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Abstract

Charcot-Marie-Tooth disease (CMT) is a group of hereditary peripheral neuropathies that can result from defects in a wide spectrum of genes. Some of these genetic defects disrupt mitochondrial fusion and fission in the peripheral neurons, ultimately leading poor axonal transport, which is one of the two major cellular phenotypes associated with CMT. While the mechanisms of how these mutated genes lead to disrupted axonal transport are not entirely understood, knowledge on this process, and the genes involved, has expanded substantially in the past decade. Currently, there is no cure for any form of CMT, and most treatments focuses on symptom management. The purpose of this paper is to provide an overview on the genetic and molecular mechanisms by which this form of CMT manifests, and to discuss potential directions for future research on treatments for mitochondrial CMT.

One Sentence Summary: Genetic defects can result in disrupted mitochondrial dynamics in peripheral neurons, leading to various forms of CMT.

Abbreviations: CMT=Charcot-Marie-Tooth disease; HMSN=hereditary motor and sensory neuropathy; NCV=Nerve-conduction velocity; NGS=Next-generation sequencing; WES=Whole-exome sequencing; AFO=Ankle Foot Orthosis; *MFN2*=Mitofusin 2; *SLC25A46*=Solute Carrier Family 25, Member 46; HDAC=histone deacetylase; *GDAP1*=Ganglioside Induced Differentiation Associated Protein 1; AR=Autosomal Recessive; AD=Autosomal Dominant; *AIFM1*=Apoptosis Inducing Factor Mitochondria-associated 1; *DHTKD1*=Dehydrogenase E1 and Transketolase Domain Containing 1; *DNM2*=Dynamin 2; *INF2*=Inverted Formin 2; *MYH14*=Myosin Heavy Chain 14

Introduction

Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy (HMSN), is a heterogenous group of genetically derived neuropathic disorders. CMT is the most common form of hereditary neuropathy and has global prevalence of 1 in 2,500, with variable prevalence depending on population genetics and geographic region (*1*). Due to the heterogeneous nature of CMT, there is multitude of types and subtypes of this neuropathy (*2*). Historically, CMT has been divided into three main types, demyelinating, axonal, and intermediate, based on underlying pathology and mode of inheritance (*3*, *4*). Recently, as the biochemical pathogenesis of the various genes implicated in CMT has become better understood, CMT typing and subtyping has moved towards classifying based on the cellular structure or function that is disrupted by the mutated gene (*5–7*). Among these subtypes of HMSN is CMT, resulting from impairments in mitochondrial dynamics (*5*, *8–10*). There are over 20 genes that, when mutated, are associated with disruptions in mitochondrial fusion, fission, or motility, and present as one of the major phenotypes of CMT (*8*, *11*).

Yet, despite the genetic variability of CMT, there are a few relatively consistent physiological and anatomical characteristics that are exhibited by nearly all CMT patients. Specifically, most CMT patients present clinically with weakness and wasting in the distal limb muscles, foot deformities (pez cavus), distal atrophy, hyporeflexia, and sensory loss (*12*). These

symptoms, along with slow disease progression during childhood or a lack of positive sensory symptoms (paresthesia, hypersensitivity, etc.) in spite of obvious sensory involvement to confirm that the disease is of hereditary origin, allow for clinical diagnosis of generalized CMT (*12*). In the past, diagnosing specific CMT types in patients has been dependent on clinical phenotype distinction and NCV testing of the motor nerves of upper-limb, as genetic testing methods had yet to be proven as an effective or efficient mode of diagnosis in a clinical setting (*13*). However, the recent advancements in the effectiveness and financial accessibility of whole-exome sequencing (WES) and next-generation sequencing (NGS) as tools for performing genetic diagnoses (*14*, *15*) has allowed such methods to be performed more extensively. These advancements in genetic sequencing has allowed for better characterization of the genes involved in CMT, along with uncovering genes that had not been previously implicated in CMT (*16*, *17*).

