

A light blue map of North America, including the United States, Canada, and Alaska, with state and provincial boundaries outlined. The text is overlaid on the map.

**2nd Symposium
of the
North American
CMT Consortium**

May 19, 20 & 21, 2005

S P O N S O R E D B Y



CHARCOT-MARIE-TOOTH ASSOCIATION

Friday May 20

Session 1: Chair; Larry Wrabetz, Brian Popko

9:00 – 9:10: Welcome: Charles Hagins CMTA

9:10-10:00: Ann Lee Beyer Plenary Lecture: Gain of abnormal function and phenotypic diversity in MPZ related neuropathies: Lawrence Wrabetz, Milan Italy

10:20-10:40: Assessment of Myelin structure in Transgenic Mouse Models of Dysmyelinating Disease: Robin L. Avila, Boston Mass

10:40-11:00: Two Distinctive Pathologies between early and late onset of CMT1B, Jun Li, Detroit MI

11:00-11:20: ER retention and aggregation induced apoptosis associated with neuropathy causing MPZ truncating mutants are abrogated by curcumin treatment, Mehrdad Khajavi, Houston, Texas

11:20-11:40: Forward Genetic Approach to Neuromuscular Abnormalities, Brian Popko, Chicago, IL

11:40-12:00: Characterization of the neuromuscular mouse mutant sprawling (Swl), Xing-Jun Chen, Chicago, IL

Session 2: Chairs: Charles Abrams, Angelika Hahn

2:00 -2:20: Genotype-Phenotype Correlations in CMTX1, Angelika Hahn, London Ontario

2:20-2:40: Connexins in Schwann cells: electrophysiologic characteristics of gap junctional coupling, Charles Abrams, New York, New York

2:40 – 3:00 Connexin-32 mutants lacking a prenylation motif are not prenylated but traffic normally in myelinating Schwann cells, Steve Scherer, Philadelphia Pa

3:00 – 3:20 Motor Unit Number Estimate of Distal and Proximal Muscles in CMT-X Accentuated Motor Unit Loss in Distal Hand Muscles, Tim Doherty, London Ontario

3:20 – 3:40 Electrophysiological Criteria Defining Charcot Marie Tooth Disease with Intermediate Nerve Conduction Velocities, Agnes Jani-Acsah, Detroit MI

Saturday, May 21

Session 3: Chairs: Vincent Timmerman, Garth Nicholson

9:00 – 9:20: Mutations in Mitofusin 2 are a major cause for autosomal dominant axonal Charcot Marie tooth Neuropathy, Vincent Timmerman, Antwerp Belgium

9:20 – 9:40: Clinical and electrophysiologic features of CMT2A with mutations in the Mitofusin 2 gene, Victoria Lawson, Salt Lake City, Utah

9:40–10:00: Mutations in the pleckstrin homology domain of dynamin 2 cause dominant intermediate Charcot Marie Tooth disease, Jeff Vance, Durham North Carolina

10:00 –10:20: Expression and intracellular localization of mutant K558E dynamin 2 in EBV transformed DI-CMTB patient B-lymphocytes, Marina Kennerson, Sydney, Australia

10:20–10:40: Mutations in the SPTLC1 protein, causing hereditary sensory neuropathy type 1, show altered localization of cytoskeletal proteins in transiently transfected SH-SY5Y neuroblastoma cells, Garth Nicholson, Sydney, Australia

Session 4: Chairs, Jun Li, Steve Scherer

11:20 –11:40: T118M Mutation In The Peripheral Myelin Protein (PMP22) gene cause partial loss of function neuropathies, Mena Scavina, Wilmington Delaware

11:40-12:00: Skin biopsies in myelin related neuropathies: bringing molecular pathology to the bedside, Jun Li, Detroit MI

12:00 –12:20: EGR2 mutations, a natural history study of 10 patients and functional analysis of neuropathy associated alleles, Wojciech Wisniewski, Houston, Texas

Session 5: Tim Doherty, Victoria Lawson

2:30 – 2:50: CMT Neuropathy score identifies two year progression in CMT1A patients, Richard Lewis, Detroit MI

2:50- 3:10: CMT and resistance training: advancements in exercise prescription, Robert Chetlin, Morgantown, W. Va

3:10 – 3:30: The prevalence of Charcot Marie Tooth Disease in the childhood population with bilateral cavovarus feet, M.K Nagai, Wilmington, Delaware

3:30 – 3:50: The lateral coleman block view assessing the correctability of the hindfoot deformity in Charcot Marie Tooth Disease, M.K. Nagai, Wilmington Delaware

Gain of abnormal function and phenotypic diversity in *MPZ*-related neuropathies

Lawrence Wrabetz

San Raffaele Scientific Institute, DIBIT, Milan, Italy

P0 is the most abundant glycoprotein of peripheral myelin. In human, diverse *MPZ* mutations result in various neuropathies, ranging from mild Charcot-Marie-Tooth (CMT) disease type 1B to the more severe forms Dejerine-Sottas syndrome (DSS) and Congenital Hypomyelination (CH). The dominant inheritance and widely varying phenotypes of *MPZ* mutations suggests gain of function mechanisms. We have provided genetic proof of principle for this idea by producing a series of transgenic mouse models of various *MPZ*-related neuropathies. Comparison of mouse models expressing either of two P0S63 mutants reveals diverse mechanisms. Deletion (S63del) or conversion of serine 63 to cysteine (S63C) in the extracellular domain results in CMT1B or DSS, respectively. Transgenic mouse models that express these mutant P0s manifest a phenotype similar to the human counterpart. However, intracellular trafficking differs among mutants. P0S63C is mostly trafficked to myelin, where it induces a packing defect, whereas P0S63del is retained intracellularly in the endoplasmic reticulum (ER), where it triggers an unfolded protein response (UPR). This indicates that the diversity of *MPZ*-related neuropathies results from various toxic gain of function mechanisms deriving from various intracellular locations.

