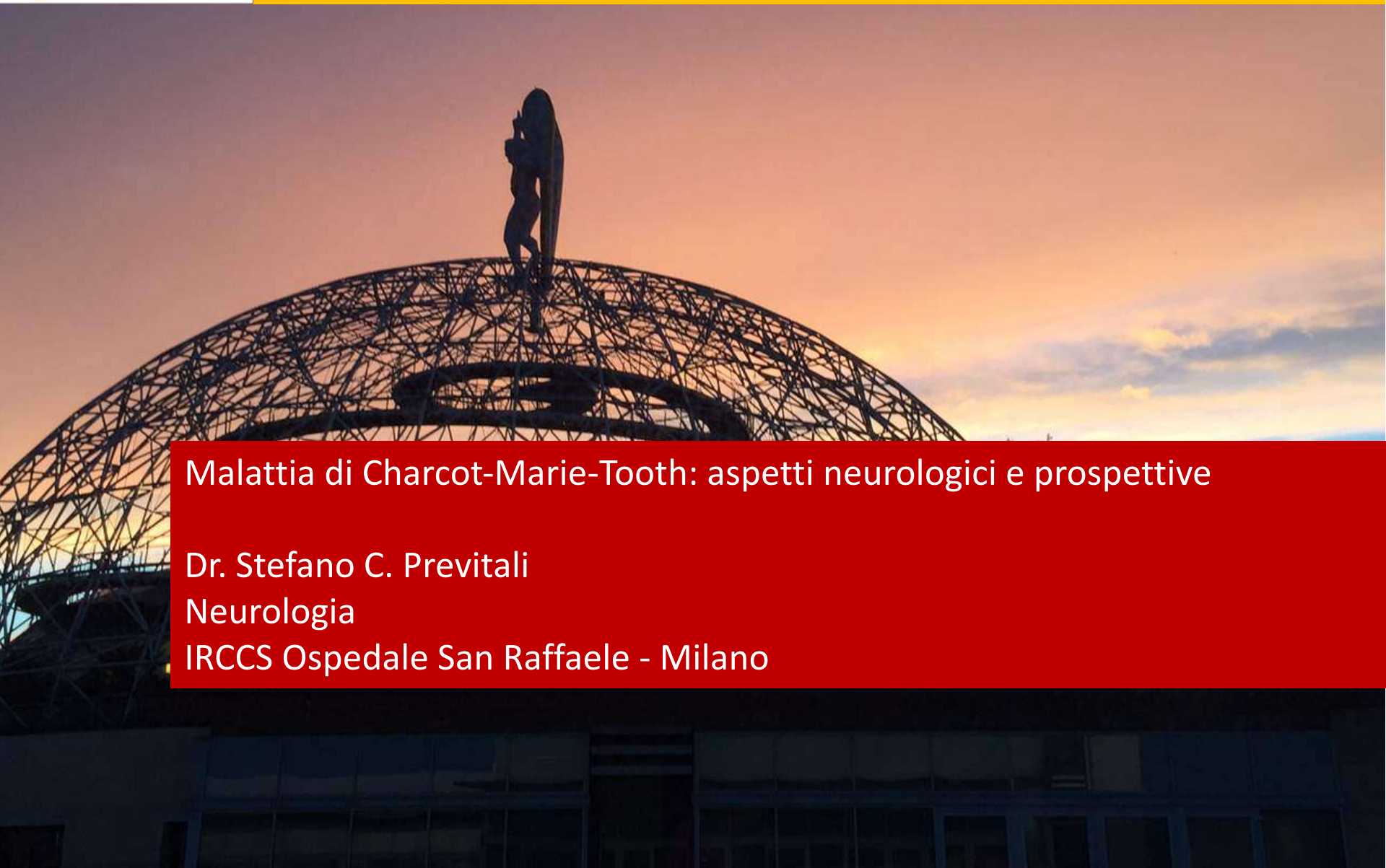
ACMT-Rete

Ospedale Fatebenefratelli

Milano, 23 Marzo 2019



Malattia di Charcot-Marie-Tooth: aspetti neurologici e prospettive

Dr. Stefano C. Previtali
Neurologia
IRCCS Ospedale San Raffaele - Milano

Neuropatie ereditarie tipo Charcot-Marie-Tooth (CMT)

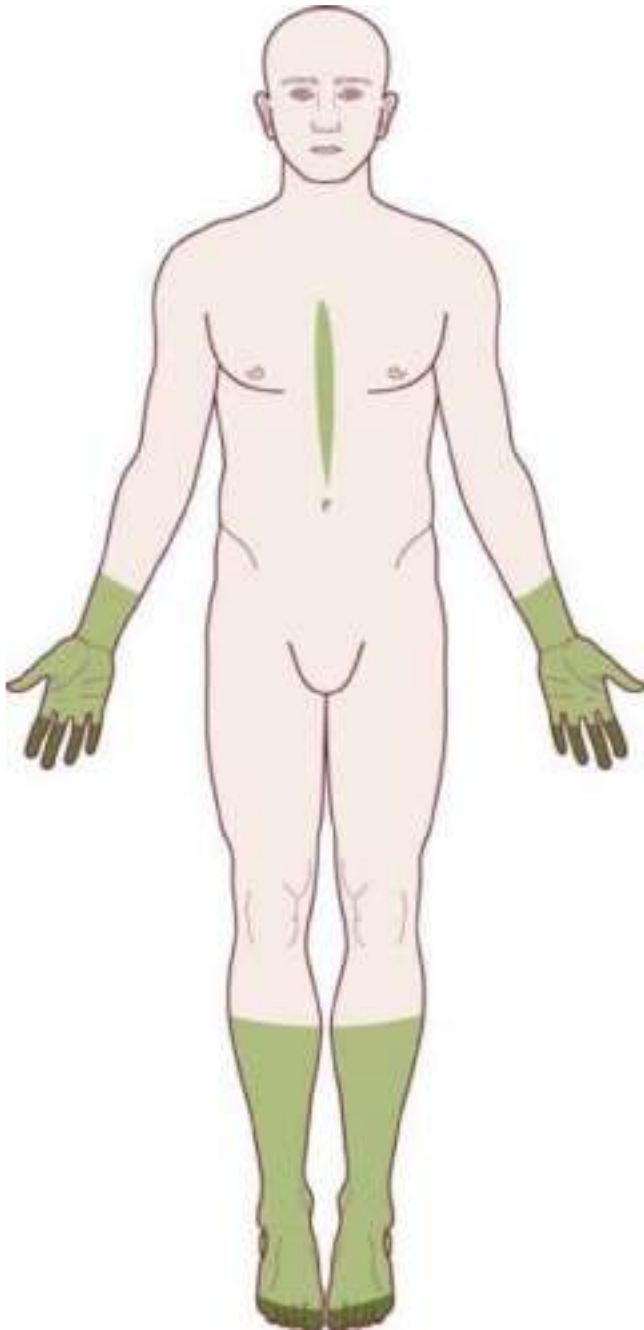
Descritte per la prima volta nel 1886 da
Jean-Martin Charcot, Pierre Marie, e Howard Henry Tooth

PREVALENZA <1/2.500
(sono quindi malattie rare)

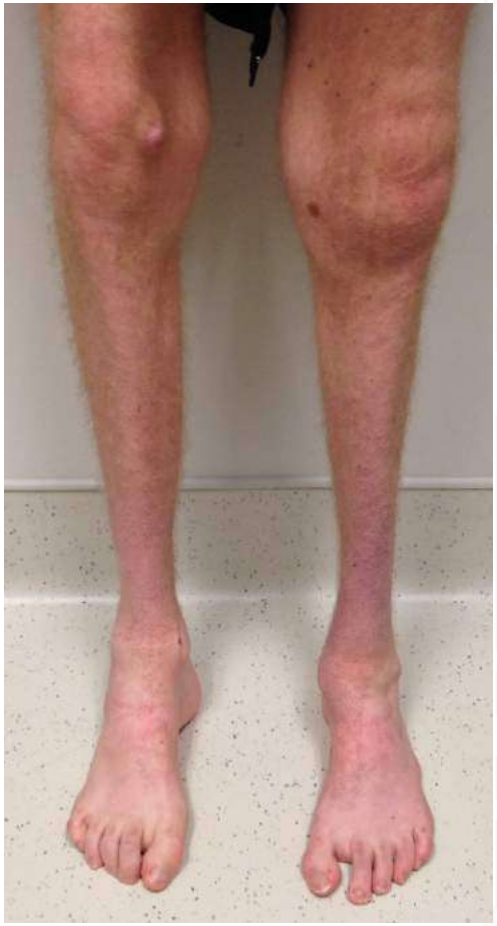
Neuropatie ereditarie: aspetti clinici

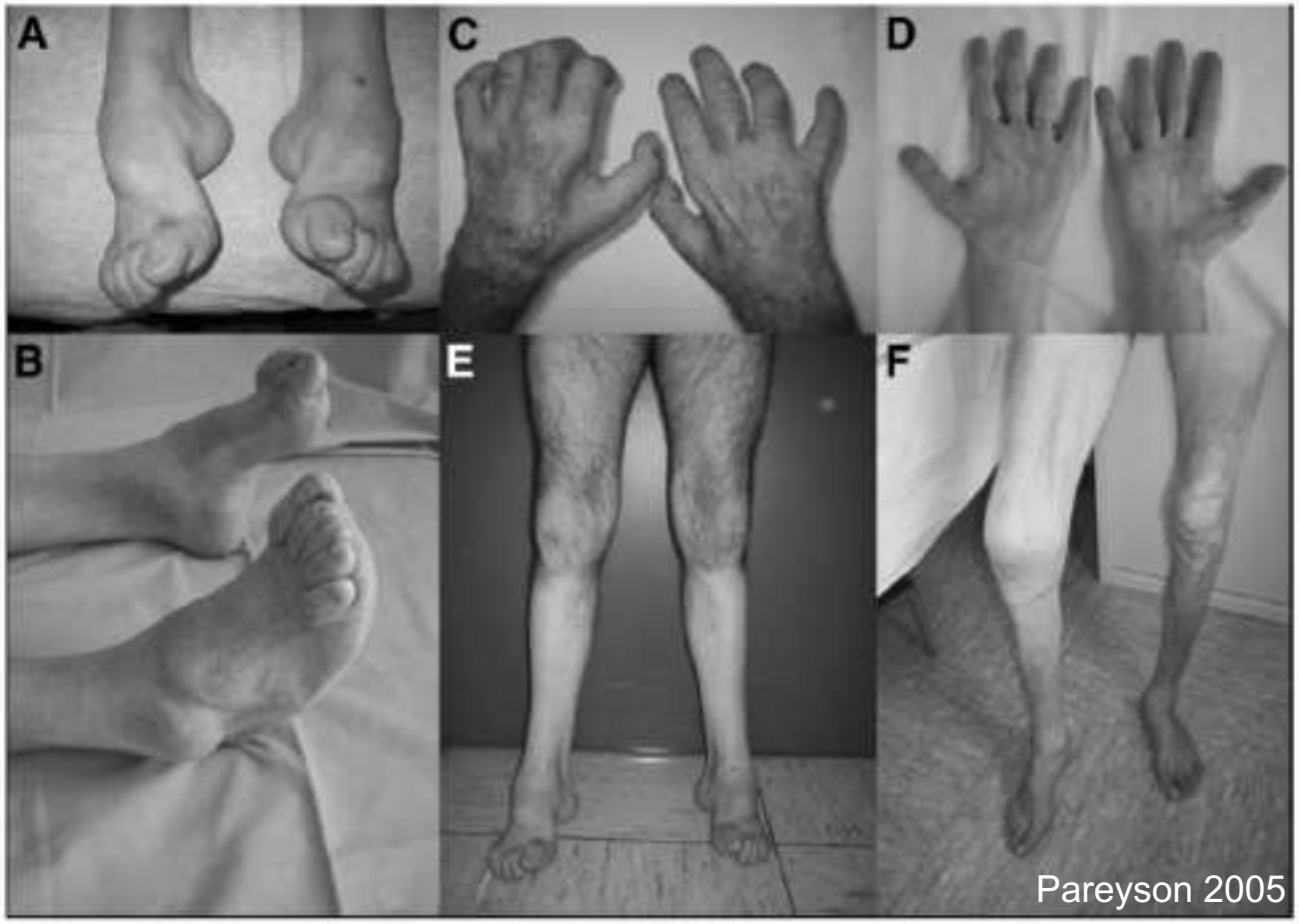
PAZIENTE:

