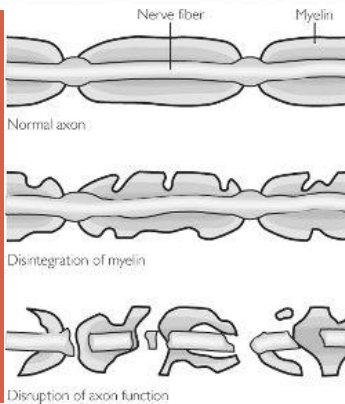


# Charcot-Marie-Tooth Disease Type 1A



JAMIE WU  
STUYVESANT HS  
SBS11QHG2 (PD 6)  
DR. M. NEDWIDEK  
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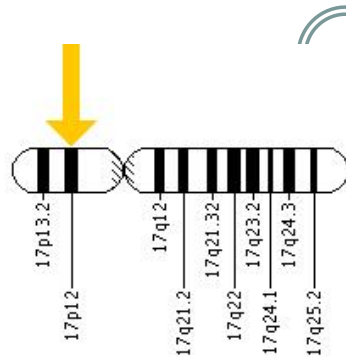
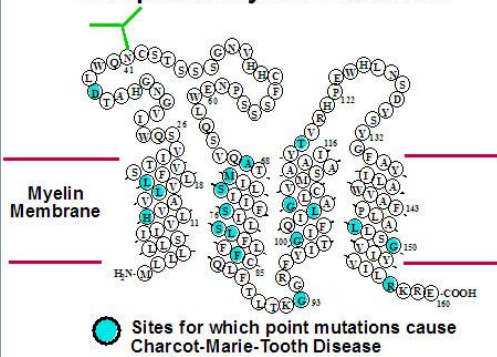
## Physiology



- Most common inherited neurological disorder (prevalence of 10 in 100,000 and is also most common type of all CMT disorders)
- Nearly full penetrance, but extreme clinical variability even within families
- Targets the peripheral nervous system—specifically causes demyelination in Schwann cells and hypertrophy (redundant wrapping of Schwann cells around axonal body); characteristic onion bulb formations around demyelinated or partially remyelinated axons
- Early onset (usually before 20 years)
- Patients become symptomatic around 5
- Distal muscle weakness and atrophy; hand and foot deformities like pes cavus; cramps, sensory loss, and tremors
- Individuals lose balance, but fewer than 5% are wheelchair bound and lifespan is not affected
- Lifespan is not affected

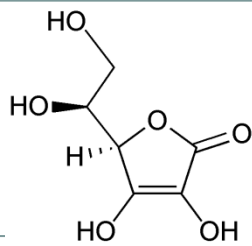
# Molecular Cause

Peripheral Myelin Protein 22



- Most commonly caused by a 1.5 Mb duplication of the peripheral myelin protein 22 (PMP22) at 17p11.2 due to unequal crossing over during meiosis
- Disease is autosomal dominant, children of affected parent have 50% chance of inheriting it
- PMP22 is a hydrophobic protein that is an important part of compact myelin; it regulates protein binding, myelin assembly, negative regulation of cell proliferation, negative regulation of neuron projection, peripheral nervous system development, and synaptic transmission
- PMP22 is processed and packaged in the ER and Golgi apparatus before becoming part of myelin sheath

- Overproduction of PMP22 prevents it from being processed correctly; unprocessed myelin disrupts Schwann cell activities and results in demyelination
- Demyelination results from misfolding of PMP22 protein caused by overexpression of PMP22 gene
- Misfolded proteins are usually refolded by molecular chaperones at ER, but if not possible they are transferred to the cytosol to be degraded by proteasomes in a process called ER-associated degradation (ERAD)
- Proteasome pathway only degrades monomeric misfolded proteins; when it is impaired or overwhelmed the misfolded proteins form toxic oligomers that inhibit proteasome function
- These misfolded and aggregated proteins are then degraded by the aggresome-autophagy pathway, another crucial system in maintaining protein control
- Accumulation of misfolded PMP22 proteins overwhelm these pathways, disrupting Schwann cell function and causing demyelination