**Assessment of Myelin Structure in Transgenic Mouse Models of Demyelinating
Disease**

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Laura Feltri³, Lawrence Wrabetz³, and Daniel A. Kirschner^{1*}

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P0 and PLP are the major structural protein of peripheral (PNS) and central (CNS) nerve myelin, respectively. EM shows that there are often changes in myelin period with packing defects in humans and mice having mutations in the genes. We have used X-ray diffraction to investigate myelin structure in sciatic and optic nerves from mice with disruption of one or both copies of the P0 gene, from mice that express P0 instead of PLP in CNS myelin, and from a mouse with a Charcot-Marie-Tooth-like neuropathy. To link our findings on unfixed nerves to EM results, we analyzed x-ray patterns from unembedded, aldehyde-fixed nerves. From the x-ray measurements, we developed novel parameters for assessing, in whole nerves, the amount of myelin and its quality (i.e., relative thickness and regularity). We found that unfixed whole nerves and, to a lesser extent, fixed but unembedded nerves, gave diffraction patterns of sufficient quality to distinguish periods, sometimes differing by a few angstroms (Å). Our findings demonstrate that x-ray diffraction can provide quantitation at a molecular level of the membrane packing defects that occur in internodal myelin in demyelinating peripheral neuropathies.

Two Distinctive Pathologies between Early- and Late- Onset of CMT1B

Bai YH, Qin P, Ghandour K, Ianokova E, Hatfield J, Kupsky WJ, Martin J, Ceuterick-de Groote C, Mazanec R, Seeman P, Shy ME, Li J. Detroit, USA.

Objective: To investigate the pathological differences between early- and late- onset neuropathies of patients with MPZ mutations.

Background: Myelin protein zero (MPZ) is the major myelin protein expressed by Schwann cells (SC). Mutations in the MPZ gene cause Charcot-Marie-Tooth disease (CMT) with two distinctive phenotypes; early- and late-onset (Shy et al 2004). We have recently demonstrated that a late-onset H10P MPZ mutation cause axonal damage with minimal physiological features of demyelination in an autopsy study (Li, et al 2004). In the present study, we investigate whether nerve pathology is distinctive between the early- and late-onset phenotypes.

Design/Method: Nerves from an additional autopsy with a late-onset MPZ mutation of T95M was studied. Sural nerve biopsy from an early onset MPZ mutation of R69C was also examined and compared with the nerves from the two late-onset patients. Peripheral nerves were studied with routine histology, immunohistochemistry, electron microscopy (EM), and immunoEM.

Results: Sciatic nerves from the late-onset MPZ mutation of T95M show pathology similar to those in H10P, including prominent axonal loss without demyelination and periaxonal accumulation of abnormal materials. There is no macrophage infiltration in the nerves of these late-onset mutations. In contrast, segmental demyelination and numerous 'onion bulbs' are conspicuous in the sural nerve from the patient with an early-onset MPZ mutation of R69C although axonal loss of the large diameter nerve fibers is severe (no fibers > 7 μ m). Macrophages are found in the areas of segmental demyelination in a few nerve fibers (<1%). Teased fiber immunohistochemistry shows voltage-gated sodium channel subtype 1.8 (Nav1.8) expressed at the nodes of Ranvier around the areas of segmental demyelination. Some of Nav1.8 form hemi-nodes reminiscent to the expression pattern of Nav1.2 during the development of myelination. Interestingly, the other group of nerve fibers has minimal or no segmental demyelination, but internodes are uniformly short. These fibers have no Nav1.8 expression at the nodes.

Conclusions: Our study demonstrates that pathological changes are distinctive between the early- and late- onset neuropathies of MPZ mutations, suggesting different pathological mechanisms involving the ultimate axonal loss in the two phenotypes. The uniform short internodes and absence of Nav1.8 in a portion of nerve fibers of the early-onset mutation are inconsistent with a segmental demyelination process; thus, may imply a possible developmental defect of myelination.

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ER retention and aggregation induced apoptosis associated with neuropathy
causing MPZ truncating mutants are abrogated by curcumin treatment

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Mutations in *MPZ*, encoding myelin protein zero the major protein constituent of peripheral myelin, can cause the adult onset inherited neuropathy Charcot-Marie-Tooth (CMT) disease as well as a more severe childhood onset Dejerine-Sottas Neuropathy (DSN) and congenital hypomyelinating neuropathy (CHN). Most *MPZ* truncating mutations associated with severe forms of peripheral neuropathy result in premature termination codons (PTCs) within the terminal or penultimate exons that are not subject to nonsense mediated decay (NMD) and are stably translated into mutant proteins with a potential dominant-negative activity. However, some truncating mutations at the 3' end of *MPZ* escape the NMD pathway and yet cause a mild peripheral neuropathy phenotype. We examined the functional properties of *MPZ* truncating proteins that escaped NMD and found that frameshift mutations associated with severe disease cause intracellular accumulation of mutant proteins, primarily within the endoplasmic reticulum (ER), that induces apoptosis. Curcumin, a chemical compound derived from the curry spice tumeric, releases the ER-retained *MPZ* mutants to the cytoplasm and is accompanied by a lower number of apoptotic cells. Our findings suggest that curcumin treatment is sufficient to relieve the toxic effect of mutant aggregation induced apoptosis and may potentially have a therapeutic role in selected forms of inherited peripheral neuropathies.

Forward Genetic Approach To Neuromuscular Abnormalities.

