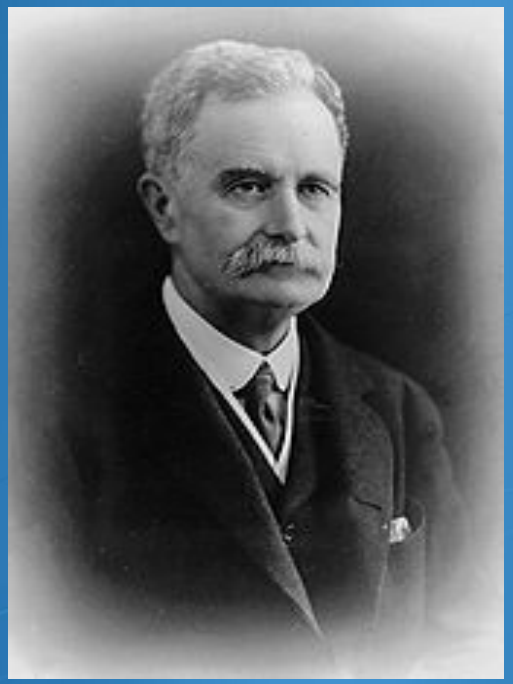
Genetica dell'apparato locomotore

Charcot-Marie-Tooth (CMT)

www.charcot-marie-tooth.org

Charcot-Marie-Tooth

Jean-Martin
Charcot
1825-1893



Pierre **Marie**
1853-1940

Howard Henry **Tooth**
1856-1925

Charcot-Marie-Tooth (CMT) disease is named after the 3 physicians who first identified it .

Patologia

Charcot-Marie-Tooth (CMT) disease is:

- the most common inherited genetic disorder that involves the peripheral nerves, affecting an estimated 150,000 people in the United States. It occurs in all races and ethnic groups, affecting about 1 in 2,500 people or 2.6 million people worldwide.
- a progressive disorder, causing people to lose normal use of their hands. arms, feet/legs.
- not usually life-threatening and does not affect the brain or intelligence.
- not contagious, but is usually passed down from one generation to the next.
- currently not curable

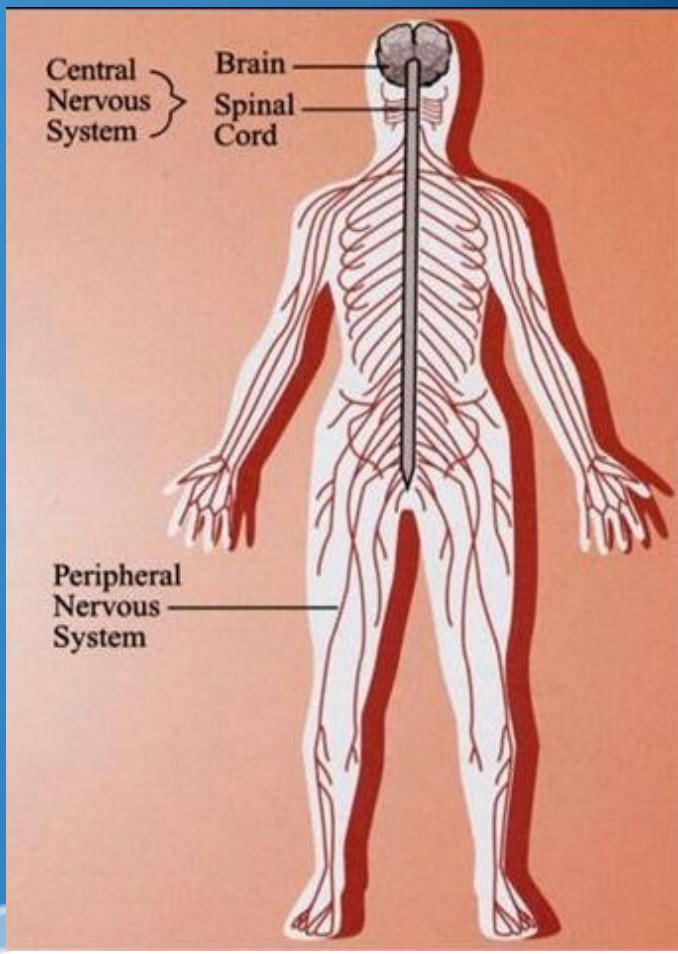
CMT - Peripheral Nervous System

★ CMT causes damage to the peripheral nerves, which link the brain and spinal cord to muscles and sensory organs.

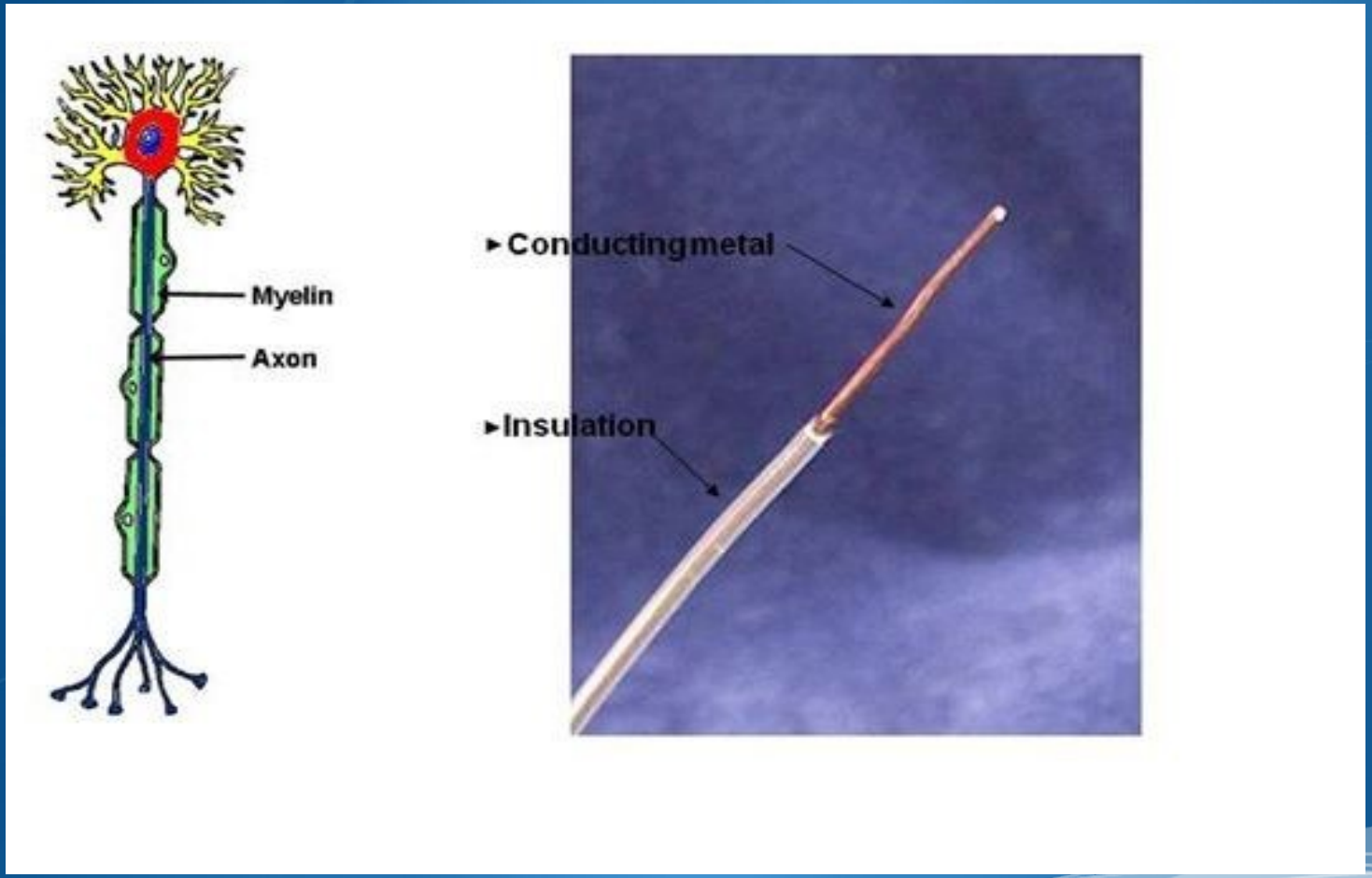
★ Peripheral Nerves carry impulses from the spinal cord to muscles.

★ Peripheral Nerves convey sensation by carrying feelings like pain & temperature from the hands and feet to the spinal cord.

★ Peripheral Nerves help control balance, by carrying information about the position of the body in space.

