Impaired Mitochondrial Mobility in Charcot-Marie-Tooth Disease

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Abstract

Charcot-Marie-Tooth (CMT) disease is the most commonly inherited neurological disorder, defined by progressive deterioration of the peripheral nerves. Clinical manifestations of CMT mutations are typically limited to peripheral neurons, the longest cells in the body. Currently, mutations in at least 80 different genes are associated with CMT and new mutations are regularly being discovered. A large portion of the proteins mutated in axonal CMT have documented roles in mitochondrial mobility. This suggests that trafficking defects may be a common underlying mechanism in CMT. This review will focus on the potential role of altered mitochondrial mobility in the pathogenesis of axonal CMT, highlighting the challenges and opportunities to this “impaired mobility” model of the disease.

Introduction

Charcot-Marie-Tooth (CMT) disease is the most commonly inherited neurological disorder, affecting ~1 in 2500 people (Skre, 1974). It is a peripheral neuropathy defined by progressive deterioration of the peripheral nerves in the distal parts of the body, specifically the feet, hands, and lower extremities. This typically results in both motor and sensory loss in the affected areas. Unraveling the pathomechanism(s) behind CMT is somewhat complicated by the fact that CMT is both genetically and clinically heterogeneous. CMT has many subtypes including X-linked, demyelinating (affecting mainly Schwann cells), axonal, and intermediate (affecting both axons and Schwann cells). For this review, we are focusing on axonal defects due to perturbations of mitochondrial mobility.

CMT variants were originally classified based purely on clinical data. However, a recent explosion in genetic data can be mined to generate some compelling hypotheses. To date, over 100 mutations across more than 40 different proteins have been implicated in axonal

and intermediate CMT. A large fraction of CMT-associated proteins are shown or predicted to affect the mobility of mitochondria or other organelles (Table 1). In this review, we will focus on the role of CMT mutations in mitochondrial mobility, and attempt to lay out an “impaired mobility” hypothesis as a “grand unified theory” for why CMT mutations only affect peripheral neurons, while at the same time highlighting what we believe to be important limitations to this model. Our belief is the insights gained from studying the effects of CMT mutations in peripheral neurons will lend insight towards the role of mitochondrial mobility in other types of neurons and neurodegenerative disorders, including aging.

CMT is a progressive disorder that affects only the longest neurons

CMT affects only the distal ends of the body - the feet, hands, and lower extremities. These axons can be as long as a meter in some individuals. Some CMT mutations also cause optic atrophy, and the optical nerve notably consists of relatively long axons (~50mm). Patients are usually born normal, but typically by age 10 have displayed major loss of function. That said, the range of age of onset can be very broad, ranging from toddler years to the 5th decade of life. The severity of the disease is directly correlated with the age of onset (Chung et al., 2006; Verhoeven, Claeys, Zuchner, et al., 2006), and the longer axons (i.e. the feet) invariably degenerate before the shorter axons (i.e. the hands). In cases where CMT patients also display optic atrophy, this occurs after loss of function in the hands (Verhoeven, Claeys, Zuchner, et al., 2006; Zuchner et al., 2006). Together, these observations indicate a disease that directly correlates the length of the axon with the speed of onset, and the speed of onset with the magnitude of the pathology.

CMT mutations largely affect mitochondrial mobility

As mentioned above, a unique peripheral nerve characteristic is their extreme length, which suggests these cells are uniquely sensitive to impaired long-distance transport. When considering the specific physiopathology of CMT mutations affecting only the longest axons in the body, this

makes sense: Any reduction in mobility will first affect the cells with the most extreme demand for mobility. Put simply, a decrease in mobility would have a greater impact on longer distance commutes than shorter ones. In support of this theory, 22 out of the 47 proteins mutated in axonal or intermediate CMT can be argued to play roles in mitochondrial mobility (Table 1).