- Deficit motori distali (piedi, mani, < faccia e tronco)
- Atrofia muscolare distale
- Deficit sensitivi distali
- Disturbi dell'equilibrio (deficit sensibilità profonda)
- Dolore
- Deformità ossee



Neuropatie ereditarie: aspetti clinici





Aspetto caratteristico gambe con aspetto di bottiglia di Champagne rovesciata e piede cavo

Esordio poco definibile, spesso presente dalla giovane età

Neuropatia sensitivo motoria (forme sensitive pure, forme motorie pure)

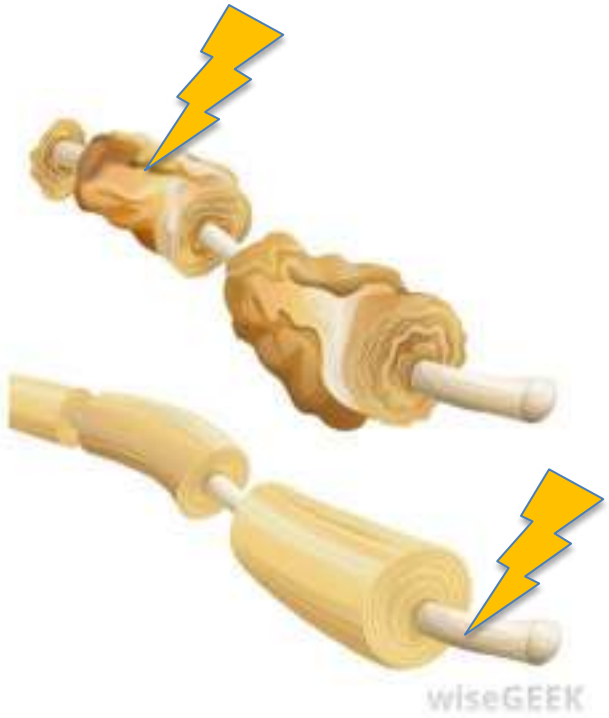
Neuropatie ereditarie: classificazione

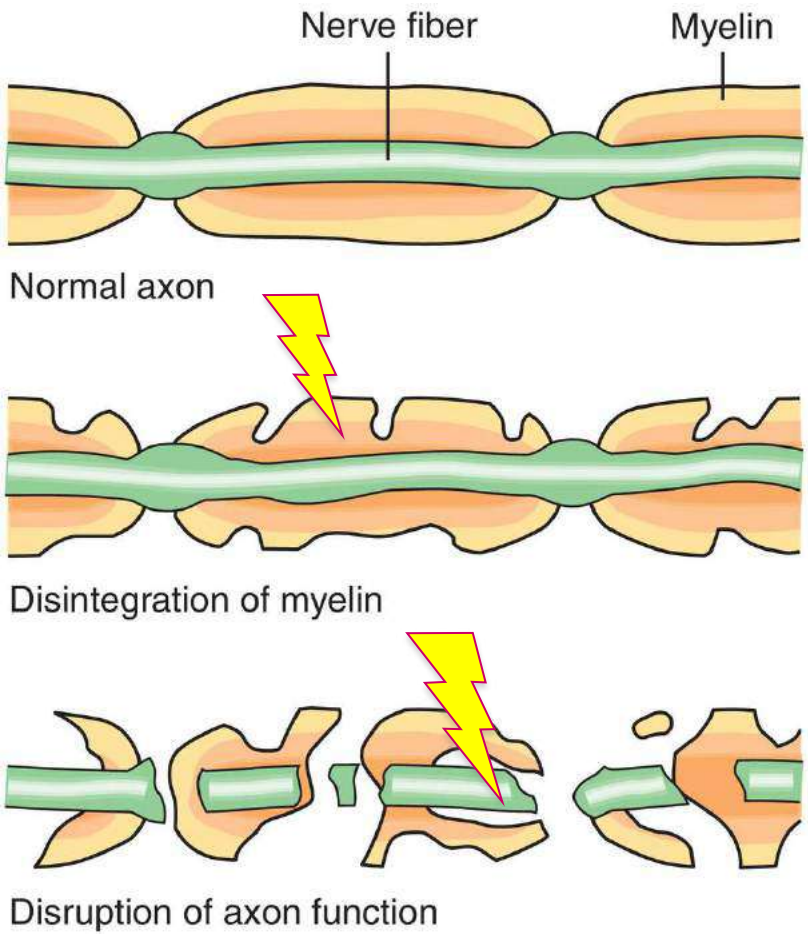
Sulla base della neurofisiologia

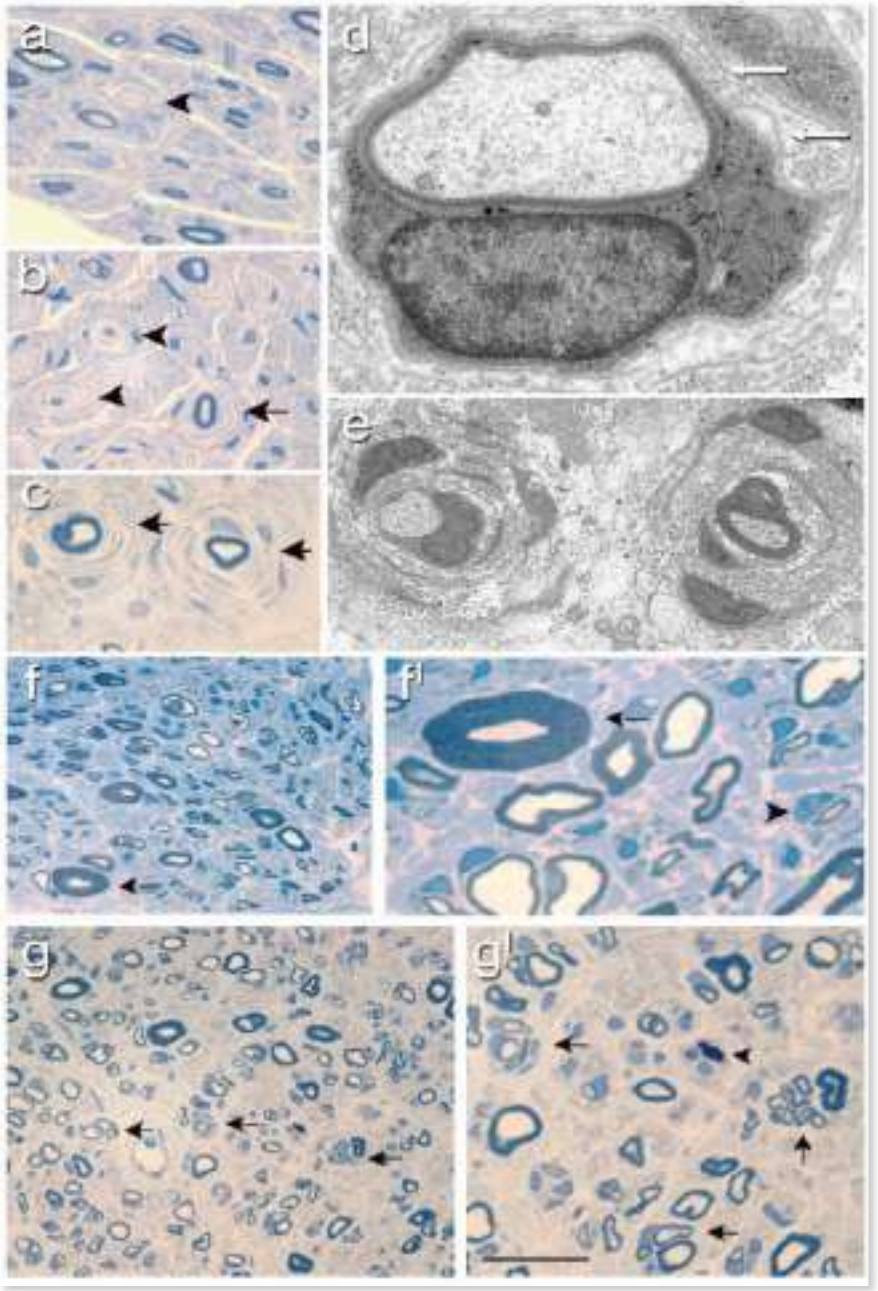
FORME DEMIELINIZZANTI (CMT1, CMT4):
velocità di conduzione motoria < 38 m/s agli arti superiori

FORME ASSONALI (CMT2)
velocità di conduzione motoria > 38 m/s agli arti superiori

FORME INTERMEDIE
velocità di conduzione motoria >25 m/s <45 m/s







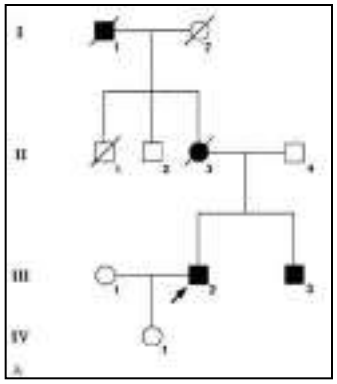
Previtali, Quattrini, Bolino; Exp Rev Mol Med 2008

Neuropatie ereditarie: classificazione

Sulla base della trasmissione

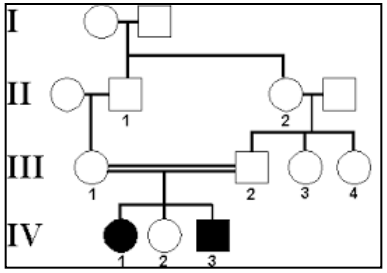
FORME DEMIELINIZZANTI
Dominanti CMT1
Recessive CMT4
X-linked CMTX

