5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 3

EAN/PNS: Novel approach in the treatment of neuropathy (Level3)

Inherited neuropathies: Emerging genetic therapies

Mary M. Reilly
London, United Kingdom

Email: M.Reilly@ion.ucl.ac.uk

UCL

International Centre for Genomic Medicine in Neuromuscular Diseases

INHERITED NEUROPATHIES: EMERGING GENETIC THERAPIES

Mary M Reilly
MRC centre for Neuromuscular Diseases,
Institute of Neurology,
Queen Square, London, UK.

1

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DISCLOSURES

IONIS TTR trial

Consultancy
Alnylam
Inflectis
Acceleron
Akcea
Myotherix

2

INHERITED NEUROPATHIES

1. Introduction
2. Barriers to therapy development
3. Classification of therapies
4. Emerging therapies

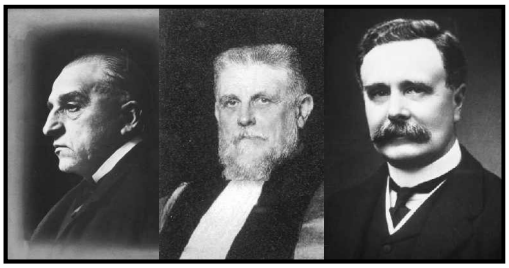
3

INHERITED NEUROPATHIES

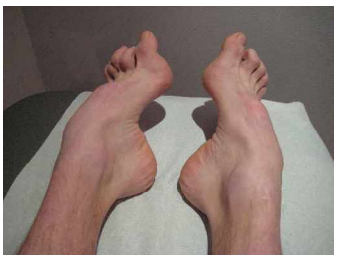
1. **Introduction**
2. Barriers to therapy development
3. Classification of therapies
4. Emerging therapies

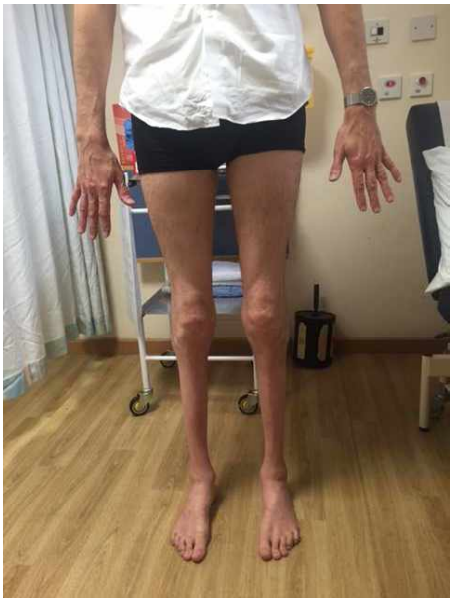
4

INHERITED NEUROPATHIES



Charcot Marie Tooth disease





5

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INHERITED NEUROPATHIES

1. Sole / primary e.g. CMT

2. Part of multisystem disorder

6

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INHERITED NEUROPATHIES

1. **Sole / primary e.g. CMT**

2. Part of multisystem disorder

7

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CMT / RELATED DISORDERS

1. Charcot-Marie-Tooth disease (CMT)

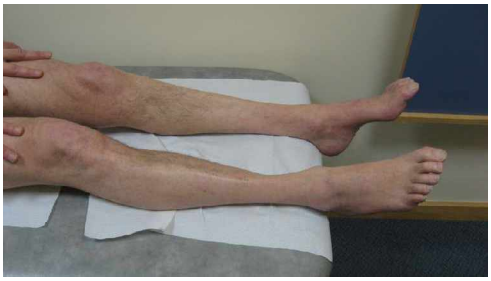
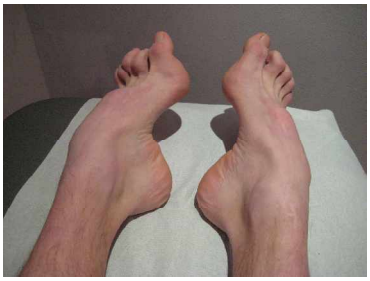
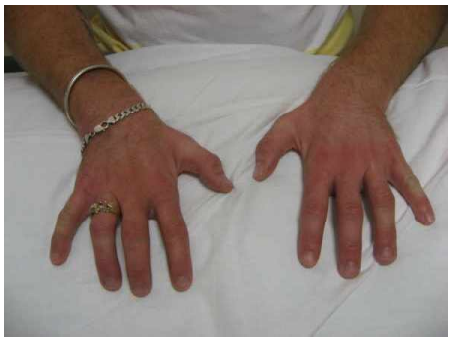
2. Hereditary Neuropathy with liability to pressure palsies (HNPP)

3. Hereditary sensory neuropathies (HSN / HSAN)

4. Distal hereditary motor neuropathies (HMN)

8

CMT / HMN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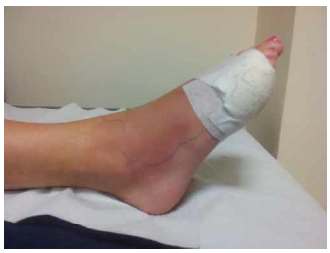
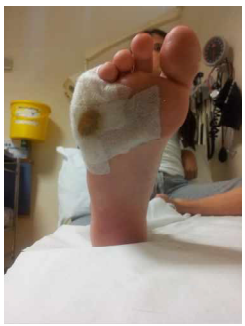
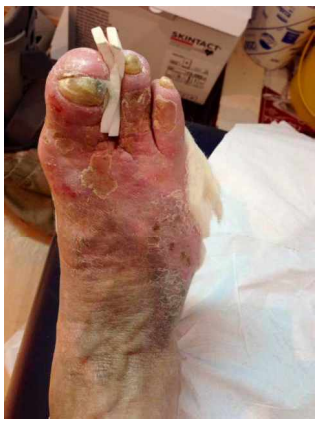
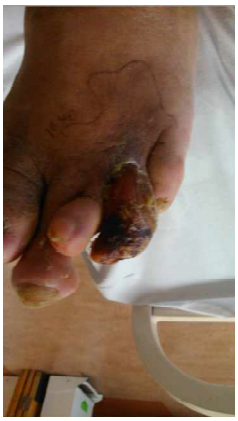
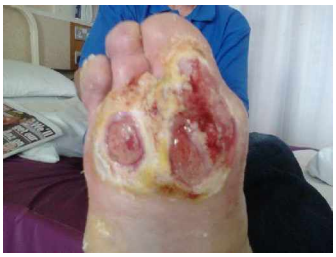
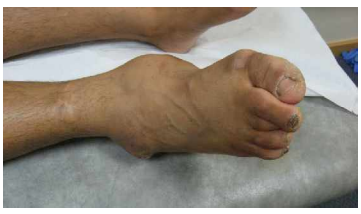
HSN

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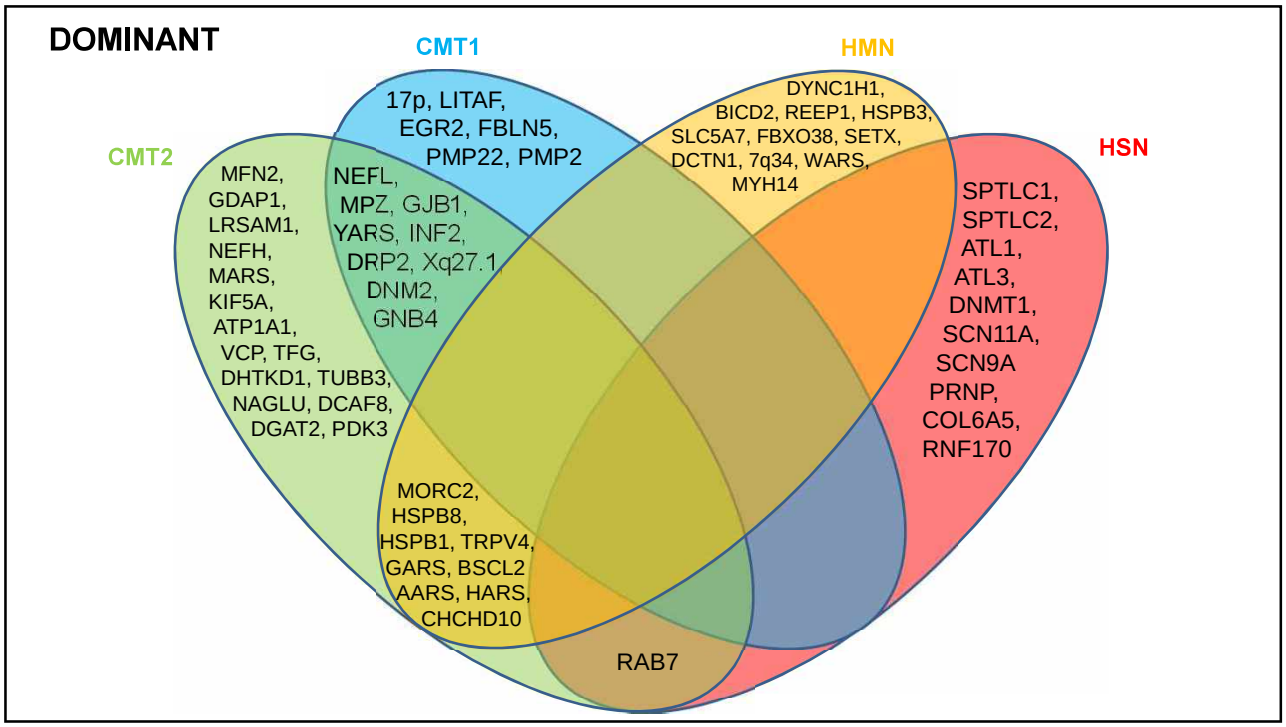
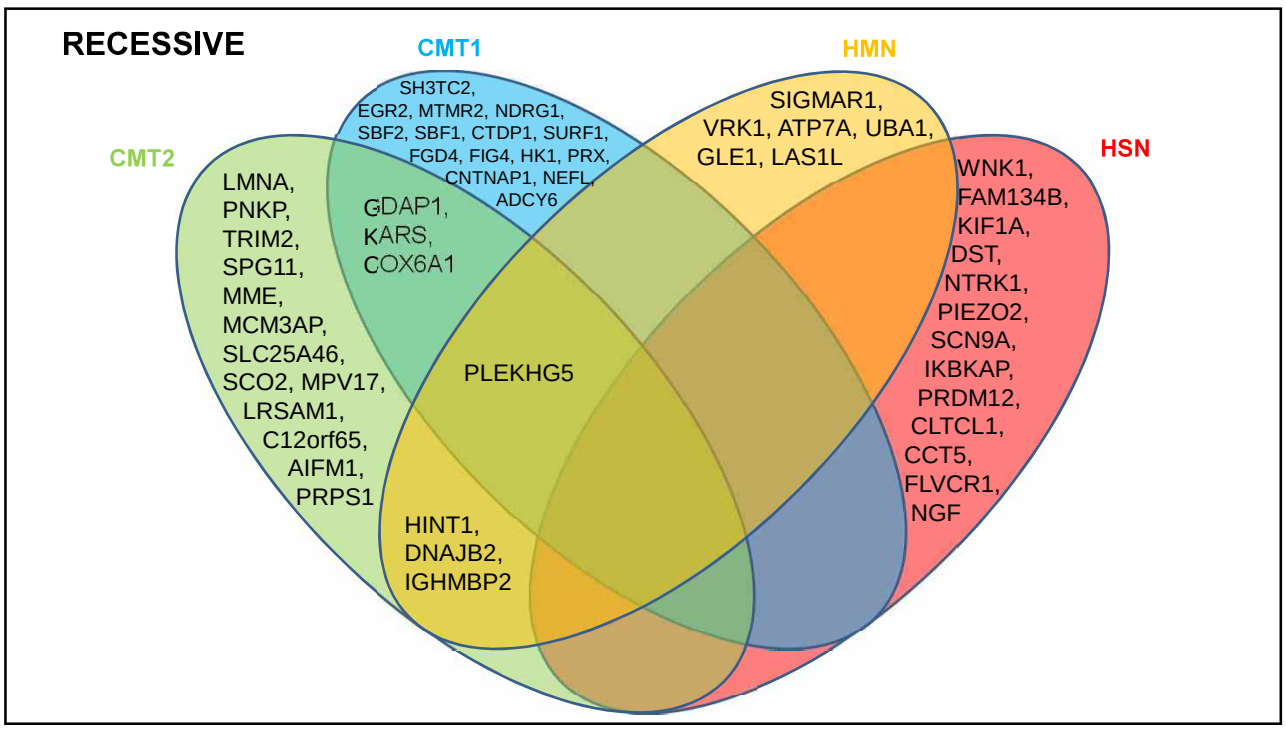

DOMINANT
CMT1
HMN
CMT2
HSN
17p, LITAF, EGR2, FBLN5, PMP22, PMP2
DYNC1H1, BICD2, REEP1, HSPB3, SLC5A7, FBXO38, SETX, DCTN1, 7q34, WARS, MYH14
MFN2, GDAP1, LRSAM1, NEFH, MARS, KIF5A, ATP1A1, VCP, TFG, DHTKD1, TUBB3, NAGLU, DCAF8, DGAT2, PDK3
NEFL, MPZ, GJB1, YARS, INF2, DRP2, Xq27.1, DNM2, GNB4
SPTLC1, SPTLC2, ATL1, ATL3, DNMT1, SCN11A, SCN9A PRNP, COL6A5, RNF170
MORC2, HSPB8, HSPB1, TRPV4, GARS, BSCL2 AARS, HARS, CHCHD10
RAB7

11


RECESSIVE
CMT1
HMN
CMT2
HSN
SH3TC2, EGR2, MTMR2, NDRG1, SBF2, SBF1, CTDP1, SURF1, FGD4, FIG4, HK1, PRX, CNTNAP1, NEFL, ADCY6
SIGMAR1, VRK1, ATP7A, UBA1, GLE1, LAS1L
LMNA, PNKP, TRIM2, SPG11, MME, MCM3AP, SLC25A46, SCO2, MPV17, LRSAM1, C12orf65, AIFM1, PRPS1
GDAP1, KARS, COX6A1
WNK1, FAM134B, KIF1A, DST, NTRK1, PIEZO2, SCN9A, IKBKAP, PRDM12, CLTCL1, CCT5, FLVCR1, NGF
PLEKHG5
HINT1, DNAJB2, IGHMBP2

12

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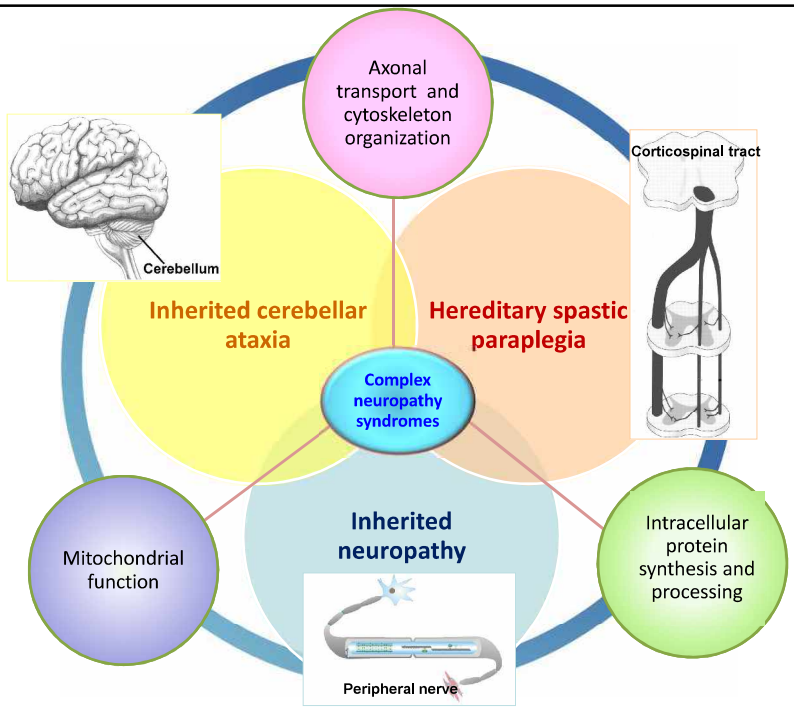
INHERITED NEUROPATHIES

1. Sole / primary e.g. CMT

2. **Part of multisystem disorder**

13



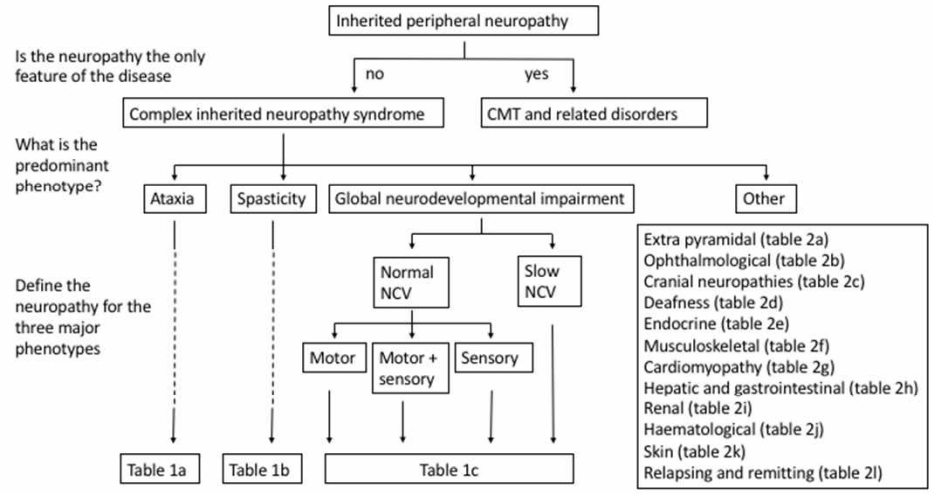
14

Peripheral neuropathy in complex inherited diseases: an approach to diagnosis

J Neurol Neurosurg Psychiatry 2017;**0**:1–18.

