# It's Not A Wrap! 4 Key Proteins Call Their Agents

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**Charcot-Marie-Tooth disease (CMT) is the most commonly inherited peripheral neuropathy disorder in humans with an incidence of about 1 in 2500. This disease involves slowly progressive atrophy and muscle weakness in the peripheral appendages. CMT affects many different types of people with varying age-of-onset and progression. There are a few different classes of CMT: CMT1, which entails demyelination and slow nerve conduction velocities (NCV's), and CMT2, which involves axonal atrophy and decreased NCV's and amplitudes. This review will focus on CMT1, which includes mutations in four different genes: PMP22, MPZ, Cx32, and EGR2. PMP22 and MPZ encode the myelin structure proteins, Cx32 encodes a gap junction protein involved in movement of molecules across the myelin sheath, and EGR2 encodes a transcription factor needed for myelin development. Current research has shown that mutations within these genes contribute significantly to symptoms seen in CMT1 patients. Understanding the mechanism behind these mutations may provide researchers with the knowledge to better comprehend the molecular basis of CMT1 in hopes of leading to an eventual cure to this debilitating disease.**

## Establishing the Groundwork

Charcot-Marie-Tooth disease (CMT) was simultaneously discovered in 1886 by three scientists: Jean Martin Charcot and Pierre Marie in France and Howard Henry Tooth in the UK. CMT is an autosomal dominant peripheral neuropathy disorder with multiple forms: CMT1, CMT2 and CMT4. CMT1, which is the primary focus of this paper, encompasses three subclasses: 1A, 1B, and 1X (X-linked). 1X is related to demyelination, which prevents successful nerve conduction signaling (<10 m/s) to the peripheral appendages as seen by the phenotypes expressed in CMT1 patients.[1] In contrast, CMT2 concerns the atrophy of axons. CMT4 involves a myotubularin related protein that is still undergoing research to pinpoint its exact molecular basis.

CMT1 is a well characterized disease in that scientists have identified and isolated four key proteins involved specifically in demyelination: PMP22, Cx32, MPZ, and EGR2. These proteins are essential to the study and understanding of CMT1.

## Stepping Out with CMT1

CMT1 exhibits a number of different symptoms affecting the peripheral appendages. Patients typically become aware of their symptoms within the first decade (within 10 years of life) in 50 percent of patients and within the first two decades (within 20 years of life) in 70 percent of patients. However, some patients did not have any noticeable symptoms until the seventh or eighth decade (within 70 to 80 years) of life.[2] Symptoms vary from mild to severe and manifest themselves in a variety of different forms such as bone deformities (hammer toes), foot drop, high arches, claw hands, and loss of balance.[3] The most evident clinical sign of CMT1 patients is muscular impairment. Many patients also experience vibration sensations in their feet and hands, as well as a decrease in large myelinated fibers.[1,18]

| Disease Type | Inheritance Pattern | Genetic Mapping | Related Gene | Pathology |
|---|---|---|---|---|
| | | | | |
| CMT1A | Autosomal dominant | 17p11.2-p12 | PMP22 | slowed NCVs; onion bulbs form |
| | Autosomal dominant | 10q21-q22 | EGR2 | slowed NCVs; onion bulbs form |
| | | | | |
| CMT1B | Autosomal dominant | 1q22-q23 | MPZ | slowed NCVs; onion bulbs form |
| | | | | |
| CMT1X | X-linked | Xq13.1 | Cx32 | slowed NCVs; onion bulbs form |

Legend:

CMT= Charcot-Marie-Tooth
PMP22= Peripheral Myelin Protein
MPZ= Myelin Protein Zero
Cx32= Connexin 32
ERG2= Early Growth Response 2
NCV= Nerve Conduction Velocity

**Figure 1: Summary Table of CMT1.** This table is an overview of CMT1, which specifically pinpoints the biological basis characterizing the disease. The most frequent inheritance pattern seen in type1 is autosomal dominance. The major pathologies seen in each subtype are all uniform, which leads one to believe that the proteins involved are closely related to one another.