As a result of the highly heterogeneous nature of this disease, there is currently no effective pharmaceutical therapy for CMT, and thus, most treatment options are limited to symptom management (*13*). Due to the gait disorders, muscular pain and weakness, and regularity of falls, CMT patients often suffer from inactivity, which has shown to potentially exacerbate the health issues, such as obesity and chronic inflammation, that are associated with such a lifestyle and the disease itself (*18–21*). Studies have shown that moderate aerobic and resistance training can help mitigate these health issues and reduce symptom severity of CMT in patients, without risk of overwork weakness in the skeletal muscles associated with excessive exercise (*21–24*). As the disease progresses, patients are often prescribed tailored foot orthoses, specifically ankle-foot orthoses (AFOs), which have shown to limit the painful effects of *pes cavus* and improve gait, ankle function, and overall walking velocity (*25*, *26*). Often patients will eventually require orthopedic surgery to correct the foot deformities that result from *pes cavus*

(*13*). While a majority of surgeons will advocate for calcaneal osteotomy and peroneal tendon transfer at a minimum, there is variability in the consensus on further procedure, and decisions on the best surgical route sometimes must be made in the operating room (*27*, *28*). In some cases, symptomatic drug therapy is prescribed to mitigate pain and other neuropathic effects experienced as a result of CMT (*13*). Due to the variable genotypes associated with CMT, effective therapy will likely need to target the specific gene, or its protein products, responsible for the disease in each patient (*5*, *29*). This genetic basis for understanding the disease, combined with the recent advancements CRISPR-Cas9, siRNA, and other modes of modulating gene expression, have allowed researchers to demonstrate potential pathways for effective therapies in the more common forms of CMT in transgenic mice models (*Mus musculus*) of the disease (*30*–*34*). The purpose of this paper is to review the genes that are most commonly associated with disruptions in mitochondrial dynamics that lead to CMT, to describe the molecular mechanisms by which this occurs, and how this knowledge may affect the development of future therapies.

Mitochondrial dynamics and their role in healthy axonal transport

Mitochondrial dynamics refers to the processes by which the cell balances mitochondrial fission and fusion in the cytosol (*35*). Fission involves the division of a single mitochondrion to form two daughter mitochondria, while fusion forms a single mitochondrion from two mitochondria. Due to this organelle's significant bioenergetic role in aerobic respiration, maintenance of tissue-specific balance of its dynamics has shown to be essential in energy production, development, apoptosis, and proliferation (*36*). Mitochondrial fission is necessary for proliferating cells to populate their offspring with a sufficient number of mitochondria, while also playing a role in apoptosis via Bax mediated cytochrome c release, and mitophagy (*37*, *38*).

Fusion is important in complementation and repair of damaged mitochondria (*37*), along the generation of a mitochondrial network which is advantageous in cells that often experience high energy demand (*36*). Neurons are among these cells with immense energy requirements, and thus, rely on mitochondrial fission, fusion, and motility for their proper function. Due to the many processes that mitochondrial dynamics are essential in, it is not surprising that disruption of fusion and fission can lead to a wide variety of human diseases. Excessive fission can allow a cell to proliferate excessively and contribute to evasion of apoptosis, potentially contributing to the development of cancer, pulmonary arterial hypertension, and patent arteriosus (*39*). Impairment of fusion, and excessive fission fragmentation of mitochondria, can lead to neurodegenerative diseases such as Familial Parkinsonism, Alzheimer's Disease, Huntington's Disease, and amyotrophic lateral sclerosis (*10*, *39*). Also, failure to meet the cell's energetic requirements due to impaired dynamics in cardiac and metabolic tissues can contribute to the development of diabetes mellitus, ischemia-reperfusion injury, and cardiomyopathy (*39*). Lastly, disruptions in mitochondrial fusion, fission, and motility can result in neuropathies, such as CMT and optic atrophy, a physiological defect occasionally observed in some CMT genes (*9–11*, *39*).