Alexander M Rossor,[1] Aisling S Carr,[1] Helen Devine,[1] Hoskote Chandrashekar,[2] Ana Lara Pelayo-Negro,[1] Davide Pareyson,[3] Michael E Shy,[4] Steven S Scherer,[5] Mary M Reilly[1]

155 (190) complex neuropathies



15

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INHERITED NEUROPATHIES

Considerations when developing therapies

16

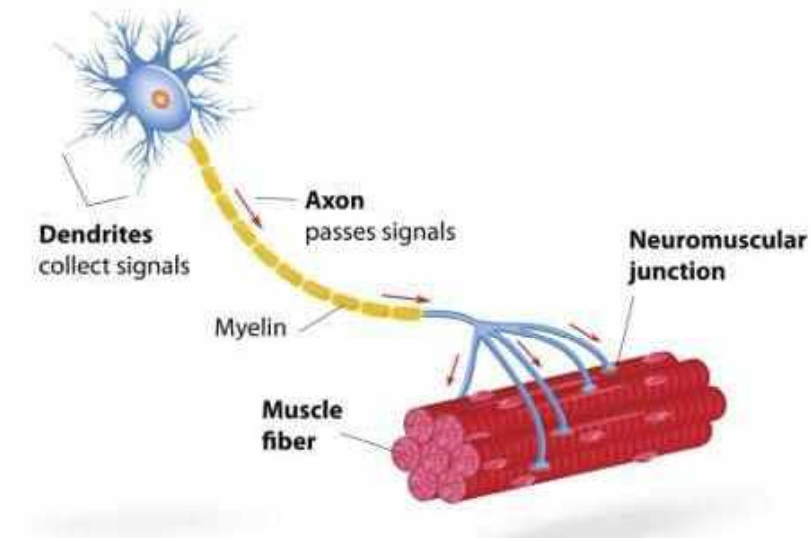
1886

1991 (Chromosome 17 duplication / PMP22)
(Lupski et al: Cell; 1991, Raeymaekers et al: Neuro Dis; 1991)

2019 (> 100 causative genes)

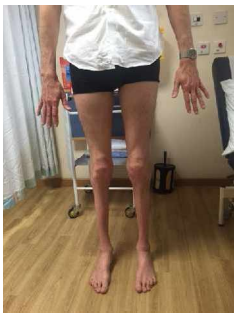
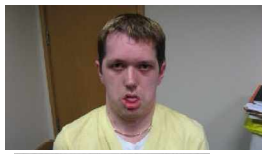
17

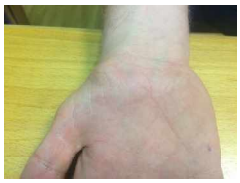
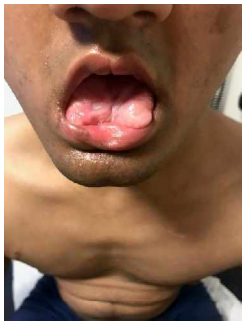
PARTICULAR CHALLENGES

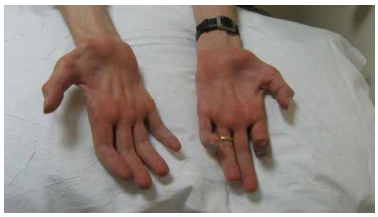


18

HUMAN DISEASE: PHENOTYPE VARIATIONS

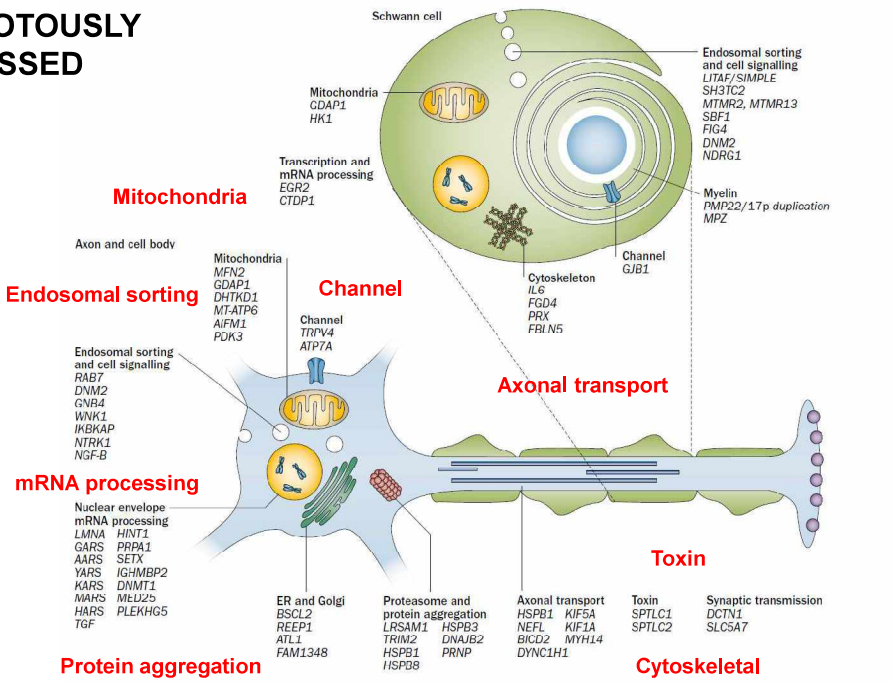





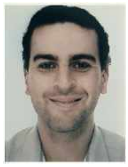
19

UBIQUOTOUSLY EXPRESSED

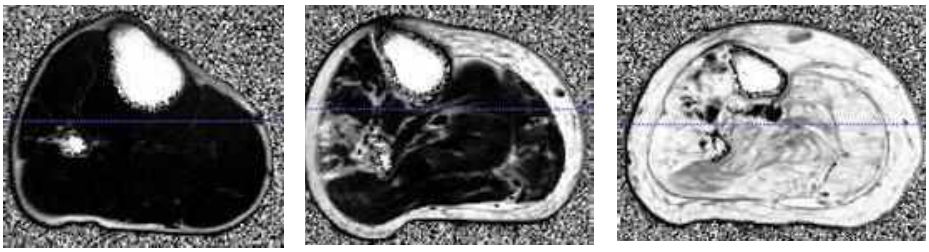


20

NEED TO TREAT EARLY



19y man CMT1A **37y man CMT1A** **53y woman CMT1A**



MRI biomarker assessment of neuromuscular disease progression: a prospective observational cohort study

Jasper M Morrow, Christopher D J Sinclair, Arne Fischmann, Pedro M Machado, Mary M Reilly, Tarek A Yousry*, John S Thornton*, Michael G Hanna*

Lancet Neurol 2016; 15: 65–77

Validation of MRC Centre MRI calf muscle fat fraction protocol as an outcome measure in CMT1A

Jasper M. Morrow, PhD, Matthew R.B. Evans, MBBS, Tiffany Grider, MS, Christopher D.J. Sinclair, PhD, Daniel Thedens, PhD, Sachit Shah, MD, Tarek A. Yousry, Dr Med Habil, Michael G. Hanna, MD, Peggy Nopoulos, MD, John S. Thornton, PhD, Michael E. Shy, MD, and Mary M. Reilly, MD

Neurology® 2018;00:1-5.

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WHOLE BODY / WHOLE LIFESPAN

22

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INHERITED NEUROPATHIES

1. Sole / primary e.g. CMT

2. Part of multisystem disorder

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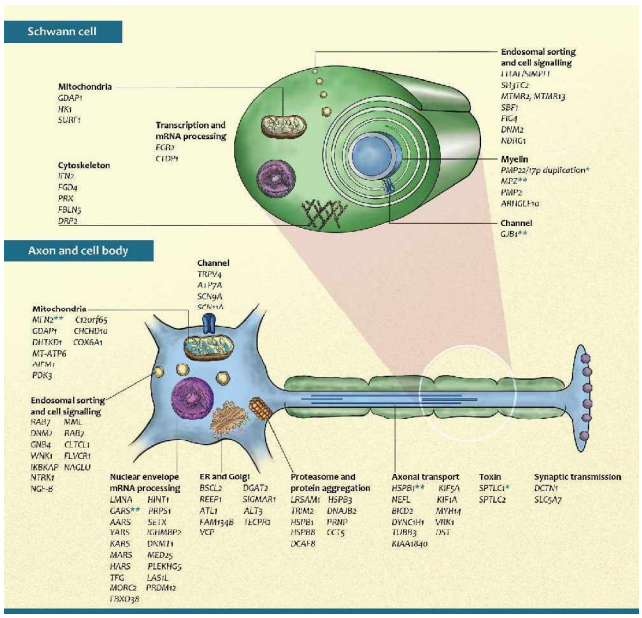
> 100 CAUSATIVE GENES

Missense
Nonsense
Deletions
Duplications
Promoter



CMT1

CMT2 / HMN / HSN

Alexander M. Rossor, Pedro J. Tomaselli, and Mary M. Reilly **Curr Opin Neurol** 2016, 29:537–548

24

Peripheral neuropathy in complex inherited diseases: an approach to diagnosis

J Neurol Neurosurg Psychiatry 2017;**0**:1–18.

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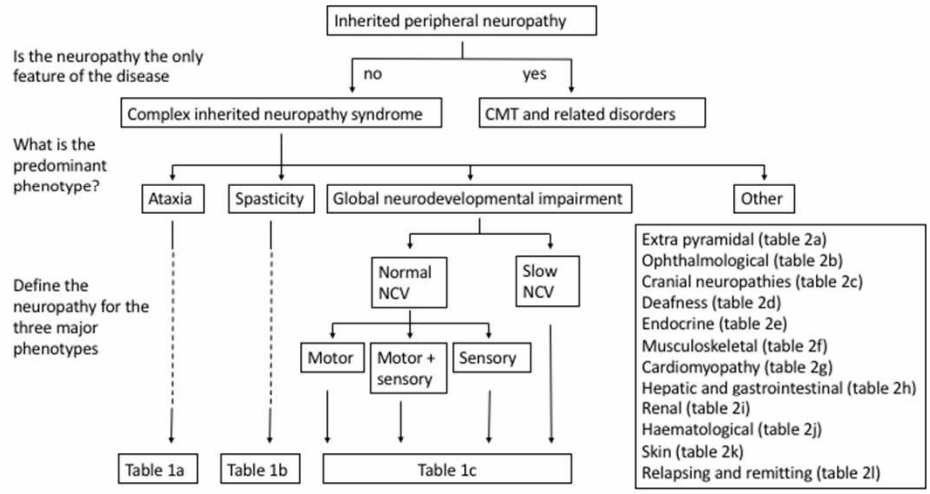
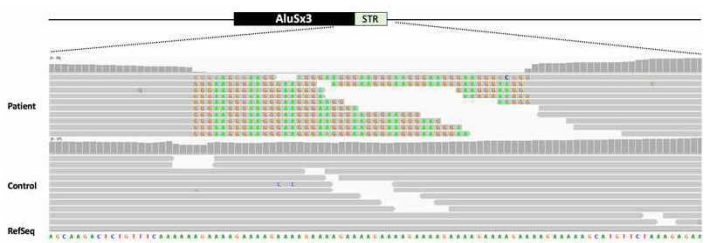


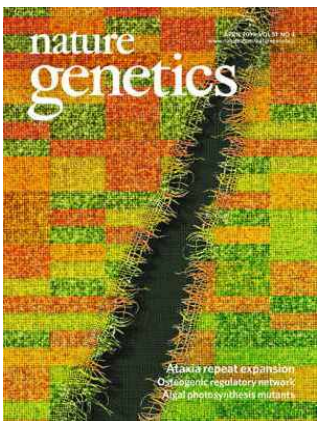
25

Biallelic expansion of an intronic repeat in *RFC1* is a common cause of late-onset ataxia

Cortese A, ...Reilly M M and Houlden H

NATURE GENETICS | VOL 51 | APRIL 2019 | 649–658 |





CANVAS cerebellar ataxia, neuropathy, vestibular areflexia syndrome

0.7% carrier frequency in Caucasian population

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INHERITED NEUROPATHIES

1. Introduction
2. **Barriers to therapy development**
3. Classification of therapies
4. Emerging therapies

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BARRIERS TO THERAPY

Pre clinical

Rigorously conducted clinical trials

Ideally 2 different animal models

Target engagement

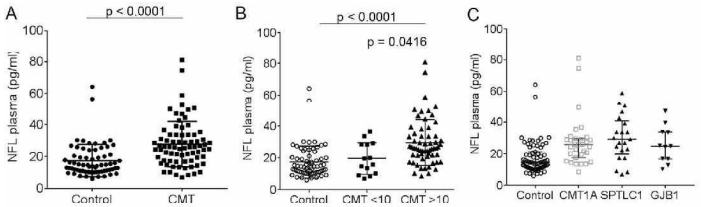
Pathology most reliable neuropathy outcome measure

28

Plasma neurofilament light chain concentration in the inherited peripheral neuropathies

Neurology® 2018;90:e1-e7.

Åsa Sandelius, PhD, Henrik Zetterberg, PhD, Kaj Blennow, PhD, Rocco Adiutori, Andrea Malaspina, PhD, FRCP, Matilde Laura, PhD, Mary M. Reilly, MD, FRCP, FRCPI,* and Alexander M. Rossor, PhD, MRCP*



Gene replacement therapy in a model of Charcot-Marie-Tooth 4C neuropathy

Natasa Schiza,[1] Elena Georgiou,[1] Alexia Kagiava,[1] Jean-Jacques Médard,[2] Jan Richter,[3] Christina Tryfonos,[3] Irene Sargiannidou,[1] Amanda J. Heslegrave,[4,5] Alexander M. Rossor,[6] Henrik Zetterberg,[4,5,7,8] Mary M. Reilly,[6] Christina Christodoulou,[3] Roman Chrast[2] and Kleopas A. Kleopa[1]

BRAIN 2019: 0; 1–15

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BARRIERS TO THERAPY

Clinical

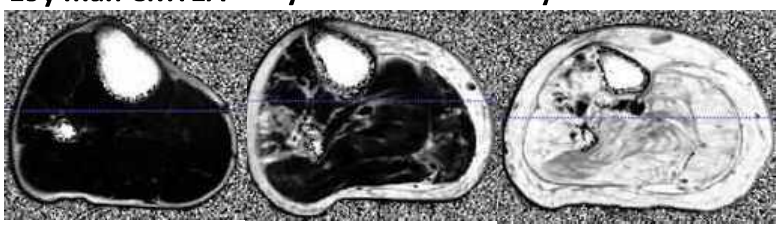
Responsive outcome measure (bridgeable biomarkers)

Evidence of target engagement

30

MRC CENTRE NEUROMUSCULAR MRI PROTOCOL

19y man CMT1A 37y man CMT1A 53y woman CMT1A



GJB1 / MFN2 / MPZ

Ongoing studies

CMT1A

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Neurology® 2018;00:1-5.

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HSN1 SPTLC1/2 mutations

Development of MRC Centre MRI calf muscle fat fraction protocol as a sensitive outcome measure in Hereditary Sensory Neuropathy Type 1

Umaiyal Kugathasan,[1] Matthew R B Evans,[1,2] Jasper M Morrow,[1,2] Christopher D J Sinclair,[1,2] John S Thornton,[1,2] Tarek A Yousry,[1,2] Thorsten Hornemann,[3] Saranya Suriyanarayanan,[3] Khadijah Owusu-Ansah,[4] Giuseppe Lauria,[5,6] Raffaella Lombardi,[5] James M Polke,[7] Emma Wilson,[1] David L H Bennett,[8] Henry Houlden,[1] Michael G Hanna,[1] Julian C Blake,[1,9] Matilde Laura,[1] Mary M Reilly[1]

J Neurol Neurosurg Psychiatry 2019;**0**:1–12.