AD



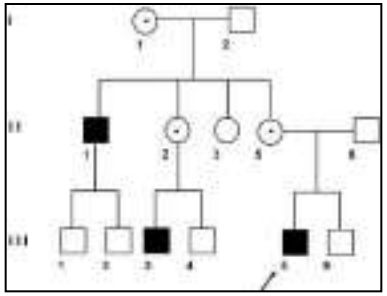
FORME ASSONALI
Dominanti CMT2
Recessive AR-CMT2
X-linked CMTX

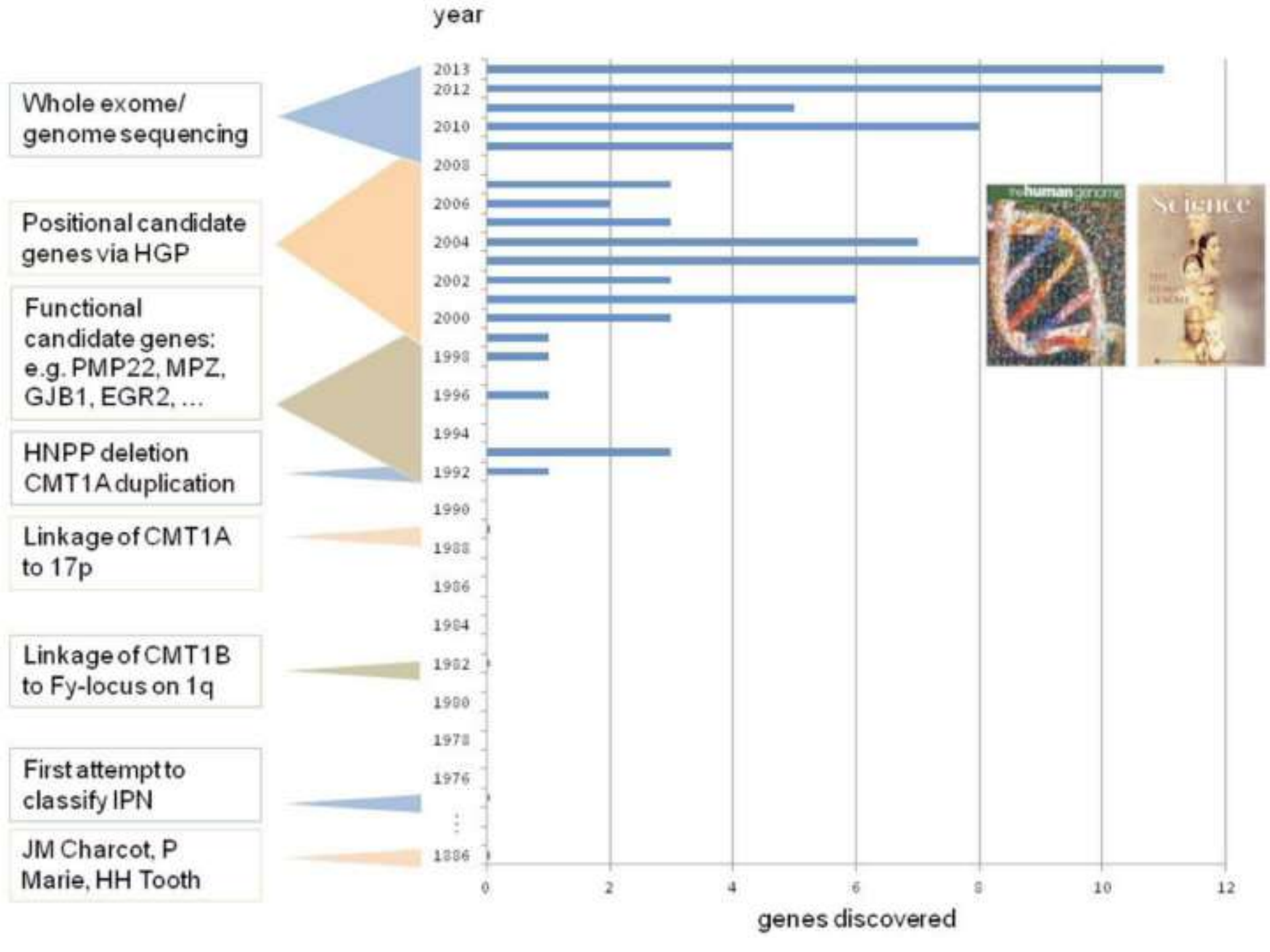
AR



FORME INTERMEDIE
Dominanti AD-I
Recessive AR-I
X-linked CMTX-i

X-linked




year
Whole exome/ genome sequencing
Positional candidate genes via HGP
Functional candidate genes: e.g. PMP22, MPZ, GJB1, EGR2, ...
HNPP deletion CMT1A duplication
Linkage of CMT1A to 17p
Linkage of CMT1B to Fy-locus on 1q
First attempt to classify IPN
JM Charcot, P Marie, HH Tooth
2013
2012
2010
2008
2006
2004
2002
2000
1998
1996
1994
1992
1990
1988
1986
1984
1982
1980
1978
1976
1886
0
2
4
6
8
10
12
genes discovered
the human genome
Science

Neuropatie ereditarie: classificazione

Oltre 100 geni noti descritti

CMT & HMSN: Demyelinating

Dominant
- CMT 1A: PMP-22; 17p12
- CMT 1B: P_0 protein; 1q23
- CMT 1C: LITAF; 16p13
- CMT 1D: EGR2; 10q21
- CMT 1E (Deafness)
  - PMP-22; 17p12
  - P_0 protein; 1q23
- CMT 1F: NEFL; 8p21
- CMT1: FBLN5; 14q32
- HNPP
  - PMP-22 (Deletion or Point); 17p12
  - KARS; 16q23
- HMSN 3 (Dejerine-Sottas)
  - PMP-22; P_0; 8q23; EGR2
- Thermosensitive
- PNS & CNS hypomyelin; SOX10; 22q13
- Sensory PN + Hearing loss; GJB3; 1p34
- Hypomyelination; ARHGEF10; 8p23
- CMT-DIF; GNB4; 3q26
- HMSN; HARS; 5q31
- HMSN; PMP2; 8q21

Recessive; Also AR-CMT1
- CMT 4A; GDAP1; 8q21
- CMT 4B1; MTMR2; 11q22
- CMT 4B2; SBF2; 11p15
- CMT 4B3; SBF1; 22q13
- CMT 4C; SH3TC2 (KIAA1985); 5q32
- CMT 4D (Lom); NDRG1; 8q24
- CMT 4E; EGR2; 10q21
- CMT 4F; Periaxin; 19q13
- HMSN-Russe (4G); HK1; 10q22
- CMT 4H; FGD4; 12q12
- CMT 4J; FIG4; 6q21
- CMT 4K; SURF1; 9q34
- HMSN 3 (Dejerine-Sottas)
  - P_0; PMP-22; EGR2; Periaxin
- HMSN + Juvenile glaucoma
- Cataracts (CCFDN); CTDP1; 18qter
- Cockayne's; 5
- Congenital hypomyelinating
  - P_0, PMP-22 & EGR-2
- Farber lipogranulomatosis; ASAH; 8p22
- CDG1a; PMM2; 16p13

CMT & HMSN: Axonal

Dominant
- CMT 2A2A; MFN2; 1p36
- ? CMT 2A1; KIF1B; 1p36
- CMT 2B; RAB7; 3q21
- CMT 2C; TRPV4; 12q24
- CMT 2D; GARS; 7p14
- CMT 2E; NEFL; 8p21
- CMT 2F/ Distal HMN; HSPB1; 7q11
- CMT 2G; See CMT 2P
- CMT 2I; P_0; 1q22
- CMT 2J; P_0; 1q22
- CMT 2K; GDAP1; 8q21
- CMT 2L; HSPB8; 12q24
- CMT 2M; DNM2; 19p13
- CMT 2N; AARS; 16q22
- CMT 2O; DYNC1H1; 14q32
- CMT 2P; LRSAM1; 9q33
- CMT 2Q; DHTKD1; 10p14
- CMT 2U; MARS; 12q13
- CMT 2V; NAGLU; 17q21
- CMT 2W; HARS; 5q31
- CMT 2Y; VCP; 9p13
- CMT 2Z; MORC2; 22q12
- CMT 2CC; NEFH; 22q12
- CMT 2DD; ATP1A1; 1p13
- CMT 2; TFG; 3q12
- CMT 2; DGAT2; 11q13
- CMT 2; MME; 3q25
- Giant axonal 2; DCAF8; 1q22
- HMSN; BAG3
- HMSN-Proximal; TFG; 3q12

CMT2 + Pyramidal
- HMSN5; 4q34
- MFN2; 1p36
- KIF5A; 12q13
- HMSN + Optic atrophy
- HMSN + Deafness
  - P_0
  - Connexin-31 (GJB3)
  - Eye + Ear dysfunction
- HMSN6A (+ Optic); MFN2; 1p36
- HSMN + Ulcero-mutilation
- HMSN; SPTLC3; 20p12
- HSMN + Ataxia; IFRD1; 7q31
- HMN 5B; BSCL2; 11q13

Recessive

AR-CMT2
- A (B1); Lamin A/C; 1q22
- B (B2); MED25; 19q13.3
- F/Distal HMN; HSPB1; 7q11-q21
- H/Pyramidal signs; 8q21.3
- K/Hoarseness; GDAP1; 8q21
- P; LRSAM1; 9q33
- R; TRIM2; 4q31
- S; IGHMBP2; 11q13
- T; MME; 3q25
- X; SPG11; 15q21
- 2A2B; MFN2; 1p36
- EGR2; 10q21
- HSJ1/DNAJB2; 2q35
- MCM3AP (GANP); 21q22
- PNKP; 19q13
- SACS; 13q12

Acrodystrophy; ATSV; 2q37

Andermann; KCC3; 15q13

Ataxia + Neuropathy
- Cough + Sensory
- Hepato-Cerebellar; SCYL1; 11q13
- SCAN

Early onset
- CMT; SCO2; 22q13
- Lethal Neonatal
- NBIA2A; PLA2G6; 22q13
- Ouvrier
- Optic; MFN2; 1p36
- Respiratory failure
  - REEP1; 2p11
  - MFN2; 1p36
- Severe; NEFL; 8p21

Episodic; SGPL1; 10q22

Giant axonal; Gigaxonin; 16q23

Neuromyotonia; HINT1; 5q31

Optic neuropathy
- HMSN + Deaf
- HMSN6B; SLC25A46; 5q22

Syndromes; HMSN+
- Childhood onset
- CNS
- Deafness

X-linked

CMT + Intermediate NCV

Dominant
- CMT-DIA; 10q24
- CMT-IB; DNM2; 19p13
- CMT-DIC; YARS; 1p35
- CMT-DID; P_0; 1q22
- CMT-DIE; INF2; 14q32
- CMT-DIF; GNB4; 3q26
- CMT-DIG; NEFL; 8p21
- CMT-X (Semi-dominant)
- CMT 1C; LITAF; 16p13
- CMT 2E; NEFL; 8p21
- Hypomyelination; ARHGEF10; 8p23