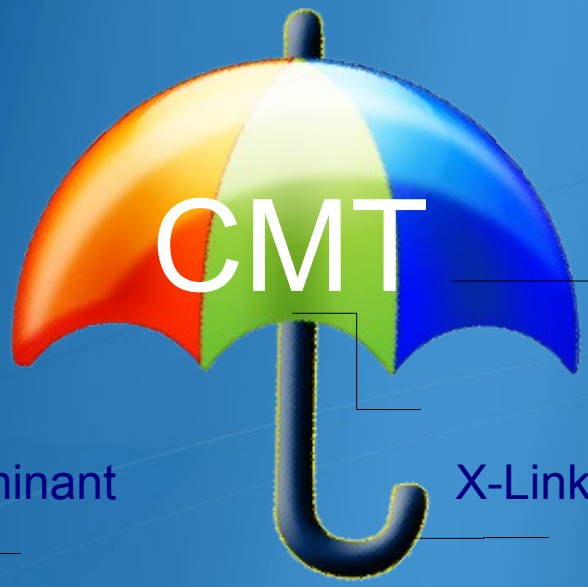


A Nerve is Like a Wire



Source: Carly Siskind, MS, CGC & Shawna Feely, MS

Tipi di CMT



Autosomal Dominant

X-Linked

Autosomal Recessive

Demyelinating (Type 1)

Axonal (Type 2)

Intermediate (Type X)

Demyelinating OR Axonal (Type 4)

source: Carly Siskind, MS, CGC & Shawna Feely, MS

Classificazione

CMT 1-an autosomal dominant disease from duplication of gene on chromosome 17 that carries info for producing the peripheral myelin protein 22

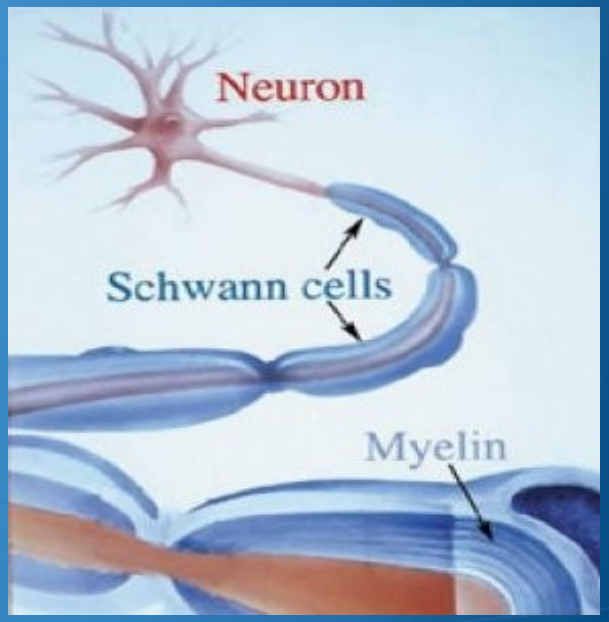
CMT 2-comes from abnormalties in the axon of the peripheral nerve cell rather than the myelin sheath

CMT 3-severe demyelinating neuropathy that begins when you are a baby

CMT 4-has several different subtypes of autosomal recessive demyelinating motor and sensory neuropathies

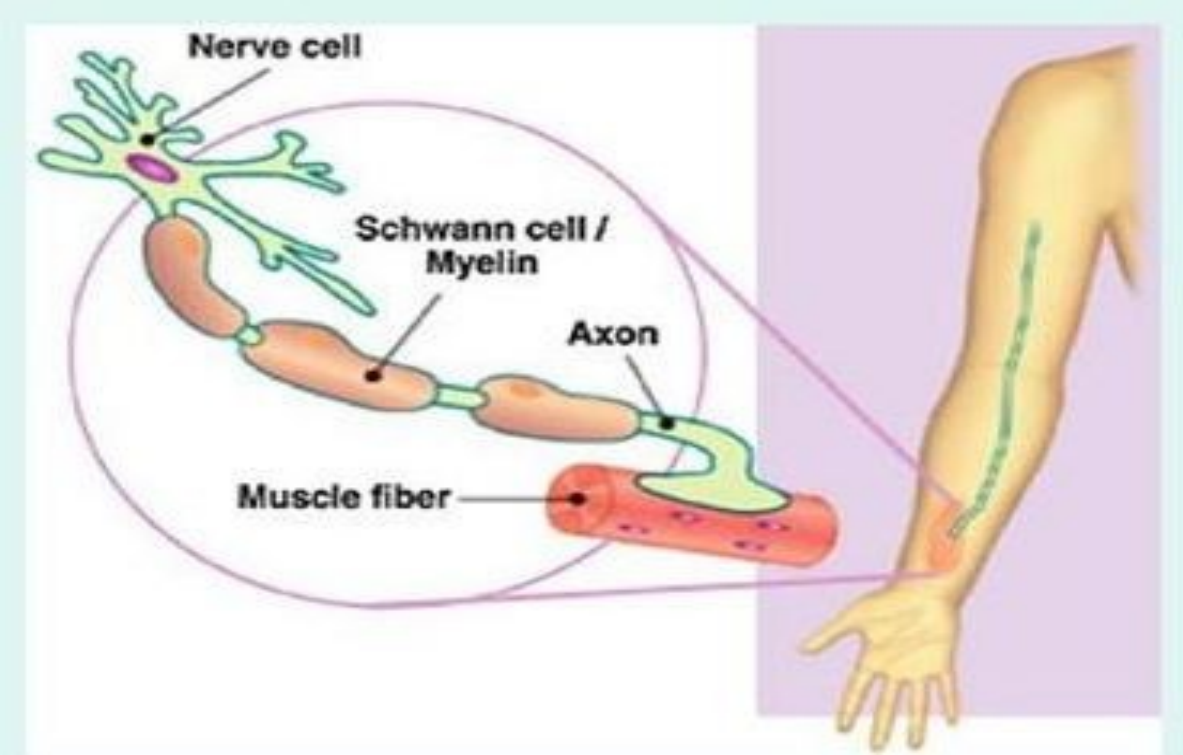
CMT X-X-linked dominant disease and caused by point mutation in the connexin-32 gene on X chromosome

What is Myelin?



- Myelin is the layer of insulation that protects nerves.
- Myelin envelops nerves, enabling them to conduct impulses from brain to different parts of the body
- Myelin, in the peripheral nervous system (PNS), is produced by specialized cells called Schwann cells
- Myelin is composed of different proteins and lipids. One of these proteins is called Peripheral Myelin Protein (PMP22)

Myelinated Peripheral Nerve



Sintomatologia

a) Weakness in feet and lower leg muscles

b) May result in foot deformities and frequently tripping and falling

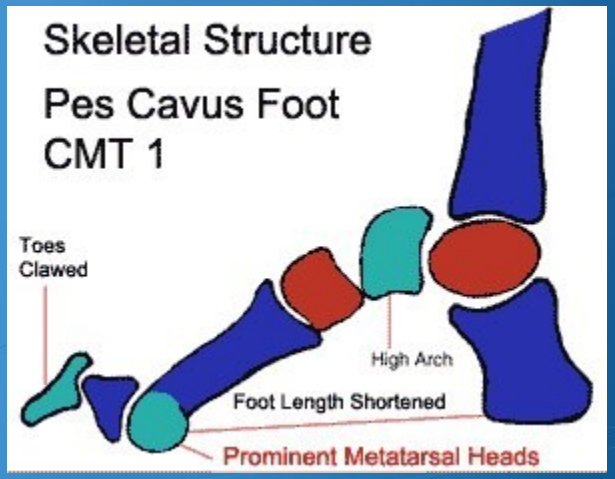
c) Your lower leg may take on an “inverted champagne bottle” from loss of muscle bulk