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INHERITED NEUROPATHIES

1. Introduction
2. Barriers to therapy development
3. **Classification of therapies**
4. Emerging therapies

32

GENETIC THERAPIES

1. Generic gene therapy
2. Target pathogenesis of disease
3. Pathway therapies

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GENETIC THERAPIES

1. **Generic gene therapy**
   - antisense oligonucleotides (AONs)
   - small interfering RNA
   - Genome editing CRISPR / Cas 9
   - viral vector-mediated gene therapy

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GENETIC THERAPIES

1. **Generic gene therapy**
   - **antisense oligonucleotides (AONs)**
   - **small interfering RNA**
   - Genome editing CRISPR / Cas 9
   - viral vector-mediated gene therapy

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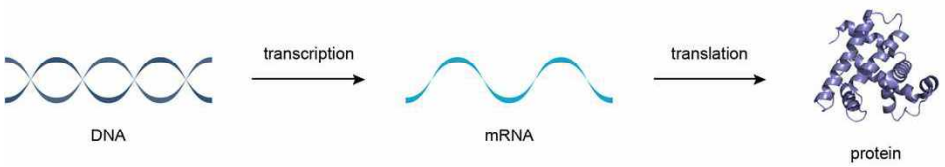
NORMAL GENETIC PROCESS



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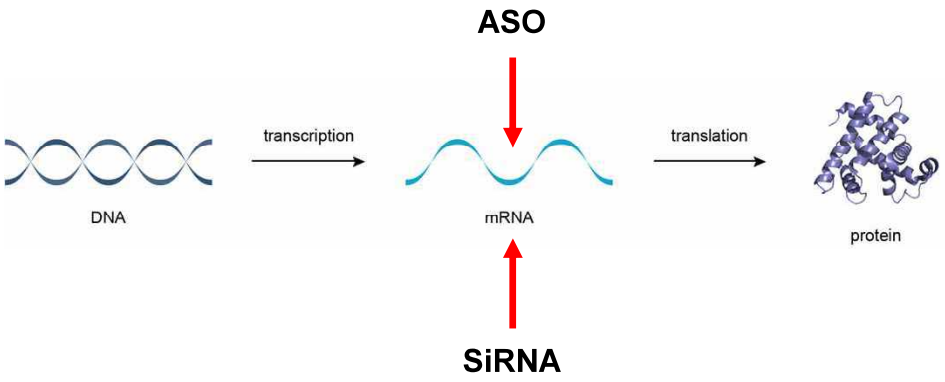
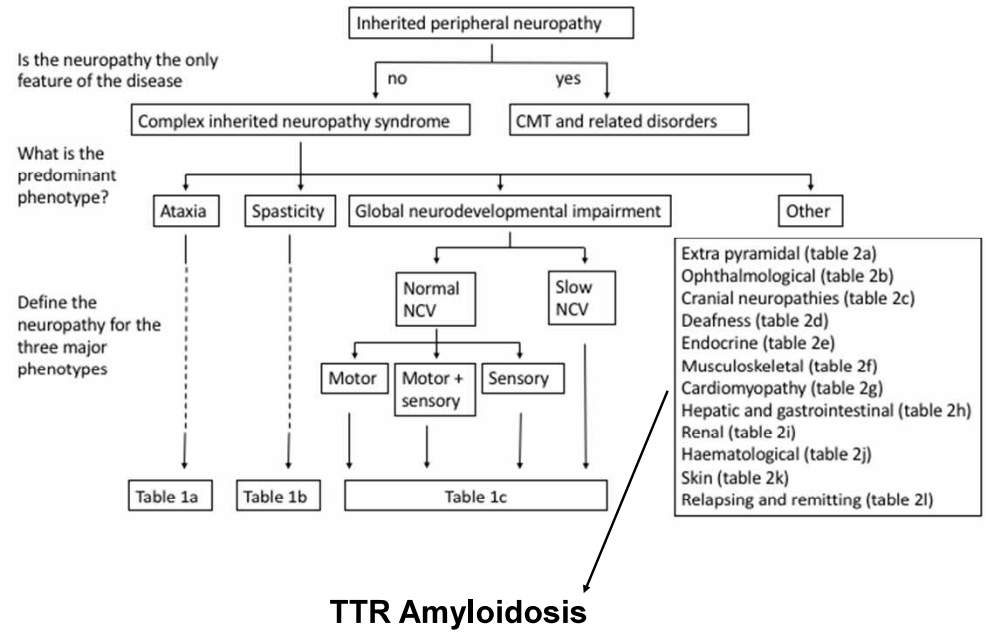
GENE SILENCING THERAPIES



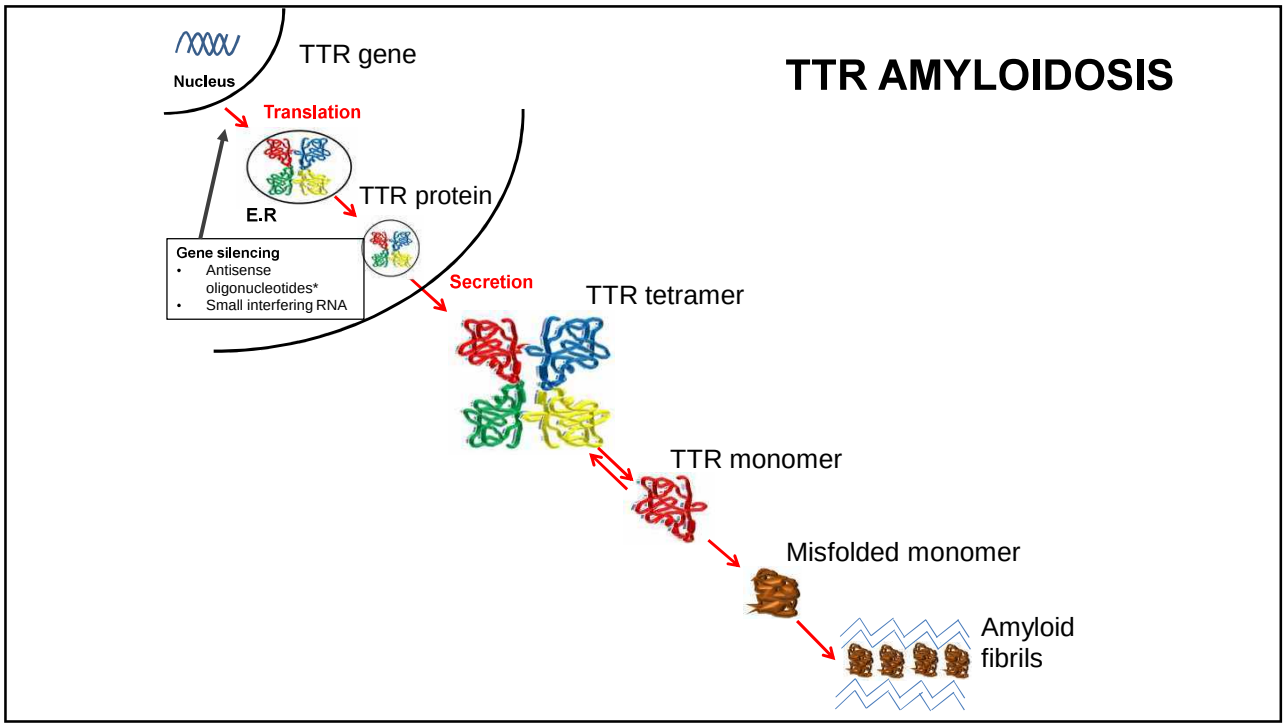
37

155 (190) complex neuropathies



TTR Amyloidosis

38



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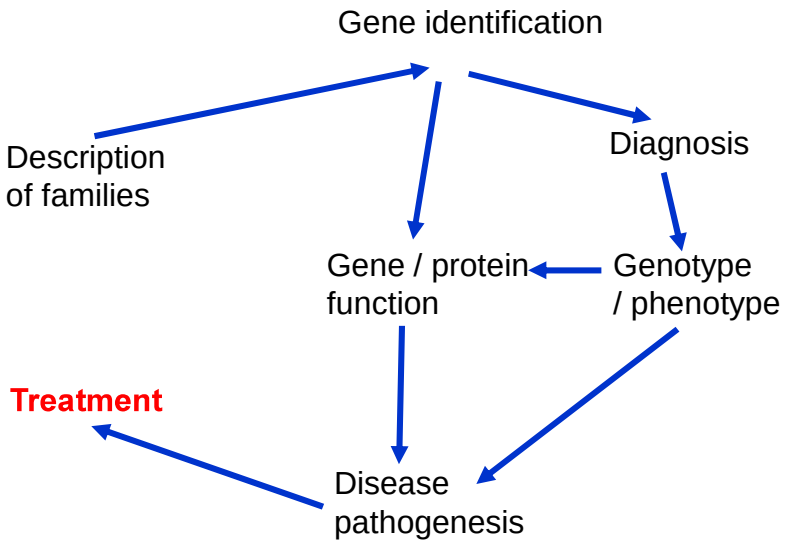
GENETIC THERAPIES

1. Generic gene therapy
2. **Target pathogenesis of disease**
3. Pathway therapies

40



41

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GENETIC THERAPIES

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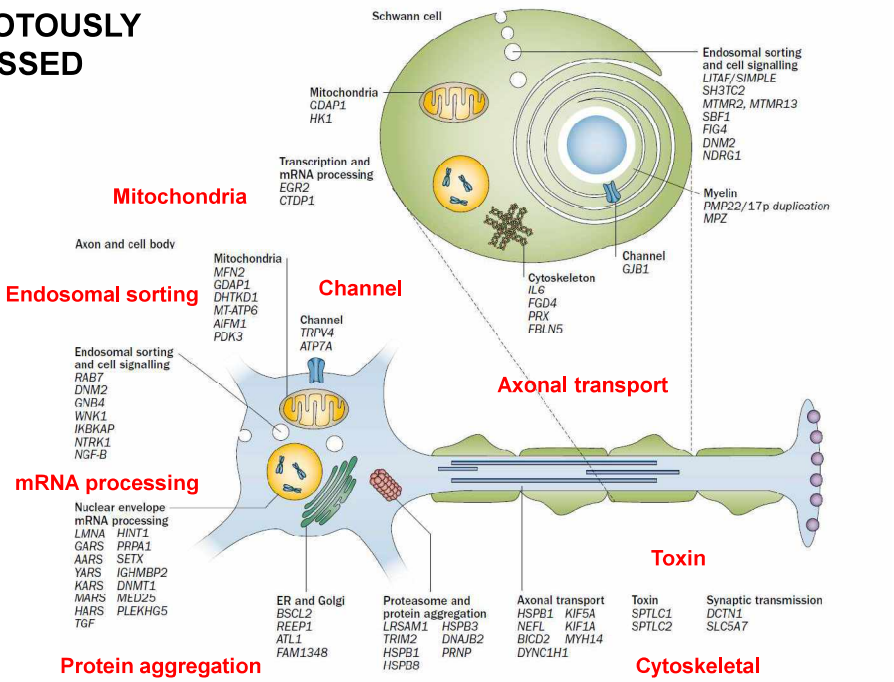
2. Target pathogenesis of disease
3. **Pathway therapies**

42

UBIQUOTOUSLY EXPRESSED



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MRC Centre for Neuromuscular Diseases

INHERITED NEUROPATHIES

1. Introduction
2. Barriers to therapy development
3. Classification of therapies
4. **Emerging therapies**

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GENETIC THERAPIES

1. Generic gene therapy
2. Target pathogenesis of disease
3. Pathway therapies

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CMT1A

1. **Generic gene therapy**
2. **Target pathogenesis of disease**
3. Pathway therapies

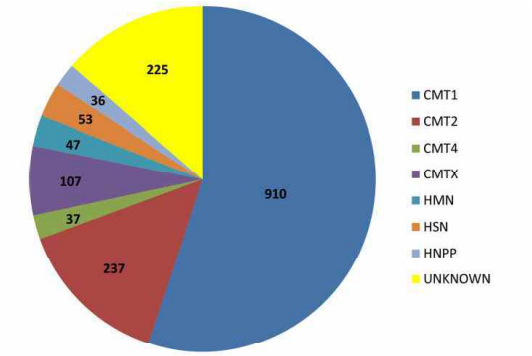
46

CMT subtypes and disease burden in patients enrolled in the Inherited Neuropathies Consortium natural history study: a cross-sectional analysis

V Fridman,[1] B Bundy,[2] M M Reilly,[3] D Pareyson,[4] C Bacon,[5] J Burns,[6] J Day,[7] S Feely,[5,8] R S Finkel,[9] T Grider,[5] C A Kirk,[2] D N Herrmann,[10] M Laurá,[3] J Li,[11] T Lloyd,[12] C J Sumner,[12] F Muntoni,[13] G Piscosquito,[4] S Ramchandren,[8,14] R Shy,[5,8] C E Siskind,[7] S W Yum,[15,16] I Moroni,[4] E Pagliano,[4] S Zuchner,[17] S S Scherer,[16] M E Shy,[5,8] on behalf of the Inherited Neuropathies Consortium

J Neurol Neurosurg Psychiatry 2014;**0**:1–6.

61% CMT1A



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CMT 1A

Onset 1st two decades

Foot weakness or deformity

Hands later

Length dependent

Slowly progressive

Foot deformity a problem

Need for walking aids

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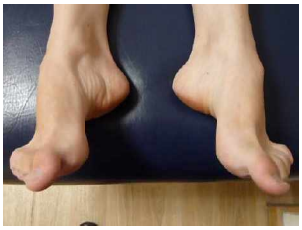
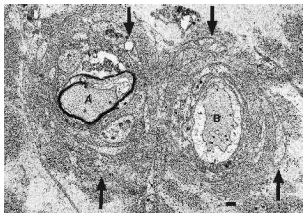
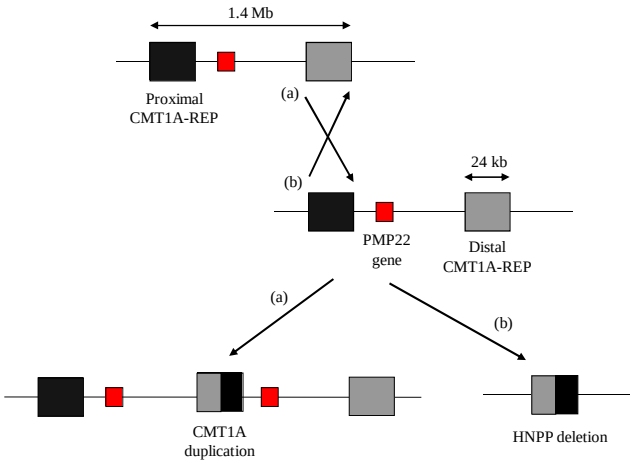
CMT1A







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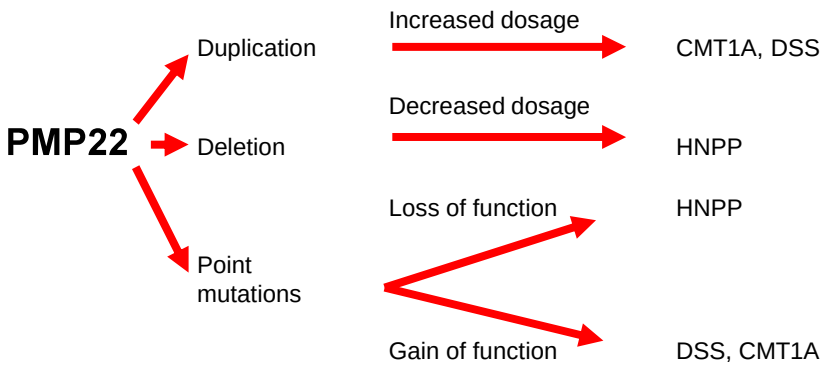
PMP22 DOSAGE AND CMT1A