Brian Popko, Jack Miller Center for Peripheral Neuropathy, Department of Neurology,
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Mutant mouse strains have been particularly useful in identifying the in vivo functions of proteins, as well as in establishing authentic models of human disease. Efforts over the past 15 years or so have resulted in the establishment of hundreds of new strains of mice with mutations in predetermined genes using reverse genetics approaches. More recently, as the DNA sequence of the mouse and human genomes has become known, efforts to identify causative genes in forward genetic screens have been greatly facilitated. These phenotypic driven screens allow for the selection of specific traits of particular biological interest. In this way, genes are identified that, by definition, play a critical role in the precise pathway of interest. We are taking such a forward genetics approach to identify and characterize mouse mutants that display evidence of neuromuscular abnormalities. These mice are being examined using an array of phenotypic screens, including behavioral, physiological, histological and molecular, that are designed to define the cellular origin of the abnormality. Moreover, comprehensive genetic screens are being exploited to identify the underlying molecular cause of the disorder. As an example of our approach, I will focus my presentation on the enervated strain of mice, which originated as a transgene-induced insertional mutation. These mice display Schwann cell-axon interaction abnormalities, neuromuscular junction irregularities, and muscle defects. We have recently identified the disrupted locus in these mice as the gene that encodes the LARGE glycosyltransferase.

Characterization of the neuromuscular mouse mutant sprawling (*Swl*)

Xiang-jun Chen and Brian Popko.

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The sprawling (*Swl*) mutant mouse arose as a radiation-induced autosomal dominant mutation on the C3H/101 hybrid mouse strain (Duchen, 1975. *Neuropath Applied Neurobiol.* 1: 89-101). These mice display an early onset sensory neuropathy. The main clinical features of *Swl* mice, detectable on the 7th to 10th day after birth, include an abnormal resting posture with the hind limbs splayed out or held stiffly in extension, a wobbly gait, and inability to grip structures by their hind paws. Heterozygous mutants have a normal life span. Nevertheless, homozygous animals die between E7.5 and E8.5, indicating that *Swl* has a late implantation or early gastrulation defect. The pathological features of heterozygous mutants include a severe reduction in the number of sensory ganglia and myelinated nerves fibers in the PNS, and an almost complete absence of muscle spindles in hindquarter muscles (Duchen and Scaravilli, 1977. *J Anat.* 123: 763-75). Electrophysiologically, these mice have normal motor function but do not show evidence of an H-reflex, which indicates that the sensory pathway, rather than the motor pathway, is compromised. Thus, the *Swl* mouse may offer an excellent animal model for human hereditary sensory neuropathies. By linkage mapping, we have determined that the *Swl* locus resides on the distal end of mouse chromosome 12, a region syntenic to human 14q32 and rat 6q32. There are 82 known genes and ESTs found in the 4.6 Mb critical region. We are currently using a variety of approaches to identify the gene responsible for the *Swl* phenotype.

GENOTYPE-PHENOTYPE CORRELATIONS IN CMTX1

Angelika Hahn, Carly Siskind, Karen Krajewski, Richard A Lewis, Michael E Shy

The X-linked form of Charcot-Marie-Tooth disease (CMTX1) is caused by mutations in the Gap Junction Beta 1 (*GJB1*) gene encoding the connexin 32 (Cx32) protein. Over 250 different mutations in *GJB1* have been identified, which affect all portions of the Cx32 protein. CMTX1 patients often have prominent axonal loss and less slowing of conduction velocities than do other forms of CMT1. Taken together, these data suggest that the different *GJB1* mutations produce a spectrum of disease severity by a common pathological mechanism - axonal degeneration. The clinical phenotype and disease progression are thought to differ between CMTX kindreds, suggesting that different mutations may cause more severe neuropathy. To address this possibility, we used the CMT Neuropathy Score (CMTNS) (Shy et al. In Press) to perform phenotype-genotype correlations on 68 male patients with 25 distinct mutations from all intracellular, extracellular and transmembrane domains of Cx32. The mean score for all patients was 14.5 (SD=7.3) with a range from 1 to 30. (Patients with mild, moderate and severe neuropathies have CMTNS of <10, 11-20 and 21-30 respectively.) Mean scores increased with each decade of life (3, 9, 10, 18, 20, 19.5, 26). To determine the onset and progression of neuropathy in individual patients, we then devised and evaluated patients with a CMT Symptom Score (CMTSS). In all patients scores increased with age. Two patients with *GJB1* deletions had similar CMTNS and CMTSS to other patients of similar age. Scores did not differ between mutations with the exception of Lys187glu, and Glu208lys in which CMTSS peaked in the fourth rather than the sixth decade. Taken together, these results suggest disability in men with CMTX1 depends more on age than mutation, and that different CMTX1 mutations do NOT produce a spectrum of disease. Rather, virtually all mutations result in a "loss" of Cx32 function since they do not differ from mutations that delete the Cx32 gene.

Connexins in Schwann cells: electrophysiologic characteristics of gap junctional coupling. C. K. Abrams, M. M. Freidin, V. K. Verselis, T. A. Bargiello, M. V. L. Bennett. Albert Einstein College of Medicine, Bronx NY, 10461

