


CMT
Demyelinating
Axonal
Intermediate
AD
AR
X-linked
AD
AR
X-linked
AD
X-linked
PMP22 dup
MPZ
PMP22
LITAF
EGR2
NEFL
EGR2
LITAF
FBLN5
GDAP1
EGR2
PRX
SH3TC2
NDGR1
FGD4
FIG4
MTMR2
MTMR13
HK1
GJB1
MFN2
MPZ
GDAP1
GARS
NEFL
RAB7
HSPB1
HSPB8
LRSAM1
DNM2
TRPV4
AARS
DYNC1H1
DHTKD1
GDAP1
LMNA
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IFN2
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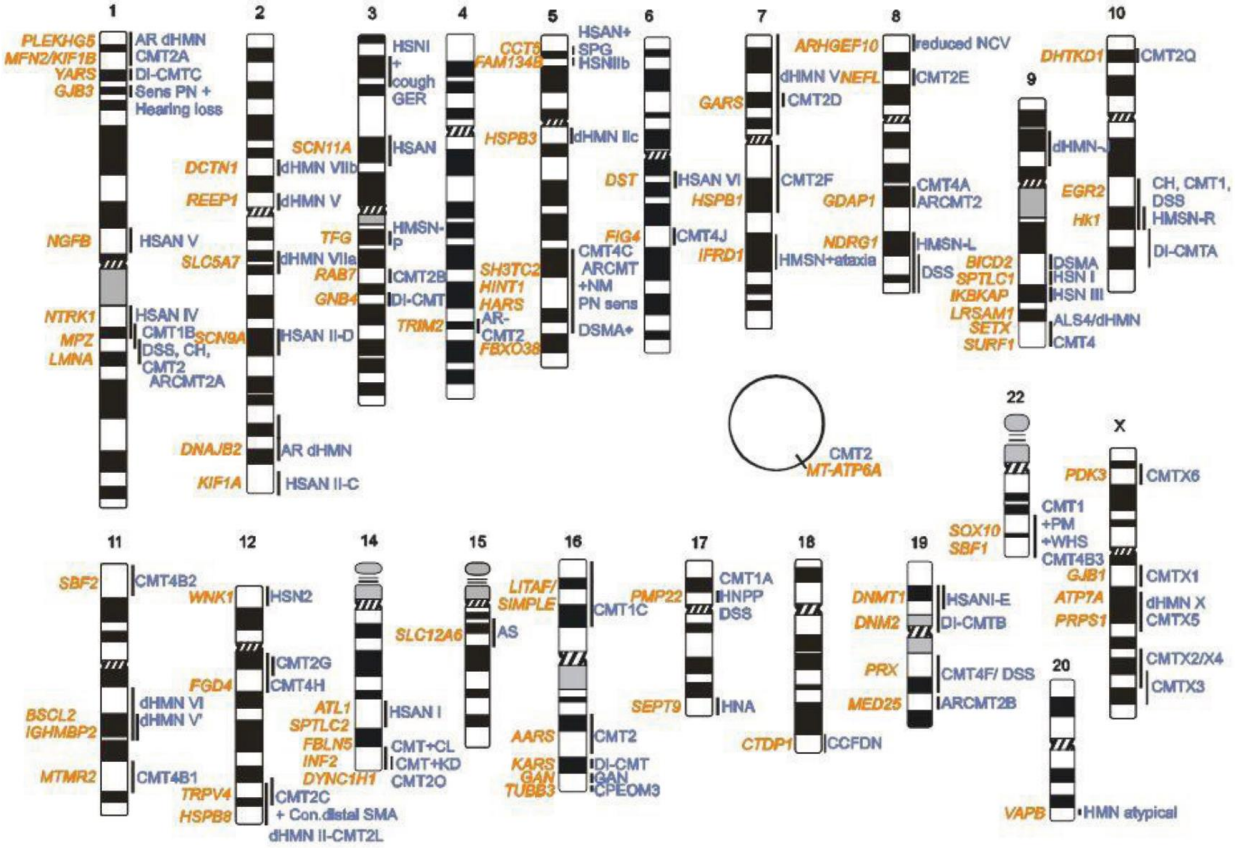
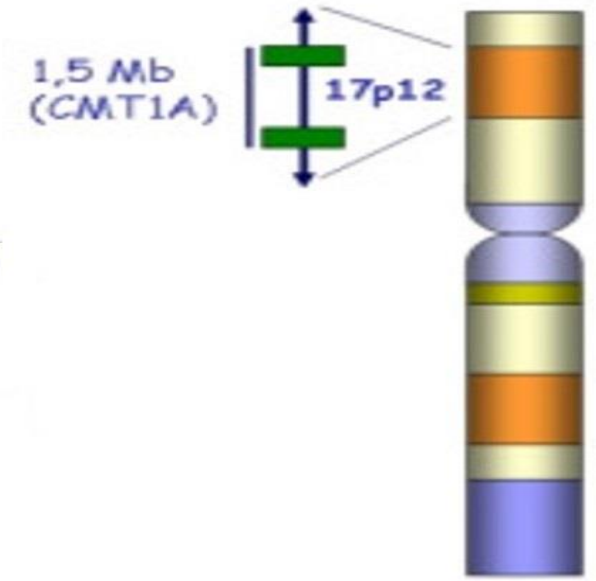