The majority of CMT studies have centered on Mitofusin 2 (MFN2) mutations, which consistently result in reduced axonal mitochondrial mobility. This has now been reproduced in mouse models and patient cell lines and tissues. Neurons expressing MFN2 CMT mutants and neurons from MFN2 CMT mouse models also show reduced axonal mitochondrial mobility (Baloh, Schmidt, Pestronk, & Milbrandt, 2007; Rocha et al., 2018; Vallat et al., 2008). Confoundingly, MFN2 is also implicated in mitochondrial fusion dynamics, and MFN2 CMT mutations cause clustering of improperly fused mitochondria (Baloh et al., 2007; Detmer & Chan, 2007; Rocha et al., 2018; Vallat et al., 2008). It is possible that this mitochondrial clustering contributes to reduced mitochondrial mobility. MFN2 is also implicated in mediating ER-mitochondria contacts - while MFN2 CMT mutants reduce ER-mitochondria contacts (Bernard-Marissal et al., 2019; Larrea et al., 2019), it is unclear whether these changes affect mitochondrial mobility.

However, there is clear evidence for a role in organelle-organelle contacts affecting mitochondrial mobility in CMT caused by mutations in the endo-lysosomal protein RAB7A. Wong et al. demonstrated reduced mitochondrial mobility due to prolonged inter-mitochondrial contacts in HeLa cells expressing CMT-mutant MFN2, RAB7A, or TRPV4 (Wong, Peng, & Krainc, 2019). RAB7A CMT mutations also increase tethering between mitochondria and endolysosomes, leading to changes in mitochondrial morphology and reduced mitochondrial mobility (Cioni et al., 2019; Wong et al., 2019; Wong, Ysselstein, & Krainc, 2018). Together, these findings are striking in that superficial interpretations of RAB7A mutations causing CMT likely focus solely on endo-lysosomal function. That mitochondria-organelle contacts can affect mitochondrial mobility and dynamics highlights the limitations of evaluating protein and organelle dysfunction in isolation.

Recently, a screen for RAB7A binding partners found that another CMT protein, INF2, is one of several actin-binding candidate interaction partners for RAB7A (Pan et al., 2020). This is particularly relevant to our discussion on CMT, inter-organelle contacts, and mitochondrial mobility for multiple reasons. First, a splice isoform of INF2 is tail-anchored to the endoplasmic reticulum (ER). Second, dominant active mutations in ER-anchored INF2 that mimic INF2 CMT mutations have been shown to increase actin-dependent mitochondrial fragmentation and decrease mitochondrial mobility (Chakrabarti et al., 2018; Korobova, Ramabhadran, & Higgs, 2013). Together, these data point towards an important role in ER-mitochondria inter-organelle contacts in somehow regulating mitochondrial mobility via the actin cytoskeleton. That INF2 also potentially interacts with RAB7A suggests that mitochondria, endo-lysosomes, and ER all contact one another via CMT-associated proteins.

All INF2 CMT mutations are predicted or shown to increase actin assembly (Bayraktar et al., 2020). While some actin-binding motor proteins likely facilitate microtubule-independent mitochondrial transport, numerous studies have shown that long-range microtubule-based mobility of mitochondria is antagonized by actin and actin-binding motor proteins (Cardanho-Ramos, Faria-Pereira, & Morais, 2020; Chada & Hollenbeck, 2004; Pathak, Sepp, & Hollenbeck, 2010; Quintero et al., 2009; Venkatesh, Mathew, & Koushika, 2019). Thus, while the effects of INF2 CMT mutations have yet to be studied in neurons, it is reasonable to expect that INF2 CMT mutations will cause an actin-dependent decrease in mitochondrial mobility in axons. Furthermore, since the ER regularly contacts many other organelles, and even appears to drive actin-assembly at ER-organelle contact sites (Chakrabarti et al., 2018; Korobova, Gauvin, & Higgs, 2014; Korobova et al., 2013; Manor et al., 2015; Schiavon et al., 2020; Yang & Svitkina, 2019), it is quite

possible INF2 CMT mutations cause aberrant actin assembly on other organelles, reducing their mobility as well (Figure 1).

Together with the newly uncovered role for RAB7A in (indirectly) modulating actin assembly (Pan et al., 2020), these observations point towards a role for multiple CMT mutations causing aberrant organelle-organelle and organelle-actin contacts, all of which cause decreased mitochondrial mobility. Whether some (or all) CMT mutations also cause decreased mobility of other organelles remains an important open question.

Figure 1: Model for how CMT mutations in INF2 reduce mitochondrial mobility. Normal INF2 is autoinhibited and thus has regulated actin-assembly activity. CMT mutations in INF2 reduce autoinhibition, resulting in excessive actin assembly on mitochondria and potentially other organelles, which in turn reduces their mobility.