Several connexins (gap junction forming proteins) are reportedly expressed in peripheral nerve and Schwann cells (SC's); these include connexin 29 (Cx29, Cx32, Cx43 and Cx45). Mutations in Cx32 lead to the X-linked form of Charcot-Marie-Tooth disease, a group of inherited peripheral neuropathies. Here we report on our continuing investigations of the patterns of electrical coupling between proliferating neonatal SC's in primary culture. In defined medium, junctional conductance (g_j) between control isolated SC pairs averaged 47 ± 16 pS ($n=25$). Treatment with Glial Growth Factor 2 (GGF2) for four to six hours increased mean g_j to 245 ± 39 pS ($n=9$, $p < 0.01$ compared with control). After 24 hours of treatment with GGF2, g_j increased to 405 ± 98 pS ($n=25$, $p < 0.001$ compared with control). Interestingly, the average conductance of cell pairs treated with a combination of GGF2 and forskolin for 24 hours was 231 ± 75 pS ($n=10$, $p < 0.05$ compared to control). Coupling between cells treated with GGF2+forskolin and GGF2 alone were not statistically significantly different. In most cell pairs, g_j was decreased by transjunctional voltage (V_j) of either polarity. The deduced G_j - V_j relation was steep and symmetric around $V_j = 0$, with a predominant unitary conductance of 35-40 pS. These characteristics are similar to those of junctions formed by Cx45. Some records contained smaller (~ 20 pS) and larger (~ 50 to 60 pS) transitions. Analysis of the unitary transition sizes of single channel sizes showed that their distribution in control cells differed significantly from that for cells treated with GGF2 for 24 hours. About 15% of junctions showed a marked asymmetry of voltage dependence. Several cell pairs showed electrophysiological characteristics similar to those expected of heterotypic, Cx43/Cx45 junctions. Treatment with GGF2 or forskolin increased levels of Cx32 in a time- and dose-dependent manner when measured by Western Blot. GGF2 and forskolin have been shown to stimulate proliferation of SC's in culture and to promote expression of several myelin specific genes such as PO, myelin basic protein, and PMP22 in cultured SC's. Thus, factors regulating SC proliferation and myelin gene expression also regulate SC connexin expression.

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Abstract Form for CMT Consortium

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CONNEXIN32 MUTANTS LACKING A PRENYLATION MOTIF ARE NOT PRENYLATED BUT TRAFFIC NORMALLY IN MYELINATING SCHWANN CELLS

Mutations in *GJB1*, the gene encoding the gap junction protein connexin32 (Cx32), cause the X-linked form of Charcot-Marie-Tooth disease type 1 (CMT1X), an inherited demyelinating neuropathy. More than 240 different mutations have been described, including two – Cys280Gly and Ser281stop – that should interrupt a CaaX motif, a potential prenylation site at the carboxy terminus. Using [³H] mevalonalactone incorporation in transiently transfected COS7 cells, we demonstrate that wild type human Cx32 is prenylated, while Cys280Gly and Ser281stop mutants are not prenylated. To examine this issue further, we generated transgenic mice that express the Cys280Gly and Ser281stop mutations in myelinating Schwann cells using a 1.1 kB rat *Mpz* promoter. In a wild type background, these mutants are properly localized in the incisures and paranodes of myelin sheaths. We are in the process of breeding transgenic animals with *Gjb1/cx32*-null mice. To the best of our knowledge, our data provide the first example that a loss of prenylation leads to loss of function. The nature of this loss of function remains to be determined; it does not appear to be the result of abnormal trafficking. Supported by the NIH (RO1 NS 42878, NS043560) and the CMTA.

Abstract for North American CMT Consortium Meeting May 2005

Title: Motor Unit Number Estimation of Distal and Proximal Muscles in CMT-X: Accentuated Motor Unit Loss in Distal Hand Muscles

Authors: Timothy Doherty, Carly Siskind, Michael E. Shy, Angelika Hahn, Karen Krajewski, Richard A. Lewis

Background: Although there are a number of myelin protein gene disorders that comprise CMT-1 and CMT-X, significant clinical differences between these disorders have not been readily identified. There are over 200 identified mutations to the gene encoding connexin-32 but to date the phenotype seems similar with all the mutations. We have investigated a large cohort of CMT-X patients in order to determine whether there is a genotype-phenotype correlation. As part of that study we have performed Motor Unit Number Estimations of the hypothenar muscles and the biceps brachii and have compared these results to those obtained on a cohort of previously studied CMT-1A patients (Lewis et al. *M&N* 28:161-7; 2003). Based on a preliminary analysis, we observe that CMT-X patients have more severe and earlier onset of distal hand muscle motor unit loss with less severe proximal motor unit loss.

Methods: The decomposition technique utilizing spike triggered averaging was performed on 70 patients with CMT-X. The results were analyzed separately for males and females and correlations with age. They were compared with results of similar studies done on 54 patients with CMT-1A

Results: The Hypothenar MUNE for the 70 CMT-X patients was 27.7 ± 26.6 (normal. 100) and the Biceps MUNE was 181 (normal > 150). For the 28 females the hypothenar MUNE was 39 and for the 42 males it was 21. The female biceps MUNE was 201 and the male was 175. The ratio of the distal MUNE and the proximal MUNE was 0.15. In comparison the ratio for CMT-1A patients was 0.31 (distal MUNE = 33; proximal MUNE = 141). No correlation with age was identified for CMT-X but MUNE decreased with age for CMT-1A (Lewis et al.).

Discussion: This preliminary analysis of the data reveal slightly greater distal motor unit loss in CMT-X than in CMT-1A. However proximal MUNE is normal in CMT-X and mildly reduced in CMT-1A. This difference suggests an accentuated distal motor unit loss in CMT-X and the pattern of nerve fiber loss appears different from that of CMT-1A. The lack of correlation with age in CMT-X is consistent with unproven observations that distal hand muscles are atrophied more frequently in younger patients with CMT-X than with other forms of CMT.

Electrophysiological Criteria Defining Charcot-Marie-Tooth Disease with Intermediate Nerve Conduction Velocities

Agnes Jani-Acsadi, Karen Krajewski, Darren Fuerst, Carly Siskind, Michael E. Shy and Richard A. Lewis
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Bradley et al (Brain 1977) identified a group of patients with CMT who had conduction velocities that were intermediate between those that we would now label as CMT-1 and CMT-2. They defined this intermediate group as having median motor velocities of between 25 and 45 m/sec. It has now become clear that although CMT-X represents many patients with intermediate slowing, the adult onset form of MPZ and newly identified genes also cause dominant and recessive intermediate CMT. There remain however a number of other patients with unknown genetic disorders.