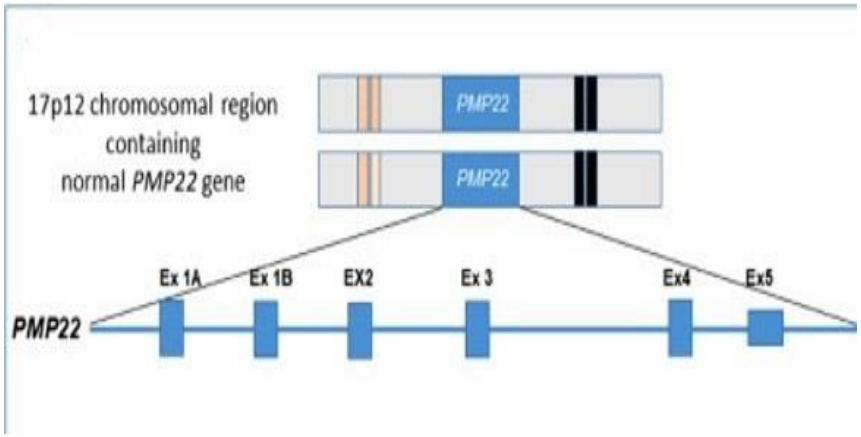
The figure shows 80 currently known genes (orange symbols) and their corresponding chromosomal loci (vertical bars). The corresponding phenotypes are indicated by blue symbols and are according to the disease nomenclature. Note that the disease names may not always correspond to information available in OMIM, GeneReviews, or in other publicly available databases.