Recessive
- CMT RIA; GDAP1; 8q21.1
- CMT RIB; KARS; 16q23
- CMT RIC; PLEKHG5; 1p36
- CMT RID; COX6A1; 12q24
- CMT XI; DRP2; Xq22

Other related names or disorders
- α-Methylacyl-CoA racemase (AMACR)
- Brachial plexopathy, Hereditary
- Childhood onset neuropathies
- CNS & Cranial nerve disorders
- Complex clinical syndromes
- Congenital Hypomyelinating
  - EGR2; 10q21
  - P_0; 1q22
  - PMP-22; 17p11
  - ARHGEF10; 8p23
- Connective tissue; EMILIN1; 2p23
- Cowchock; AIFM1; Xq26
- Dejerine-Sottas (HMSN 3)
- Focally folded myelin sheaths
  - CMT 4B; MTMR2; 11q23
  - CMT 4B2; SBF2; 11p15
  - CMT 4E; EGR2; 10q21
  - CMT 4F; Periaxin; 19q13
  - P_0; 1q22
  - Juvenile glaucoma
- Hereditary
  - Motor neuropathies

Charcot-Marie-Tooth (CMT)

Features
- Associated
- Childhood
- Childhood CMT
- Comparative
- General
- Molecules
- Pathology

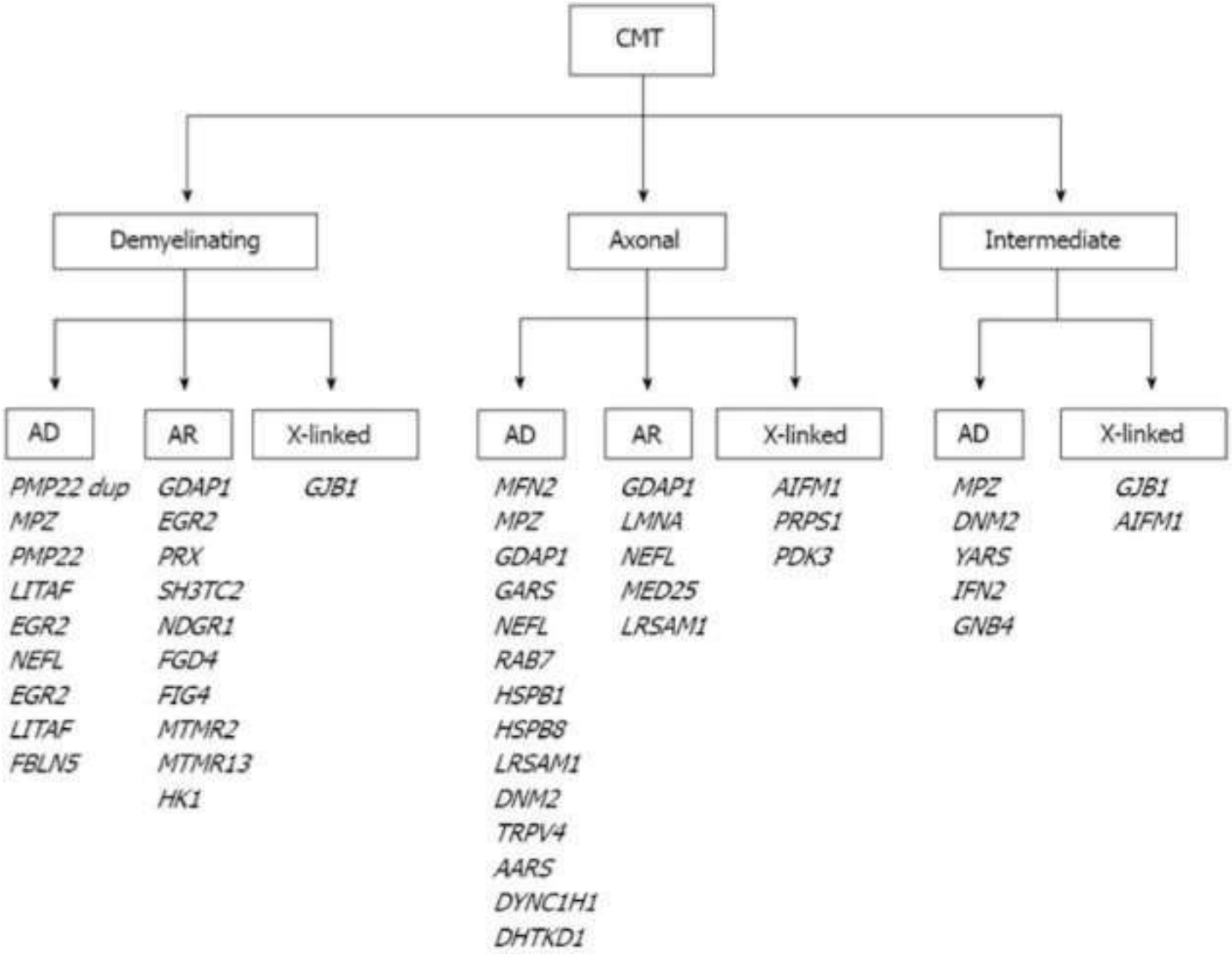
Myelin proteins

External link; Mutation database

Charcot (left) & Babonski at the Salpêtrière clinic.

http://neuromuscular.wustl.edu/time/hmsn.html

Neuropatie ereditarie: classificazione



CMT: un gene, molti fenotipi

*PMP*22, peripheral myelin protein 22

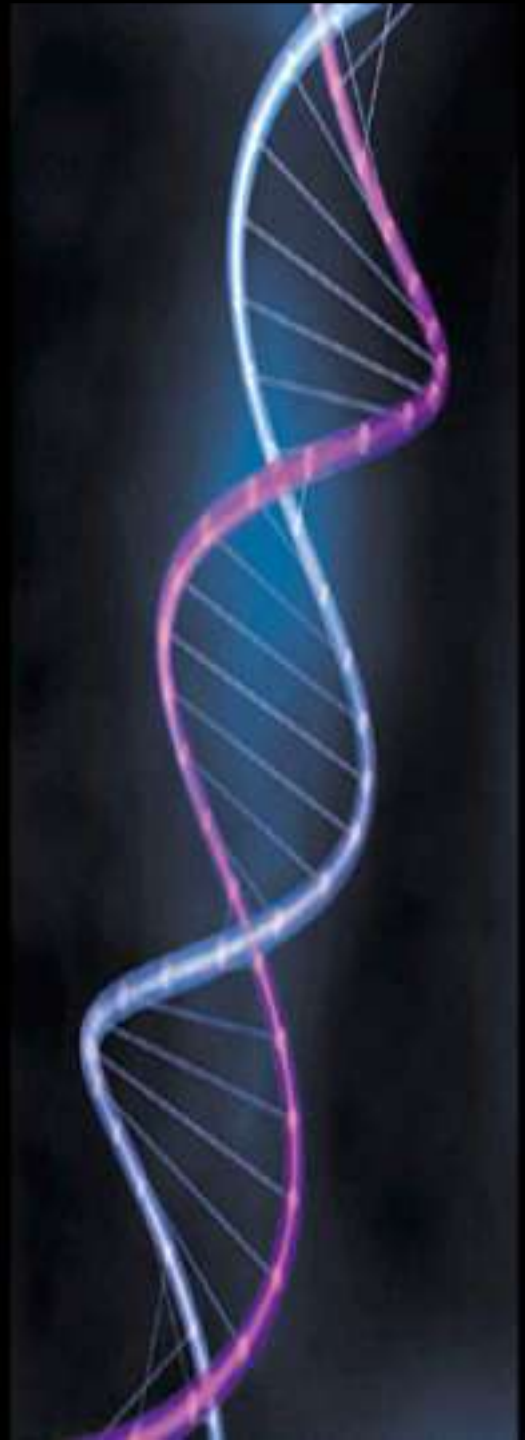
CMT1A	demyelinating
HNPP	demyelinating
DSS	demyelinating
CHN	demyelinating

MPZ, Myelin protein zero

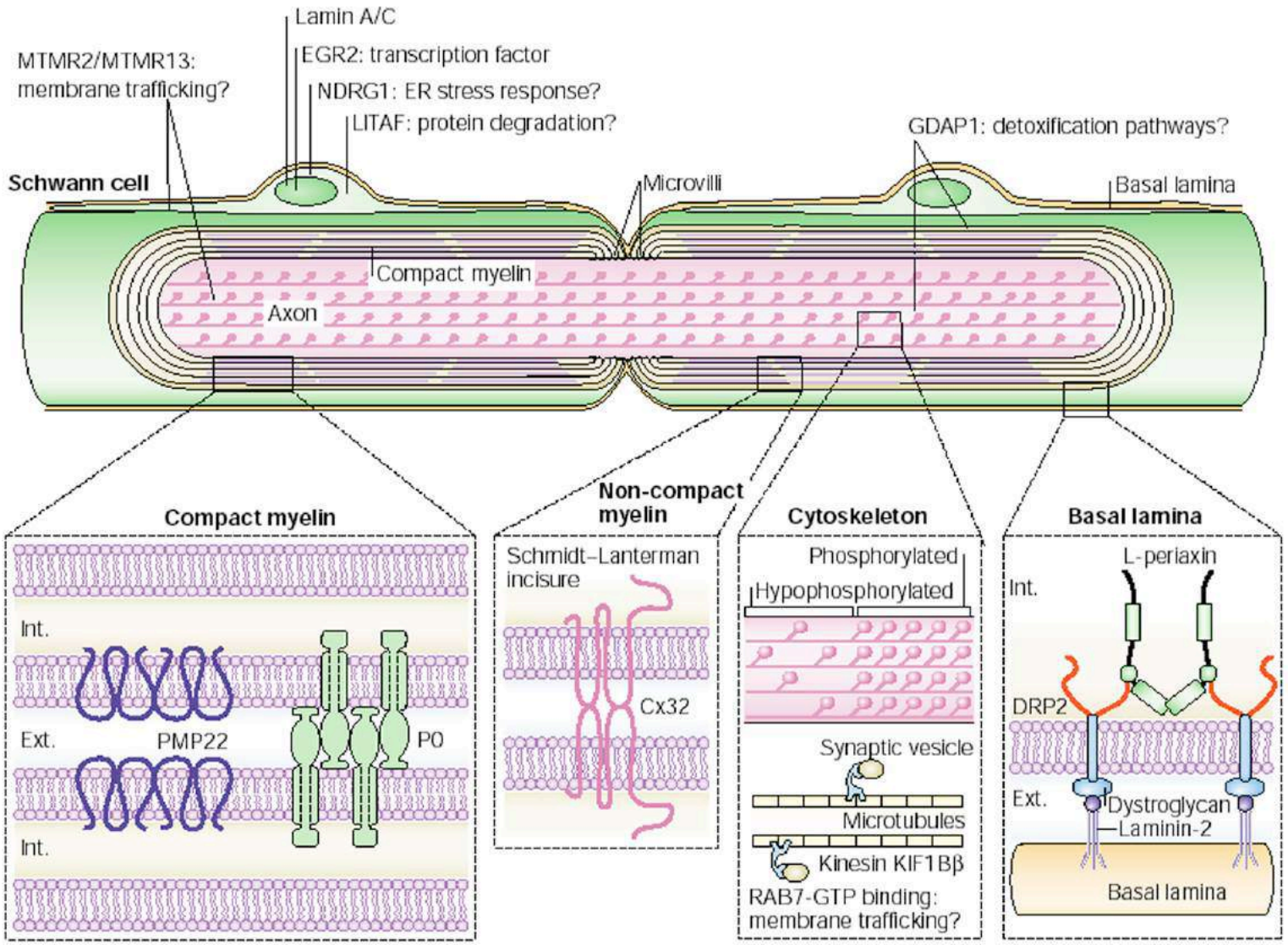
CMT1B	demyelinating
DSS	demyelinating
CHN	demyelinating
CMT2	axonal
HNPP/CMT4B like	demyelinating
I-CMT	intermediate