To be meaningful the term Intermediate CMT should define a group of patients with distinct characteristics that separate it from CMT-1 and CMT-2. This study is designed to determine whether there are electrodiagnostic features that best discriminate patients with CMT-Int from CMT-1 and CMT-2 and are able to guide genetic testing and help to characterize the relative effects of these mutations on the function of myelin and the axon.

We have analyzed median and ulnar nerve conduction velocities, median and ulnar CMAPs and sensory nerve conduction data of 335 patients with CMT based on their first electrophysiological testing as entered in the CMT Database at Wayne State University (158 subjects with CMT1A, 14 subjects with CMT1B, 55 with CMTX and 75 patients with unknown type of CMT).

We have found that both median and ulnar NCV and CMAP values were a significant predictor for the diagnosis type. Age was only a significant predictor of the median and ulnar CMAP values but not for MNCV (ANOVA).

Median sensory NCV was also a significant predictor for the type of CMT, with IM CMT patients having higher average sensory NCV values independent from age.

Narrowing our data to the IM-range CMT criteria we have earlier identified as 35 to 45 m/sec, we have found that there was a clear separation of patients with Cx32, Adult onset MPZ and Early Onset MPZ mutations based on their Median CMAP values. This was consistent with our prior observation that Early Onset MPZ patients have a severe, more uniform conduction slowing with lower CMAP values than Adult Onset MPZ or Cx32 patients. Connexin 32 patients however within the same MNCV range showed lower MCMAP values when compared to the adult onset MPZ patients.

Further studies need to be done to characterize the group of patients with IM nerve conduction velocities with so far unknown genetic diagnosis, to guide genetic testing and help to elaborate the pathophysiology of myelin and axon interaction behind the phenotypic and genotypic variability

MUTATIONS IN MITOFUSIN 2 ARE A MAJOR CAUSE FOR AUTOSOMAL DOMINANT AXONAL CHARCOT-MARIE-TOOTH NEUROPATHY.

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Based on electrophysiological criteria CMT can be subdivided in a demyelinating and axonal subgroup. CMT1 patients have nerve conduction velocities (NCV) lower than 38 m/s in the upper limbs, while CMT2 patients have normal or slightly reduced NCVs. Molecular genetic studies have identified 8 CMT2 loci (CMT2A to CMT2G, and CMT2L). Linkage studies already indicated that the CMT2A locus on chromosome 1p35-p36 is a major locus since several large CMT2 families showed conclusive linkage to this locus. Initially, a missense mutation in the kinesin superfamily motor protein KIF1B β gene was reported in a single Japanese CMT2 family as the gene involved in CMT2A. However, KIF1B β mutations were subsequently excluded in 7 CMT2A-linked families. In these CMT2A families and in isolated CMT2 patients, Züchner et al. (2004) recently reported 10 different mutations in mitochondrial GTPase mitofusin 2 (MFN2). We screened an additional cohort of >300 unrelated families and individuals with distinct CMT phenotypes (including CMT2, CMT1 and intermediate CMT) for mutations in MFN2. In 29 probands we found 23 different mutations that were absent in control individuals. Interestingly, mutations were almost exclusively observed in CMT2 patients indicating that MFN2 mutations are a major cause of CMT2. We will discuss the clinical and electrophysiological features of the CMT patients harbouring MFN2 mutations. These observations will help to draw guidelines for diagnostic molecular genetic screening of MFN2. We wish to thank all clinicians who provided us with CMT families for this study.

Clinical and Electrophysiologic Features of CMT2A with Mutations In the Mitofusin 2 Gene

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Background: Axonal neuropathy linked to the CMT2A locus was originally associated with a mutation in the KIF1B gene [1]. However, mutations in this gene have not been described associated with any other CMT2A families. Recently, mutations in the MFN2 gene, encoding the mitochondrial GTPase mitofusin 2 (Mfn2), have been identified as causative of CMT2A in 7 families [2]. We report three additional CMT2A families associated with novel mutations in highly conserved regions of the Mfn2 GTPase domain.

Methods: We performed a standardized neuromuscular and nerve conduction examination, genotyped known CMT loci, and analyzed the MFN2 gene by direct sequencing in three pedigrees and 10 additional probands affected with axonal CMT.

Results: Sequencing of the MFN2 gene revealed a novel mutation in each family (c.818T>G, c.638T>C, and c.314C>T), each resulting in the substitution of an amino acid residue in a highly conserved region of the GTPase. The largest family demonstrated an age-independent variable expression such that approximately one quarter of individuals with the mutation presented with features mild enough as to remain occult even with electrophysiologic evaluation.

Conclusion: Our results confirm that the majority cases of CMT linked to the CMT2A locus are due to MFN2 mutations. The phenotype is largely indistinguishable from KIF1B-related CMT and from CMT2E and CMT2F. At least in some families, as many as 25% of individuals with MFN2 mutations may be asymptomatic and have a normal electrophysiologic exam, although a detailed neuromuscular exam suggests the trait. Given the frequency of MFN2 mutations among CMT2 probands (3/13, or 23%), genetic testing of CMT2 patients should begin with a screen of the MFN2 gene.

Keywords: CMT2A, mitochondria, KIF1B, mitofusin

References

- [1] Zhao C, Takita J, Tanaka Y, et al. (2001) Charcot-Marie-Tooth disease type 2A caused by mutation in a microtubule motor KIF1Bbeta. *Cell*, 105(5), 587-597.
- [2] Zuchner S, Mersyanova IV, Muglia M, et al. (2004) Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. *Nat Genet*, 36(5), 449-451.