Usually the focus of mitochondria's role in CMT has been primarily on MFN2 and GDAP1, with a lesser focus on motor proteins (KIF1B, KIF5A, DYNC1H1, DCTN2) and some cytoskeletal proteins (NEFL). Here we have introduced INF2 and RAB7A as CMT-associated proteins likely involved in mitochondrial mobility and dynamics. However, the proteins mutated in CMT that play roles in mitochondrial function (particularly mitochondrial dynamics) extend beyond those listed above (see Table 1 for a full list).

Why do mobility defects only affect peripheral neurons in CMT patients?

Hopefully we have convinced the reader that many CMT mutations likely reduce mitochondrial mobility. Given the extreme lengths of peripheral axons, it is tempting to conclude that a reduction in mobility due to CMT mutations simply affects longer axons more severely (the

“impaired mobility model” of CMT). One can easily reconcile two key features of CMT using the impaired mobility model:

1. **The progressive nature of the disease:** This suggests that damage must be accumulating over time. One can imagine that damage accumulates most severely in longer axons, due to reduced turnover of damaged mitochondria resulting from reduced mitochondrial mobility. Interestingly, one could imagine that reduced mobility of other organelles associated with turnover (e.g. lysosomes) could also cause increased accumulation of damaged mitochondria in longer axons.
2. **The longest peripheral axons (i.e. the feet) progressively degenerate prior to the next-longest axons (i.e. the hands):** This further supports the impaired mobility model, wherein damage accumulates first in the longest axons due to the more demanding, “longer commute” resulting in faster accumulation of damaged mitochondria.

Unfortunately, while this model is compelling, it appears to be overly simplistic. The weakness in relying on mobility alone as an explanation can best be highlighted by comparing the lengths of different axons both within and between species. For example, the longest axon in mice is approximately 2cm, whereas in humans the longest axon is ~60 times longer. Just as striking, some unaffected axons in the human CNS may be longer than the mouse’s longest axon. The very same mutation in humans and mice can cause CMT, yet no defects are found in the brains of human CMT patients. Meanwhile, the motor proteins, cytoskeletal tracks, and mitochondria of mice and humans are all roughly the same size, and all possess roughly the same biophysical properties (e.g. velocity, force generation, etc.) when transporting their organelles across long distances (Figure 2).

Figure 2: The relative scales of axons in humans versus mice. While microtubules, motor proteins, and mitochondria have nearly identical sizes in mice and men, the length of the axons can be very different. At the same time, axons in the mouse sciatic nerve are not as long as some of the longer axons within the human brain. For example, it is known in the macaque there are direct connections from the frontal eye fields in the anterior bank of the arcuate sulcus to the primary visual cortex, which in the macaque is ~5cm, and probably as long as 12.5cm in humans. Notably, for most CMT patients the pathology is often constrained to only peripheral neurons. Since the same mutations can cause CMT in mice and men, the distances mitochondria must travel can only provide a partial explanation for the physiopathology of these mutations.

Any analysis of mobility must consider not just distance but also time. A laboratory mouse only lives for ~1-2 years at most, while humans may not even experience symptoms until adolescence or adulthood. Perhaps the difference in relative magnitude of both time and space can perhaps at least partially be explained by interspecies differences in metabolism and oxidative stress? There is clearly a “missing variable” that also likely underlies differences in lifespan between species. Thus, CMT may serve as a “model disease” to better understand age-related neurodegeneration. It is well established mitochondria play myriad roles at the pre-synapse, including calcium signing, ATP production, intra- and intercellular signaling, and the biosynthesis of signaling molecules (Devine & Kittler, 2018). Perhaps perturbed transport of mitochondria to the pre-synapse of peripheral neurons in CMT provides an opportunity to better understand other neurodegenerative disorders associated with defective presynaptic mitochondria, including Alzheimer’s, ALS, Parkinson’s, Friedreich’s ataxia, and hereditary spastic paraplegia (Devine & Kittler, 2018).

But even considering the impaired mobility model for CMT within a single organism has some issues. It is difficult to imagine how reductions in mobility as high as 1000% (Baloh et al., 2007; Rocha et al., 2018) could have a severe effect on only the longest axons, but not other axons that, while shorter than the peripheral neurons, are still very long compared to the ~25nm step size of a motor protein. It is not obvious that a truck unable to survive regular trips from California to Washington, DC will be perfectly fine for routes between California and Seattle, Washington.