GBJ1, Connexin 32

CMTX1	demyelinating
I-CMT	intermediate
CMT2	axonal

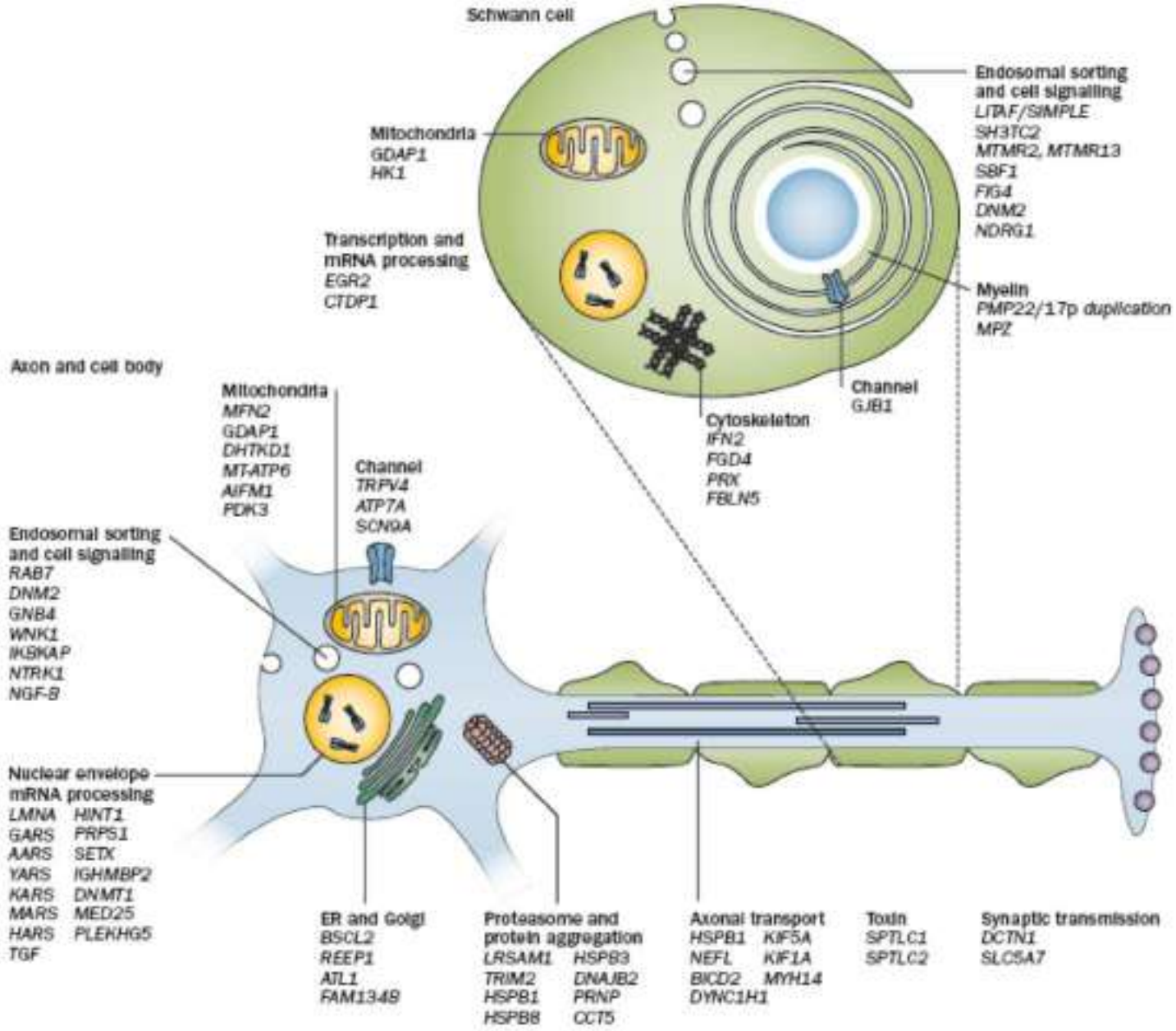


CMT: una neuropatia, molteplici pattern molecolari



Suter and Scherer, Nature Neurosci. 2003

CMT: una neuropatia, molteplici pattern molecolari

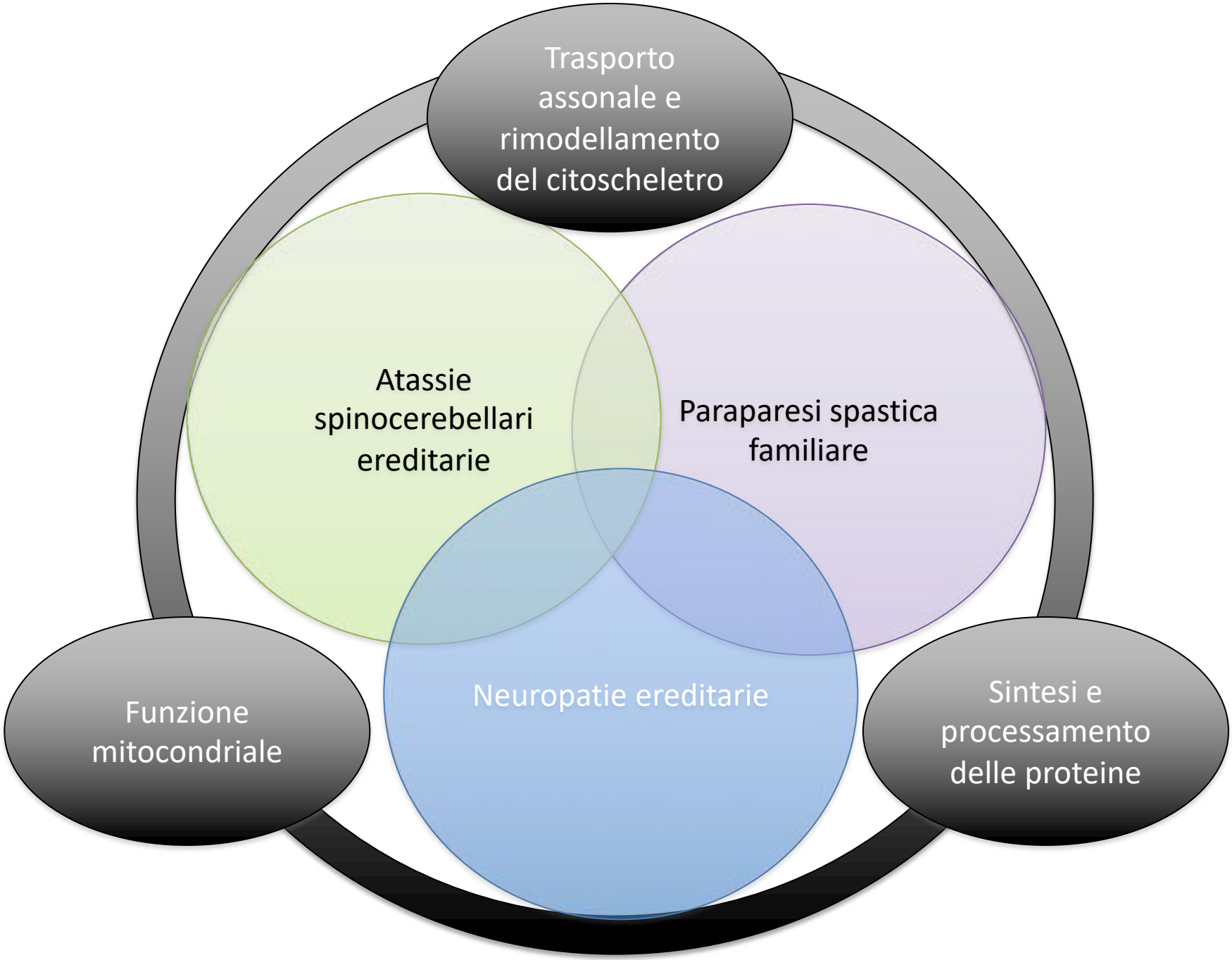


Rossor, Nat Rev Neurol 2013

HSN/HSAN
sensitive

CMT
sensitivo-
motorie

HMN/dSMA
motorie


Trasporto assonale e rimodellamento del citoscheletro
Atassie spinocerebellari ereditarie
Paraparesi spastica familiare
Neuropatie ereditarie
Funzione mitocondriale
Sintesi e processamento delle proteine

Come distinguere e diagnosticare le diverse forme di CMT ?