d) Occurs in adolescent or early adulthood

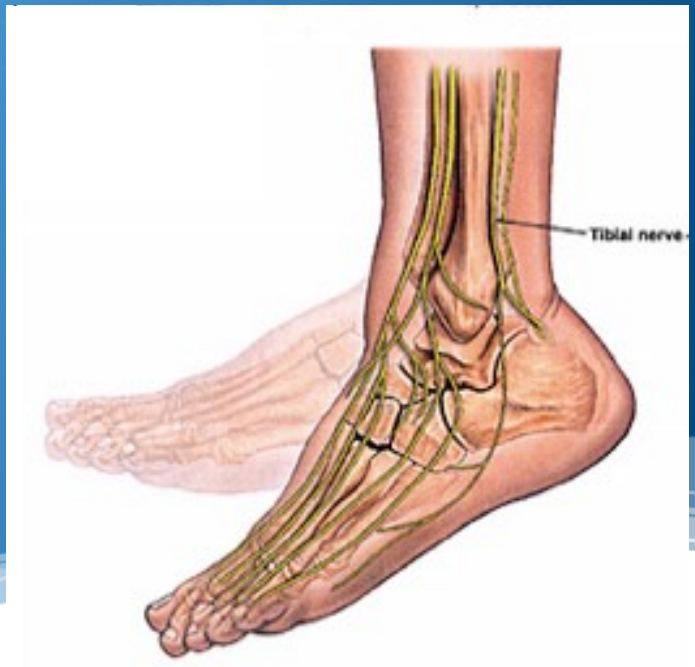
e) Progression of disease is gradual

Characteristics and Symptoms

- High Arches



- Muscle weakness in lower legs: foot drop, poor balance and sprained ankles



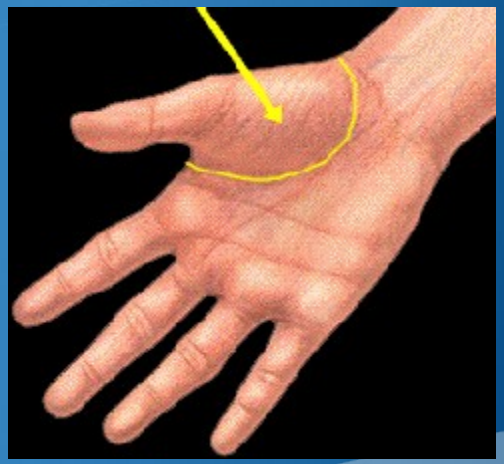
Characteristics and Symptoms

- Muscle atrophy in hands causes manual dexterity difficulty. Tremor.

Question

How would this affect everyday life ?

Thenar muscles



Weakness in fingers

Characteristics and Symptoms

- Loss of nerve function can lead to tingling, burning sensation in hands and feet (painful neuropathy)

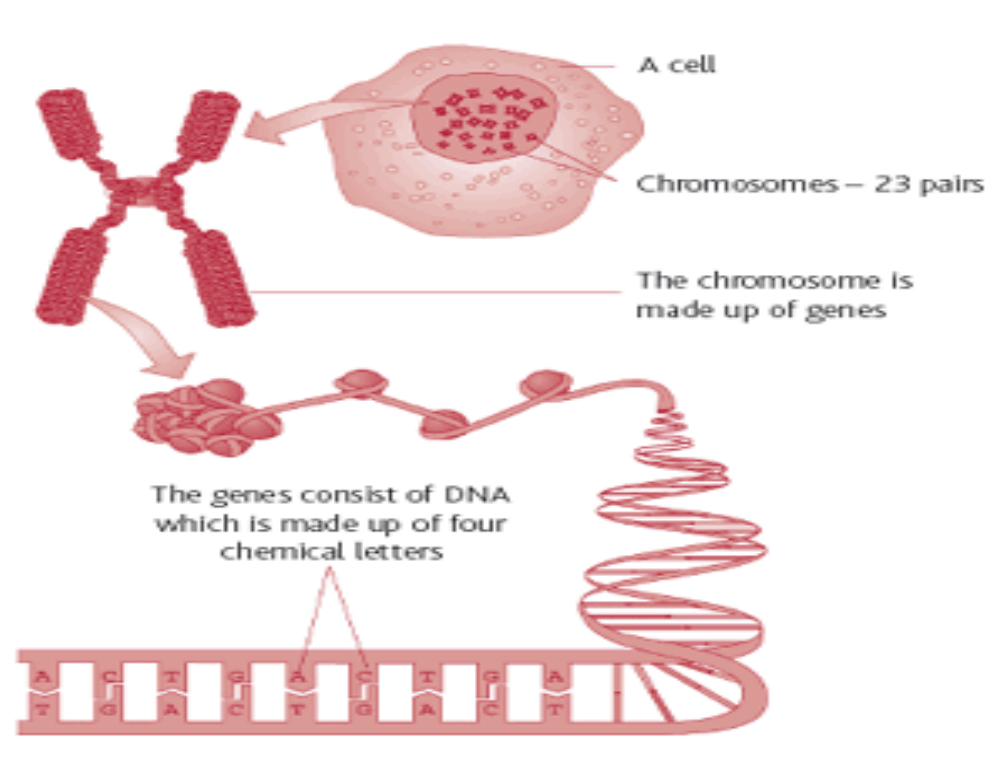
- Additional Symptoms: fatigue, breathing problems, scoliosis, kyphosis…..

Treatments

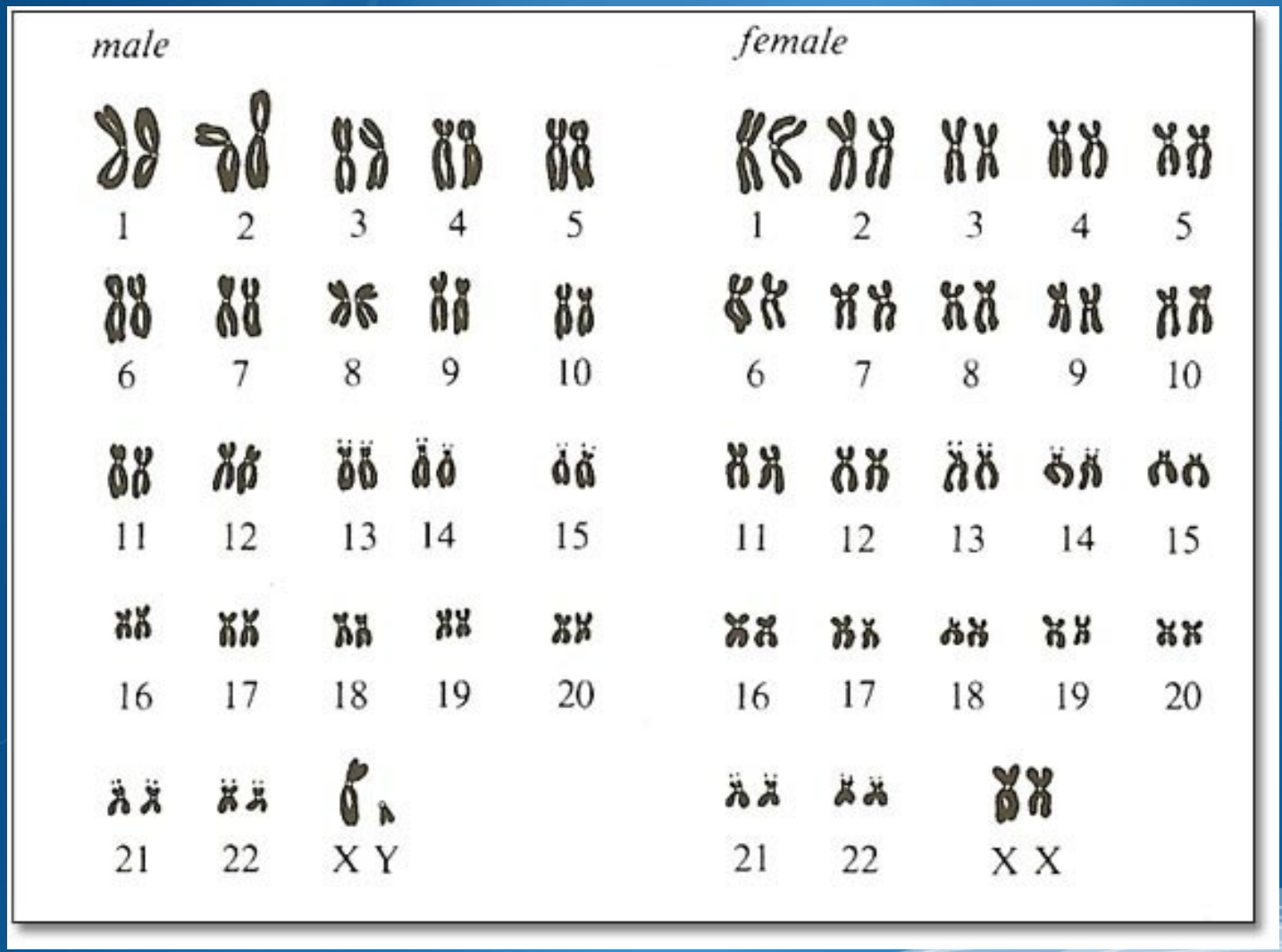
- Physical Therapy
- Moderate Activity
- AFOs or leg braces
- Occupational Therapy
- Surgery