The primary belief is that peripheral neuropathy is due to limited anterograde and retrograde axonal transport, resulting from poor mitochondrial motility (*11*). This disruption in mitochondrial motility is often attributed to either, dysfunction in fission preventing mitochondria from becoming small enough for transport through the axon, or due to a failure in fusion leading to dysfunctional mitochondria that fail to pass through mitochondrial transport checkpoints (*9*). However, due to the many roles of mitochondrial dynamics in the neurons, disruptions in fusion and fission have also been implicated in alterations of other cellular systems in many genotypes of CMT (*9*).

Genes associated with disrupted mitochondrial dynamics in CMT

Table 1. Genes involved with mitochondrial dynamics and associated with Charcot-Marie-Tooth disease

Gene	Protein	Primary mode of inheritance	Clinical Classification	Location in the cell	Role in mitochondrial dynamics
MFN2	Mitofusin 2	Autosomal Dominant	CMT2A2A CMT2A2B CMT6A	Outer mitochondrial membrane	Fusion of outer membrane
SLC25A46	Solute Carrier Family 25, Member 46	Autosomal Recessive	CMT6B	Integrated in outer mitochondrial membrane	Inhibition of membrane fusion and cristae remodeling
GDAP1	Ganglioside Differentiation Associated Protein 1	Autosomal Recessive (most common) and Autosomal Dominant (rare)	CMT2K CMT2A CMTRIA CMT4A	Outer mitochondrial membrane	Membrane fission, mitochondrial trafficking, Ca^{2+} homeostasis, mitochondrial-lysosomal membrane contacts
AIFM1	Apoptosis-inducing factor mitochondrion-associated 1	X-linked recessive	CMTX4	Mitochondrial intermembrane space	Regulation of apoptosis
DHTKD1	E1 subunit of mitochondrial 2-oxoglutarate-dehydrogenase complex	X-linked dominant	CMT2Q	Mitochondrial matrix	Mitochondrial energy production,
DNM2	Dynamin 2	Autosomal Dominant	CMT2M, CMTDIB	Cytosol; Plasma membrane	Membrane fission
INF2	Inverted Formin 2	Autosomal Dominant	CMTDIE	ER-mitochondrial membrane contact sites	Membrane fission
MYH14	Myosin Heavy Chain 14	Autosomal Dominant	CMT2	Cytosol	Membrane fission

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Mitofusin 2 (MFN2)

The *MFN2* gene encodes the Mitofusin-2 protein (MFN2), a dynamin-related GTPase found on the outer mitochondrial membrane, and is primarily involved with outer mitochondrial membrane fusion (*40*). Beyond this, MFN2 also plays a role in mitochondrial transport, direct lipid transfer to the mitochondria, and mitophagy (*9*). Mutation of *MFN2* is one of the three more common causes of CMT, accounting for approximately 6% of all cases and 20% of axonal CMT cases (*41*). While homozygous loss of function in *MFN2* is embryonic lethal (*42*), mutations associated with CMT are heterozygous and have an autosomal dominant pattern of inheritance, exhibiting a dominant negative effect (*2*). There are over 100 mutations that lead to this form of CMT, most of which are found in or near the GTPase domain of *MFN2*, leading to GTPase dysfunction in MFN2 (*11*). Due to this protein's wide breadth in functionality, the mechanisms by which this mutation results in the neuropathic phenotype in CMT patients is still uncertain (*41*). The first proposed mechanism is the deficiency in performing outer mitochondrial membrane fusion, resulting from loss of GTPase function in MFN2 (*11*). Second, there is some evidence that loss of MFN2 downregulated *p53* expression, resulting in an evasion of apoptosis and increased mitophagy in the neurons (*43*). Third, studies have shown data that indicates that MFN2 mutations may impair mitochondria-associated ER membranes ability to synthesize myelin, and may disrupt the formation of synaptic vesicles in the peripheral neurons leading to some of the phenotypes associated with this form of CMT (*44*). Lastly, mutated *MFN2* is associated with decreased mitochondrial motility, preventing proper distribution throughout the neuron, which could explain CMT typically having greater severity in the distal-most areas of the limbs (*11*).