Clinical and Electrophysiologic Features of CMT2A with Mutations in the Mitofusin 2 Gene

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CMT2A has recently been associated with mutations in the MFN2 gene encoding the mitochondrial GTPase, mitofusin 2, the human homolog to the yeast and Drosophila gene, *fuzzy onions* (*Fzo1*). Yeast studies have determined that *Fzo1* is required for mitochondrial fusion. Both *Fzo1* and *Mfn2* are thought to mediate fusion through an evolutionarily conserved GTPase, comprised of 4 domains. Mitochondrial fusion balances fission events in the cell to maintain mitochondrial morphology, which is thought necessary for normal mitochondrial function. Yeast literature also indicates that a biologic consequence of mitochondrial fusion defects is loss of mitochondrial DNA (mtDNA), leading to respiratory incompetence of the cell. Mitochondrial DNA loss using Southern blot has not been demonstrated in mammalian cells with fusion defects due to mutations introduced in mammalian MFN2, but changes in mitochondrial morphology have been demonstrated. We have identified three novel MFN2 mutations in Utah families with axonal CMT. These missense mutations result in amino acid residue substitutions in highly conserved regions of the GTPase, including one in the G1 domain motif. To investigate the cellular effect of these mutations *in vivo*, we are examining the mitochondrial morphology in fibroblast cell lines cultured from skin biopsies of patients from each of the three families. In addition, we are quantifying mtDNA in genomic DNA derived from blood and fibroblasts using the sensitive real-time quantitative PCR technique. Preliminary results suggest that mtDNA is diminished in patients relative to a nuclear single copy gene in genomic DNA derived from blood. Early microscopic images of patient fibroblasts also suggest the abnormal fragmented mitochondrial morphology as is seen in yeast and mouse fibroblasts with mitochondrial fusion defects.

Keywords: CMT2A, mitochondria, KIF1B, mitofusin

Mutations in the pleckstrin homology domain of dynamin 2 cause dominant intermediate Charcot-Marie-Tooth disease

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Charcot-Marie-Tooth (CMT) disease is a clinically and genetically heterogeneous group of peripheral neuropathies. CMT has historically been divided into the predominantly demyelinating and axonal forms, CMT1 and CMT2. CMT 1 is characterized by slow nerve conduction velocities (NCV), while in CMT2 NCVs are at or near normal (≥ 45 m/s). However, some CMT families with NCVs between normal to 25 m/s have been designated as intermediate CMT. Autosomal dominant, "intermediate" types of CMT have been linked to three different chromosomal loci; DI-CMTA, DI-CMTB, and DI-CMTC. We refined the DI-CMTB locus on chromosome 19p12–13.2 to 4.2 Mb in three unrelated CMT families originating from Australia, Belgium and North America. After screening candidate genes, we identified in all families unique mutations in dynamin 2 (*DNM2*). *DNM2* belongs to the family of large GTPases and is part of the cellular fusion/fission apparatus. In transiently transfected cell lines we showed that the mutations in *DNM2* significantly diminish binding of *DNM2* to membranes and clathrin-coated vesicles, by altering the conformation of the $\beta 3/\beta 4$ loop of the pleckstrin homology (PH) domain. Also, the microtubule network was disturbed in cells transfected with mutant *DNM2* constructs. Additionally, in the Australian and Belgian pedigrees, which carry two different mutations affecting the same amino acid, K558, we found co-segregation of CMT with neutropenia, which has not previously been associated with CMT neuropathies. In conclusion, we identified *DNM2* as the gene underlying an intermediate CMT neuropathy. The detected mutations caused functional and structural deficits of the early endosomal transport and microtubule organization. *DNM2* now represents the third protein causing CMT that contains a GTPase domain and is related to fusion/fission of cellular membranes, suggesting an exceptional role of these pathways for CMT and for neuropathies in general.

Expression and Intracellular Localization of Mutant K558E Dynamin 2 in EBV Transformed D1-CMTB Patient B-lymphocytes.

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Dominant intermediate Charcot-Marie-Tooth (D1-CMTB) was originally mapped by our group to chromosome 19p11.2-p12. In a collaborative effort, mutations in the Dynamin 2 (Dyn2) gene were recently reported in three families with D1-CMTB. Dynamin 2 is a ubiquitously expressed, 100 kDa GTPase required for receptor mediated endocytosis (RME). RME is initiated in all cells when hormones or transmitters bind to cell surface receptors and the complex is internalized via clathrin-coated pits. In addition to RME, Dyn2 has multiple roles in cellular functions ranging from endocytosis of caveolae, phagocytosis and budding from the trans golgi network, regulation of actin assembly, apoptosis and cell proliferation through the p53 transcription factor and a role in centrosome cohesion. There are three known mutations in the Dyn2 gene which cause amino acid changes in the pleckstrin homology (PH) domain of the protein: 1652_1659+1delATGAGGAGg, K558E and K558del. The PH domain of Dyn2 binds the lipid PtdIns(4,5)P2 thereby targeting the protein to sites of RME. We hypothesize that mutations in the Dyn2 PH domain at K558E produce a protein that is altered in its ability to appropriately target the correct subcellular compartment, due to altered lipid or protein binding. We have examined Dyn2 expression and cellular localization in EBV transformed B-lymphocytes from D1-CMTB patients which carry the K558E point mutation. Preliminary results suggest that the punctuate staining for Dyn2 that is characteristic of RME is considerably altered in the patient cells. This cell culture system provides us with a model to study the biological and cellular effects of the mutant K558E Dyn2 protein in these cells.

Mutations in the SPTLC1 protein, causing hereditary sensory neuropathy type 1, show altered localization of cytoskeletal proteins in transiently transfected SH-SY5Y neuroblastoma cells.