CMT: Back to Basics

Charcot-Marie-Tooth disease is caused by inherited mutations in the genes involved with the structure and function of the peripheral nerves



Chromosomes



Chromosomes

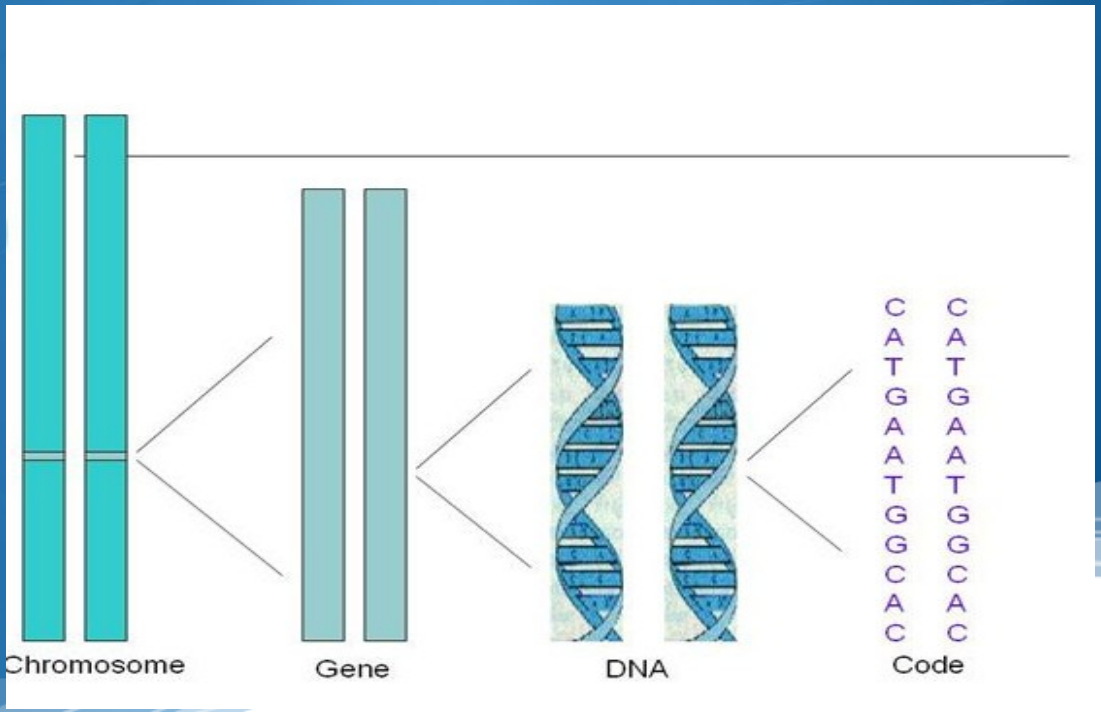
Chromosome = bookcase

Genes = books on the bookcase

DNA = letters which give the book its meaning

If there is a typo in the book or if there are missing or extra pages, the book's message (code) might be changed

A mutation in the DNA of a gene = typo in a book



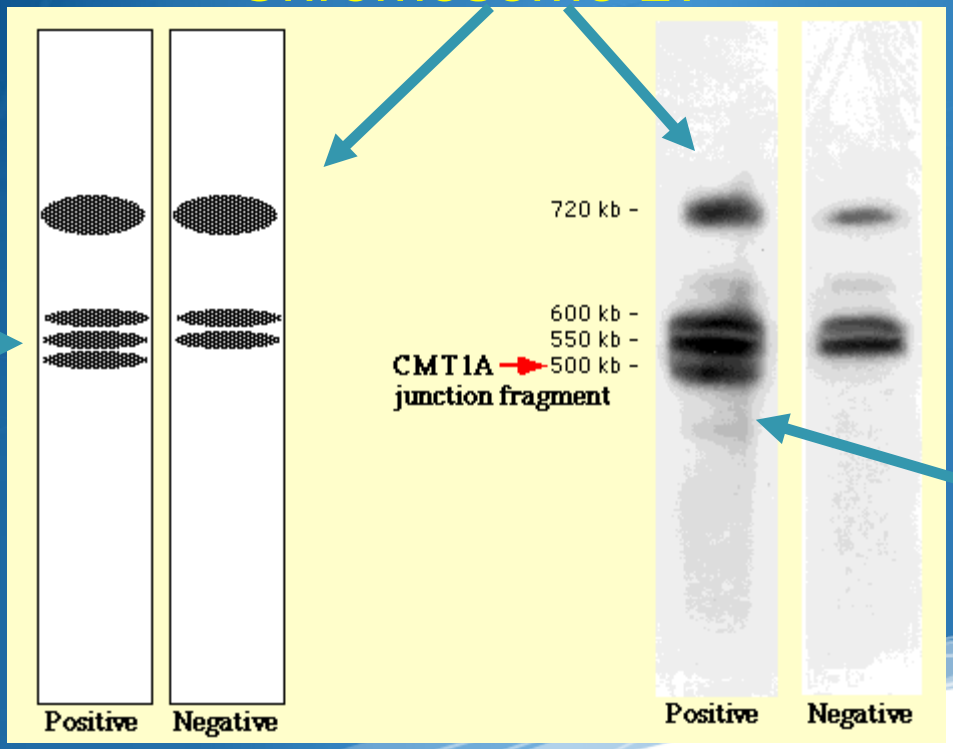
Source: Carly Siskind, MS, CGC & Shawna Feely, MS

CMT & Genetic Mutations

Charcot-Marie-Tooth disease is caused by inherited mutations in the genes involved with the structure and function of the peripheral nerves

Chromosome 17

PMP22 gene duplication

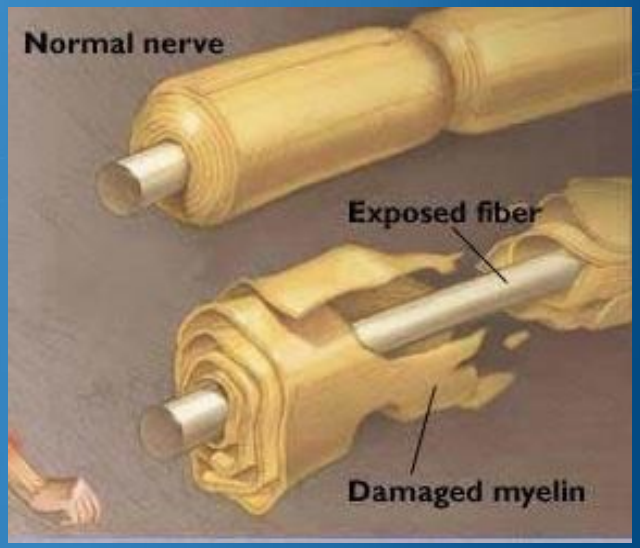


PMP22 gene duplication

PMP22 vs. *PMP22*

CMT1A is caused by a duplication of the *PMP22* gene in every cell

- PMP22- a protein found in myelin
- *PMP22* – duplicated gene in CMT1A
- *PMP22* gene duplication :
  - ➔ over-production of PMP22 protein
  - ➔ deterioration of myelin sheath



PMP-22

The official name of this gene is
“peripheral myelin protein 22”
PMP22 is the gene's official symbol