## Epidemiology

Approximately 80 percent of CMT patients express the demyelinating form known as Type 1.[4] The onset of CMT1 typically occurs in late childhood or adolescence and progresses in severity throughout adulthood.[5] Patients usually have a normal lifespan. Male and female patients are affected according to the inheritance patterns of each type of disease. For example, CMT1X (X-linked), which involves the mutated Connexin 32 gene, tends to affect men more severely than women. This is due to the fact that men inherit only one X chromosome and therefore express only one X chromosome guaranteeing its expression.[6]

## Stepping Out in Comfort

Successful diagnosis of CMT1 is the first step on the road to relief. Although there are no cures for this disease quite yet, scientists are constantly in pursuit of this goal. Therapeutic strategies have been devised to provide patients with temporary aid for their ailments. Treatments come in a variety of forms, most notably through orthopedics, surgery, physical and occupational therapy, and medication such as non-steroidal anti-inflammatory drugs and analgesics for temporary relief of minor to moderate pain.[3] Genetic testing is also available to families who express or are positive for the CMT allele in order to identify the potential of inheritance in one's offspring.[3]

Future therapies include genetic alterations of the affected gene(s), gene-replacement therapy, antisense and antigene technologies, immune-modulating therapy through the elimination of cells in the immune system, and the use of adenovirus injections.[3,4]

While many of these techniques may hold the key to a possible cure, they also pose a very legitimate threat in the form of severe side effects. None of the aforementioned therapies are currently being utilized in humans. Much more information is needed in order to perform them successfully. Uncertainty about proper dosages, accessibility of peripheral nerves, toxic effects such as those that occur in immune-modulating technique, are all considerations that have prevented comprehensive usage of these therapies to date.[4]

## Seeking the Hot Spot

CMT1 is characterized by demyelination of the myelin sheath in the peripheral nerves. Subcategories of CMT1 that will be discussed in this review include 1A, 1B, and 1X. CMT1A is associated both with a duplication of a locus in chromosome 17p11.2-p12, which contains the myelin gene PMP22, and also with a point mutation in this gene.[7] Additionally, EGR2, which is a zinc-finger protein located on chromosome 1q22-q23, is included in this subcategory as well.[8] CMT1B includes a mutation in the myelin protein zero (MPZ), which is the structural protein of the myelin sheath. CMT1X is associated with the

**Figure 2: Biological Model of 3 Key Proteins Associated with CMT1 located on a Neuron.** Three peripheral proteins involved in CMT1 are connexin 32 (Cx32), which is the X-linked form, myelin protein zero (MPZ), involved in CMT1B, and peripheral myelin protein 22 (PMP22), involved in CMT1A. Cx32 is a gap junction protein that sits in between the schwann cell membranes and allows for passage of small molecules. MPZ is located on the myelin sheath and it serves as a glue for the sheath. PMP22 is also located in the myelin sheath and aids in the structural formation of it. In conclusion, a myelin sheath is constructed of schwann cell membranes that wrap around the axon of a neuron and serve to protect and aid in the transfer of signals throughout the peripheral nervous system.

mutated gene, Connexin 32 (Cx32), which functions as a gap junction protein.[2] It is located at chromosome Xq13-22.[2]

The main pathological similarity between the four proteins is seen by degradation of the myelin sheath, resulting in severely reduced nerve conduction velocities and the presence of onion bulb formations, which result in incorrectly organized Schwann cell membrane processes.[9]

**Pinpointing PMP22**

A major step in unraveling the genetic basis of CMT1 was identifying the duplication of chromosome 17.[10] PMP22 is a dosage-sensitive gene that had previously emerged as an attractive candidate for causing CMT1 because it is expressed in Schwann cells and was earlier mapped to chromosome 17p11.2-p12.[10] PMP22 is a glycoprotein that comprises an estimated 2-5 percent of the total myelin protein.[11] Being a small, but functionally significant protein, PMP22 is largely confined to the compact myelin.[11] Structurally, PMP22 is predicted to be an integral membrane protein with four putative membrane-spanning domains (see figure 2).[11] Additionally, the expression of PMP22 is controlled by Schwann cells.[11]

Until recently, the biological model of PMP22 was relatively vague. It was known that CMT1A was associated with a duplication of chromosome 17, or a point mutation of the PMP22 locus.[11,12] It had been hypothesized by Sereda *et al.* that CMT1A is caused by increased expression of the gene for PMP22.[10] Furthermore, Adlkofer *et al.* hypothesized that PMP22 is required for the correct development of peripheral nerves.[11]