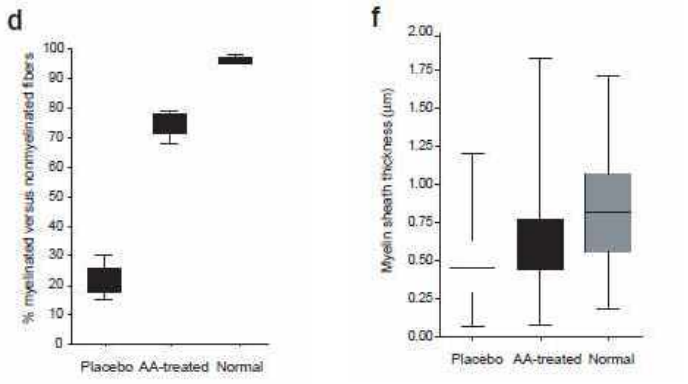
In vitro models, animal models, humans

50

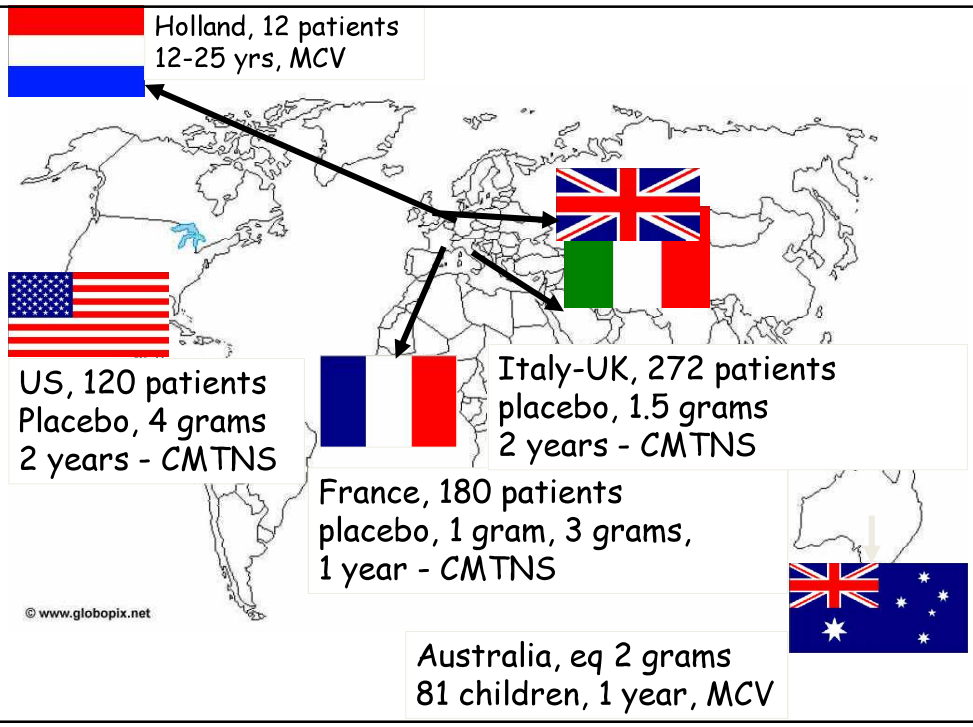
Ascorbic acid treatment corrects the phenotype of a mouse model of Charcot-Marie-Tooth disease

Edith Passage[1,5], Jean Chrétien Norreel[1,2,5], Pauline Noack-Fraissignes[1], Véronique Sanguedolce[1], Josette Pizant[1], Xavier Thirion[3], Andrée Robaglia-Schlupp[1], Jean François Pellissier[4] & Michel Fontés[1]

VOLUME 10 | NUMBER 4 | APRIL 2004 NATURE MEDICINE



51



52

Ascorbic acid in Charcot–Marie–Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial

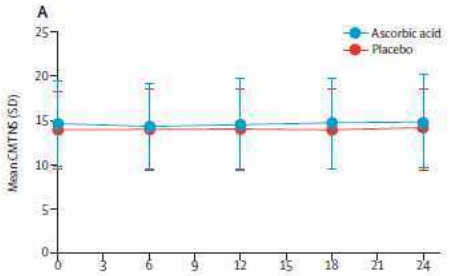
Davide Pareyson, Mary M Reilly, Angelo Schenone, Gian Maria Fabrizi, Tiziana Cavallaro, Lucio Santoro, Giuseppe Vita, Aldo Quattrone, Luca Padua, Franco Gemignani, Francesco Visioli, Matilde Laurà, Davide Radice, Daniela Calabrese, Richard A C Hughes, Alessandra Solari, for the CMT-TRIAAL and CMT-TRAUK groups*

Lancet Neurol 2011; 10: 320–28

272 patients

2 years

1.5 gram AA daily



Lack of responsiveness of the CMT neuropathy score (CMTNS)

53

Effect of ascorbic acid in patients with Charcot–Marie–Tooth disease type 1A: a multicentre, randomised, double-blind, placebo-controlled trial

Joëlle Micallef, Shahram Attarian, Odile Dubourg, Pierre-Marie Gonnaud, Jean-Yves Hogrel, Tanya Stojkovic, Rafaelle Bernard, Elisabeth Jouve, Severine Pitel, Francois Vacherot, Jean-Francois Remec, Laurent Jomir, Eric Azabou, Mahmoud Al-Moussawi, Marie-Noelle Lefebvre, Laurence Attolini, Sadek Yaici, Daniel Tanesse, Michel Fontes, Jean Pouget, Olivier Blin

Lancet Neurol 2009; 8: 1103–10

Ascorbic acid in Charcot–Marie–Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial

Davide Pareyson, Mary M Reilly, Angelo Schenone, Gian Maria Fabrizi, Tiziana Cavallaro, Lucio Santoro, Giuseppe Vita, Aldo Quattrone, Luca Padua, Franco Gemignani, Francesco Visioli, Matilde Laurà, Davide Radice, Daniela Calabrese, Richard A C Hughes, Alessandra Solari, for the CMT-TRIAAL and CMT-TRAUK groups*

Lancet Neurol 2011; 10: 320–28

High-Dosage Ascorbic Acid Treatment in Charcot-Marie-Tooth Disease Type 1A

Results of a Randomized, Double-Masked, Controlled Trial

Richard A. Lewis, MD; Michael P. McDermott, PhD; David N. Herrmann, MD; Ahmet Hoke, MD, PhD; Lora L. Clawson, MSN, CRNP; Carly Siskind, MS; Shawna M. E. Feely, MS; Lindsey J. Miller, MS; Richard J. Barohn, MD; Patricia Smith, BS; Elizabeth Luebbe, MS; Xingyao Wu, MD, PhD; Michael E. Shy, MD; for the Muscle Study Group

JAMA Neurol. 2013;70(8):981-987.

54

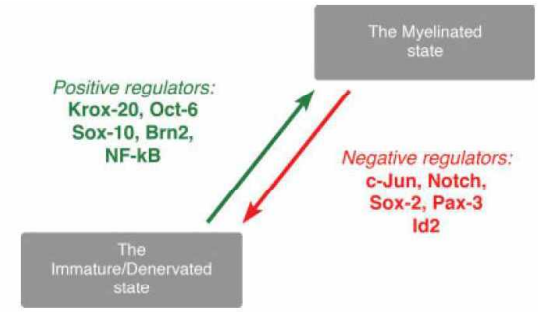
Antiprogesterone Therapy Uncouples Axonal Loss from Demyelination in a Transgenic Rat Model of CMT1A Neuropathy

Gerd Meyer zu Horste, MD,[1] Thomas Prukop,[1] David Liebetanz, MD,[2] Wiebke Mobius, PhD,[1] Klaus-Armin Nave, PhD,[1] and Michael W. Sereda, MD[1,3]

Ann Neurol 2007;61:61–72

Progesterone antagonists reduce PMP22 expression
(Ulipristal acetate trial ongoing)

Progesterone



GLIA 56:1552–1565 (2008)

55

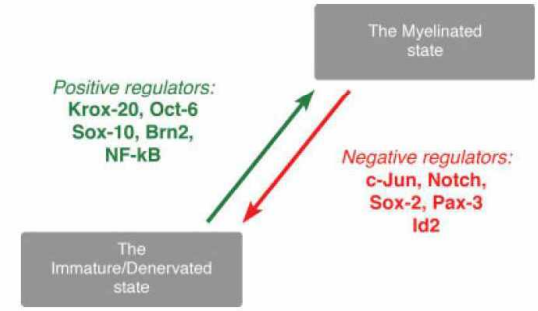
Soluble neuregulin-1 modulates disease pathogenesis in rodent models of Charcot-Marie-Tooth disease 1A

Robert Fledrich[1,6], Ruth M Stassart[1,2,6], Axel Klink[1], Lennart M Rasch[1], Thomas Prukop[1,3], Lauren Haag[4], Dirk Czesnik[4], Theresa Kungl[1], Tamer A M Abdelaal[1], Naureen Keric[1,5], Christine Stadelmann[2], Wolfgang Brück[2], Klaus-Armin Nave[1] & Michael W Sereda[1,4]

NATURE MEDICINE VOLUME 20 | NUMBER 9 | SEPTEMBER 2014

Axonally overexpressed neurogulin-1 drives diseased Schwann cells towards differentiation and axonal preservation
(not in clinical trials in CMT1A)

Neuregulin-1



GLIA 56:1552–1565 (2008)

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PHARNEXT

Polytherapy with a combination of three repurposed drugs (PXT3003) down-regulates *Pmp22* over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy

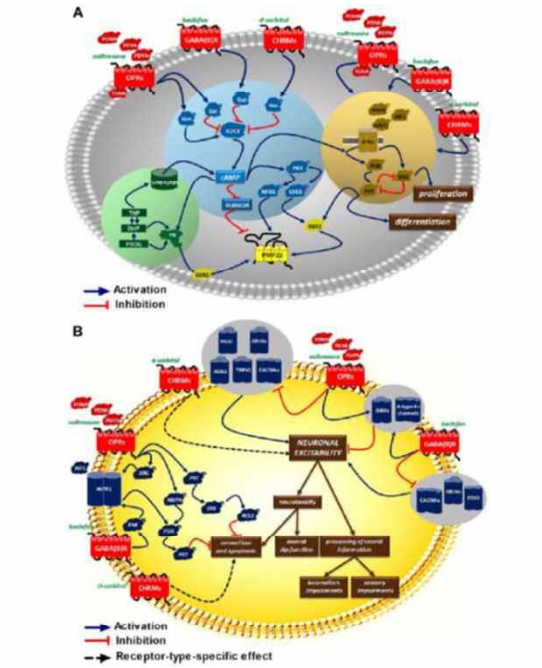
Ilya Chumakov[1], Aude Milet[1], Nathalie Cholet[1], Gwenal Primas [1], Aurlie Boucard [1], Yannick Pereira[1], Esther Graudens[1], Jonas Mandel[1], Julien Laffaire[1], Julie Foucquier[1], Fabrice Glibert[1], Viviane Bertrand[1], Klaus-Armin Nave[2], Michael W Sereda[2,3], Emmanuel Vial[1], Mikal Cuedj [1], Abdolphe Haji[1], Serguei Nabirotchkin[1] and Daniel Cohen[1*]

Orphanet Journal of Rare Diseases 2014, **9**:201

Hypothesis polytherapy to normalise PMP22 gene expression and improve axonal dysfunction (Pleiotropic)

Baclofen, Naltrexone, D-sorbitol

Action on G-protein coupled receptor signalling pathways - suppress PMP22



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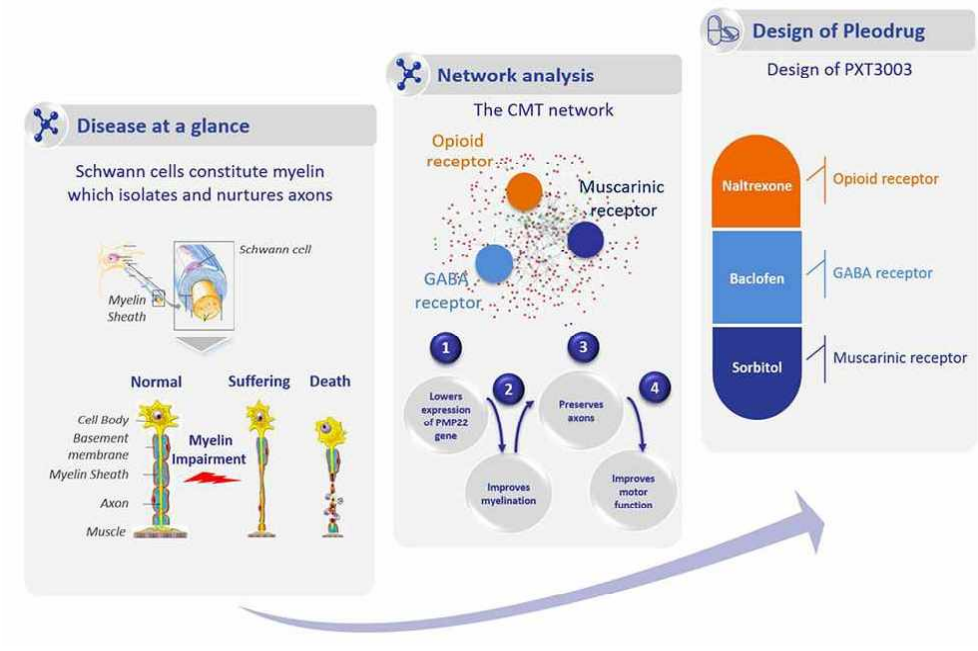

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An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot-Marie-Tooth disease type 1A

Shahram Attarian[1*], Jean-Michel Vallat[2], Laurent Magy[3], Benoît Funalot[2], Pierre-Marie Gonnaud[4], Arnaud Lacour[5], Yann Péréon[6], Odile Dubourg[7], Jean Pouget[1], Joëlle Micallef[1], Jérôme Franques[1], Marie-Noëlle Lefebvre[1], Karima Ghorab[1], Mahmoud Al-Moussawi[1], Vincent Tiffreau[1], Marguerite Preudhomme[1], Armelle Magot[1], Laurène Leclair-Visonneau[1], Tanya Stojkovic[7], Laura Bossi[8], Philippe Lehert[9,10], Walter Gilbert[11], Viviane Bertrand[12†], Jonas Mandel[12], Aude Milet[12], Rodolphe Hajj[13], Lamia Boudiaf[12], Catherine Scart-Grès[12], Serguei Nabirotchkin[12], Mickael Guedj[12†], Ilya Chumakov[12] and Daniel Cohen[12*]

Orphanet Journal of Rare Diseases (2014) 9:199

PXT3003 is safe and well tolerated

80 patients placebo controlled 1 year study

CMTNS / ONLS

High dose suggested improvement in ONLS and CMTNS

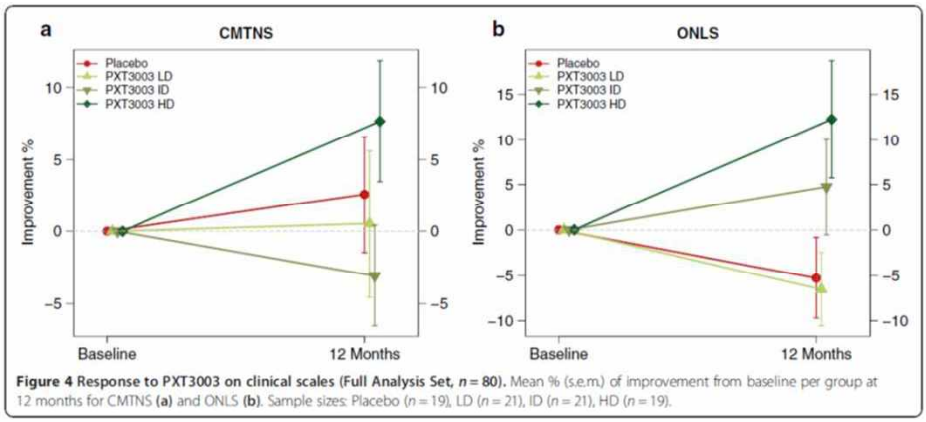

Figure 4 Response to PXT3003 on clinical scales (Full Analysis Set, *n* = 80). Mean % (s.e.m.) of improvement from baseline per group at 12 months for CMTNS **(a)** and ONLS **(b)**. Sample sizes: Placebo (*n* = 19), LD (*n* = 21), ID (*n* = 21), HD (*n* = 19).

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PHASE III STUDY

Efficacy and safety of PXT3003 in patients with CMT1A: International Pivotal Phase III trial.

Initial results presented PNS Genoa last week

2 doses versus placebo (3/6mg Baclofen, 0.35/0.7mg naltrexone, 105/210mg sorbitol)

Randomisation 323 1:1:1

15 months mild moderate severity (maximum CMTNS 18)

Primary endpoint ONLS

10 meter walk, CMTNS etc.

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PHASE III STUDY

Efficacy and safety of PXT3003 in patients with CMT1A: International Pivotal Phase III trial.