Mutations in *MFN2* can be classified clinically as CMT2A2A, CMT2A2B, and CMT6A (*5*, *9*). The clinical phenotype of CMT patients with a mutated *MFN2* gene is highly variable in severity and in presence of certain symptoms, where up to 25% of patients are asymptomatic of the mutation (*2*). Aside from the loss of sensory and motor nerve function in the distal limbs, *pes cavus*, and hammertoes that are observed in most forms of CMT, patients with this form of the disease have also exhibited retinal degeneration leading to loss of visual acuity, sensorineuronal hearing loss, and signs of central nervous system involvement due to upper motor neuron impairment (*41*).

As is the case with all forms of CMT, there is no therapy available that can resolve the negative symptoms of *MFN2* mutations in patients. Thus, most current treatment involves the symptom management strategies previously described in this review. Additionally, due to the mitochondrial involvement of this form of CMT, coenzyme Q10 supplementation is often prescribed with the intent of mitigating the effects mitochondrial dysfunction. However, data that supports the effectiveness of this is limited at best (*29*). Current routes of therapeutic research focus on MFN2 modulation through various agonists of the protein or genetic manipulation (*41*). Recent research has demonstrated that MFN2 activation by MiM111, a small organic molecule, could reverse neuromuscular defects and promote axonal regeneration in *MFN2* knockout mice models (*31*). While the results of this study need to be further replicated before moving to clinical trials, it provides the first potential therapeutic method by which *MFN2* associated CMT can be effectively treated in adolescent patients.

Solute Carrier Family 25, Member 46 (SLC25A46)

SLC25A46 encodes a member of a solute carrier family of proteins, and complexes with proteins involved in mitochondrial membrane fusion and cristae remodeling (*45*). Interestingly, while this protein is predicted to be involved in solute transport across the mitochondrial membrane, due to it being a part of a solute carrying protein family, it has not been reported or observed to be involved in performing this function specifically (*46*, *47*). CMT resulting from mutations in *SLC25A46* typically exhibit an autosomal recessive mode of inheritance (*48*). While research on *SLC25A46*$^{-/-}$ mice models supports the belief that the neurodegenerative effects of *SLC25A46* loss of function results in dysregulation of mitochondrial fusion and fission, and subsequent neuronal metabolic dysfunction, the specific role that this protein plays in these processes is less understood (*49*). Prevailing evidence suggests that SLC25A46 serves as a negative regulator of mitochondrial fusion by interacting with MFN1/2 and OPA1, as *SLC25A46* knockdown cells exhibit hyperfused mitochondria and elevated levels of MFN1/2 (*9*, *50*).

Clinically, CMT associated with a loss of function in SLC25A46 is classified as CMT6B, (*9*). Individuals who have mutations in *SLC25A46* exhibit a wide spectrum of clinical presentations, likely due to variation in degree of loss of function in the SLC25A46 protein product (*47*). All patients reported thus far with a loss of function mutation in *SLC25A46* exhibit optic atrophy, and a CMT phenotype that is similar to those with mutations in *MFN2* (*47*). There is currently no approved therapy for CMT associated with *SLC25A46*. Recently, however, there has been progress in research regarding the development of potential therapies for CMT resulting from a loss of function in *SLC25A46*. Suda et al. demonstrated that a homolog of histone deacetylases 1 and 2 (HDAC1 and HDAC2) in *Drosophila*, Rpd3, serves as a negative regulator of SLC25A46 (*51*). They then observed a recovery in motor and locomotive activity when the

functionality of Rpd3 was reduced in *SLC25A46* knockdown *Drosophila* (*51*). The existence of multiple chemicals that inhibit the action of HDAC 1 and HDAC2 establishes this a promising pathway for future research into therapies for this form of CMT (*52*). Additionally, Yang et al. developed an adeno-associated virus (AAV) vector containing *Slc25a46*, and transduced the gene into *Slc25a46*$^{-/-}$ mice (*53*). While there were limitations and issues with this study in reference to dose dependency and longevity of therapeutic action, it still demonstrated that AAV vector gene therapy could be a viable method for treating CMT resulting from loss of *SLC25A46* (*53*).