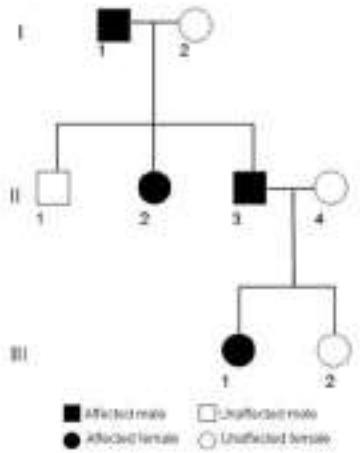
Neuropatie ereditarie: diagnosi

1. Forme primarie (CMT)
2. Neuropatie che appartengono a disordini multisistemici

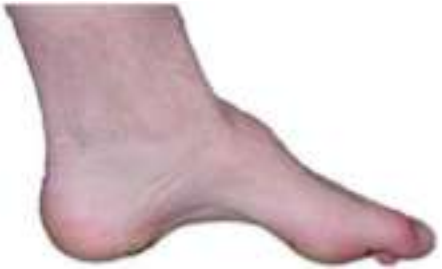
Neuropatie ereditarie: diagnosi

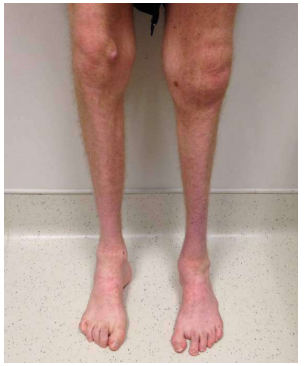
Ereditarietà

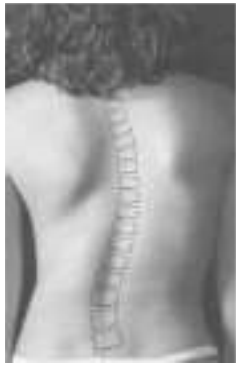
1. Autosomica Dominante
2. Autosomica Recessiva
3. X-linked
4. Sporadica



- Progressione lenta
- Simmetrica e distale
- Deformità scheletriche

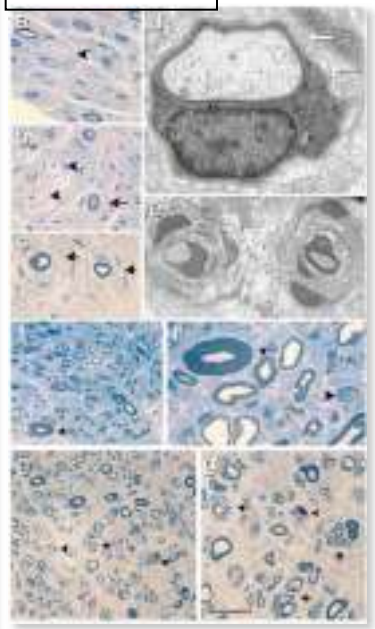


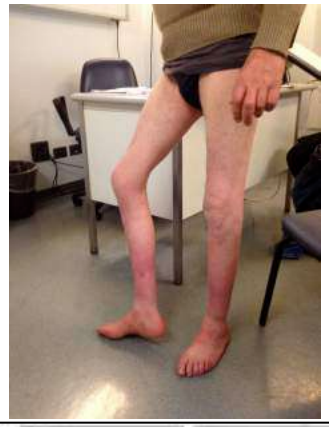


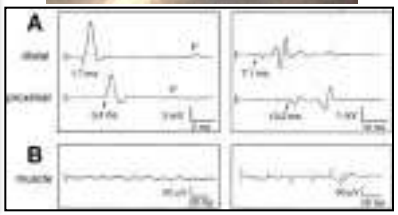


Neuropatie ereditarie: diagnosi

fenotipo







Identificazione del gene

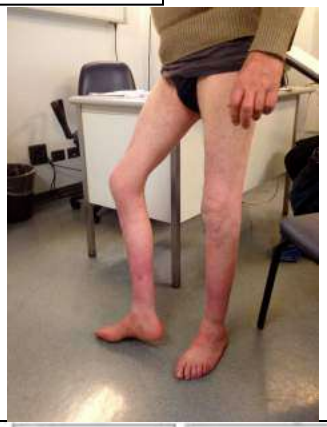
diagnosi

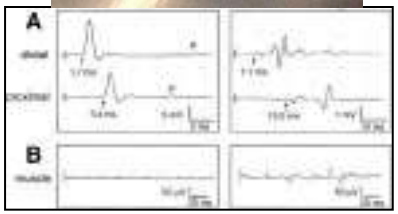
terapia

- CMT1A 70% di CMT1
50% di tutte CMT
- CMT1B 5-10% di CMT1
assonali tardive
- CTX 10% di tutte le CMT
demielinizzanti in uomo,
assonali in donna
- CMT2A segni piramidali
- CMT4A, 4B paralisi corde vocali
- CMT4C scoliosi
- CMT4B2 glaucoma
- CMT1D, 4B nervi cranici
- CMTX5 sordità

The new age

fenotipo





Identificazione del gene

diagnosi

terapia

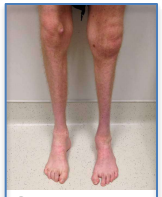
ORIGINAL ARTICLE

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S., David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D., Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc., David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D., Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D., Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S., Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

N ENGL J MED 362;13 NEJM.ORG APRIL 1, 2010

Possibile flowchart di analisi: utilizzo di pannelli NGS



Sospetto CMT

demielinizzante

assonale

Duplicazione/delezione PMP22

Se positivo

Se negativo

Diagnosi CMT1A HNPP

Pannello NGS per CMT

(OSR: AARS , ARHGEF10, ATP7A, BSCL2, CTDP1, DCTN1, DNAJB2, DNM2, DYNC1H1, EGR2, FBLN5, FGD4, FIG4, GAN, GARS, GDAP1, GJB1, GJB3, HARS, HK1, HSPB1, HSPB3, HSPB8, IGHMBP2, INF2, KARS, KIF5A, LITAF, LMNA, LRSAM1, MED25, MFN2, MPZ, MTMR2, NDRG1, NEFL, PLEKHG5, PMP22, POLG, PRPS1, PRX, REEP1, SBF2, SETX, SH3TC2, SLC5A7, SOX10, SPTLC1, SPTLC2, SURF1, TDP1, TRPV4, VCP, YARS)

Se positivo

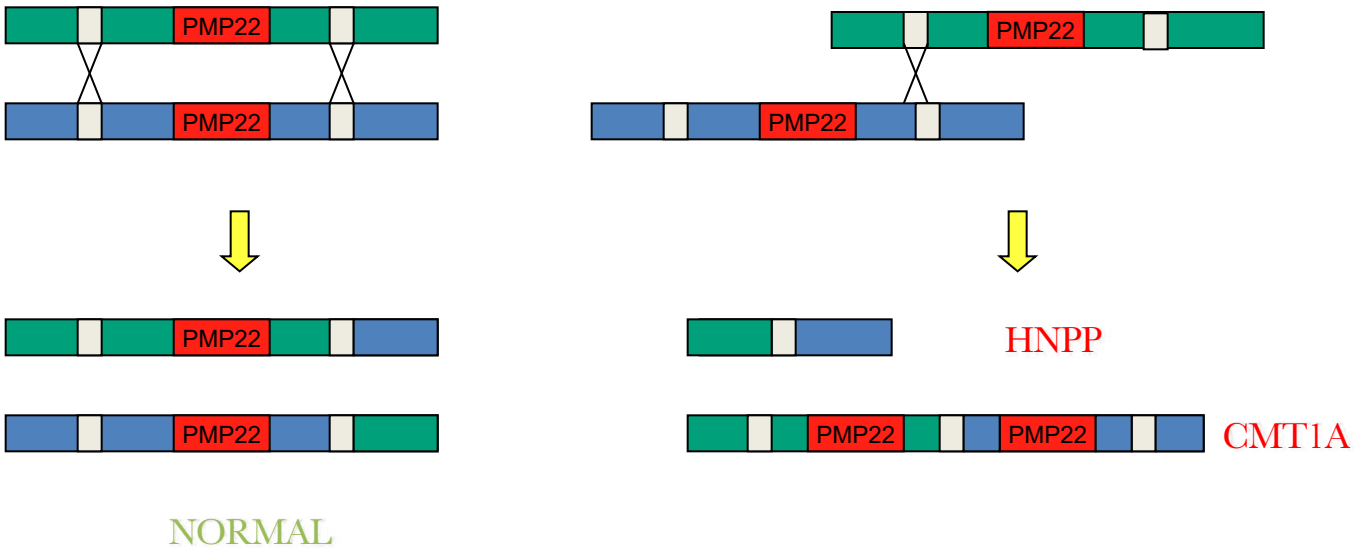
Se negativo

Diagnosi CMT

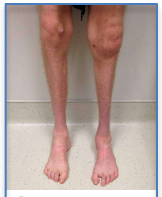
WES (esoma)
WGS (genoma)

HNPP

- Causata dalla delezione del gene PMP22 (presenza di una sola copia del gene; o mutazioni puntiformi)



Possibile flowchart di analisi: utilizzo di pannelli NGS



Sospetto CMT

demielinizzante

assonale

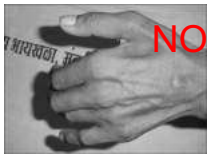
Duplicazione/delezione PMP22

Se positivo

Diagnosi CMT1A HNPP

Se negativo

Male
X-linked pedigree
Split hand syndrome



Pannello NGS per CMT
(OSR: AARS , ARHGEF10, ATP7A, BSCL2, CTDP1, DCTN1, DNAJB2, DNM2, DYNC1H1, EGR2, FBLN5, FGD4, FIG4, GAN, GARS, GDAP1, GJB1, GJB3, HARS, HK1, HSPB1, HSPB3, HSPB8, IGHMBP2, INF2, KARS, KIF5A, LITAF, LMNA, LRSAM1, MED25, MFN2, MPZ, MTMR2, NDRG1, NEFL, PLEKHG5, PMP22, POLG, PRPS1, PRX, REEP1, SBF2, SETX, SH3TC2, SLC5A7, SOX10, SPTLC1, SPTLC2, SURF1, TDP1, TRPV4, VCP, YARS)

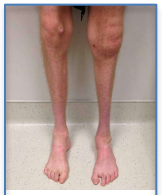
Se positivo

Diagnosi CMT

Se negativo

WES (esoma)
WGS (genoma)

Sequenziamento dell'esoma o del genoma



Sospetto CMT

WES
WGS

Step 1
Known neuropathy mutation
(OMIM, HGMD)

Yes → Definite cause

No

Step 2
Minor allele frequency <0.0001
(NHBLI ESP6500 Exome, dbSNP, 1K Genome)

Yes → Novel Variants

Yes

Step 3
Functional impact or
Conserved amino acid
(Polyphen 2, SIFT, GERP score)

Yes → Possible cause

Yes

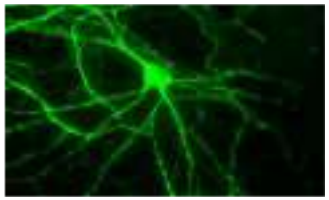
Step 4
Variant tracks with neuropathy in family

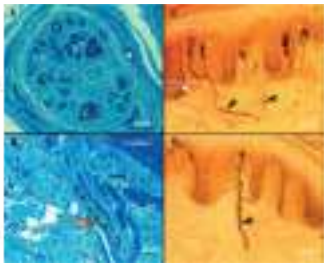
Yes → Probable cause

Yes

Step 5
Variant tracks with neuropathy in other families
Cell culture studies show functional impact