Initial results presented PNS Genoa last week

Met the primary end point reduction 0.37-point ONLS

10 meter walk reduction 0.47 sec

Issue with high dose crystallisation so low dose x 2 used for part of trial

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A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale

R C Graham, R A C Hughes

See Editorial Commentary, p 899 J Neurol Neurosurg Psychiatry 2006;77:973–976. doi: 10.1136/jnnp.2005.081547

0-12 scale

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? Yes☐ No☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their hands or arms? Yes☐ No☐ Not applicable ☐

Arm Grade
0=Normal
1=Minor symptoms in one or both arms but not affecting any of the functions listed
2=Disability in one or both arms affecting but not preventing any of the functions listed
3=Disability in one or both arms preventing at least one but not all functions listed
4=Disability in both arms preventing all functions listed but purposeful movement still possible
5=Disability in both arms preventing all purposeful movements

SCORE=____

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0=Walking/climbing stairs/running not affected
1=Walking/climbing stairs/running is affected, but gait does not look abnormal
2=Walks independently but gait looks abnormal
3=Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4=Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)
5=Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6=Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7=Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

SCORE=____

Overall Neuropathy Limitation Scale=arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability))

TOTAL SCORE=____

Is there any disorder, other than peripheral neuropathy, which affects the above functions Yes☐ No☐
If yes please describe:

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Ascorbic acid in Charcot–Marie–Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial

Lancet Neurol 2011; 10: 320–28

*Davide Pareyson, Mary M Reilly, Angelo Schenone, Gian Maria Fabrizi, Tiziana Cavallaro, Lucio Santoro, Giuseppe Vita, Aldo Quattrone, Luca Padua, Franco Gemignani, Francesco Visioli, Matilde Laurà, Davide Radice, Daniela Calabrese, Richard A C Hughes, Alessandra Solari, for the CMT-TRIAAL and CMT-TRAUK groups**

	Ascorbic acid		Placebo		p value
	Patients	Mean change (95% CI)	Patients	Mean change (95% CI)	
Timed 10 m walk test (s)	118	0·76 (0·08 to 1·44)	109	1·12 (–0·38 to 2·61)	0·81
Nine-hole peg test (s; average of both sides)	118	0·11 (–0·59 to 0·80)	106	0·85 (0·33 to 1·37)	0·07
Overall neuropathy limitations scale score*	118	0·11 (–0·07 to 0·29)	109	0·09 (–0·07 to 0·25)	0·99

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Responsiveness of clinical outcome measures in Charcot–Marie–Tooth disease

European Journal of Neurology 2015, **22:** 1556–1563

G. Piscosquito[a], M. M. Reilly[b], A. Schenone[c], G. M. Fabrizi[d], T. Cavallaro[d], L. Santoro[e], F. Manganelli[e], G. Vita[f,g], A. Quattrone[h], L. Padua[i], F. Gemignani[j], F. Visioli[k,l], M. Laurà[b], D. Calabrese[a], R. A. C. Hughes[b], D. Radice[m], A. Solari[a] and D. Pareyson[a] for the CMT-TRIAAL and CMT-TRAUK Group*

Table 3 Responsiveness of activity limitation scales

		Mean (SD)				
	N	Baseline	24 months	Change	*P* ([a])	SRM
9-HPT (s)[b]	119	23.5 (5.8)	24.2 (7.1)	0.75 (2.66)	**< 0.001**	0.28
T10-MW (s)	121	8.6 (4.7)	8.9 (4.1)	0.31 (1.64)	**< 0.001**	0.19
ONLS	122	3.1 (1.2)	3.3 (1.2)	0.13 (0.88)	0.10	0.15

[a]*P* values for mean change; [b]average of both sides. Values in bold are significant.

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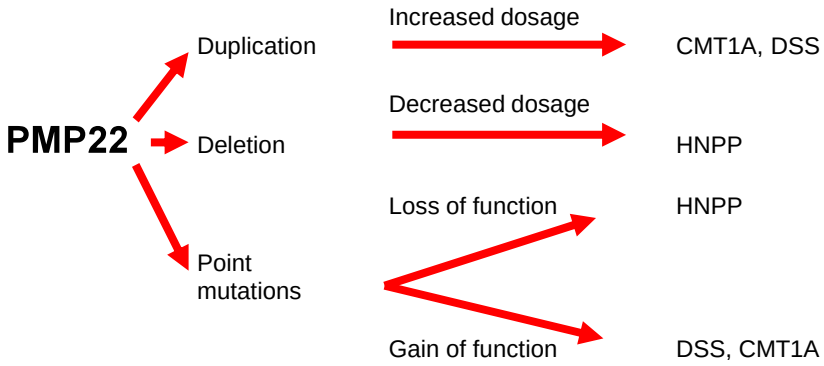
PMP22 DOSAGE AND CMT1A



In vitro models, animal models, humans

65

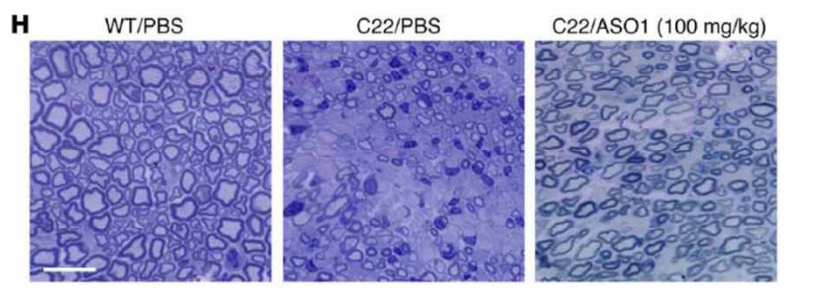
PMP22 antisense oligonucleotides reverse Charcot-Marie-Tooth disease type 1A features in rodent models

Hien Tran Zhao,[1] Sagar Damle,[1] Karli Ikeda-Lee,[1] Steven Kuntz,[1] Jian Li,[2] Apoorva Mohan,[1] Aneeza Kim,[1] Gene Hung,[1] Mark A. Scheideler,[3] Steven S. Scherer,[2] John Svaren,[4] Eric E. Swayze,[1] and Holly B. Kordasiewicz[1]

J Clin Invest. 2018;128(1):359–368.

Successful ASO treatment C22 mice / CMT1A rat

Behavioural / NCS / Pathology / PMP22 expression



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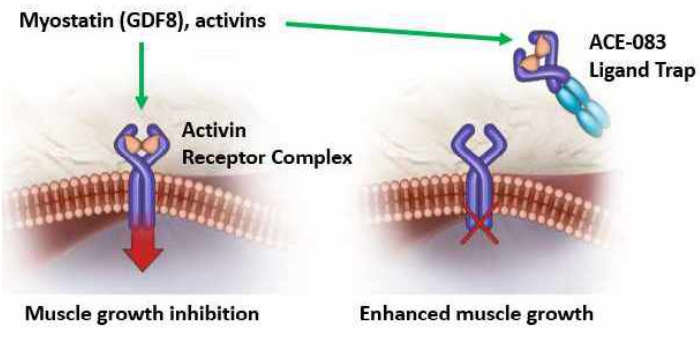
ACE-083 – A Locally-Acting Muscle Therapeutic

- ACE-083 is a locally-acting protein therapeutic in the TGF-β superfamily consisting of a modified form of human follistatin that binds GDF8 (myostatin) *plus* other negative regulators of skeletal muscle
- Designed to be locally injected in affected muscles to increase muscle mass and strength
- Increased muscle mass demonstrated in healthy volunteers[1] and patients with FSH muscular dystrophy[2]
- Tibialis anterior and biceps were selected as initial muscle targets for a locally acting therapeutic



[1] *Glasser CE, et al. Muscle Nerve. 2018; 57:921-926*
[2] *Statland J, et al. World Muscle Society 2018 Poster 365*

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ACCELERON ACE-083 CMT Program Update

- ACE-083 is a locally-acting muscle therapeutic, acting on myostatin plus other inhibitors of muscle growth; it is being investigated in FSHD and CMT (clinicaltrials.gov NCT03124459)
- Part 1 data in CMT presented at AAN May, 2019
  - ACE-083 injected into tibialis anterior bilaterally for 3 months had a favorable safety profile
  - Mean % increases of >12% total muscle volume and >15% in contractile muscle volume (MRI)
  - Mean absolute decrease in fat fraction of >3% at 200-240 mg/muscle
- Placebo-controlled Part 2 topline data expected Q1 2020
- Primary endpoint: muscle volume
- Secondary endpoints: function and quality of life
- 24-month open-label extension study is evaluating alternative dosing regimens

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GENETIC THERAPIES

1. Generic gene therapy
2. Target pathogenesis of disease
3. Pathway therapies

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GENETIC THERAPIES

1. **Generic gene therapy**
2. Target pathogenesis of disease
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GENETIC THERAPIES

1. **Generic gene therapy**
   - antisense oligonucleotides (AONs)
   - small interfering RNA
   - **Genome editing CRISPR / Cas 9**
   - viral vector-mediated gene therapy

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GENETIC THERAPIES

1. **Generic gene therapy**
   - antisense oligonucleotides (AONs)
   - small interfering RNA
   - Genome editing CRISPR / Cas 9
   - **viral vector-mediated gene therapy**

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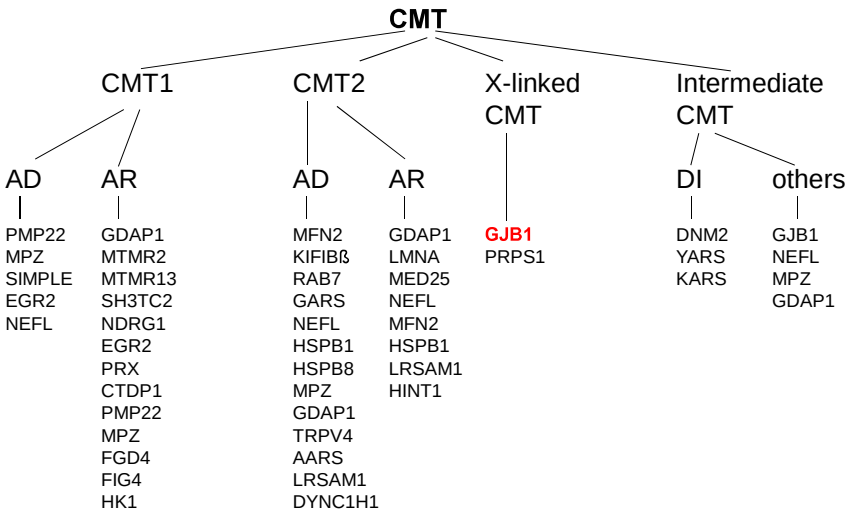
CMT



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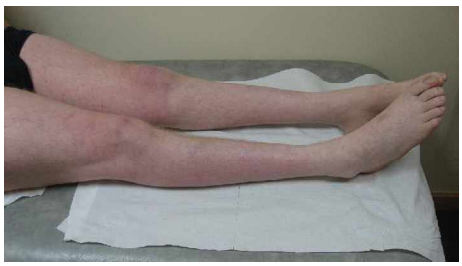
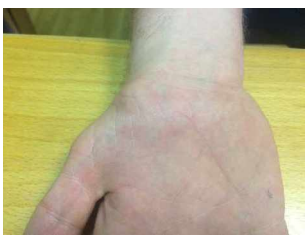
UCL

CMT

MRC Centre for Neuromuscular Diseases

24 year old man, family history males > females, no male to male





Left median MRC 2/5
CMAP **2.3** µv; MCV 29 ms

Left ulnar MRC 4/5
CMAP **6.3** µv: MCV 34 ms

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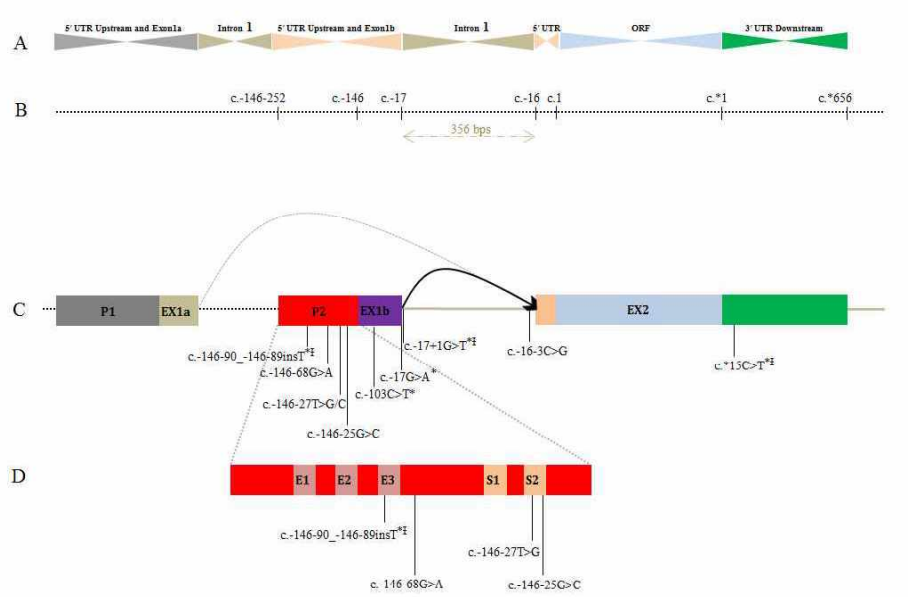
Mutations in noncoding regions of *GJB1* are a major cause of X-linked CMT

Pedro J. Tomaselli, MD, MSc*
Alexander M. Rossor, MRCP, PhD*
Alejandro Horga, MD, PhD
Zane Jaunmuktane, FRCPath
Aisling Carr, MRCP, PhD
Paola Saveri, BSc
Giuseppe Piscosquito, MD
Davide Pareyson, MD
Matilde Laura, MD, PhD
Julian C. Blake, FRCP
Roy Poh, PhD
James Polke, PhD
Henry Houlden, FRCP, PhD
Mary M. Reilly, FRCP, FRCPI, MD

Neurology® 2017;88:1-9

11.4% (25/194) of CMTX1 is due to non coding mutations

75

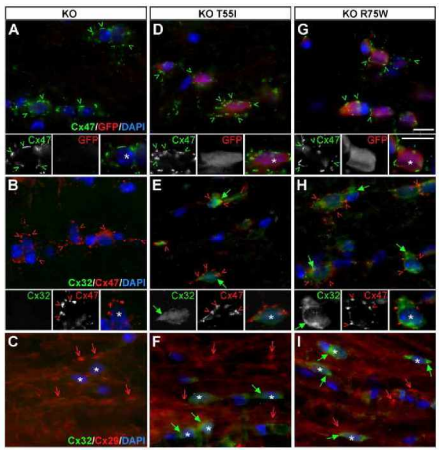


76

Connexin32 Mutations Cause Loss of Function in Schwann Cells and Oligodendrocytes Leading to PNS and CNS Myelination Defects

Irene Sargiannidou,[1] Natalie Vavlitou,[1] Sophia Aristodemou,[2] Andreas Hadjisavvas,[2] Kyriacos Kyriacou,[2] Steven S. Scherer,[3] and Kleopas A. Kleopa[1]

The Journal of Neuroscience, April 15, 2009 • 29(15):4736 – 4749



77

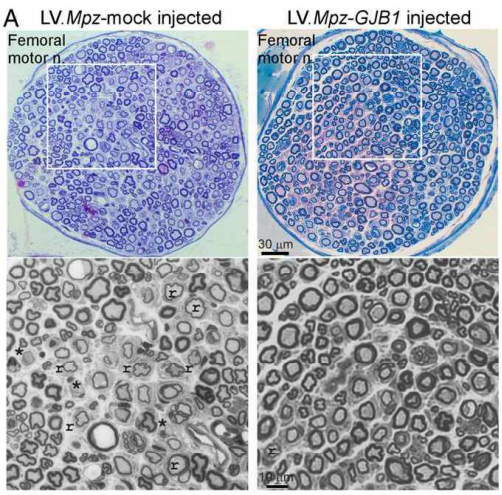
Intrathecal gene therapy rescues a model of demyelinating peripheral neuropathy

Alexia Kagiava[a], Irene Sargiannidou[a], George Theophilidis[b], Christos Karaiskos[a], Jan Richter[c], Stavros Bashiardes[c], Natasa Schiza[a], Marianna Nearchou[d], Christina Christodoulou[c], Steven S. Scherer[e], and Kleopas A. Kleopa[a,f,1]

PNAS | Published online March 28, 2016 | E2421–E2429

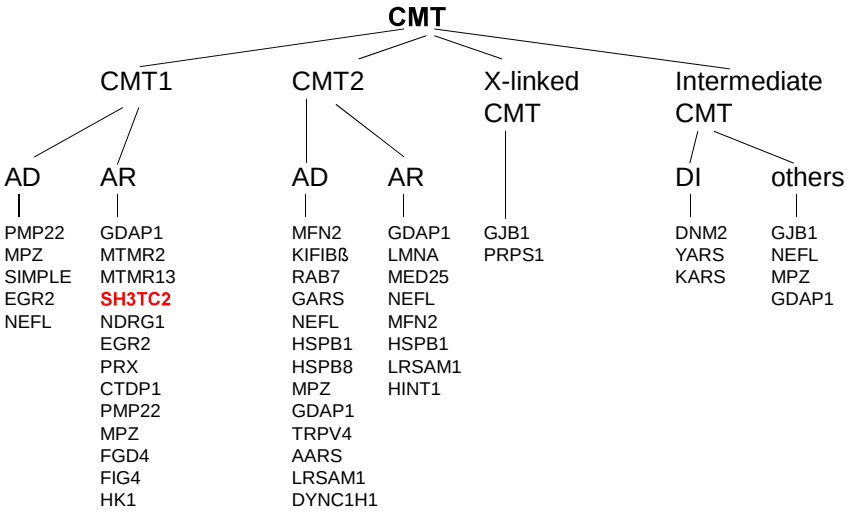
Further update confirm these results PNS 2019