Researchers knew that the PMP22 locus was duplicated, but it was the research by Sereda *et al.* that provided the experimental evidence that one cause of CMT1A is increased expression of the gene for PMP22.[10] Sereda *et al.* used transgenic rats to test the genetic, behavioral, morphological, and electrophysiological criteria that PMP22 overexpressing rats develop a peripheral neuropathy that closely mimics CMT1A.[10] One of the results of the transgenic rat model showed that $PMP22^{+/+}$ rats have a normal gait, while the $PMP22^{+/-}$ rats develop an unsteady gait and show signs of muscle weakness.[10] In the same study, they also observed severely reduced NCVs in the $PMP22^{+/-}$ rats, which is a hallmark of CMT1.[10] Based on these results, the researchers used RT-PCR to quantitative PMP22 overexpression in the $PMP22^{+/-}$ rats.[10] It was noticed that the degree of overexpression correlated with the

severity of the visual phenotype. $PMP22^{+/-}$ rats with the lowest PMP22 mRNA levels were not visibly affected, whereas the $PMP22^{+/-}$ rats with the highest PMP22 mRNA levels failed to sustain their body weight when attempting to move. [10]

Based on the results of the transgenic rat model, the researchers were able to link human CMT1A with the overexpression of the PMP22 gene located with the duplicated region of 17p11.2.[10]

The second landmark study, executed by Adlkofer *et al.,* showed that PMP22 is required for correct development of peripheral nerves, the maintenance of axons and the determination of myelin thickness and stability. [11] The research team used gene-targeting techniques in embryonic stem cells to inactivate the PMP22 gene in mice. One result of their study, using light and electron microscopy, showed that $PMP22^{-/-}$ mice have myelin and axon abnormalities, such as prominent myelin thickening, redundant myelin loops, axon compression, and the formation of onion bulbs. [11] The researchers observed pathology in the $PMP22^{+/-}$ mice remarkably similar to that of CMT1 patients. [11] This study pinpointed the exact function of PMP22 through their results.

The two studies of PMP22, explained above, show that the phenotype observed in CMT1A patients can be caused by either an overexpression of PMP22 or the lack of expressed PMP22.

**Zeroing in on MPZ**

Myelin Protein Zero (MPZ) is the structural protein of the myelin sheath that accounts for >50 percent of the total peripheral nervous system myelin protein.[3] Through observations and experimental procedures, it is known that MPZ is involved in cell-cell interactions and may initiate adhesion of membrane surfaces.[1] MPZ has been mapped to chromosome 1q22-q23, in the region of the locus for CMT1B.[2]

Analyses of MPZ knockout mice and mice null for MPZ and myelin protein performed by Martini *et al.* hypothesized that MPZ plays a critical role in the structure and function of the peripheral nerve myelin.[13] $MPZ^{-/-}$ mice demonstrated abnormal, poorly compacted myelin within four days of birth as opposed to $MPZ^{+/-}$ mice, which displayed normal myelination of Schwann cells. [13] However, demyelination and onion bulb formations were present at four months of age and became more apparent at one year. [13] The nature and position of the MPZ mutation could explain the loss-of-function even if only one of the alleles carries the mutation and some normal protein is produced.[13] These differences in phenotypes show that there are some variants to the disease when compared.[13]

In summary, MPZ mutations are a common cause of demyelination as seen in CMT1B patients as well as the knockout mice. These observations led the scientists to conclude that MPZ does indeed play a critical role in the structure and function of the myelin sheath. [13]

**Growing up with EGR2**

The early growth response two gene (EGR2) is a zinc-finger protein that plays a role in the regulation of cellular proliferation and differentiation.[14] This protein is critical for peripheral nerve myelination in the fact that it encodes for myelin proteins and enzymes required for synthesis of normal myelin lipids.[15] EGR2 has been mapped to chromosome 10q21q22 and contains two coding axons. Recessive and dominant missense mutations have been recognized in EGR2 associated with myelinopathy phenotypes, including CMT1.[3]

In order to pinpoint the involvement EGR2 has in myelin formation, Warner *et al.* hypothesized that EGR2 may be a transcription factor affecting late myelin genes and that human myelinopathies of the peripheral nervous system may result from mutations in EGR2.[14] In order to prove their hypothesis correct, they performed a knockout mice experiment that was directly related to EGR2. $EGR2^{-/-}$ mice displayed hypomyelination of the peripheral nervous system and Schwann cells were blocked at an early stage of differentiation (with expression of late myelin genes decreased or absent).[14] These observations suggest that EGR2 may control myelination in the peripheral nervous system. The fact that CMT1 is associated with mutations in the same gene further supported their contention that this disorder represents a spectrum of related clinical findings due to an underlying defect in myelination. [14]