When considering these conundrums, it is helpful to consider alternative mechanisms for replenishing mitochondria in neurons, many of which are reviewed elsewhere (Misgeld & Schwarz, 2017; Yu & Pekkurnaz, 2018). Briefly, mitochondrial rejuvenation is speculated to be at least partially mediated via local translation in the axon. Interestingly, multiple CMT mutations affect local translation machinery (Table 1). More recent work showed that mitochondria serve as a stable compartment for mediating biogenesis, in particular at synapses (Rangaraju, Lauterbach, & Schuman, 2019). This raises a chicken vs. egg question: Does reduced mitochondrial mobility impair local translation needed for synaptic and therefore neuronal health and maintenance? Or does impaired local translation lead to damaged mitochondria that cannot be replaced without sufficient mobility? That CMT is caused by mutations disrupting both mobility and local translation indicates these two processes are uniquely related in long axons.

Conclusion and open questions

One open question is how the overall distribution of mitochondria is altered in CMT neurons, and how that relates to axonal maintenance. A recent study showed mitochondria tend to distribute along the length of axons with regular spacing, and that inter-mitochondrial feedback mediates their positioning and movement. Is this feedback-based positioning altered in CMT? Do mutations affecting mobility result in CMT via a “domino effect” caused by defects in

relatively local repositioning between axonal mitochondria, which then cascades with increasing defects as a function of increasing axonal length? How much longer does it take mitochondria in CMT patients to traverse the entire length of an axon? Is there a reduction in the turnover rate of mitochondria in CMT patients? How do any and all of these factors affect mitochondria at the pre-synapse of CMT peripheral neurons, likely the most important subpopulation of mitochondria in these cells? These are surprisingly open questions we expect to be addressed in the coming years using animal and cell models of CMT.

Table 1: Genes mutated in axonal and intermediate CMT. Genes that play a role in organelle trafficking and/or mitochondrial function are marked with an asterisk.

Gene/CMT subtype	Function	References
AARS1/CMT2N	Catalyzes the attachment of alanine to tRNA.	(Bansagi et al., 2015; Dohrn et al., 2017; McLaughlin et al., 2012; Weterman et al., 2018; Z. Zhao et al., 2012)
ATP1A1/CMT2DD	Catalyzes the hydrolysis of ATP coupled with the exchange of sodium and potassium ions across the plasma membrane.	(Lassuthova et al., 2018)
BAG3/CMT2*	Acts as a nucleotide-exchange factor promoting the release of ADP from the HSP70 and HSC70 proteins thereby triggering client/substrate protein release. Has anti-apoptotic activity. Plays a role in cytoskeletal proteostasis and dynamics.	(S. J. Kim et al., 2018; Shy et al., 2018)
BSCL2/CMT2*	Plays a crucial role in the formation of lipid droplets. Mediates the formation and/or stabilization of endoplasmic reticulum-lipid droplet contacts. Binds anionic phospholipids including phosphatidic acid.	(Chaudhry et al., 2013)

DCTN2/CMT2*	Component of a large macromolecular complex required for the cytoplasmic dynein-driven movement of organelles along microtubules. Pays a role in prometaphase chromosome alignment and spindle organization during mitosis.	(Braathen et al., 2016)
DGAT2/CMT2	Required for synthesis and storage of intracellular triglycerides.	(Hong et al., 2016)
DHTKD1/CMT2Q	Catalyzes the overall conversion of 2-oxoglutarate to succinyl-CoA and CO ₂ .	(Baets, De Jonghe, & Timmerman, 2014; Dohrn et al., 2017; Z. H. Zhao, Chen, Zhou, & Wang, 2019)
DNAJB2/CMT2T	Functions as a co-chaperone, activating the ATPase activity of chaperones of the HSP70/heat shock protein 70 family. Contributes to the ubiquitin-dependent proteasomal degradation of misfolded proteins.	(Gess et al., 2014; Lupo et al., 2016)
DNM2/CMT2M; CMTDIB*	Plays an important role in vesicular trafficking processes, in particular endocytosis. Involved in producing microtubule bundles. Involved in cytokinesis.	(Bitoun et al., 2008; Echaniz-Laguna et al., 2007; González-Jamett et al., 2014; Haberlová et al., 2011; Saghira et al., 2018)
DYNC1H1/CMT2O*	Acts as a motor for the intracellular retrograde motility of vesicles and organelles along microtubules. Plays a role in mitotic spindle assembly and metaphase plate congression.	(Weedon et al., 2011)
GARS1/CMT2D	Catalyzes the attachment of glycine to tRNA	(Hamaguchi, Ishida, Iwasa, Abe, & Yamada, 2010; James et al., 2006; Morelli et