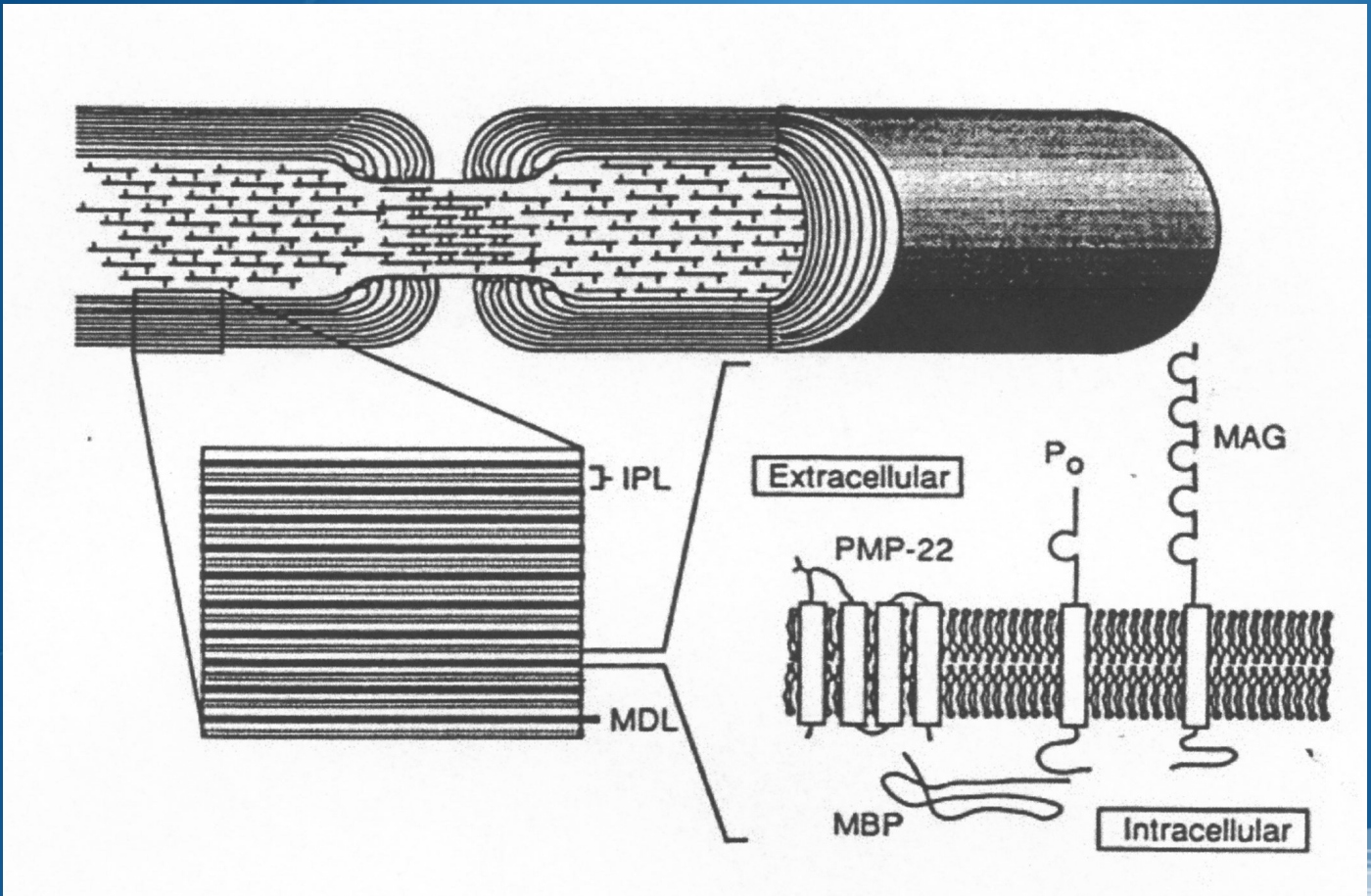
What is the normal function of thePMP22 gene?

The PMP22 gene provides instructions for making a protein called peripheral myelin protein 22. This protein is found in the peripheral nervous system, which connects the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, heat, and sound.

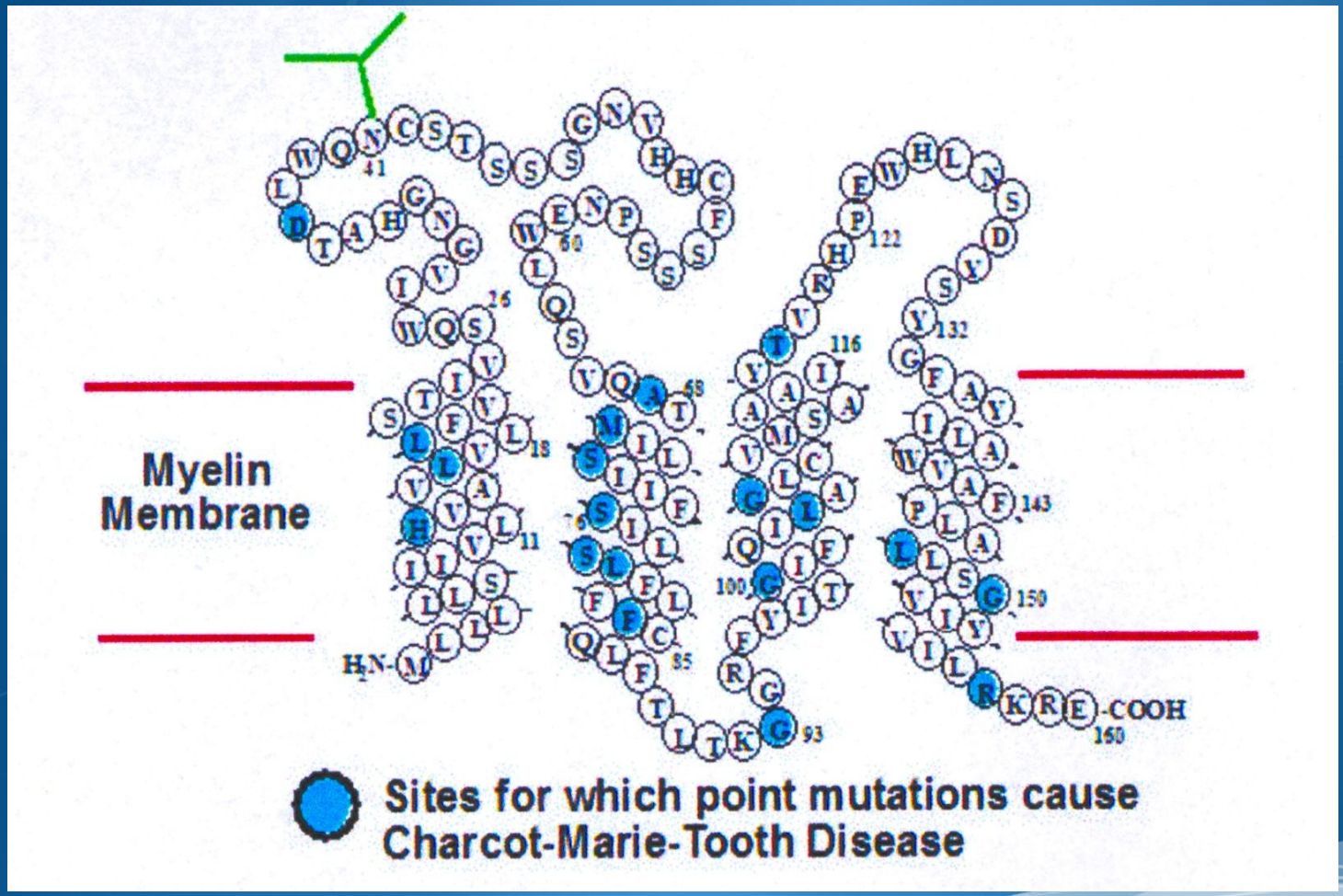
Peripheral myelin protein 22 is a component of myelin, a protective substance that covers nerves and promotes the efficient transmission of nerve impulses. The protein is produced primarily by specialized cells called Schwann cells that wrap around and insulate nerves. Within Schwann cells, peripheral myelin protein 22 plays a crucial role in the development and maintenance of myelin. The PMP22 gene may also play a role in Schwann cell growth and differentiation (the process by which cells mature to carry out specific functions).

Before it becomes part of myelin, newly produced peripheral myelin protein 22 is processed and packaged in specialized cell structures called the endoplasmic reticulum and the Golgi apparatus. Completion of these processing and packaging steps is critical for proper myelin function.

Assoni, mielina, PMP-22



PMP-22


Myelin Membrane
H2N-M
-COOH
Sites for which point mutations cause Charcot-Marie-Tooth Disease

How are changes in the PMP22 gene?

Mutations in the PMP22 gene cause forms of Charcot-Marie-Tooth disease known as types 1A and 1E.

An extra copy of the PMP22 gene in each cell is the most common genetic change that causes type 1A Charcot-Marie-Tooth disease. The extra gene leads to an overproduction of peripheral myelin protein 22, which prevents the protein from being processed correctly.

A reduced amount of functional peripheral myelin protein 22 impairs the formation of myelin.

The unprocessed peripheral myelin protein 22 may also disrupt other Schwann cell activities, which leads to instability and loss of myelin (demyelination).

Demyelination reduces the ability of the peripheral nerves to activate muscles used for movement or relay information from sensory cells back to the brain, causing the signs and symptoms of type 1A Charcot-Marie-Tooth disease.