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Mutations in the sphingolipid biosynthesis enzyme, serine palmitoyltransferase (SPT) long chain sub unit 1 (SPTLC1), cause hereditary sensory neuropathy type 1 (HSN1). HSN1 is the most common hereditary disorder of peripheral sensory neurons, involving the progressive degeneration of lower limb sensory. Mammalian SPTLC1 encodes a 53-kDa protein, and is a type I integral membrane protein. There are now 4 known mutations in the SPTLC1 gene which cause the following changes in the amino acid sequence: C133Y, C133W, V144D and G387A. We have used an anti-LCB1 antibody to examine the subcellular localization of the SPTLC1 in wild type transfected and mutant SPTLC1 transfected neuroblastoma cells. There is a significant accumulation of SPTLC1 protein in the ER region and in the neurite processes in SH-SY5Y cells expressing the V144D mutation. The β -actin cellular architecture appears altered in both differentiated and undifferentiated neuronal cells expressing the different SPTLC1 mutations. These changes were not present in cells expressing the wild type or endogenous SPTLC1. These results support our hypothesis that axonal degeneration in HSN1 is caused by the mutations in the SPTLC1 protein, which result in altered localization of SPTLC1 and cytoskeletal proteins leading to failed or altered axonal transport.

Abstract Form for CMT Consortium

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AXONAL DISORGANIZATION IN A MOUSE MODEL OF CMT1A.

How demyelination and remyelination affect the function of myelinated axons is a key problem in demyelinating neuropathies. We have examined this issue in *Trembler-J* mice, a model of CMT1A, caused by a missense mutation in *Pmp22*. In teased fibers, one can observe that myelin internodes have different lengths and thickness, even unmyelinated segments - the consequences of repeated episodes of demyelination and remyelination. Paranodal axo-glial junctions appeared to be formed properly, with well localized Caspr staining. Kv1.1 and Kv1.2 channels, however, were often improperly organized - instead of being confined to the juxtaparanodal region, they were often present in the membranes at the paranode or even node. Nodes of Ranvier appeared normal, containing Nav1.6, ankyrin-G, β IV spectrin, and KCNQ2. In demyelinated segments, these proteins clustered in heminodes bordering the myelinating Schwann cells, but did not diffuse in the paranodes, internodes or demyelinated compartments. We did not observe a shift toward an immature phenotype in these mice, such as the expression of Nav1.2 at nodes. This suggested that the sequestration of the juxtaparanodal K⁺ channels is highly dependent on myelin integrity, while the clustering of nodal and paranodal protein depend on the formation of an axo-glial contact. The shape of the nerve activity recorded from these mice was in keeping with the morphology of the fibers: delayed, dispersed and decreased in amplitude. Interestingly, Nav1.8, a tetrodotoxin-resistant voltage-gated sodium channel, was found at nodes in the *Trembler-J* mice. It is normally absent from wild-type nodes. However, the presence of this subunit was not associated with a resistance of nerve activity to tetrodotoxin blocks. This suggested that other Nav channel sensitive to tetrodotoxin may have a more prominent role than Nav1.8 in AP regeneration at nodes.

This study shows that understanding the axonal changes taking place concomitantly to myelin alteration in CMTA might help understanding the neurological phenotypes, and finding new therapies.

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SKIN BIOPSIES IN MYELIN RELATED NEUROPATHIES; BRINGING MOLECULAR PATHOLOGY TO THE BEDSIDE

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Abstract

Skin biopsy is a minimally invasive procedure and has been utilized in the evaluation of non-myelinated, but not myelinated nerve fibers, in sensory neuropathies. We therefore evaluated myelinated nerves in skin biopsies from normal controls and patients with Charcot-Marie-Tooth (CMT) disease caused by mutations in myelin proteins. Light microscopy, electron microscopy, and immunohistochemistry routinely identified myelinated dermal nerves in glabrous skin that appeared similar to myelinated fibers in sural and sciatic nerve. Myelin abnormalities were observed in all patients with CMT. Moreover, skin biopsies detected potential pathogenic abnormalities in the axolemmal molecular architecture previously undetected in human neuropathies. Finally, myelin gene expression in both mRNA and protein levels was evaluated by real-time PCR and immuno-EM. PMP22 was increased in CMT1A (*PMP22* duplication) and decreased in patients with hereditary neuropathy with liability to pressure palsies (*PMP22* deletion). Taken together, our data suggest that skin biopsy may in certain circumstances replace the more invasive sural nerve biopsy in the morphological and molecular evaluation of inherited and other demyelinating neuropathies.

***EGR2* mutations: a natural history study of 10 patients and functional analysis of neuropathy associated alleles**

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We ascertained 10 patients with *EGR2* mutations and examined the natural history of the disease by regarding progression and respiratory compromise [mean follow-up 17.5+/-10]. These patients were from an AD, 3 from AR family and in 4 patients the sporadic neuropathy was associated with *de novo* mutations. Even the same mutations caused different phenotypes; e.g. heterozygous R359W caused CMT1, DSN and CHN in three different families. Respiratory compromise in the form of documented restrictive pulmonary disease was present in 3/7 (43 %) of the patients, in one case resulting in respiratory failure and death at 6 years. Cranial nerve findings were present in 60 % and involved the facial nerve, cranial nerve III, IX and XII. The progression of the disease was rapid, moderate or mild, depending upon the mutation. Interestingly, the toxic gain of function mutations resulted in moderate to severe progression, whereas the homozygous loss of function mutation in the AR family had minimal, if any, progression of the neuropathy. *In vitro* functional studies were performed, including transcription activity assays and localization studies utilizing constructs generated by *in vitro* mutagenesis. We did not find a correlation between mutations and outcome, thus it is extremely difficult to prognosticate patients with *EGR2* mutations. However our study confirmed that respiratory compromise and cranial nerve dysfunction are commonly associated with *EGR2* mutations and can be useful in guiding molecular diagnostic.