Researchers Nagarajan *et al* performed a subsequent study that included mutant EGR2 genes as well. They had hypothesized that ERG2 mutants dominant-negatively inhibit wild-type EGR2 expression of essential myelin genes to levels of sufficiently low to result in the abnormal myelination observed through knockout mice experiments.[15]

What they found through observations of the EGR2$^{-/-}$ mice was that they displayed disrupted hindbrain segmentation and development and a block of Schwann cell differentiation at an early stage. [15] Because EGR2 heterozygous mice are phenotypically normal, it was surprising that the disease followed a dominant mode of inheritance in families with neuropathy caused by EGR2 DNA binding domain mutations.[15] Taken together, mutations in EGR2 do not generate simple loss-of-function alleles, but that these mutant alleles behave dominantly to disrupt wild-type EGR2 function. [15]

In conclusion, the scientists demonstrated that EGR2 coordinates the peripheral nerve myelination program by inducing genes encoding myelin proteins and enzymes required for myelin lipid assembly.[15] Furthermore, they revealed that DNA binding domain ERG2 mutants cause myelinopathy by dominantly inhibiting wild-type EGR2 induction of newly identified target genes.[15]

**X-tra Important Information on CMT1X**

Further study of the genotypes of CMT led scientists to identify another form of the disease: X-linked CMT. The occurrence of X-linked CMT is 3.1 per 100,000, or 10 percent of all CMT patients.[6] The X-linked form is located on the X chromosome and predominantly affects men because they inherit only one X chromosome and therefore it is expressed. While men are the more severely affected, females also suffer from the disease, and this discovery suggests that if dominance is defined by the expression of the disease in the majority of its carriers, CMT1X is a dominant disease. [6]

X-linked was mapped to chromosome Xq13.1 and upon further research, scientists were able to identify that a gap junction protein called Cx32 was also located on that chromosome.[16] Cx32 was first cloned in 1986. [16] In the early 1990's, only twelve Connexin genes had been identified. By the year 2000, fifteen have already been successfully identified and cloned. [16] Connexin is found in myelinating Schwann cells, and this knowledge, in conjunction with the knowledge that CMT1 is related to demyelination, prompted further research into Connexin.[5]

**Connexin32 Connection**

Cx32 is part of the Connexin family, which is a group of membrane proteins that form gap junction channels between cells.[17] These channels operate in the Schwann cells as a sort of bridge, in order to dramatically reduce the diffusion difference between the Schwann cell nucleus and the cytoplasm.[5]

Cx32 is comprised of six hemichannels, which together are called a connexon. The union of two connexons creates a channel through which ions and other molecules can be transported in and out of the cell allowing for intercellular communication and signaling.[17] Research has revealed that connexons are integral to the creation of signals through electronic coupling between neurons and gilial cells.[17] Cx32 is structurally composed of two extracellular loops, four transmembrane segments and three cytoplasmic domains (See Figure 2).[16]

Mutations in Cx32 have been found to cause CMT1X. Over 200 mutations have been identified for the connexin gene and the most common of them is the missense mutation. Frame shift microinsertions, amino acid deletions, and nonsense mutations have also been identified in relation to the disease, but at smaller rates of occurrence.[3] All of the mutations are believed to affect the entire portion of the protein rather than a section, and are believed to prevent the gap junctions from functioning properly, if at all.[17]

Armed with the knowledge of what role gap junction proteins play in the cell, researchers hypothesized that mutations to Cx32 would likely lead to decreased functionality of the hemichannels as well as difficulties in the Schwann cell's ability to maintain the spatial buffering of potassium that is necessary to prevent an equilibrium with sodium.[17]

**Traffic Jam!**

In 1997, a research group at the University of Pennsylvania Medical Center decided to study the cellular localization of nine different Cx32 mutants in mammalian cells in order to see if the mutations had any relation to the trafficking of the protein.[18] Through the use of immunocytochemical localization of Cx32, Deschenes *et. al* was able to identify three different ways that the mutations affect trafficking, which he categorized in three classes.[18]

The first class is defined by the mutant 175fs, which is a frame shift mutation that cuts Cx32 by 43 amino acids, therefore altering the last 67 residues and the fourth transmembrane domain.[18] This mutation resulted in a complete loss of Cx32 expression—no protein was

detected in the wild-type sample, leading researchers to believe that this particular mutation plays a role in translation or produces a degradation of Cx32.[18]

The second class is defined by a number of mutations such as R15Q and V139M which allow a small amount of the protein to be transported to the plasma membrane, but still impaired the myelination process leading them to believe that this mutation either affects the formation of gap junctions or causes the protein itself to be misrouted.[18] Additional dye-coupling and electrophysiological studies must be preformed to determine which of these options is correct.