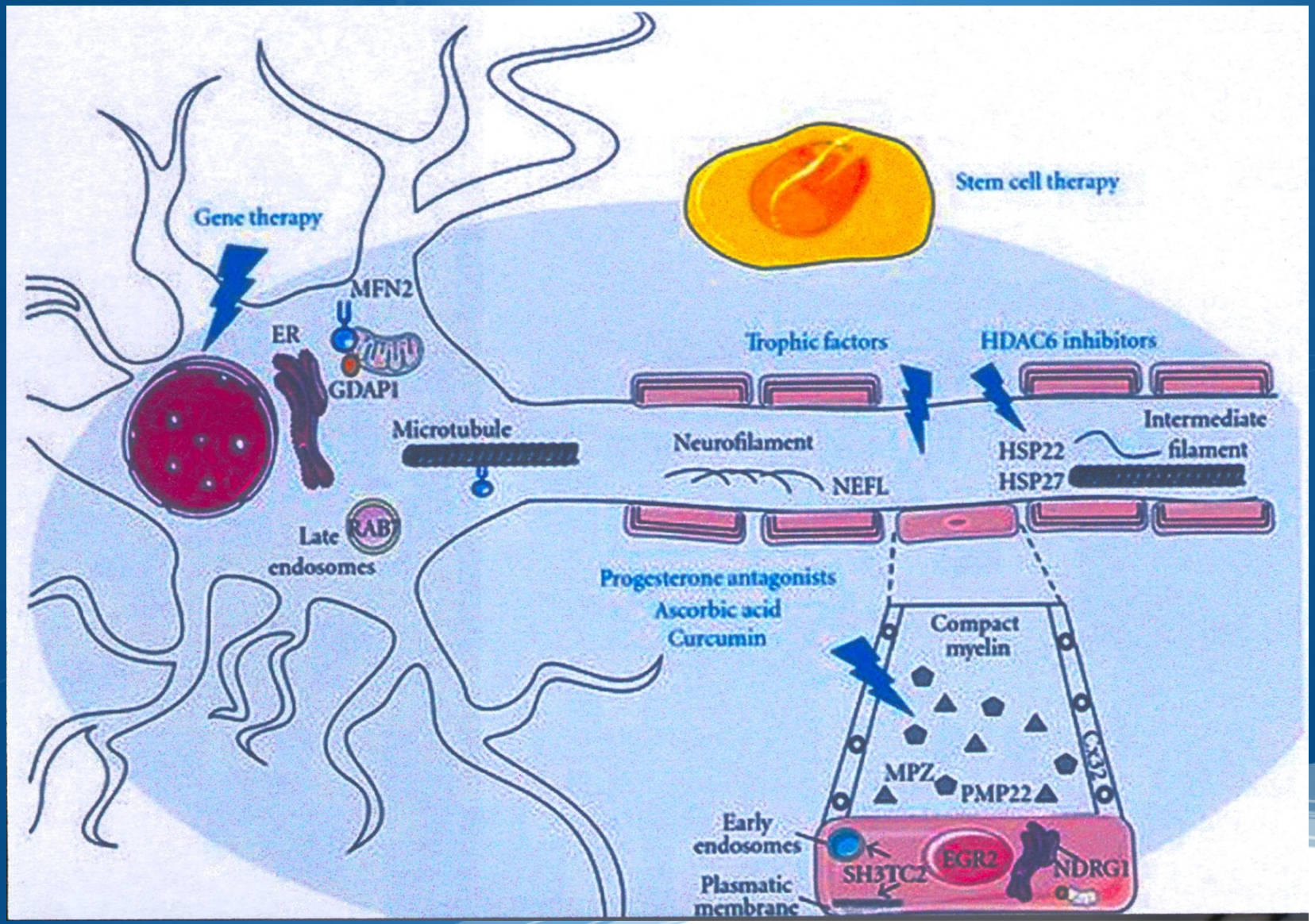
CMT type 1E

Hearing loss is experienced by some people with a form of type 1 Charcot-Marie-Tooth disease called type 1E.

Type 1E is associated with particular amino acid substitutions and deletions in the PMP22 gene.

The most frequently reported mutation causing hearing loss replaces the amino acid alanine with the amino acid proline at protein position 67 (also written as Ala67Pro).

Neurone e cellula di Schwann



Cell localization of some CMT proteins at the Schwann cell or the neuronal axon.

(a) PMP22 and P0 are structural proteins located at the compact myelin and Cx32 at the noncompact myelin in the paranode (and also at the Schmidt-Lanterman incisures). Some other demyelinating CMT-associated molecules are SHT3TC2 at the plasmatic membrane and related to early endosomes and endosome recycling, the transcription factor ERG2 working in early promyelination programme, and NDRG1 that is ubiquitously expressed and has been proposed to play a role in growth arrest and cell differentiation, possibly as a signaling protein shuttling between the cytoplasm and the nucleus. Proteins mainly related to axonal CMT are associated with neurofilaments (NEFL), late endosomes (RAB7), mitochondria, endoplasmic reticulum and microtubules (MFN2 and GDAP1), or intermediate filaments (HSP22 and HSP27).

(b) A ray sign indicates the main location where drugs or advanced therapies are acting.

Changes in the PMP22 gene

Type 1A Charcot-Marie-Tooth disease is also caused by mutations that add, delete, or change the building blocks (amino acids) used to make peripheral myelin protein 22. The altered protein is probably processed at a slower rate, and some of the protein is processed abnormally. These disruptions of peripheral myelin protein 22 processing impair the normal functions of the Schwann cell, leading to demyelination and producing the signs and symptoms of type 1A Charcot-Marie-Tooth disease.

Paralisi Pressoria

Loss of one copy of the PMP22 gene from each cell is the most common genetic cause of hereditary neuropathy with liability to pressure palsies. Deletion of one copy of the PMP22 gene (also called reduced gene dosage) probably decreases the amount of peripheral myelin protein 22 available for myelin production. This disorder is also caused by PMP22 gene mutations that produce an abnormally small protein, which is rapidly broken down. Other mutations change one of the amino acids used to make peripheral myelin protein 22, producing an unstable protein. A reduction in the amount of stable protein leads to the loss of myelin. Demyelination results in increased sensitivity to pressure on the nerves, causing the signs and symptoms of hereditary neuropathy with liability to pressure palsies.

Gene PMP22

Where is the PMP22 gene located?