Yes → Definite cause





LA RICERCA DI UNA TERAPIA

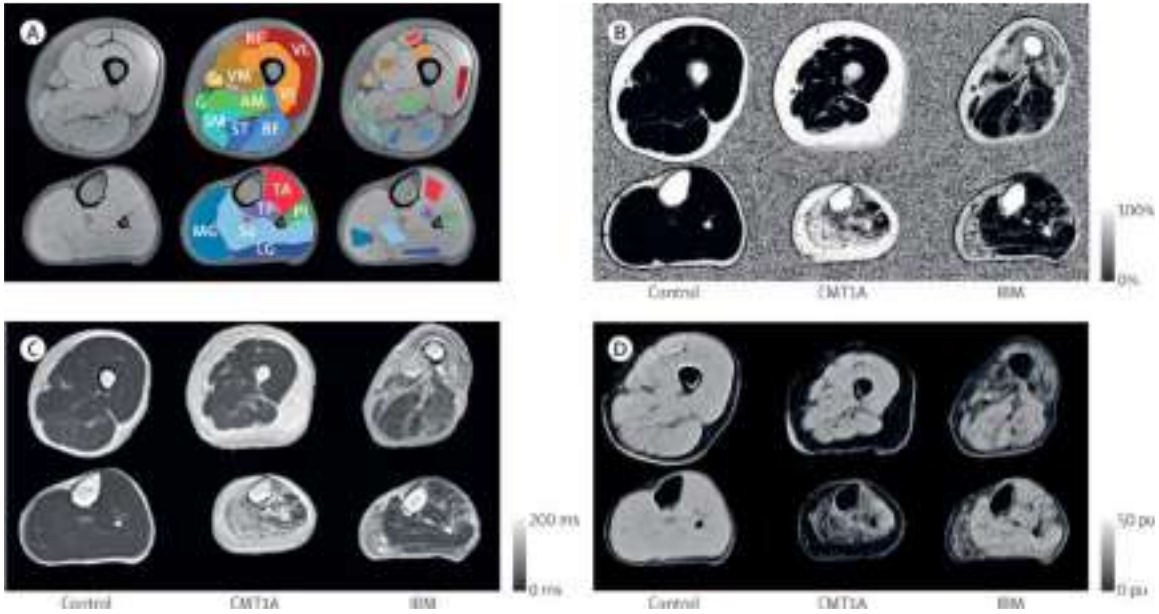
Misure di outcome in CMT

CMT Neuropathy Score – Version 2

Patient Name: _____ **Date:** _____ **Evaluator:** _____

Parameter	0	1	2	3	4	Score
Sensory symptoms[1]	None	Symptoms below or at ankle bones	Symptoms up to the distal half of the calf	Symptoms up to the proximal half of the calf, including knee	Symptoms above knee (above the top of the patella)	
Motor symptoms legs[2]	None	Trips, catches toes, slaps feet. Shoe inserts	Ankle support or stabilization (AFOs). Foot surgery[3]	Walking aids (cane, walker)	Wheelchair	
Motor symptoms arms	None	Mild difficulty with buttons	Severe difficulty or unable to do buttons	Unable to cut most foods	Proximal weakness (affect movements involving the elbow and above)	
Pinprick sensibility[1,3]	Normal	Decreased below or at ankle bones	Decreased up to the distal half of the calf	Decreased up to the proximal half of the calf, including knee	Decreased above knee (above the top of the patella)	
Vibration[4]	Normal	Reduced at great toe	Reduced at ankle	Reduced at knee (tibial tuberosity)	Absent at knee and ankle	
Strength legs	Normal	4+,4 or 4- on foot dorsiflexion or plantar flexion	≤3 on foot dorsiflexion or ≤3 on foot plantar flexion	≤3 on foot dorsi and ≤3 on plantar flexion	Proximal weakness	
Strength arms	Normal	4+,4 or 4- on intrinsic hand muscles[5]	≤3 on intrinsic hand muscles[6]	<5 on wrist extensors	Weak above elbow	
Ulnar CMAP (Median)	>6mV (>4mV)	4-5.9mV (2.8-3.9)	2-3.9 mV (1.2-2.7)	0.1-1.9 mV (0.1-1.1)	Absent (Absent)	
Radial SAP amplitude, antidromic	≥15μV	10 - 14.9 μV	5 - 9.9 μV	1 - 4.9 μV	<1 μV	
CMTSS Subtotal						
CMTES Subtotal						
CMTNS Total						

Misure di outcoma in CMT



Morrow 2015

Strength Myometer

9 hole-peg test

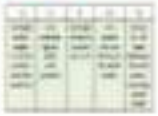
FDT

Sensation

Long jump

6 min walking test

Foot posture index



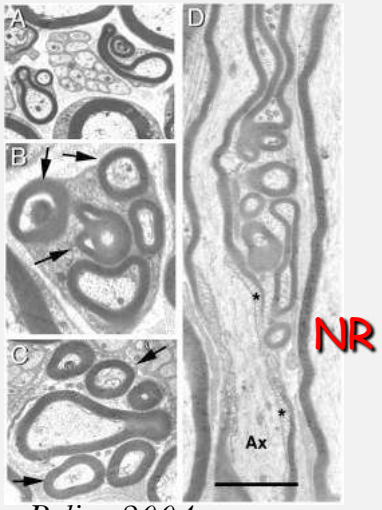
Lunge test

Balance - BOT-2

SCOPRIRE I MECCANISMI MOLECOLARI

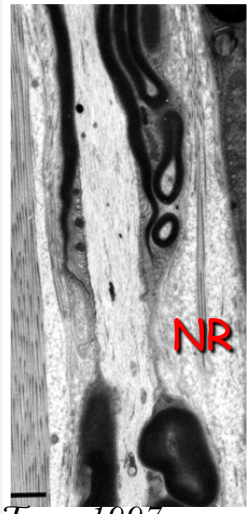
Regolazione della quantità di mielina

Mouse CMT4B



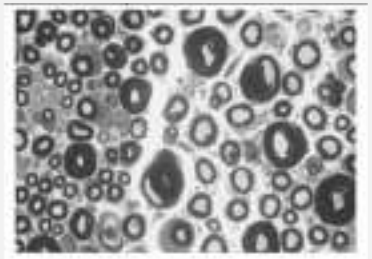
Bolino 2004

Human CMT4B

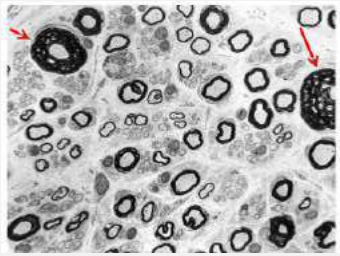


Tyson 1997

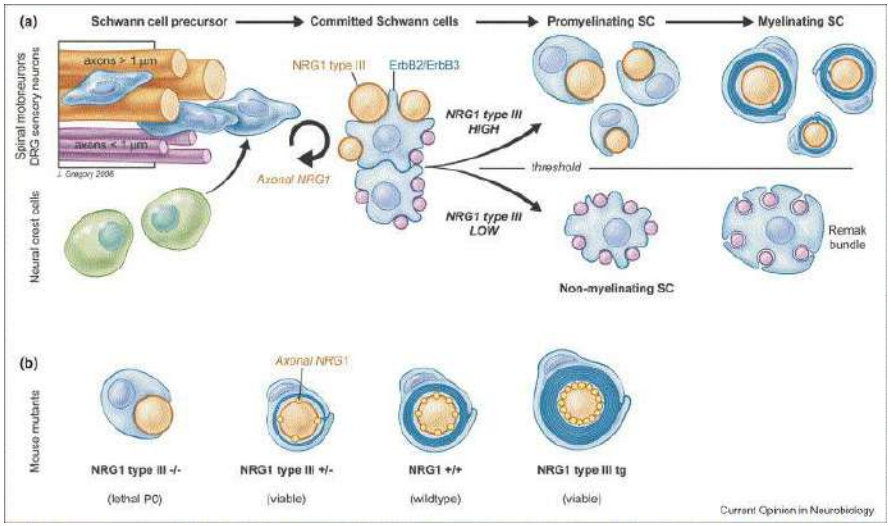
Mouse HNPP



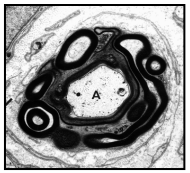
Human HNPP



Bolino 2016



CMT with Hypermyelination



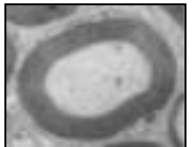
Niacin (activator)

downregulation

TACE secretase

NRG1-III axons
ErbB2/B3 Schwann cells

MYELIN



Regolazione della quantità di mielina

Published online: October 31, 2016

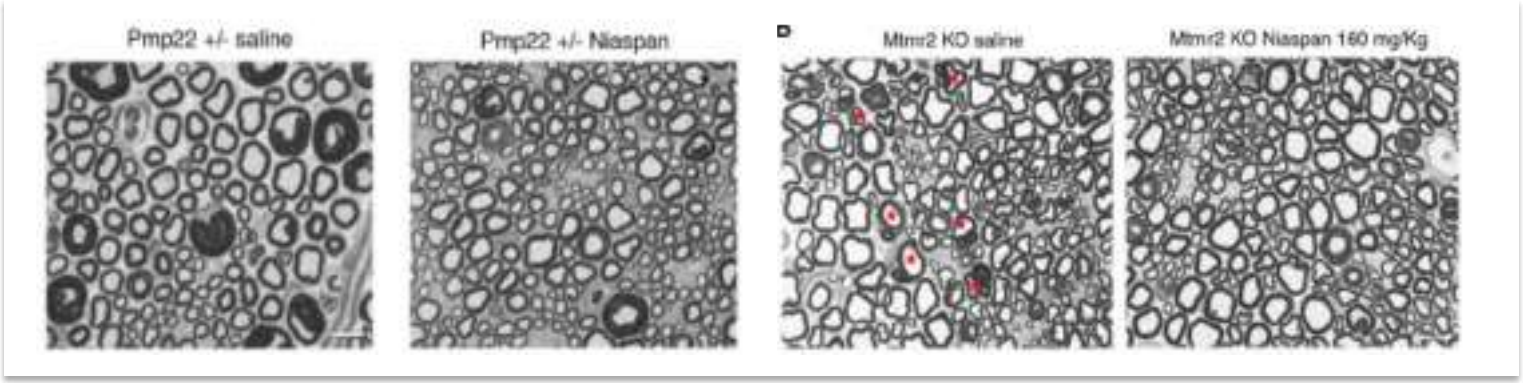
Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

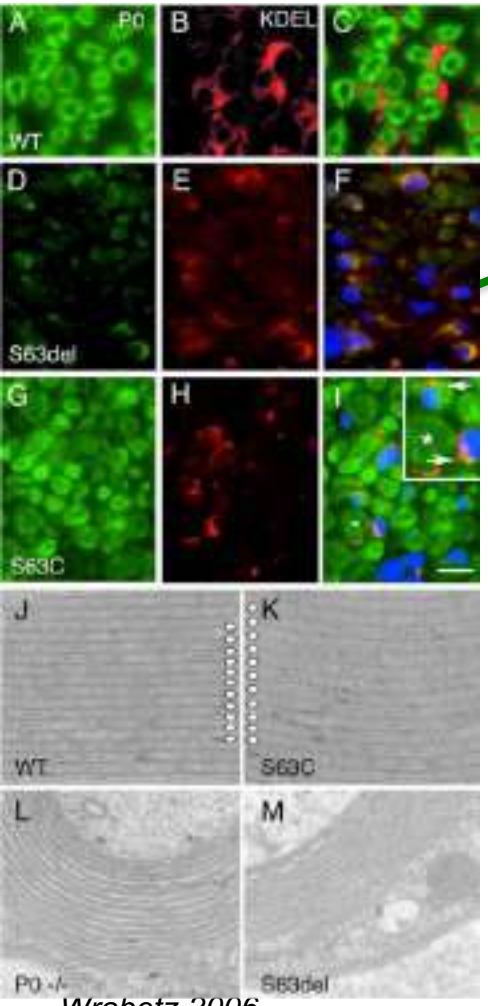
Niacin-mediated Tace activation ameliorates CMT neuropathies with focal hypermyelination