Also NEFL is a responsive biomarker



78

CMT

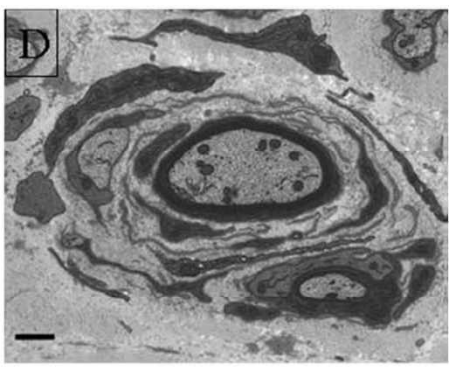


79

The phenotype of Charcot–Marie–Tooth disease type 4C due to *SH3TC2* mutations and possible predisposition to an inflammatory neuropathy

Henry Houlden [a,*], Matilde Laura [a], Lionel Ginsberg [b], Heinz Jungbluth [c], Stephanie A. Robb [d], Julian Blake [a,e], Susan Robinson [f], Rosalind H.M. King [b], Mary M. Reilly [a]

Neuromuscular Disorders 19 (2009) 264–269

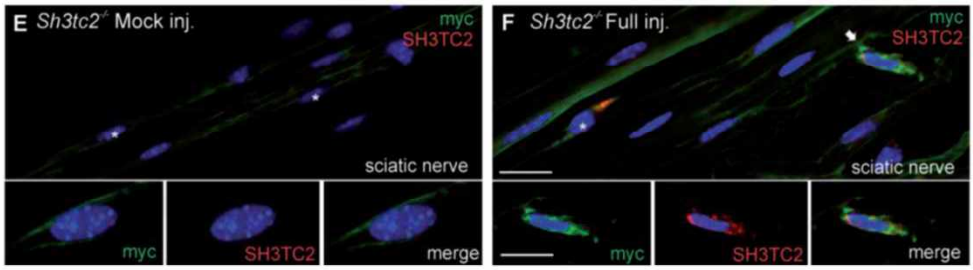


80

Gene replacement therapy in a model of Charcot-Marie-Tooth 4C neuropathy

Natasa Schiza,[1] Elena Georgiou,[1] Alexia Kagiava,[1] Jean-Jacques Médard,[2] Jan Richter,[3] Christina Tryfonos,[3] Irene Sargiannidou,[1] Amanda J. Heslegrave,[4,5] Alexander M. Rossor,[6] Henrik Zetterberg,[4,5,7,8] Mary M. Reilly,[6] Christina Christodoulou,[3] Roman Chrast[2] and Kleopas A. Kleopa[1]

BRAIN 2019: 0; 1–15



NEFL responsive biomarker

81

UCL

MRC Centre for Neuromuscular Diseases

GENETIC THERAPIES

1. Generic gene therapy
2. **Target pathogenesis of disease**
3. Pathway therapies

82

UCL

MRC Centre for Neuromuscular Diseases

GENETIC THERAPIES

1. Generic gene therapy
2. **Target pathogenesis of disease example 1.**
3. Pathway therapies

83

Charcot–Marie–Tooth disease: frequency of genetic subtypes and guidelines for genetic testing

Sinead M Murphy,[1,2,3] Matilde Laura,[1,2] Katherine Fawcett,[4,5] Amelie Pandraud,[1,2] Yo-Tsen Liu,[1,2] Gabrielle L Davidson,[1,2] Alexander M Rossor,[1,2] James M Polke,[3] Victoria Castleman,[1,2] Hadi Manji,[1,2] Michael P T Lunn,[1,2] Karen Bull,[1,2] Gita Ramdharry,[1,2] Mary Davis,[4,5] Julian C Blake,[6,7,8] Henry Houlden,[1,2] Mary M Reilly[1,2]

J Neurol Neurosurg Psychiatry (2012). doi:10.1136/jnnp-2012-302451

Frequency of mutations in the genes associated with hereditary sensory and autonomic neuropathy in a UK cohort

G. L. Davidson · S. M. Murphy · J. M. Polke · M. Laura · M. A. M. Salih · F. Muntoni · J. Blake · S. Brandner · N. Davies · R. Horvath · S. Price · M. Donaghy · M. Roberts · N. Foulds · G. Ramdharry · D. Soler · M. P. Lunn · H. Manji · M. B. Davis · H. Houlden · M. M. Reilly

J Neurol Published online: 01 February 2012

The distal hereditary motor neuropathies

Alexander M Rossor,[1] Bernadett Kalmar,[2] Linda Greensmith,[2] Mary M Reilly[1]

J Neurol Neurosurg Psychiatry 2012;**83**:6–14.

PRE PANEL DIAGNOSTIC RATE

65% Diagnosis

(PMP22, MPZ, GJB1, MFN2 >90%)

Charcot-Marie-Tooth Disease Subtypes and Genetic Testing Strategies

Anita S.D. Saporta, MD,[1] Stephanie L. Sottile, BA,[1] Lindsey J. Miller, MS,[1] Shawna M.E. Feely, MS,[1] Carly E. Siskind, MS,[1] and Michael E. Shy, MD[1,2]

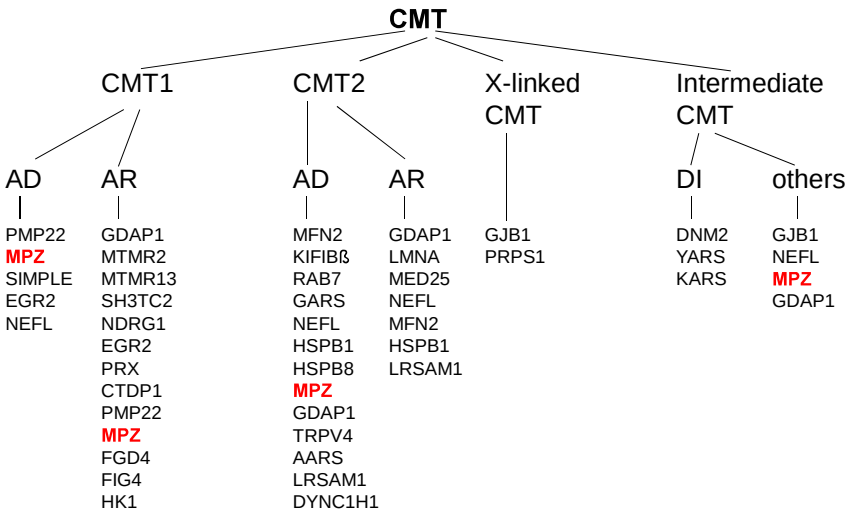
ANN NEUROL 2011;69:22–33

Charcot-Marie-Tooth disease: Frequency of genetic subtypes in a German neuromuscular center population

Burkhard Gess*, Anja Schirmacher, Matthias Boentert, Peter Young

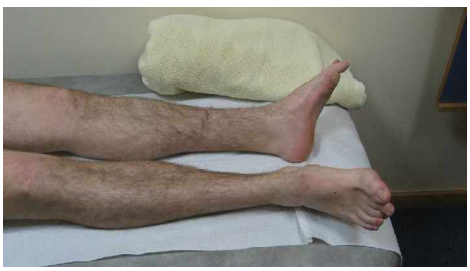
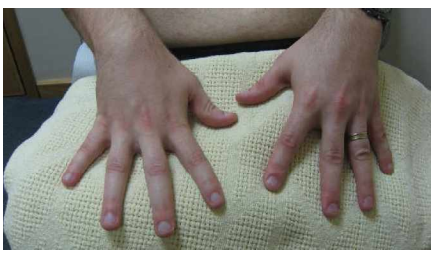
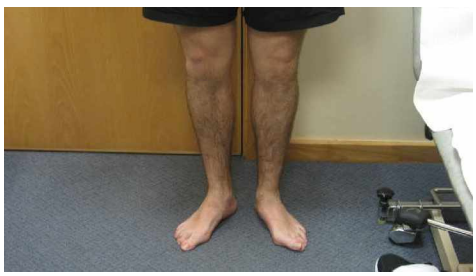
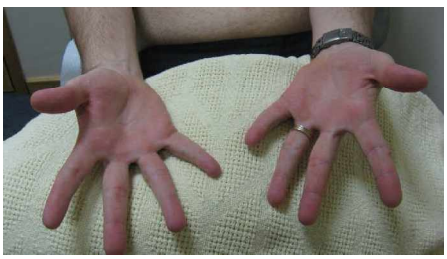
Neuromuscular Disorders 23 (2013) 647–651

84


CMT
CMT1
CMT2
X-linked CMT
Intermediate CMT
AD
AR
AD
AR
DI
others
PMP22
MPZ
SIMPLE
EGR2
NEFL
GDAP1
MTMR2
MTMR13
SH3TC2
NDRG1
EGR2
PRX
CTDP1
PMP22
MPZ
FGD4
FIG4
HK1
MFN2
KIFIBß
RAB7
GARS
NEFL
HSPB1
HSPB8
MPZ
GDAP1
TRPV4
AARS
LRSAM1
DYNC1H1
GDAP1
LMNA
MED25
NEFL
MFN2
HSPB1
LRSAM1
GJB1
PRPS1
DNM2
YARS
KARS
GJB1
NEFL
MPZ
GDAP1

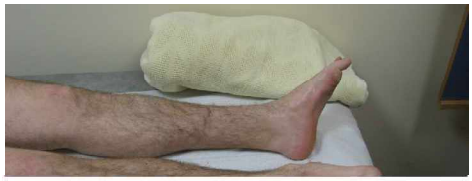
85

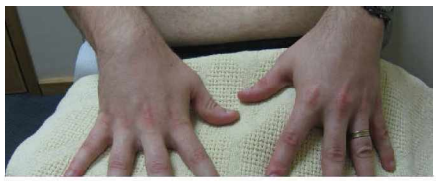
CMT1B

86

CMT1B

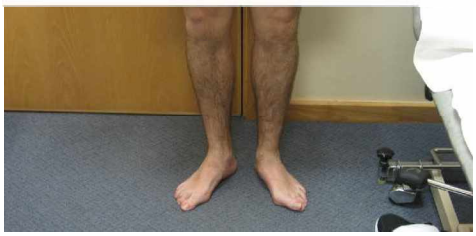




DOI: 10.1093/brain/awh048 *Brain* (2004), **127**, 371–384

Phenotypic clustering in MPZ mutations

Michael E. Shy,[1,2] Agnes Jáni,[1] Karen Krajewski,[1,2] Marina Grandis,[1,2] Richard A. Lewis,[1] Jun Li,[1] Rosemary R. Shy,[3] Janne Balsamo,[4] Jack Lilien,[4] James Y. Garbern[1,2] and John Kamholz[1,2]



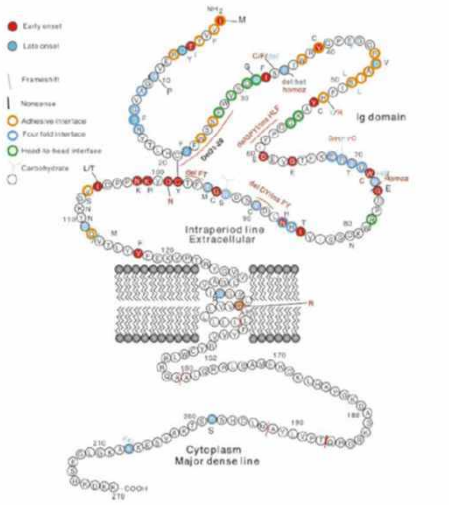
87

CMT1B (MPZ)

1. Early onset
   MNCVs < 15 m/s

2. Late onset
   MNCVs 30-60 m/s

(Shy et al, Brain 2004)



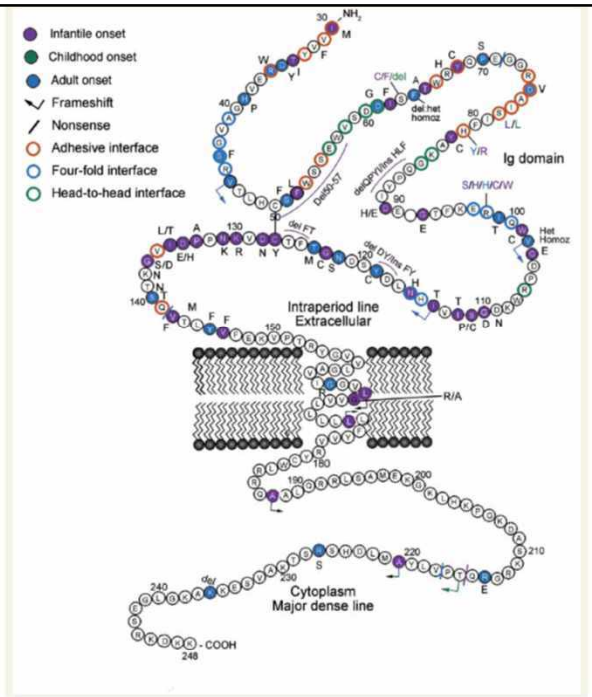
88

Genotype–phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the *MPZ* gene

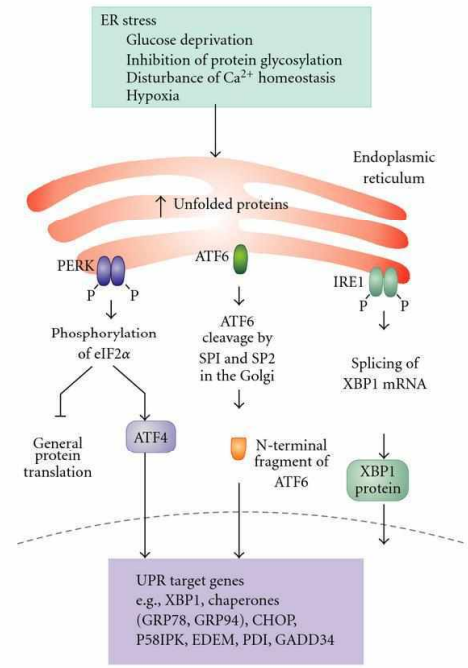
Oranee Sanmaneechai,[1,2] Shawna Feely,[1] Steven S. Scherer,[3] David N. Herrmann,[4] Joshua Burns,[5] Francesco Muntoni,[6] Jun Li,[7] Carly E. Siskind,[8] John W. Day,[8] Matilde Laura,[9] Charlotte J. Sumner,[10] Thomas E. Lloyd,[10] Sindhu Ramchandren,[11] Rosemary R. Shy,[1] Tiffany Grider,[1] Chelsea Bacon,[1] Richard S. Finkel,[12] Sabrina W. Yum,[3,13] Isabella Moroni,[14] Giuseppe Piscosquito,[15] Davide Pareyson,[15] Mary M. Reilly[9] and Michael E. Shy[1] for the Inherited Neuropathies Consortium - Rare Disease Clinical Research Consortium (INC-RDCRC)

BRAIN 2015: Page 1 of 13

103 MPZ patients



89



International Journal of Cell Biology
Volume 2010, Article ID 214074, 23 pages
doi:10.1155/2010/214074

90

Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit

Indrajit Das,[1] Agnieszka Krzyzosiak,[1] Kim Schneider,[1] Lawrence Wrabetz,[2]*
Maurizio D'Antonio,[2] Nicholas Barry,[1] Anna Sigurdardottir,[1] Anne Bertolotti[1]†

SCIENCE 10 APRIL 2015 • VOL 348 ISSUE 6231

Perk Ablation Ameliorates Myelination in S63del-Charcot–Marie–Tooth 1B Neuropathy

Nicolò Musner[1,*], Mariapaola Sidoli[1,2,*], Desireè Zambroni[3], Ubaldo Del Carro[3], Daniela Ungaro[3], Maurizio D'Antonio[4], Maria L. Feltri[1,2,5], and Lawrence Wrabetz[1,2,5]

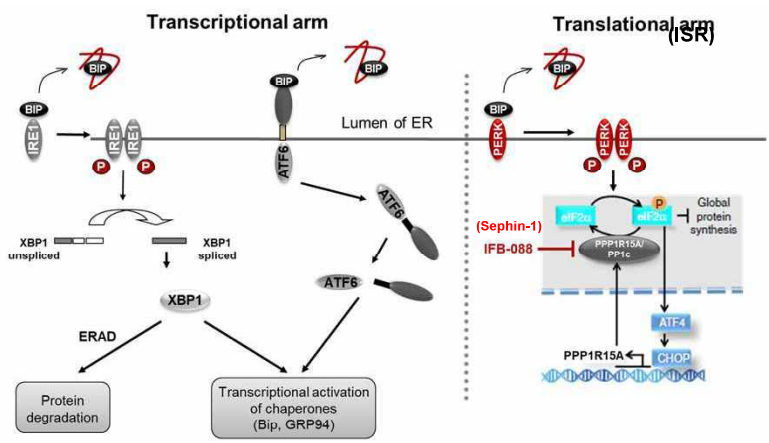
ASN Neuro
March-April 2016: 1–18

Successful treatment of a 2nd MPZ mouse model presented PNS Genoa 2019

91

INFLECTIS

THE UNFOLDED PROTEIN RESPONSE (UPR)