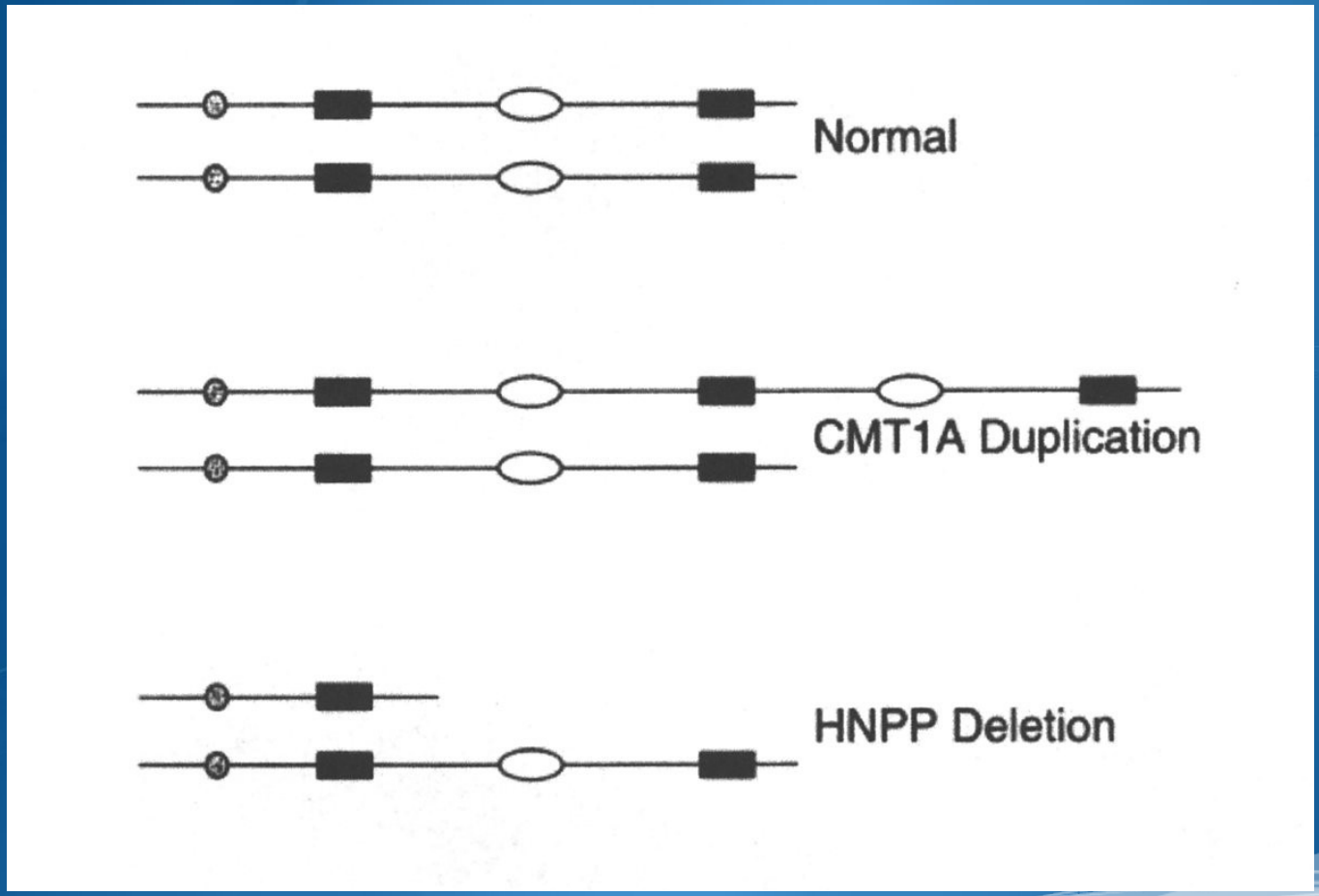
Cytogenetic Location: 17p12

Molecular Location on chromosome 17: base pairs 15,229,776 to 15,265,356

The PMP22 gene is located on the short (p) arm of chromosome 17 at position 12.

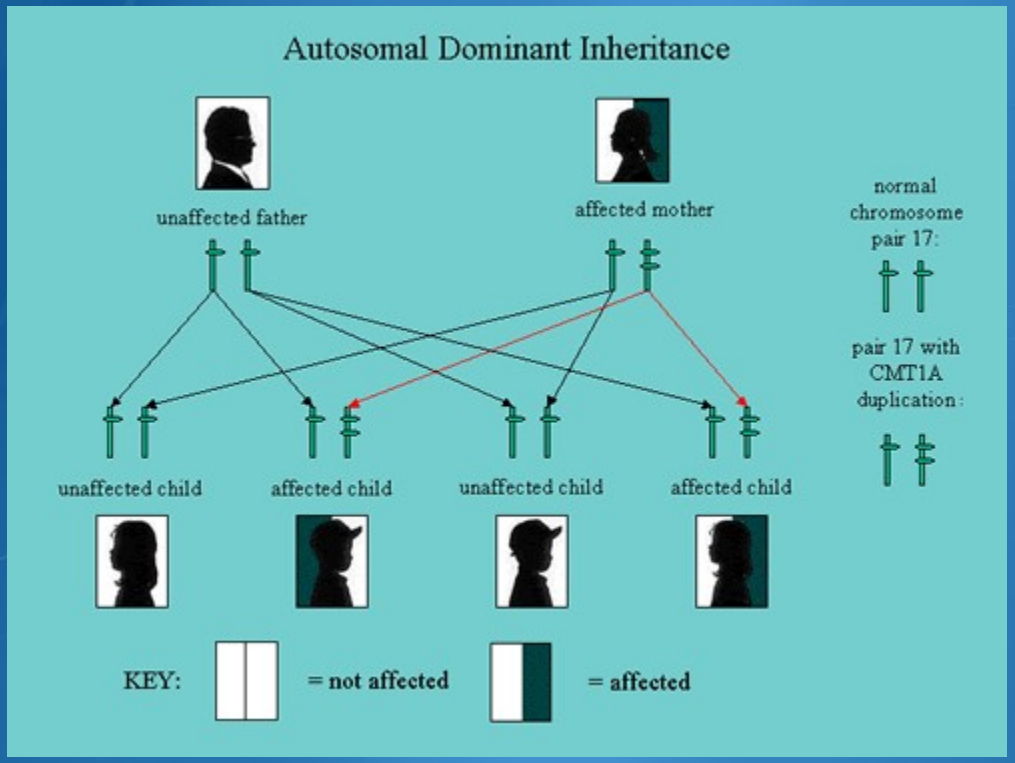
More precisely, the PMP22 gene is located from base pair 15,229,776 to base pair 15,265,356 on chromosome 17.

Mutazioni cluster PMP-22

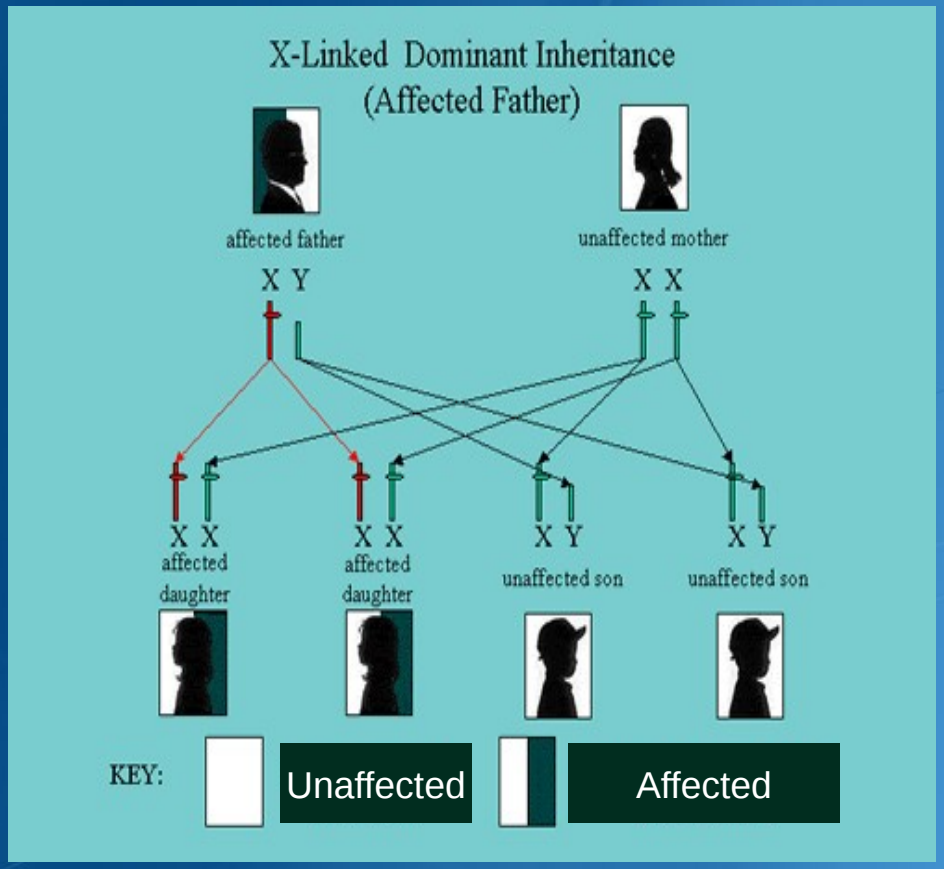


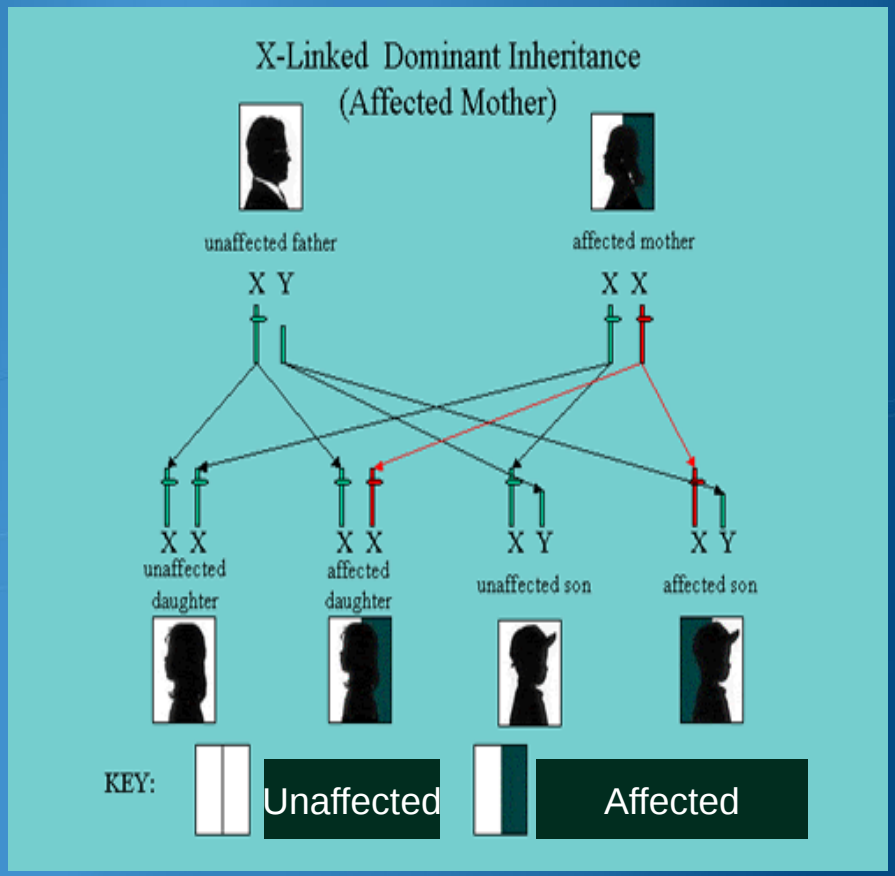
Inheritance Patterns

Autosomal Dominant (CMT1A)