Ganglioside Induced Differentiation Associated Protein 1 (GDAP1)

GDAP1 encodes for the GDAP1 protein, which is anchored to the outer mitochondrial membrane and plays a role in mitochondrial fission (*54*, *55*). A CMT phenotype typically results from autosomal recessive (AR) mutations in this gene, but rare autosomal dominant (AD) mutations do exist (*54*). *GDAP1* has been found to be expressed in both the axons and Schwann cells (*56*). The presence of GDAP1 in axons and Schwann cells suggest that both axonal degradation and demyelination might contribute the GDAP1-related CMT (*9*). Additionally, there is evidence showing that GDAP1 plays a role in regulating the *trans*-Golgi network, and membrane contact sites between the mitochondria and the lysosome (*57*, *58*). High rates of defects in these organelles suggests that disruptions in these functions may also play a role in the pathophysiology of GDAP1-related CMT. On top of its role in mitochondrial fission, GDAP1 has also shown to have a role in mitochondrial trafficking and Ca^{2+} homeostasis in the peripheral neurons (*59*). Due to the many roles that this protein plays in the mitochondria of the cell, it is

not surprising that there are over 80 mutations associated with *GDAP1* that have been reported (*60*).

Clinically, mutated *GDAP1* can be classified as CMT2K, CMT2A, CMTRIA, or CMT4A (*5*, *9*). AR mutations in *GDAP1* tend to produce a more severe CMT phenotype and an earlier onset of symptoms of disease, with some patients developing dysphonia and respiratory dysfunction (*60*). Patients with AD *GDAP1*-related CMT typically experience less severe muscle wasting and weakness, relative to AR (*60*). However, correlations between patient genotype and clinical phenotype are difficult to make, as there is variability in symptom severity and age of symptom onset between patients with the same mutations in *GDAP1* (*60*).

Despite the many cellular functions that are likely disrupted in GDAP1-related CMT patients, recent research presents a potential therapeutic route for this form of CMT. In pre-symptomatic *Gdap1*$^{-/-}$ mouse models, administration of the mitochondrial uncoupler florfenicol and the antioxidant MitoQ can prevent the onset of CMT disease symptoms by preventing oxidative damage to metabolic and redox proteins in the peripheral nerves (*61*). However, administration of florfenicol failed to improve motor function in *Gdap1*-null mice that had already begun to exhibit neuropathic symptoms (*61*).

Apoptosis Inducing Factor Mitochondrion-Associated 1 (AIFM1)

The *AIFM1* gene encodes the AIFM1 flavoprotein, which is an FAD-dependent NADH oxidoreductase that is essential in disassembling the nucleus during caspase-independent apoptosis (*62*). In a healthy cell, AIFM1 has a variety of functions that are dependent on its location in the cell (*63*). In healthy cells, following synthesis in the cytosol, AIFM1 is transported to the mitochondria, where it is inserted into the IMM at its N-terminus (*64*). Once

inserted into the IMM, AIFM1 can function in a variety of roles in mitochondrial respiration. Early studies on AIFM1 suggested that it functioned as a superoxide-producing NADH oxidase, while more recent research points to AIFM1 serving as a rotenone-sensitive NADH: ubiquinone oxidoreductase (*64*). Recent evidence has also shown AIFM1 to modulate mitochondrial morphology and oxidative phosphorylation by interacting with the mitochondrial intermembrane space importer, Mia40 (*64*). Additionally, AIFM1 has shown to interact with mitochondrially localized PTEN, preventing oxidation of PTEN and allowing for the negative regulation of Akt-dependent growth factor signaling (*65*). Upon apoptotic insult to the cell, AIFM1 is released from the IMM to the cytosol, where it generates reactive oxygen species (ROS) and promotes the release of cytochrome C into the cytosol (*63*). When localized to the plasma membrane, following Fas ligand binding, AIFM1 has shown to promote the externalization of phosphatidylserine, allowing for recognition and phagocytosis by macrophages (*66*). Lastly, AIFM1 facilitates caspase-independent apoptosis by translocating to the nucleus and binding to DNA and activating endonuclease activity to promote chromatin condensation and large scale DNA degradation (*63–65*).