		al., 2017; Motley et al., 2011; W. Xie, Schimmel, & Yang, 2006)
GDAP1/CMT2K; CMTRIA; CMT4A*	Regulates the mitochondrial network by promoting mitochondrial fission. Proposed roles in mitochondrial transport, redox processes, calcium homeostasis, and energy production.	(Ammar et al., 2003; Auer-Grumbach et al., 2008; Auranen et al., 2013; Baránková et al., 2007; Baxter et al., 2002; Cassereau et al., 2011; Cuesta et al., 2002; Di Maria et al., 2004; Dohrn et al., 2017; Fusco et al., 2011; He et al., 2018; Ho et al., 2017; Kabzińska et al., 2007; Mai et al., 2019; Manganelli et al., 2015; Martí et al., 2017; Martin, Maradei, & Velasco, 2015; Masingue et al., 2018; Moroni et al., 2009; Qin et al., 2019; Rougeot et al., 2008; Rzepnikowska & Kocharński, 2018; Sahin-Calapoglu, Soyoz, Calapoglu, & Ozcelik, 2009; Sahin-Calapoglu, Tan, Soyoz, Calapoglu, & Ozcelik, 2009; Senderek et al., 2003; Vital et al., 2012; Xin, Puffenberger, Nye, Wiznitzer, & Wang, 2008; Yoshimura et al., 2017; Zhang et al., 2004; Zimoń et al., 2011; Zimoń et al., 2015)
HARS1/CMT2W	Catalyzes the attachment of histidine to tRNA.	(Baets et al., 2014)
HINT1/CMT2	Hydrolyzes purine nucleotide phosphoramidates with a single phosphate group.	(Baets et al., 2014; Dohrn et al., 2017; Laššuthová et al., 2015; Zimoń et al., 2015)
HSPB1/CMT2F*	Functions as a molecular chaperone maintaining denatured proteins in a folding-competent state. Plays a role in stress resistance and actin organization.	(Amornvit, Yalvac, Chen, & Sahenk, 2017; Chung et al., 2008; Dohrn et al., 2017; Ho et al., 2017; Houlden et al., 2008; Liu et al., 2005; Solla

	Regulates numerous biological processes including phosphorylation and axonal transport of neurofilament proteins.	et al., 2010; Tang et al., 2005; Weeks et al., 2018)
HSPB8/CMT2L*	Displays temperature-dependent chaperone activity. Forms complex with BAG3.	(Nicholson, Kennerson, Brewer, Garbern, & Shy, 2009)
IGHMBP2/CMT2S	5' to 3' helicase that unwinds RNA and DNA duplexes. Acts as a transcription regulator.	(Cottenie et al., 2014; Dohrn et al., 2017; Wagner et al., 2015; Yuan et al., 2017)
JPH1/CMT2K	Contributes to the formation of junctional membrane complexes which link the plasma membrane with the endoplasmic or sarcoplasmic reticulum in excitable cells. Provides a structural foundation for functional cross-talk between the cell surface and intracellular calcium release channels.	(Kanwal & Perveen, 2019; Pla-Martín et al., 2015)
KIF1B/CMT2A1*	Motor for anterograde transport of mitochondria.	(Bissar-Tadmouri et al., 2004; Nakagawa & Takashima, 2003)
KIF5A/CMT2*	Microtubule-dependent motor required for slow axonal transport of neurofilament proteins. Contributes to the vesicular transport of VAPA, VAPB, SURF4, RAB11A, RAB11B and RTN3 proteins in neurons.	(Dohrn et al., 2017)
LMNA/CMT2B1	Plays an important role in nuclear assembly, chromatin organization, nuclear membrane and telomere dynamics.	(Chaouch et al., 2003; De Sandre-Giovannoli et al., 2002; Dohrn et al., 2017; Hamadouche et al., 2008; Liang, Grogan, Ackerman, & Goodsell, 2016; Zhang et al., 2010)