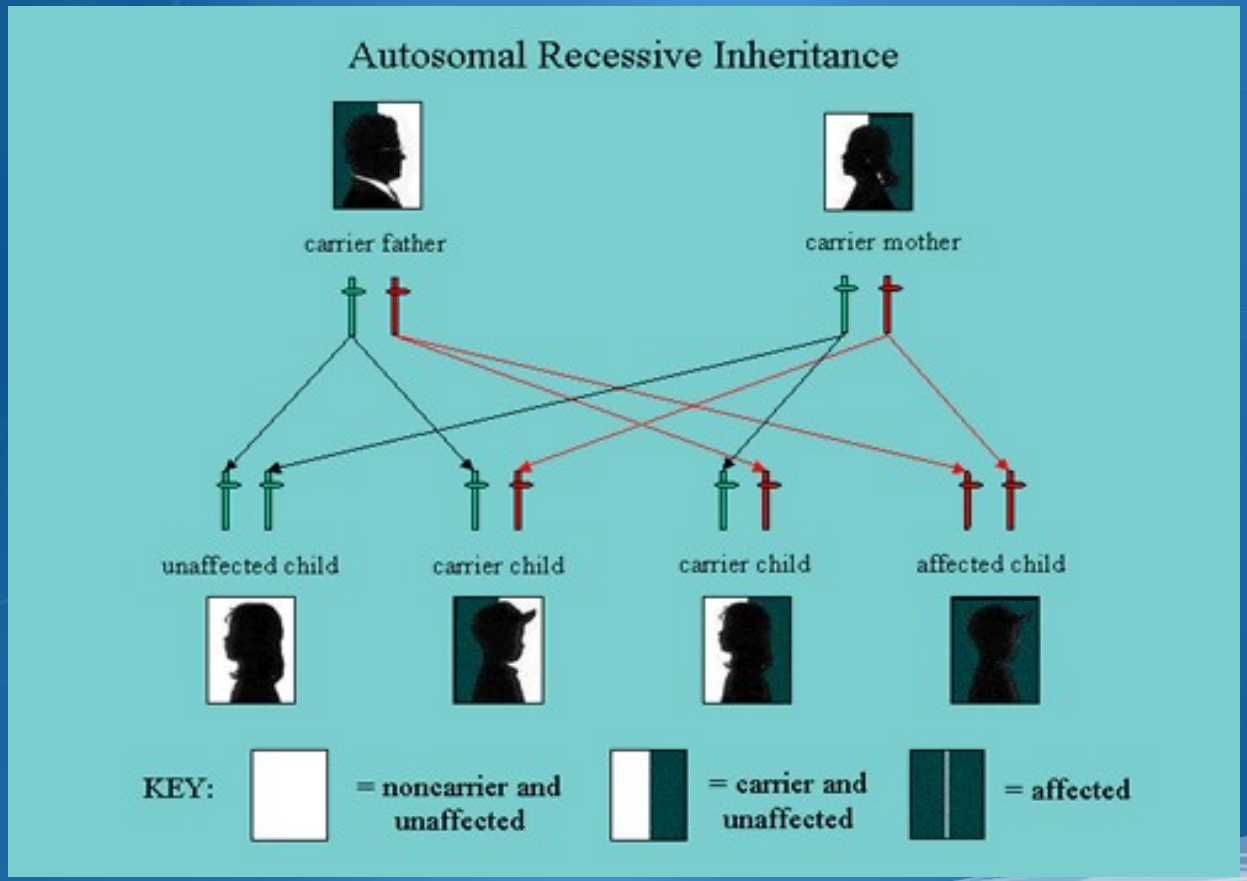


X-linked Inheritance

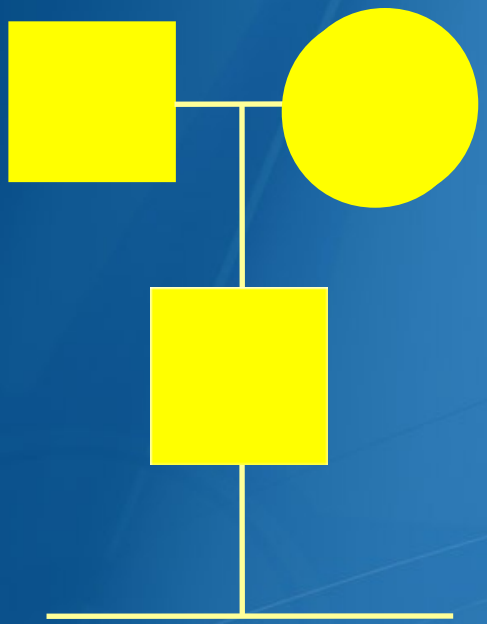


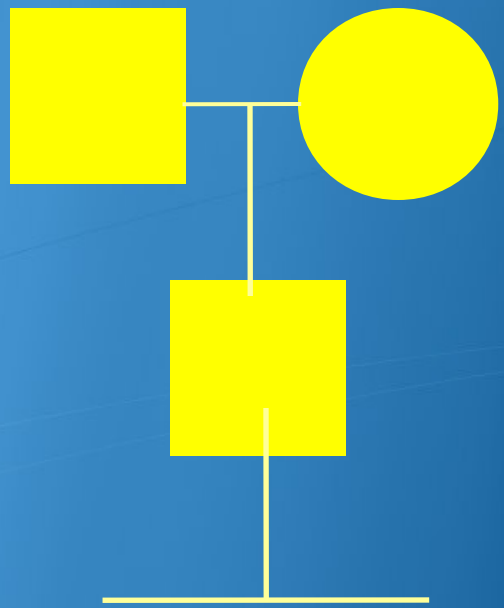


Autosomal Recessive (Type 4)



Activity





…….Put the initials of your father in the square and the initials of your mother in the circle.

……..Put your initials in either the circle or square, depending if you are male or female.

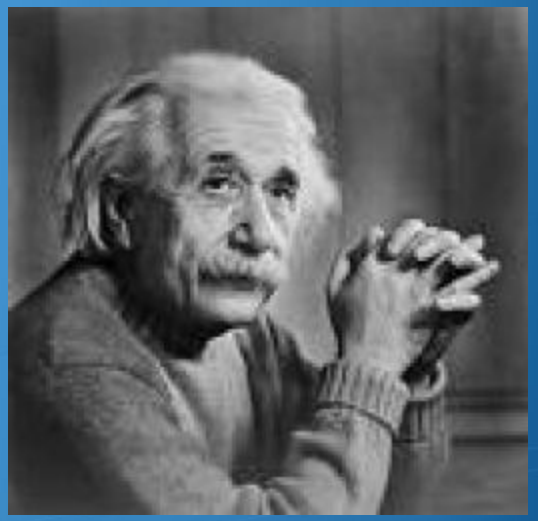
……..Roll the dice once to determine how many children you will have. Decide on the sex.

…….Take the coin and flip it. Heads-the child has CMT, and Tails-child does not have CMT. …….Do this for every child. M

Everyone Has Different Abilities

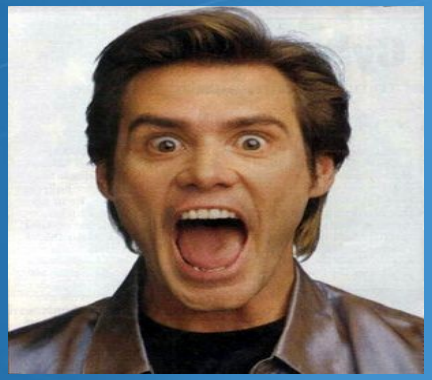
Franklin D. Roosevelt: Polio
Weihenmayer: Blind

Erik



Albert Einstein : Aspergers

Tom Cruise:
Dyslexia



Jim Carrey: Depression

Gerry Jewel:
Cerebral Palsy