In addition to causing CMT, mutations in this gene can result in a spectrum of recessive X-linked, hereditary neurological disorders (*62*, *67–69*). Therefore, the phenotype of patients with mutations in the *AIFM1* gene varies from progressive muscular wasting, to neurological deficits and premature death (*70*). Clinically, HMSN resulting from mutations in *AIFM1* is classified as CMT4X, also known as Cowchock syndrome. CMT4X is only observed in males, due to its recessive X-linked mode of inheritance, and is typically characterized by muscle wasting, sensory loss, and weakness with greater involvement of the lower limbs than of the upper limbs (*71*). Furthermore, patients with CMT4X exhibit motor axonal neuropathy more

often than sensory axonal neuropathy (*71*). The mechanisms by which mutations in *AIFM1* result in CMT are not well understood. However, there is evidence that the CMT phenotype results from isolated *AIFM1* loss of function in the motor neurons, leading to excessive apoptosis in these cells (*62*). Due to the FAD-dependent nature of AIFM1, supplementation with the FAD precursor, riboflavin, has been attempted as a therapeutic option in multiple case studies (*72–74*). The results of these case studies yielded variable outcomes ranging from no clinical benefit (*73*) to temporarily slowing disease progression (*72*) and clear improvement of ataxia (*74*).

Dehydrogenase E1 and Transketolase Domain Containing 1 (DHTKD1)

The *DHTKD1* gene encodes the DHTKD1 protein, which constitutes the E1 subunit of the alpha-ketoadipic acid dehydrogenase complex (also known as the 2-oxoglutarate dehydrogenase complex), a rate-limiting enzyme of the citric acid cycle (TCA) (*75*, *76*). This complex catalyzes the formation of succinyl-CoA from α-ketoglutarate, allowing for further degradation and energy production via the TCA (*76*). Alternatively, the 2-oxoglutarate dehydrogenase complex (OGDHC) can be inhibited in response to low cellular amino acid content, allowing for α-ketoglutarate to be utilized in amino acid biosynthesis (*77*).

Due to its considerable role in aerobic respiration, it is not surprising that the OGDHC is found in a wide variety of tissues and organisms, with DHTKD1-conatining OGDHC characterizing one of two known tissue-specific isozymes that exist in addition to canonical OGDHC (*78–80*). Silencing of *DHTKD1* in HepG2 and NCI-N87 cells has shown to decrease in mitochondrial energy production and mitochondrial biogenesis, while increasing apoptosis and levels of reactive oxygen species (*81*). HAP1 cells that underwent CRISPR/Cas9 mediated knockout of *DHTKD1* exhibit a decreased capacity for mitochondrial respiration and oxidative

phosphorylation that is consistent with the protein's role in aerobic respiration (*82*). Interestingly, these HAP1 *DHTKD1*$^{-/-}$ cells had higher basal phosphorylation states of p38 and AKT, markers for MAPK and PI3K signaling respectively (*82*). Despite this finding, these knockout cells did exhibit an increase in proliferation relative to wild-type HAP1 cells, suggesting the increase in growth factor signaling pathways may serve as compensatory mechanism for the decrease in metabolic capacity from the loss of DHTKD1 (*82*). Additionally, the mitochondrial morphology was altered in these knockout cells as they had a decrease in number and length of cristae, while showing signs of an increase in the number of mitochondria (*82*). Sciatic nerves, taken from *Dhtkd1*$^{-/-}$ mice, exhibit axonal loss and a reduction in large myelinated fibers (*83*). Additionally, the Schwann cells of these *Dhtkd1*$^{-/-}$ mice showed signs of functional impairment (*83*). At an organismal level, *Dhtkd1*$^{-/-}$ mice exhibited decreased muscle strength and motor tolerance, along with sensory reduction, which is consistent with the clinical presentation of CMT patients with DHTKD1 deficiencies (*83*, *84*).