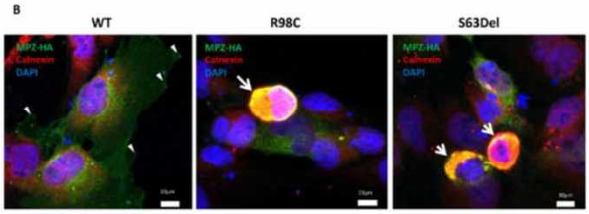


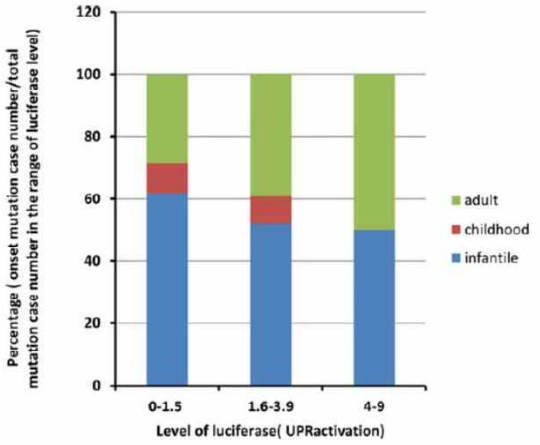
92

Myelin protein zero mutations and the unfolded protein response in Charcot Marie Tooth disease type 1B

Yunhong Bai[1,a], Xingyao Wu[1,a], Kathryn M. Brennan[1], David S. Wang[1], Maurizio D'Antonio[2], John Moran[3,4], John Svaren[3,4] & Michael E. Shy[1]

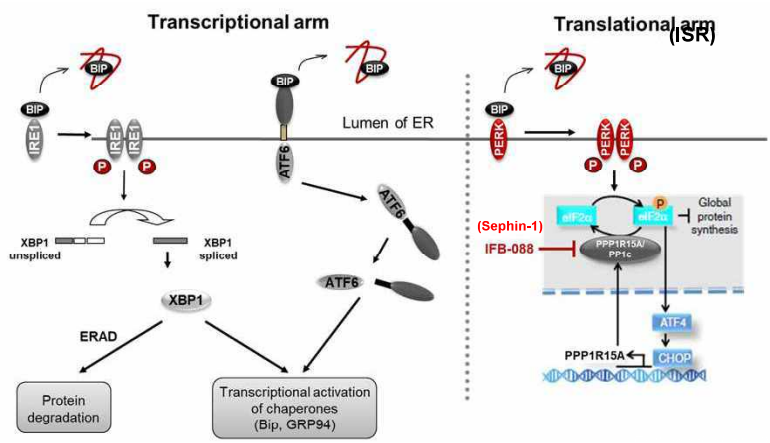
Annals of Clinical and Translational Neurology 2018; 5(4): 445–455





93

THE UNFOLDED PROTEIN RESPONSE (UPR)



Updated results PNS Genoa 2019 including evidence of activation of UPR in CMT1A
Promising data treating CMT1A c3 transgenic mice

94

UCL MRC Centre for Neuromuscular Diseases

GENETIC THERAPIES

1. Generic gene therapy
2. **Target pathogenesis of disease example 2.**
3. Pathway therapies

95

CMT / RELATED DISORDERS

1. Charcot-Marie-Tooth disease (CMT)
2. Hereditary Neuropathy with liability to pressure palsies (HNPP)
3. **Hereditary sensory neuropathies (HSN / HSAN)**
4. Distal hereditary motor neuropathies (HMN)

96

HSN1

AD sensory neuropathy

Onset early teens sensory complications

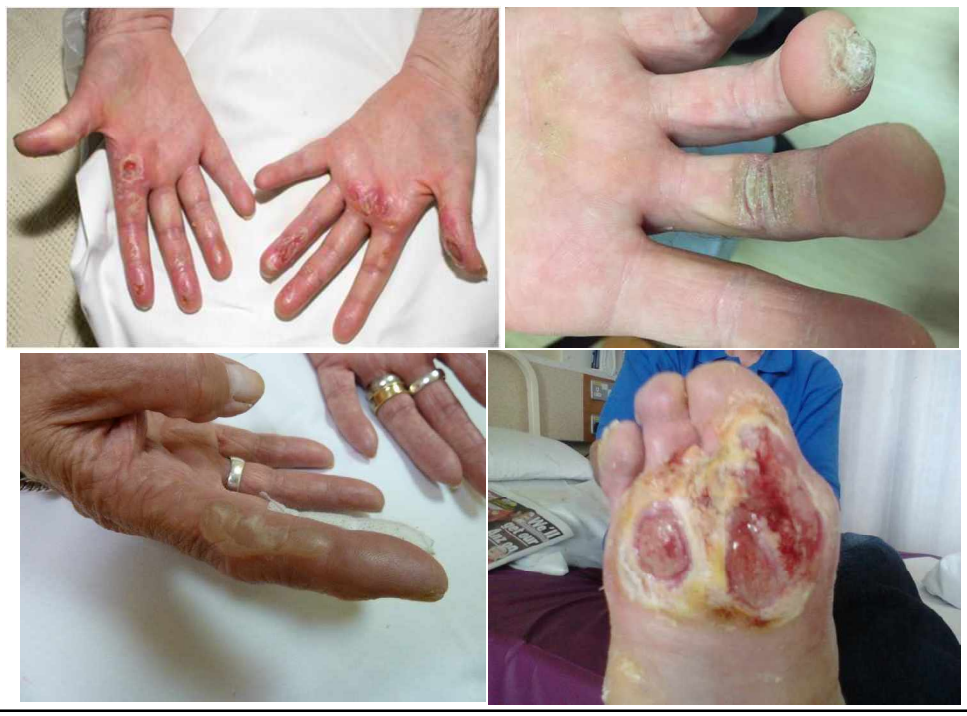
Neuropathic pain very common

Very frequent sensory complications

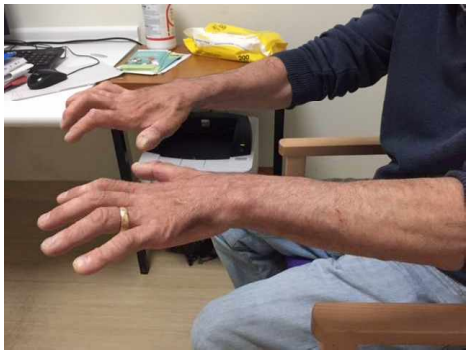
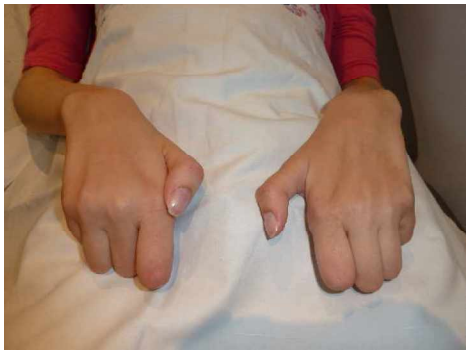
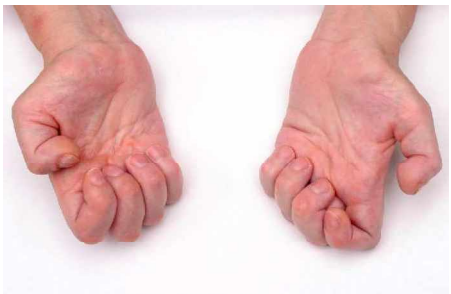
Motor involvement variable

No significant autonomic involvement

97



98


99

Mutations in *SPTLC1*, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I

Jennifer L. Dawkins[1], Dennis J. Hulme[1], Sonal B. Brahmbhatt[1], Michaela Auer-Grumbach[2] & Garth A. Nicholson[1]

nature genetics • volume 27 • march 2001

SPTLC1 is mutated in hereditary sensory neuropathy, type 1

Khemissa Bejaoui[1], Chenyan Wu[1,3], Margaret D. Scheffler[1], Geoffry Haan[1], Peter Ashby[2], Lianchan Wu[1,3], Peter de Jong[3] & Robert H. Brown, Jr.[1]

nature genetics • volume 27 • march 2001

Mutations in the *SPTLC2* Subunit of Serine Palmitoyltransferase Cause Hereditary Sensory and Autonomic Neuropathy Type I

Annelies Rotthier,[1,3,14] Michaela Auer-Grumbach,[4,14] Katrien Janssens,[1,3,14] Jonathan Baets,[2,3,5] Anke Penno,[6,7] Leonardo Almeida-Souza,[1,3] Kim Van Hoof,[1,3] An Jacobs,[1,3] Els De Vriendt,[2,3] Beate Schlotter-Weigel,[8] Wolfgang Löscher,[9] Petr Vondráček,[10] Pavel Seeman,[11] Peter De Jonghe,[2,3,5] Patrick Van Dijck,[12] Albena Jordanova,[2,3] Thorsten Hornemann,[6,13] and Vincent Timmerman[1,3,*]

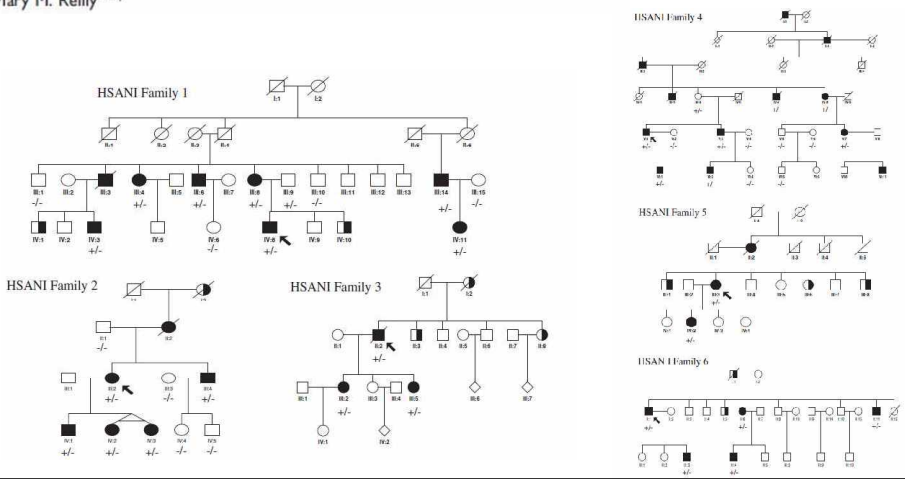
The American Journal of Human Genetics *87*, 513–522, October 8, 2010

100

doi:10.1093/brain/awh712 Brain (2006), 129, 411–425

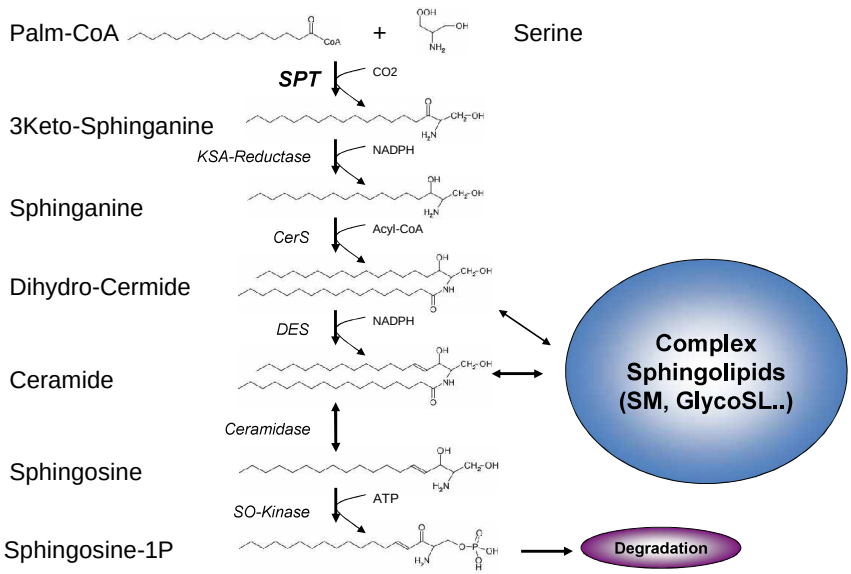
Clinical, pathological and genetic characterization of hereditary sensory and autonomic neuropathy type I (HSAN I)

Henry Houlden,[1,4,5] Rosalind King,[5] Julian Blake,[2,4,10] Mike Groves,[1,3] Seth Love,[6] Cathy Woodward,[1] Simon Hammans,[7] James Nicoll,[7] Graham Lennox,[8] Dominic G. O'Donovan,[8] Carolyn Gabriel,[9] P. K. Thomas[1] and Mary M. Reilly[1,4,*]



101

HSN1



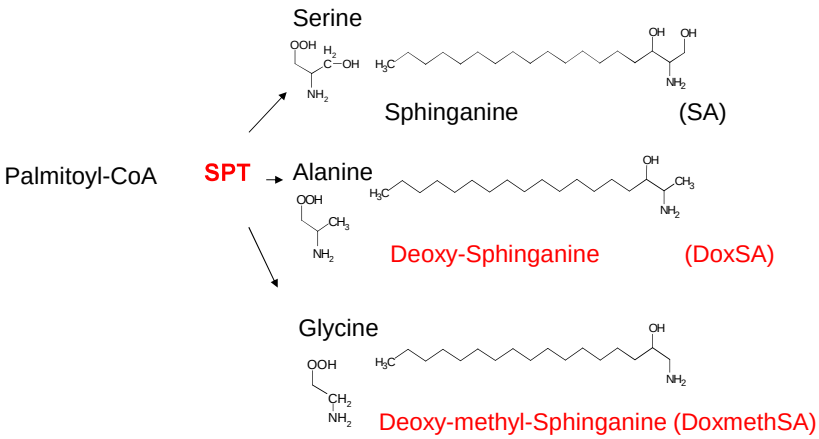
102

Hereditary Sensory Neuropathy Type 1 Is Caused by the Accumulation of Two Neurotoxic Sphingolipids*[S]•

Received for publication, December 10, 2009, and in revised form, January 15, 2010 Published, JBC Papers in Press, January 22, 2010, DOI 10.1074/jbc.M109.092973

Anke Penno[‡§], Mary M. Reilly[¶], Henry Houlden[¶], Matilde Laurá[¶], Katharina Rentsch[‡], Vera Niederkofler[‖], Esther T. Stoeckli[‖], Garth Nicholson[**], Florian Eichler[‡‡], Robert H. Brown, Jr.[‡‡§§], Arnold von Eckardstein[‡§], and Thorsten Hornemann[‡§1]

JOURNAL OF BIOLOGICAL CHEMISTRY 285, NO. 15, pp. 11178–11187, April 9, 2010

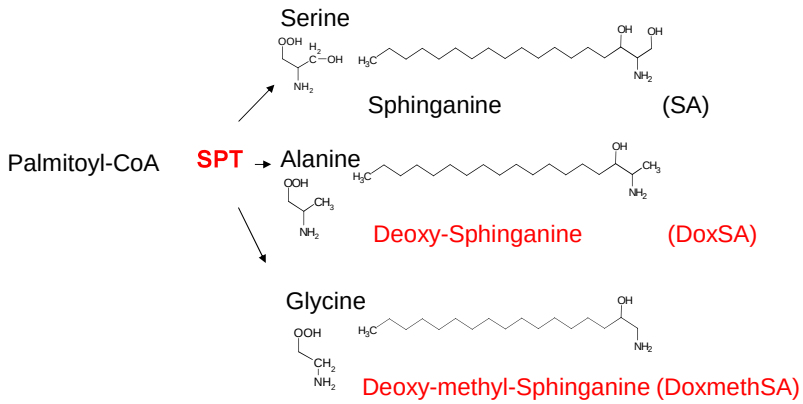


103

Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1

Kevin Garofalo,[1] Anke Penno,[2] Brian P. Schmidt,[1] Ho-Joon Lee,[3] Matthew P. Frosch,[4] Arnold von Eckardstein,[2] Robert H. Brown,[5] Thorsten Hornemann,[2] and Florian S. Eichler[1]

J Clin Invest. 2011;121(12):4735–4745.