LRSAM1/CMT2G	E3 ubiquitin-protein ligase. Bacterial recognition protein that defends the cytoplasm from invasive pathogens. Potential role in mitophagy?	(Dohrn et al., 2017; Guernsey et al., 2010; Nicolaou et al., 2013)
MARS1/CMT2U	Catalyzes the attachment of methionine to tRNA.	(Baets et al., 2014; Y. Sun et al., 2017)
MED25/CMT2B2	A coactivator involved in the regulated transcription of nearly all RNA polymerase II-dependent genes.	(Leal et al., 2018; Leal et al., 2009; Tazir, Bellatache, Nouioua, & Vallat, 2013)
MFN2/CMT2A2*	Mitochondrial outer membrane GTPase that mediates mitochondrial clustering and fusion. Involved in the clearance of damaged mitochondria via mitophagy. Potential roles in mitochondria-ER contacts and mitochondrial transport.	(Ando et al., 2017; Bannerman, Burns, Xu, Miers, & Pleasure, 2016; Beręsewicz et al., 2017; Bergamin et al., 2014; Braathen, Sand, Lobato, Hoyer, & Russell, 2010; Brožková et al., 2013; Calvo et al., 2009; Cartoni & Martinou, 2009; Chapman, Bennett, Ramesh, De Vos, & Grierson, 2013; B. O. Choi et al., 2015; Del Bo et al., 2008; Di Meglio et al., 2016; Dohrn et al., 2017; El Fissi et al., 2018; Engelfried et al., 2006; Feely et al., 2011; Finsterer, Fiorini, Scorza, & Scorza, 2018; Iapadre et al., 2018; Kijima et al., 2005; Kotruchow, Kabzińska, Hausmanowa-Petrusewicz, & Kochański, 2013; Larrea et al., 2019; Lawson, Graham, & Flanigan, 2005; Loiseau et al., 2007; Lv et al., 2013; Lv et al., 2015; McCorquodale et al., 2011; Milley et al., 2018; Muglia et al., 2007; Neupauerová, Grečmalová, Seeman, & Laššuthová, 2016; Neusch et al., 2007;

		Ouvrier & Grew, 2010; S. Y. Park et al., 2012; Rudnik-Schöneborn et al., 2016; Tan et al., 2016; Verhoeven, Claeys, Züchner, et al., 2006; Vielhaber et al., 2013; Vital et al., 2012; Wang et al., 2015; Werheid et al., 2016; Y. Xie et al., 2016; Xu et al., 2019; Zuchner et al., 2006)
MME/CMT2T	Biologically important in the destruction of opioid peptides. Able to cleave angiotensins. Involved in the degradation of atrial natriuretic factor.	(Auer-Grumbach et al., 2016; Fujisawa et al., 2017)
MORC2/CMT2Z	Essential for epigenetic silencing by the HUSH complex.	(Albulym et al., 2016)
MPV17/CMT2EE*	Non-selective channel that modulates membrane potential under normal conditions and oxidative stress, and is involved in mitochondrial homeostasis. Involved in mitochondrial deoxynucleoside triphosphates pool homeostasis and mitochondrial DNA maintenance.	(Y. R. Choi et al., 2015)
MPZ/CMT2J; CMTDID; CMT1B	Mediates adhesion between adjacent myelin wraps and ultimately drives myelin compaction.	(Avila et al., 2010; Bergamin et al., 2014; Bienfait et al., 2006; Bissar-Tadmouri et al., 1999; Blanquet-Grossard et al., 1996; Brozková, Mazanec, Haberlová, Sakmaryová, & Seeman, 2010; Chavada, Rao, Martindale, & Hadjivassiliou, 2012; Choi et al., 2011; De Jonghe et al., 1999; Dohrn et al., 2017; Gallardo et al., 2009; Hayasaka et al., 1993; He et al., 2018; Høyer et al., 2014; Høyer, Braathen, Eek, Skjelbred, & Russell, 2011;