Timmerman et al.,*Genes* 2014, *5*, 13-32

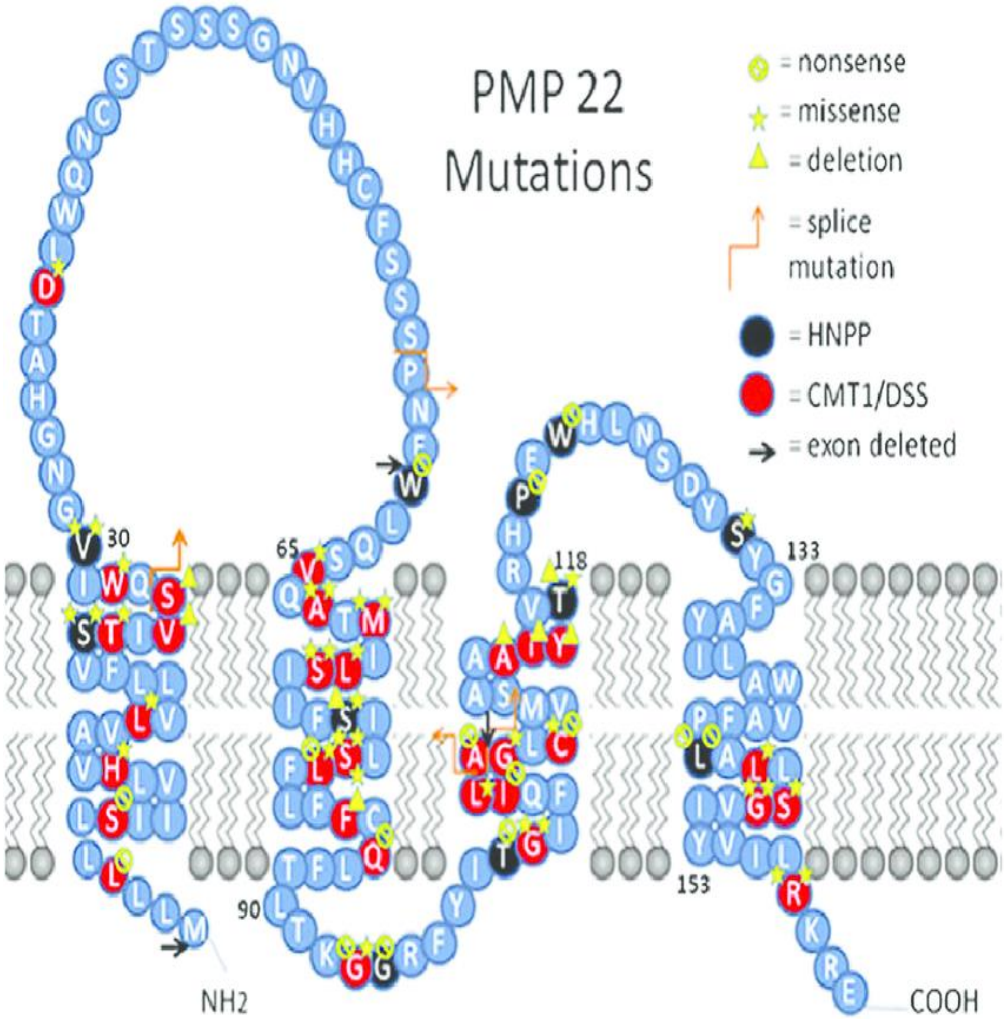
Peripheral myelin protein (*PMP22)* gene

- *PMP22* gene is present on chromosome 17p11.2.
- Spans approximately 40kb.
- The gene containssix exons conserved in both humansand rodents, two of which are 5'untranslated exons (1a and 1b) andresult in two different RNA transcriptswith identical coding sequences.
- The PMP22 gene has 2 promoters that lead to translation of 2 transcripts containing different noncoding exons, 1A and 1B, which makes it tissue-specific and highly regulated.
- The two transcripts differ in their 5'untranslated regions and have theirown promoter regulating expression.





Duplication
Deletion
point mutations
splice mutation
missense mutation
nonsense mutation