Abstract for CMT meeting

Title: CMT NEUROPATHY SCORE IDENTIFIES TWO YEAR PROGRESSION IN CMT-1A PATIENTS

Authors: Richard A. Lewis, Michael McDermott, Karen Krajewski, David Herrmann, Michael E. Shy

Background: Charcot-Marie-Tooth (CMT) disorders are considered to be insidiously progressive, typically beginning in childhood. However, whether the progression occurs primarily in the first 3 decades of life or uniformly progresses over the lifetime of the patient is not well characterized. The sensitivity of existing measures of disability and impairment to change over time is unknown. The CMT Neuropathy Score (CMTNS) has been developed to track the clinical disability of patients with CMT. It is a 36-point scale including 9 categories of sensory and motor symptoms and signs of upper and lower extremities and compound motor action potential and sensory amplitudes of the ulnar or median nerves. It was designed to determine length dependent changes in clinical status. As a scale to assess clinical status at a single time point, the score has been shown to have excellent inter- and intra-rater reliability (Shy et al. in press). We examined the responsiveness of CMTNS as well as the Neuropathy Impairment Score (NIS), a 296 point quantitative scale of the neurological examination, over a two-year follow-up period in patients with CMT-1A.

Methods: We calculated CMTNS and the NIS of 60 patients with PMP-22 duplication who were seen for at least 2 visits at the Wayne State University CMT clinic.

Results: Both CMTNS and NIS showed significant changes over 2 years. CMTNS increased an average (SD) of 1.3 (2.2) points over 2 years ($p \leq 0.0002$). NIS increased 5.0 (8.8) points over 2 years ($p \leq 0.0004$). Mean changes in both scales were not statistically significant over one year, although there was a trend toward progression (CMTNS: 0.8 (2.8), $p = 0.09$; NIS: 1.9 (8.5), $p = 0.18$). The number of patients in different age groups was too small to detect any specific age in which progression occurs more rapidly.

Conclusion: Progression of CMT-1A can be detected over 2 years by both CMTNS and NIS. This supports the feasibility of 2-year treatment trials using either or both of these scales as outcome measures. Since CMTNS combines symptoms, signs and electrophysiology and NIS is based solely on the neurologic examination, the two scales may be complementary.

**CMT & RESISTANCE TRAINING: ADVANCEMENTS IN EXERCISE
PRESCRIPTION**

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Resistance training improves muscle strength, muscle fiber morphology and functional ability in CMT patients, but standard administration of an exercise prescription is uncommon and long-term exercise adherence is unexplored. The purpose of this presentation is to address the following questions regarding exercise and exercise prescription: (1) Can patients with CMT exercise safely? (2) Is exercise an effective intervention in patients with CMT? (3) Does exercise provide additional benefits for patients with CMT beyond improved performance? (4) What are the components of exercise prescription for CMT patients and how might important exercise variables (e.g. volume, intensity, mode) be quantified or determined? (5) What are the effects of *detraining* in patients with CMT? Answers will be presented, supported by relevant literature and recent data from our investigations. Some of our findings were presented at a previous CMT Consortium, describing beneficial changes in strength, timed motor performance of activities of daily living (ADLs), and muscle fiber morphology. Our current results have demonstrated the following: CMT patients have increased risk factors for heart disease; patient strength and timed motor performance of ADLs can be used as the basis for exercise prescription, and; detraining reverses performance gains in patients with CMT. We will also discuss future directions and further potential benefits of exercise training in this patient population.

THE PREVALENCE OF CHARCOT-MARIE-TOOTH DISEASE IN THE CHILDHOOD POPULATION WITH BILATERAL CAVOVARUS FEET

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The purpose of this retrospective chart review was to determine the prevalence of CMT amongst the general pediatric and adolescent population who have bilateral cavovarus feet. Eight hundred and three charts were reviewed (January 1994 to December 2003). One hundred and forty eight patients met study criteria. All patients had bilateral cavovarus feet and normal cognitive and motor development. Patients were excluded if they had an existing medical problem associated with bilateral cavovarus feet; or had a known chromosomal alteration(s) other than those associated with CMT. Charcot-Marie-Tooth disease was diagnosed following a clinical assessment by a board certified orthopaedic surgeon and a board certified neurologist, and diagnostic testing. Testing included plain radiographs, nerve conduction velocity studies, and/or the Athena Diagnostics CMT DNA Duplication Detection Test (Athena Diagnostics Inc.). The existence of a proband required a confirmation of the diagnosis by a positive nerve conduction velocity study and/or a positive CMT DNA Duplication Detection Test. The results revealed that the probability of a patient with bilateral cavovarus feet being diagnosed with CMT, regardless of family history is 76%. A family history of CMT significantly increases the probability to 92%. It is recommended that all patients, regardless of clinical signs or symptoms, with bilateral cavovarus feet, particularly in the presence of a proband, be investigated for CMT.

THE LATERAL COLEMAN BLOCK VIEW: ASSESSING THE CORRECTABILITY OF THE HINDFOOT DEFORMITY IN CHARCOT-MARIE-TOOTH DISEASE

M.K Nagai, MD, PhD, Zaza Azmaipairashvili, MD, Eric, C. Riddle, PA-S, Mena Scavina, DO, and S. Jay Kumar MD.

Operative correction of cavovarus foot deformity in Charcot-Marie-Tooth disease is challenging. This progressive peripheral sensory and motor neuropathy commonly involves the forefoot, midfoot, hindfoot, and toes. This paper describes a new imaging technique, the lateral Coleman Block view, that allows the surgeon to assess the flexibility of the hindfoot in patients with Charcot-Marie-Tooth disease, to determine the best operative procedure to correct the deformity. Twenty-five patients (41 feet) with Charcot-Marie-Tooth disease and cavovarus foot deformity were evaluated using the lateral Coleman Block view. The Coleman Block view proved useful in determining the optimal surgical procedure(s) to perform to correct this complex deformity.