Alessandra Bolino[1,2,*], Françoise Piguet[1,2,†], Valeria Alberizzi[1,2], Marta Pellegatta[1,2], Cristina Rivellini[1,2], Marta Guerrero-Valero[1,2], Roberta Noseda[1,2], Chiara Brombin[3], Alessandro Nonis[3], Patrizia D'Adamo[2], Carla Taveggia[1,2] & Stefano Carlo Previtali[1,2,4]

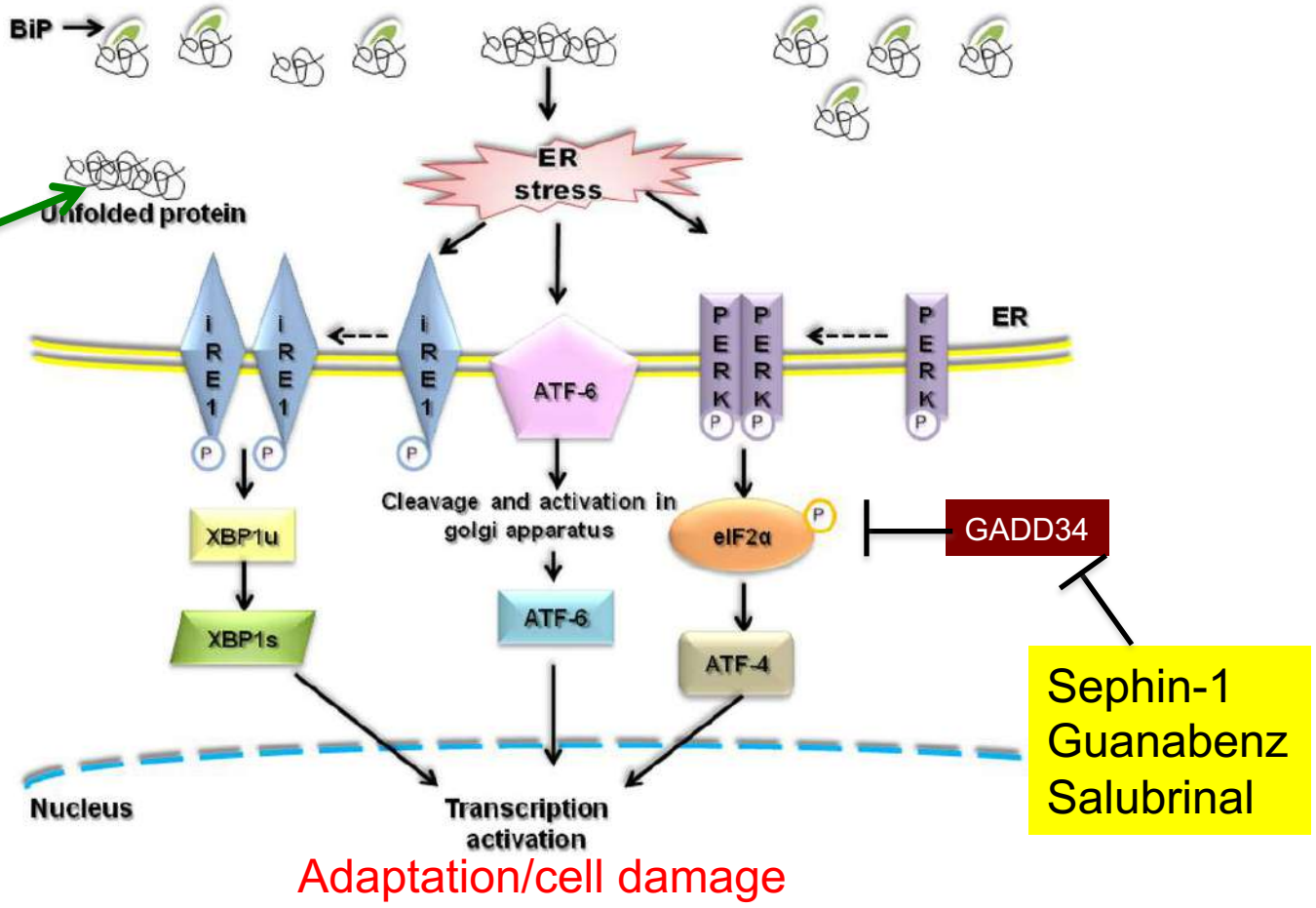


Regolazione della quantità di proteine

Mouse CMT1B

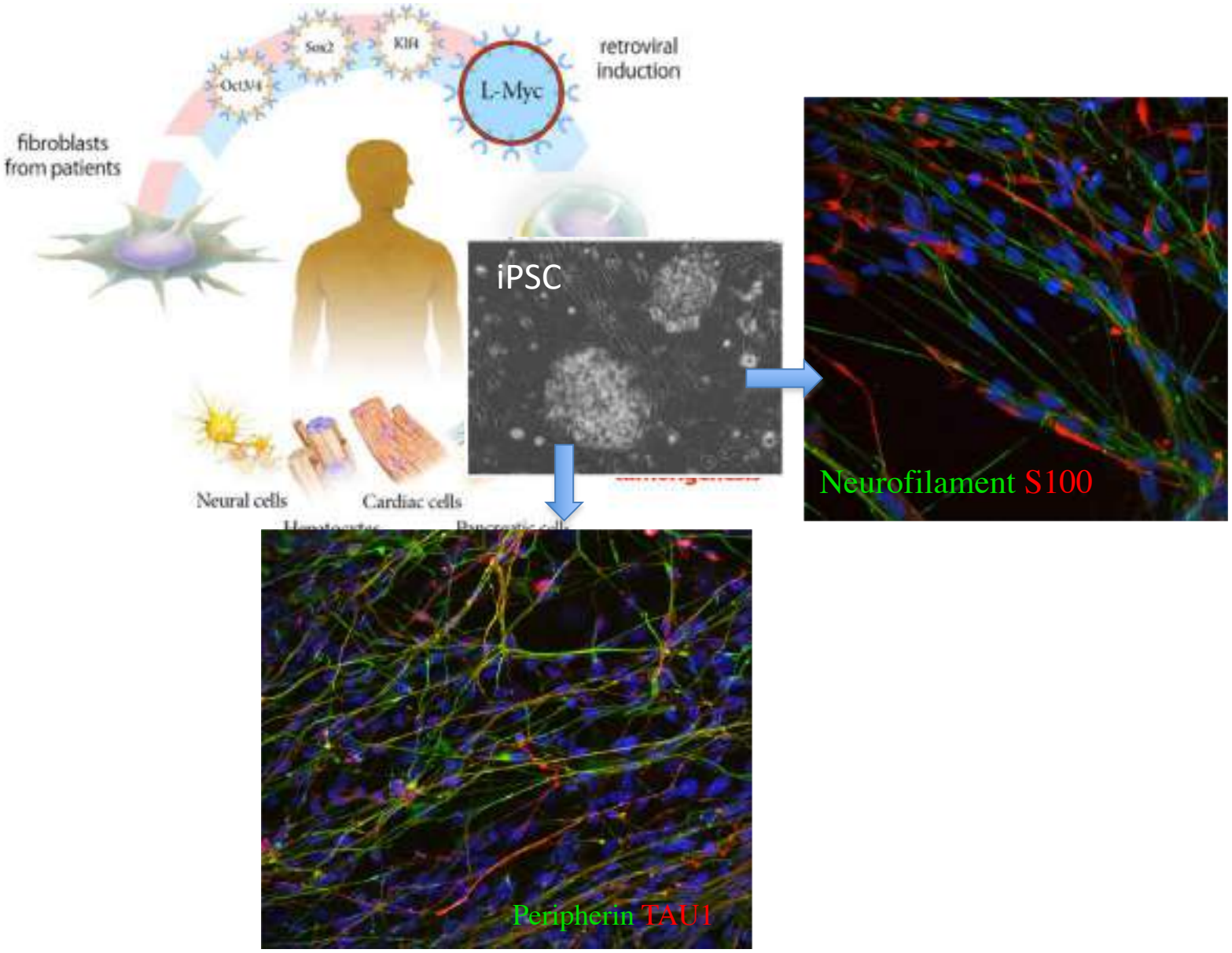


Wrabetz 2006



Adaptation/cell damage

Terapia cellulare e genetica



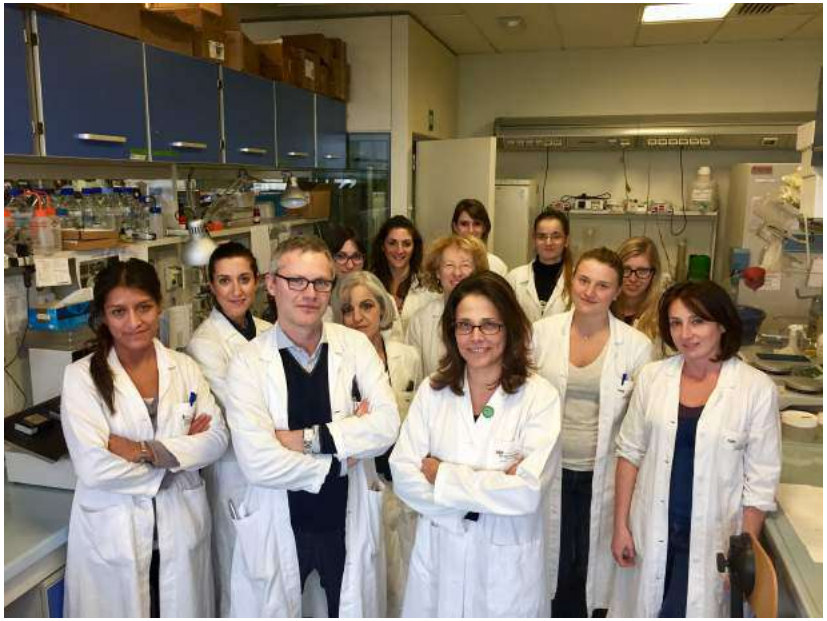
ClinicalTrials.gov

PXT3003 is a rational design, fixed combination of low-dose (RS) baclofen, naltrexone hydrochloride and D-sorbitol.
Pharnext SA
Long Term Safety and Tolerability
Charcot-Marie-Tooth Type 1A (CMT1A)

Study of ACE-083 in Patients With Charcot-Marie-Tooth Disease CMT1 and CMTX
Phase 2
Anti-miostatin
Acceleron Pharma, Inc.

Study of Phase I/IIa Trial Evaluating scAAV1.tMCK.NTF3 for Treatment of CMT1A
(NT3 expression in muscle, secretion as neurotrophic factor)
Nationwide Children's Hospital

acknowledgments



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