# Treatment/Management



- Treatment focuses on symptomatic management
- Diagnosis includes EGM and NCV, but genetic testing is definitive way
- Orthoses (supportive devices) are used to cure deformities, but more severe cases may require orthopedic surgery
- Physical and occupational therapy (strength training, stretching, stamina training, aerobic exercise) is the preferred treatment
- Low-impact or no-impact exercises are recommended
- Caffeine, nicotine, neurotoxic drugs, and excessive alcohol exacerbate symptoms and should be avoided
- Limits: physical treatment programs are most useful if begun early, before muscle atrophy and nerve degeneration progress beyond help to the point of disability. There is no cure, so disease continues to progress clinically.
- Cures being studied: trophic/nerve growth factors that prevent nerve degeneration, promote nerve regeneration, and sensory improvement. Limited by poor delivery methods, short half-lives, and great variety of PNS nerves and trophic factors
- Progesterone antagonists, as progesterone have been shown to increase PMP22 gene expression. Onapristone reduced PMP22 mRNA levels and resulted in clinical and neuropathological improvements, but all current progesterone antagonists are too toxic to be used in human body
- Ascorbic acid induces myelination and reduced severity of neuropathy in transgenic mice, but 2 year trial showed no significant neuropathy improvements in humans

# Proposed Cure/Limits



- Focuses on the augmentation of the proteasome and aggresome-autophagy pathways
- Presence of oleuropein, main polyphenol of extra virgin olive oil, during aggregation of human amylin prevented its cytotoxicity. Electron microscopy images showed that oleuropein interferes with amylin aggregation, resulting in different molecular pathway that skips the formation of toxic aggregates. Cytoprotective and proteasome characteristics of oleuropein could be useful when applied to CMT1A
- An inhibitor molecule of Usp14, a deubiquinating enzyme that inhibits proteasome function by trimming the ubiquitin chain on the substrate, has caused enhanced degradation of several proteasome substrates in cultured cells. IU1, the inhibitor, accelerated the degradation of oxidized proteins and enhanced resistance to cytotoxic stress
- Chemical compounds B2 and B5 induce aggresome formation and reduce cytotoxicity resulting from misfolded proteins—compounds prevent proteasome dysfunction and have proven to lessen cellular pathology in Huntington's and Parkinson's disease
- Rapamycin (RM), an antibiotic, induces autophagy activation and promotes myelination in explant cultures from mouse models of CMT1A
- Limits: proposal is limited by the unknown nature of many of these compounds, as they are recently discovered and still under study. However, scientists are discovering many compounds that promote proteasome and aggresome-autophagy function, which could theoretically be used to treat CMT1A. My proposal is to test the efficacy and safeness of these compounds in treating CMT1A using transgenic mice that have a Pmp22 duplication (a model of the PMP22 gene in humans) and that express clinical features and manifestations of CMT1A. If tests are successful, then clinical trials with human could be attempted.

# References



## **Physiology Slide**

### Content:

Thompson, 7<sup>th</sup> Edition

<http://www.ncbi.nlm.nih.gov/books/NBK1205/>

<http://www.ncbi.nlm.nih.gov/books/NBK1205/>

### Images:

Demyelination: <http://medical-dictionary.thefreedictionary.com/demyelination>

Hand: <http://charcotmarietoothdisease.org/charcot-marie-tooth-disease-information/charcot-marie-tooth-disease-basic-guide/>

Foot: [http://en.wikipedia.org/wiki/File:Charcot-marie-tooth\\_foot.jpg](http://en.wikipedia.org/wiki/File:Charcot-marie-tooth_foot.jpg)

## **Molecular Cause**

### Content:

Thompson, 7<sup>th</sup> Edition

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291304/#R27>

<http://www.ncbi.nlm.nih.gov/books/NBK1205/>

### Images:

Chromosome: <http://ghr.nlm.nih.gov/gene/PMP22>

Protein: [http://structbio.vanderbilt.edu/sanders/Research\\_Julia\\_Ver\\_1/Research.html](http://structbio.vanderbilt.edu/sanders/Research_Julia_Ver_1/Research.html)

## **Proposal**

### Content:

<http://www.hindawi.com/journals/np/2012/171636/>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291304/#R27>

## **Treatment/Management**

### Content:

Thompson, 7<sup>th</sup> Edition

[http://www.ninds.nih.gov/disorders/charcot\\_marie\\_tooth/detail\\_charcot\\_marie\\_tooth.htm](http://www.ninds.nih.gov/disorders/charcot_marie_tooth/detail_charcot_marie_tooth.htm)

<http://www.hindawi.com/journals/np/2012/171636/>

### Images:

Orthoses: <http://lowerextremityreview.com/article/active-stance-orthoses-functional-relevance-of-the-arch>

Ascorbic Acid: [http://commons.wikimedia.org/wiki/File:Ascorbic\\_acid\\_structure.png](http://commons.wikimedia.org/wiki/File:Ascorbic_acid_structure.png)