CMT resulting from a loss of function in DHTKD1 is classified at CMT2Q and patients exhibit an X-linked mode of inheritance (*85*, *86*). There have only been 8 reported cases of CMT associated with mutations in *DHTKD1* (*84–86*). These patients present clinically with symmetrical muscle wasting, mild sensory impairment, decreased motor NCV's in the lower or limbs depending on the patient (*84*, *85*). Currently, there is no treatment for any disease resulting from mutations in *DHTKD1*. Furthermore, due to the observation of overexpressed *DHTKD1* by various types of tumors, therapeutic research associated with this gene typically involves inhibiting its function, instead of rescuing it (*87*).

Dynamin 2 (DNM2)

The *DNM2* gene encodes the Dynamin 2 (DNM2) protein, a member the dynamin superfamily of large GTPases (*9*, *88*). DNM2 has been implicated in a variety of cellular processes, primarily in clathrin-mediated endocytosis with respect to endosomal trafficking and rearrangement of the actin cytoskeleton (*88*, *89*). Additionally, this protein has been shown to play a role in mitochondrial fission but is not essential for the process to occur (*90*). Similar to other members of the dynamin protein family, DNM2 contains five domains that provide different functions. The first is an N-terminal GTPase domain, which is proceeded by middle domain that contains an actin-binding motif (*88*). This middle domain is followed by a pleckstrin homology (PH) domain that allows for DNM2 to bind to phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] in response to growth factor signaling (*91*). After the PH domain is a GTPase effector domain (GED), which serves to provide a GAP functionality to DNM2 (*88*). Lastly, DNM2 has a proline/arginine-rich C-terminal domain that allows for binding to SH3-domains on associated proteins (*88*).

DNM2 has shown to play a role in receptor-mediated endocytosis by activating the MAPK pathway, along with ERK1 and 2, in response to epidermal growth factor binding on the plasma membrane (*89*). Due to its role in growth factor signaling, gain of function mutations in *DNM2* can be oncogenic, as increased DNM2 activity has been observed in a variety of cancers (*92–95*). Conversely, the role of DNM2 in mitochondrial fission is less understood. There is evidence to suggest that DNM2 is involved in scission of the mitochondrial membrane, following constriction by DRP1, and knockdown of DNM2 has been associated with elongated mitochondria (*96*). However, conflicting studies have failed to produce a change in rates of

mitochondrial fission following DNM2 knockdown, suggesting that the protein may be dispensable in this process (*90*, *97–99*).

Along with being a well-documented oncogene, mutations in *DNM2* have been found to cause CMT and centronuclear myopathy (CNM) (*9*). Historically, mutations in *DNM2* leading to CMT were observed to result in a loss of function, while gain of function mutations were associated with CNM (*100*, *101*). Recently, however, a gain of function mutation in *DNM2* has also been implicated in DMN2 associated CMT (*102*). Most mutations in *DNM2* that have been documented in CMT patients are in the PH domain, typically resulting in a disruption to DNM2 binding to $PI(4,5)P_2$ (*100*, *101*). While disruptions in mitochondrial fission may contribute to the pathogenesis of CMT associated with DNM2 (*88*, *100*), a majority of research points to dysfunction in clathrin-mediated endocytosis and vesicular trafficking as the primary culprit in the disease (*101*, *103*, *104*).

Clinically, DNM2-associated CMT can be classified as CMT type 2M (CMT2M) or CMT dominant intermediate type B (CMTDIB), with patients presenting with axonal or demyelinating and axonal clinical phenotype respectively (*103*). CMTDIB and CMT2M exhibit an autosomal dominant mode of inheritance, and patients with either form experience loss of sensation, muscle weakness, and atrophy (*105*). Additionally, DNM2-associated CMT patients have been reported to ptosis, ophthalmoparesis, cataract, pes cavus, hyposthenia of extensor muscles, reduction of deep tendon reflexes, fatty infiltration of muscle bellies of the lower limbs, and mild cognitive impairment (*103*, *106–108*). The role of hyperactive DNM2 in cancer and CNM creates issues in the development of potential therapies for DNM2-associated CMT, as treatments would likely require stimulation of DNM2. Thus, minimal research has been conducted with regard to therapies that might restore the functionality of DMN2.