The third class of mutations is characterized by trafficking problems that result in an accumulation of Cx32 in intracellular compartments and prevent expression in the membrane, where they should normally be located.[18] Deschenes *et. al* discovered accumulations in the cytoplasm, endoplasmic reticulum (ER), and in the golgi apparatus in the form of plaques, leading them to believe that trafficking is definitely affected by such mutations.[18] While they were able to discover that trafficking was affected, questions still remained as to whether it was conformational changes or monomer problems with the formation of the hemichannels that were at the root of the problem.[18]

**Open Wide!**

A second study performed in 2002 by Abrams *et. al* delved a little more deeply into the implications of mutations in Cx32 in their research on the affects of voltage on hemichannels.[5] Hemichannels are voltage sensitive and have the potential to open and close in response to their environment. Abrams *et. al* suspected that hemichannels of the cell remain closed to prevent stress and death that would otherwise be caused by the collapse of ionic gradients and the influx of $Ca^{2+}$ if the channels remained open.[5] This loss of control can affect cell-signaling capabilities. This idea was further elucidated by Seunghoon *et.al.* This research group proposed that the Cx32 mutation is involved in the impairment of transduction of signals arising from normal glial-neuronal interactions, resulting in demyelination through analysis of cell permeability.[19]

With the knowledge that the channels open as the cell is excited, Abrams *et. al.* sought to measure how easily the channels opened and how excited they needed to be to do so. Their study revealed that less change in voltage is needed to open the channels when the mutation is present. Additionally, when the mutations present, the hemichannels are less sensitive to voltage than the unaffected channels.[18] They also found that oocytes with the mutant had increased conductance at inside positive potentials in comparison to the wild-types, and they also learned that hemichannels in the surface membrane of the mutant type have higher open probability than the wild-type.[18] Their results led them to hypothesize that an increase in open hemi-channels could be detrimental to the Schwann cells causing loss of function in peripheral nerves of people with the mutation.[18]

More research must be done on Connexin32 to fully understand its role in CMT1X, but researchers have come a great distance thus far, and the more knowledge that can be accumulated about Cx32, the more researchers will be able to devise different therapies to potentially treat CMT1X sufferers.

**What's New in 2002?**

Based on the research in the last several years, researchers have been able to render a new biological model. In contrast the past decade when these four mutant proteins were only understood at a very basic level, today, we are able to understand these proteins on more complex levels in terms of their molecular function and mutational behavior.

From this new model many new hypotheses have been generated. For each protein, the exact cause of the mutation and its exact interaction with the demyelination of the myelin sheath is unknown. In the past, information about myelin structure and composition was limited to a few techniques such as electron microscopy studies.[20] Currently, molecular biology techniques and genetic analysis of myelin genes have been developed providing some clues about the biological basis of the myelin sheath.[20] But the big question still remains as to how the myelin sheath is formed and held together. Future experiments will obviously be performed to attempt to elucidate this particular question.[20] Future hypotheses are: What causes the mutations, how are the proteins mutated, how can different types of mutations produce the same problems and how could scientists potentially repair these mutations on the molecular level. As mentioned previously, new therapeutic techniques such as genetic alterations of the affected gene(s), gene-replacement

therapy, antisense and antigene technologies are currently being explored and new knowledge about the affected proteins will undoubtedly aid in the development of these therapies. [3,4]

## Wrapping Up!

With each scientific discovery, new facets of CMT1 are being illuminated. Current research is being done to understand the molecular basis of the mutated proteins and once this has been discovered, more effective treatments can be created for patients. As we progress further and further into the future, technological advancements are greatly improved leading to hopes of a speedy cure so patients won't have to be all wrapped up in this debilitating disease.


## Acknowledgements

*We would like to thank Dr. D. for his assistance in the comprehension of our disease topic. We also extend our gratitude to Jen McGuire and Svetla Stamenova for their generous time and help in the completion of our paper. Lastly, we would like to thank Finch Medical School Library for their abundant supply of journal sources.*


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