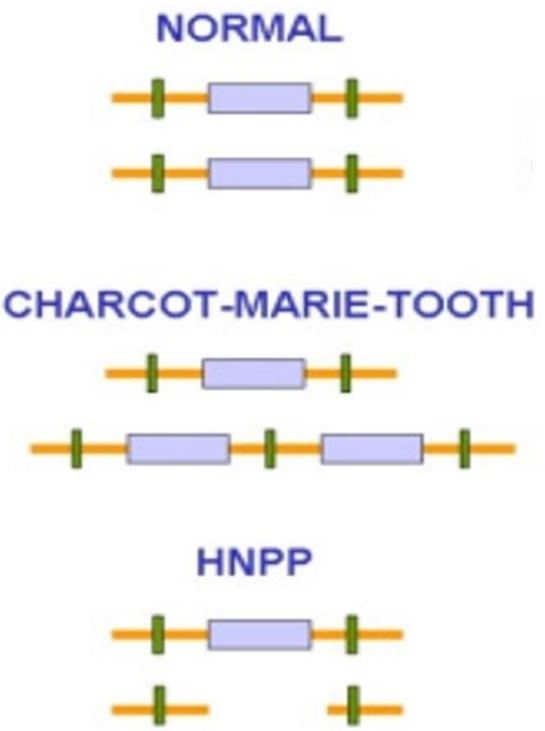


In the CMT1 category, about 60% to 80% of the cases are CMT1A and have a mutation of the *PMP22* gene at 17p12–p11.2 that encodes peripheral myelin protein 22 (PMP22).

The mutation in about 75% of these individuals is a duplication of one of the two *PMP22* genes.

The duplication of a 1.4 Mb DNA fragment encompassing the *PMP22* gene on chromosome 17p11.2 is associated with over 70% of CMT1 cases.

The *PMP22* gene duplication frequently occurs by inter-chromosomal exchange during spermatogenesis and, to a lesser extent, by intrachromosomal exchange during



Myelin protein zero (P0, MPZ)

- Mutations in the *MPZ* gene at chromosome 1q22.1, which encodes myelin protein zero (P0, MPZ), produce the same clinical characteristics as *PMP22*gene mutations and have been classified as CMT1B.
- Myelin protein zero is expressed in Schwann cells and comprises about half the total protein of the myelin sheath of peripheral nerves. It has adhesive properties and probably links layers of the myelin sheath to each other.
- Interestingly, not only *PMP22* mutations but some *MPZ* mutations also produce Dejerine–Sottas disease.
- In other words, mutations of different genes for myelin sheath proteins produce a very similar clinical phenotype.
- Overall, *MPZ* mutations account for approximately 8% of all cases of autosomal dominant CMT.

Gap junction protein connexin 32(GJB1)

- Mutations of the *GJB1* gene at Xp13.1, which encodes the gap junction protein connexin 32, are responsible for CMT, specifically CMT1X.
- Connexin32 (Cx32) is a member of a family of proteins that span membranes.
- Generally,six connexin molecules form a circular, doughnutlike aggregate (hemichannel) in the membrane of one cell that combines with a connexin hemichannel in the membrane of another cell to form a channel (gap junction) that connects the two cells.
- Gap junctions allow ions and small molecules to flow from one cell to another.
- Cx32 may form gap junctions that connect the folds of myelin sheaths of the peripheral nerves and enable nutrients and small molecules to be distributed throughout the myelin sheath.
- The phenotype associated with *GJB1* mutations is a demyelinating peripheral neuropathy that closely resembles CMT1, although axon loss has been noted in

Diagnosis

- The diagnosis is established by **electromyography** examination (which shows that the velocity of nerve impulse conduction is decreased and the time required to charge the nerve is increased) and nerve biopsy.
- Genetic markers have been identified for some, but not all forms of the disease.

Treatment

- Although there's no cure for CMT, there are treatments that can be used to effectively manage its symptoms. Those treatments have allowed many people with the disease to lead active, productive lives.

Suggested Reading

1. Human Molecular Genetics – Tom Stratchen & Andrew P. Read. Pub: John Wiley & Sons.
2. An introduction to Genetic Analysis – Griffith, Miller, Suzuki, Lewontin, Gelbard. Pub: W.H. Freeman & Co.
3. Genomes 2 – T.A. Brown, Pub: Wiley-Liss. John W. & Sons.
4. Emery's Elements of Medical Genetics– R.F. Mueller, I.D. Young, Pub: Churchill
5. An Introduction to Human Molecular Genetics – J.J. Pasternak, Pub: Fitzgerald Science