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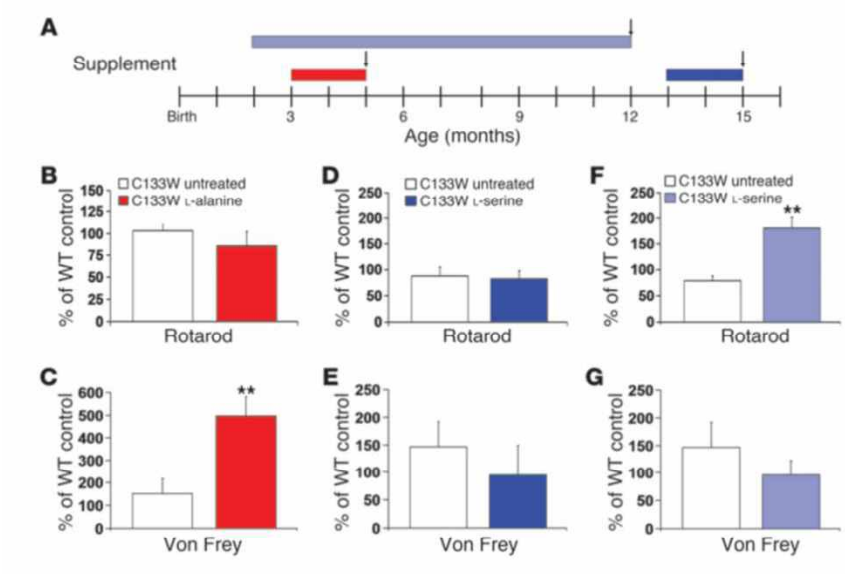


105

Randomized trial of L-serine in patients with hereditary sensory and autonomic neuropathy type 1

Vera Fridman, MD, Saranya Suriyanarayanan, PhD, Peter Novak, MD, PhD, William David, MD, PhD, Eric A. Macklin, PhD, Diane McKenna-Yasek, BSN, Kailey Walsh, BS, Razina Aziz-Bose, BA, Anne Louise Oaklander, MD, PhD, Robert Brown, MD, DPhil,* Thorsten Hornemann, PhD,* and Florian Eichler, MD*

Neurology® 2019;92:e1-e12.

Trial of serine in 18 HSN1 patients (16 completed)

No difference in primary outcome (number progressing >1 CMTNS)

Improvement in CMTNS in serine treated

Small study / better outcome measures

106

GENE

Patient cohorts: nature of disease

Outcome measures

Candidate therapies

Trial centre

Trial ready

Animal model

Trials

Pre-clinical studies

THERAPY

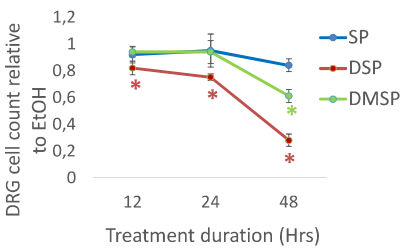
107

Hereditary sensory neuropathy type 1-associated deoxysphingolipids cause neurotoxicity, acute calcium handling abnormalities and mitochondrial dysfunction *in vitro*

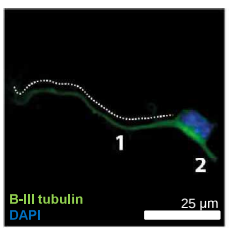
Emma R. Wilson[a,b], Umaiyal Kugathasan[a,b], Andrey Y. Abramov[c], Alex J. Clark[d], David L.H. Bennett[d], Mary M. Reilly[b,c], Linda Greensmith[a,b,1], Bernadett Kalmar[a,*,1]

Neurobiology of Disease 117 (2018) 1–14

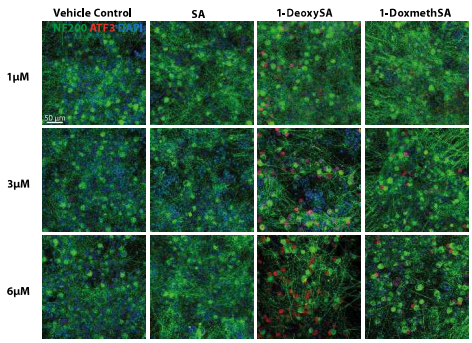
DRG



Motor neurones



IPSc



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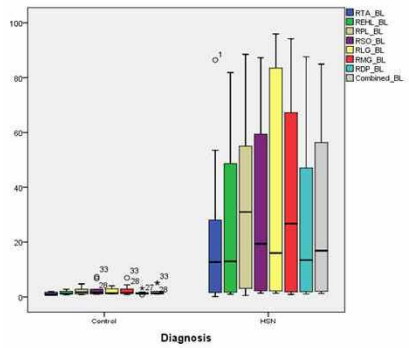
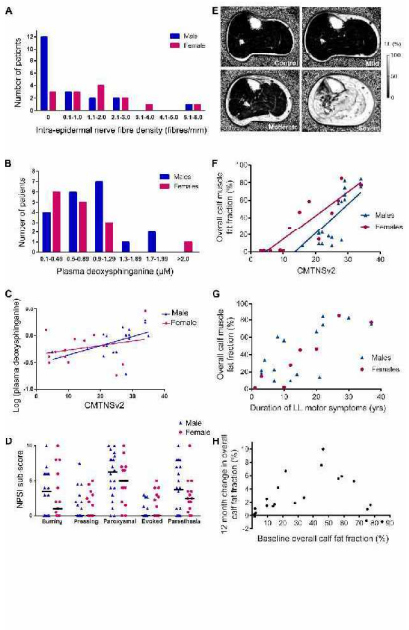
Development of MRC Centre MRI calf muscle fat fraction protocol as a sensitive outcome measure in Hereditary Sensory Neuropathy Type 1

Umaiyal Kugathasan,[1] Matthew R B Evans,[1,2] Jasper M Morrow,[1,2] Christopher D J Sinclair,[1,2] John S Thornton,[1,2] Tarek A Yousry,[1,2] Thorsten Hornemann,[3] Saranya Suriyanarayanan,[3] Khadijah Owusu-Ansah,[4] Giuseppe Lauria,[5,6] Raffaella Lombardi,[5] James M Polke,[7] Emma Wilson,[1] David L H Bennett,[8] Henry Houlden,[1] Michael G Hanna,[1] Julian C Blake,[1,9] Matilde Laura,[1] Mary M Reilly[1]

J Neurol Neurosurg Psychiatry 2019;**0**:1–12.





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Hereditary Sensory Neuropathy Serine trial (SENSE trial)

2019 under review NIHR Efficacy and Mechanism (EME) Programme

MRI muscle as primary outcome measure

56 patients (28 in each arm)

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GENETIC THERAPIES

1. Generic gene therapy
2. Target pathogenesis of disease
3. **Pathway therapies**

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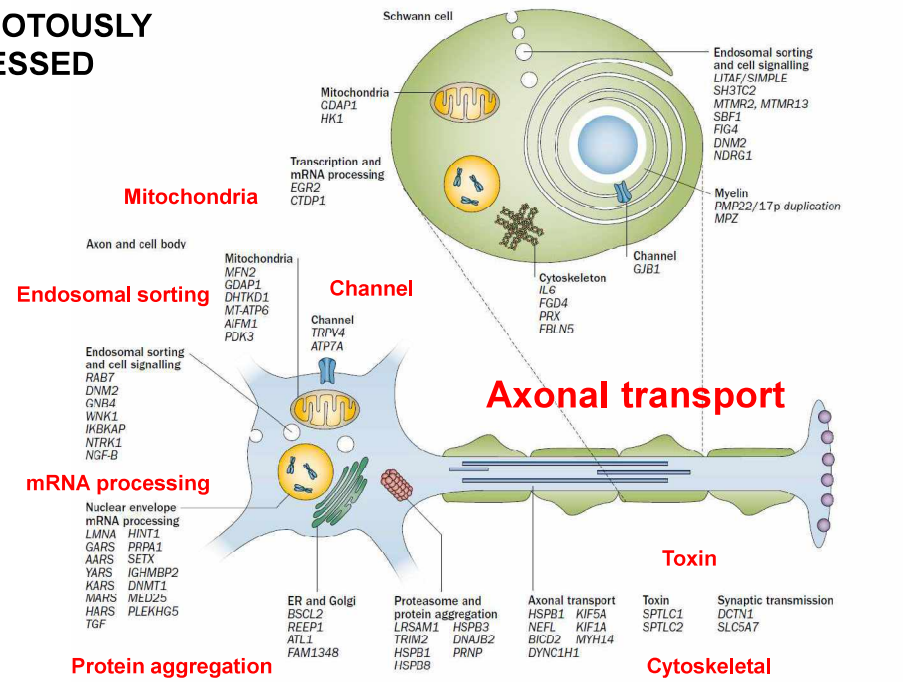
UBIQUOTOUSLY EXPRESSED



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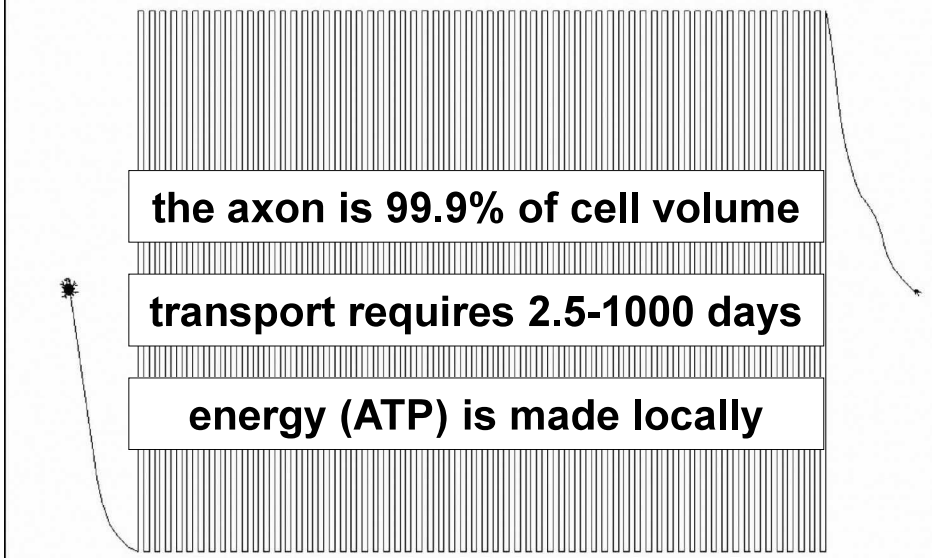
AXONOPATHIES



50 μ neuron with a 10μ axon, 1 m long - PJH

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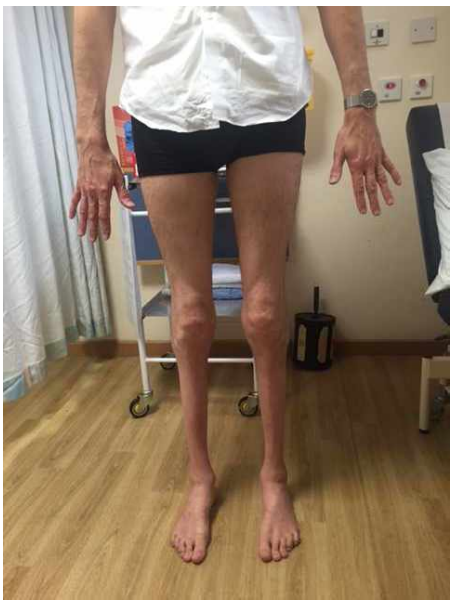

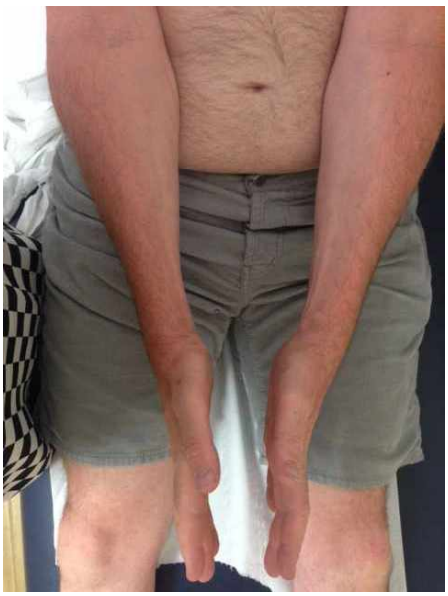

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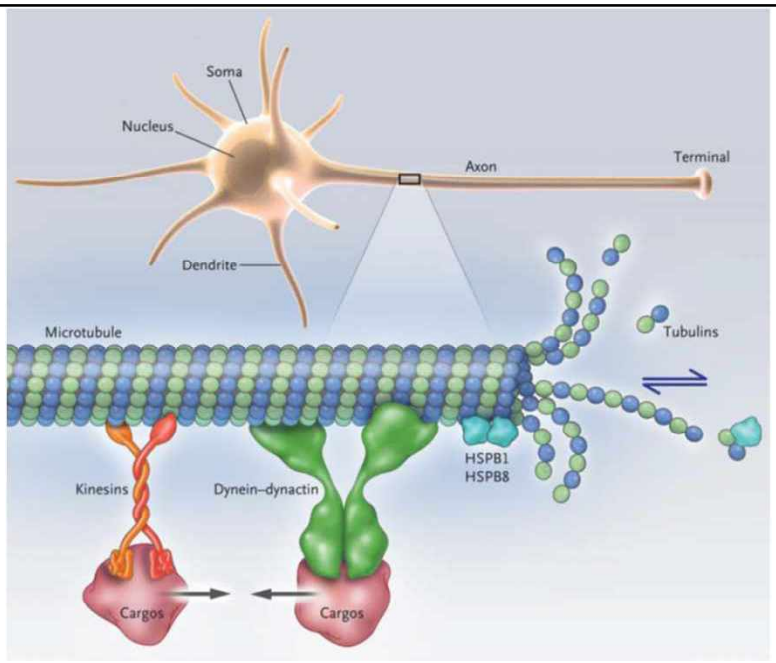

Erika L.F. Holzbaur, Ph.D., and Steven S. Scherer, M.D., Ph.D. N ENGL J MED 365;24 NEJM.ORG DECEMBER 15, 2011

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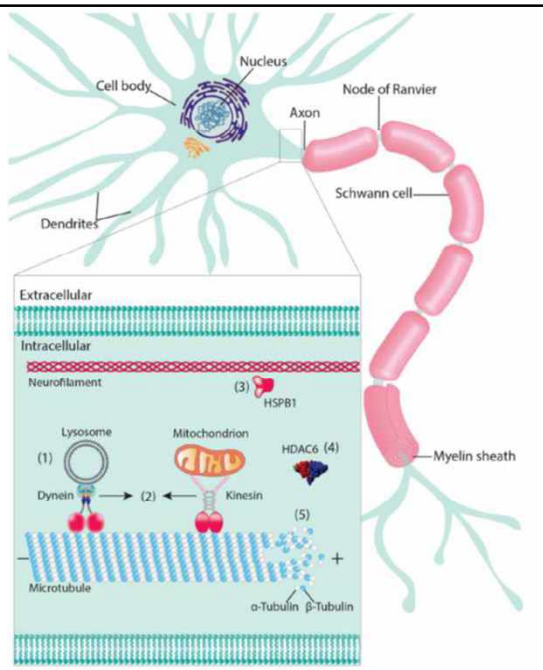

Robert Prior, Lawrence Van Helleputte, Veronick Benoy, Ludo Van Den Bosch Neurobiology of Disease xxx (2017) xxx–xxx

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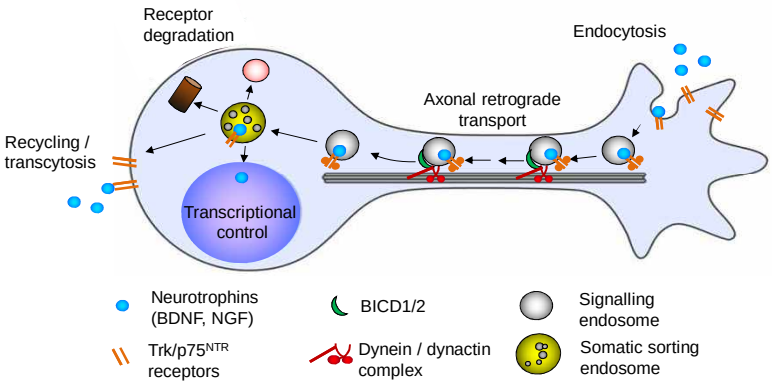

Mutations in *BICD2* Cause Dominant Congenital Spinal Muscular Atrophy and Hereditary Spastic Paraplegia

Oates E*, Rossor A* …… North K, Reilly M M
.

The American Journal of Human Genetics *92*, 1–9, June 6, 2013

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INHERITED NEUROPATHIES

1. Introduction
2. Barriers to therapy development
3. Classification of therapies
4. Emerging therapies

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ACKNOWLEDGEMENTS

Current team

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MRC Centre for Neuromuscular Diseases

International Centre for Genomic Medicine in Neuromuscular Diseases

NIH

MDA Muscular Dystrophy Association

cmt United Kingdom Together we are stronger

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