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MT-ATP6/CMT2*	Mitochondrial membrane ATP synthase. Key component of the proton channel.	(Pitceathly et al., 2012)
NAGLU/CMT2V	Involved in the degradation of heparan sulfate.	(Tétreault et al., 2015)
NEFH/CMT2CC*	Component of neurofilaments, the most abundant cytoskeletal component of myelinated axons.	(Bian et al., 2018)
NEFL/CMT2E*	Component of neurofilaments, the most abundant cytoskeletal component of myelinated axons. Regulates mitochondrial morphology.	(Berciano et al., 2016; Bhagavati, Maccabee, & Xu, 2009; Dohrn et al., 2017; Fabrizi et al., 2007; Fu & Yuan, 2018; Horga et al., 2017; Luo et al., 2003; Lupski, 2000; Miltenberger-Miltenyi et al., 2007; Shin et al., 2008; Werheid et al., 2016; Xu et al., 2019)

PNKP/CMT2B2	Plays a key role in the repair of DNA damage, functioning as part of both the non-homologous end-joining and base excision repair pathways.	(Leal et al., 2018)
RAB7A/CMT2B*	Key regulator in endo-lysosomal trafficking. Plays roles in growth-factor-mediated cell signaling, nutrient-transporter mediated nutrient uptake, neurotrophin transport in the axons of neurons and lipid metabolism. Regulates mitochondrial fission, mitophagy, and mitochondria-lysosome tethering.	(Manganelli et al., 2015; Meggouh, Bienfait, Weterman, de Visser, & Baas, 2006; Zhang et al., 2010)
SPG11/CMT2X*	Plays a role in neurite plasticity by maintaining cytoskeleton stability and regulating synaptic vesicle transport.	(Montecchiani et al., 2016)
TRIM2/CMT2R*	E3 ubiquitin-protein ligase that mediates the ubiquitination of NEFL and of phosphorylated BCL2L11.	(Baets et al., 2014; Pehlivan et al., 2015)
TRPV4/CMT2C*	Non-selective calcium permeant cation channel involved in osmotic sensitivity and mechanosensitivity. Some data supporting a role in regulating mitochondrial motility.	(Deng et al., 2010; Dohrn et al., 2017; Klein et al., 2003; Manganelli et al., 2015)
VCP/CMT2Y*	Necessary for the fragmentation of Golgi stacks during mitosis and for their reassembly after mitosis. Involved in the formation of the transitional endoplasmic reticulum. Plays a role in the regulation of stress granule clearance. Involved in DNA damage response. Essential for the maturation of ubiquitin-containing autophagosomes and	(Gonzalez et al., 2014)

	the clearance of ubiquitinated protein by autophagy and mitophagy.	
C1ORF194/CMTDI	May affect intracellular Ca^{2+} homeostasis.	(S. C. Sun et al., 2019)
GNB4/CMTDIF	Modulator/transducer in various transmembrane signaling systems.	(Baets et al., 2014; Miura et al., 2017; Soong et al., 2013)
INF2/CMTDIE*	Mediates actin polymerization at ER-mitochondria contact sites. Regulates mitochondrial morphology and motility.	(Boyer, Benoit, et al., 2011; Boyer, Nevo, et al., 2011; Caridi et al., 2014; Dohrn et al., 2017; Echaniz-Laguna & Latour, 2019; Fu et al., 2019; Jin et al., 2015; Mademan et al., 2013; H. J. Park et al., 2014; Rodriguez et al., 2013; Vallat, Mathis, & Funalot, 2013; Werheid et al., 2016)
SLC12A6/CMTDI	Mediates electroneutral potassium-chloride cotransport.	(Lupo et al., 2016)
YARS1/CMTDIC	Catalyzes the attachment of tyrosine to its corresponding tRNA	(Jordanova et al., 2006; W. Xie, Nangle, Zhang, Schimmel, & Yang, 2007)
COX6A1/CMTRI*	A subunit of the cytochrome c oxidase complex	(Tamiya et al., 2014)
KARS1/CMTRIB	Catalyzes the aminoacylation of tRNA-Lys in the cytoplasm and mitochondria	(McLaughlin et al., 2010)
PLEKHG5/CMTRIC	Activates the nuclear factor kappa B (NFKB1) signaling pathway. Also implicated in distal spinal muscular atrophy.	(H. J. Kim et al., 2013)

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