Inverted Formin 2 (INF2)

The *INF2* gene encodes the Inverted Formin 2 (INF2) protein (*109*). Formins are a family of proteins that catalyze the nucleation of actin monomers and accelerate the elongation of actin filaments (*110*). There are two documented splice variants of INF2, one that localizes to the Golgi and one that localized to the ER to engage in mitochondrial fission (*109*, *111*). INF2 is activated through the c-Jun N-terminal kinase (JNK) pathway, which results in an increased expression of *INF2*, allowing for actin polymerization near ER-mitochondria contact sites (*109*). The formation of actin filaments at these contact sites allows for binding and mitochondrial membrane constriction by myosin motor proteins (*9*).

The pathogenesis of INF2-associated CMT is poorly understood. CMT mutations in *INF2* result in mitochondrial elongation, while constitutive activation induced hyper fission of mitochondria, suggesting hyper fusion as cause of neuronal dysfunction (*8*, *111*). Alternatively, there is evidence to suggest that INF2-associated CMT is the result of disrupted dynein-mediated endocytic vesicular transport (*109*, *112*).

INF2-associated CMT is clinically classified as autosomal dominant intermediate CMT (CMTDIE) (*9*). In addition to sensory loss and distal muscle weakness, patients with mutations in *INF2* often exhibit sensorineuronal hearing loss and glomerulosclerosis (*9*, *109*). It is difficult to study potential therapies and their targets, due to the lack of understanding of the disrupted cellular mechanisms behind the pathogenic variants of *DRP1* in associated CMT patients.

Myosin Heavy Chain 14 (MYH14)

The *MYH14* gene encodes the Myosin Heavy Chain 14 (MYH14) protein, which is also referred to as Non-Muscle Myosin II C (NMIIC) (*9*). Myosins constitute a diverse superfamily of motor proteins that are found in nearly all eukaryotic cell types (*113*). While myosin proteins are most known for their role in vertebrate muscular contraction, these molecular motors are also involved in other cellular processes such as, cell-substrate contacts, cytokinesis, phagocytosis, and cell crawling (*114*). A majority of myosins are class II and can be divided into muscle and non-muscle myosin II (*113*). While muscle myosin II is exclusively found in skeletal, cardiac, and smooth muscle cells, non-muscle myosin II is expressed in muscle and non-muscle cells (*113*). Non-muscle myosin II is a hetero-hexameric protein that is comprised of a myosin heavy chain (NMII) homodimer, two myosin light chains, and two regulatory light chains (*115*, *116*).

The *MYH9, MYH10,* and *MYH14* genes code for the myosin heavy chains that can constitute non-muscle myosin II (*116*, *117*). *MYH9* is only known to produce a single mRNA transcript, while *MYH10* and *MYH14* can each give rise to four different splice variants (*117*). All three isoforms of NMII have shown to play a role in mitochondrial fission by inducing constriction at the site of fission, following recruitment by INF2-mediated actin polymerization (*118*, *119*). While inhibition or knockdown of MYH9, MYH10, and MYH14 leads to elongation in mitochondrial morphology, loss of function mutations in each isoform can produce a variable phenotype at an organismal level. Nullifying mutations in *MYH9/10* are typically associated with cardiopulmonary, renal, and developmental defects, along with a high rate of metastasis in multiple carcinomas (*120–125*). Furthermore, approximately 50% of patients that inherit pathogenic variants in *MYH9* experience delayed onset sensorineuronal deafness (*120*).

Similarly, mutations in *MYH14* are known to be associated with metastatic cancers, and to cause autosomal dominant nonsyndromic hereditary hearing loss (ADNSHL) (*126–128*).

Hereditary peripheral neuropathy associated with MYH14 was first reported in a large Korean family in 2011 (*129*). There have since been multiple reports of CMT due to mutations in *MYH14*, in families across the globe (*119*, *130–132*). Furthermore, the most prevalent mutation in *MYH14* in these CMT patients is c.2822G>T, which results in the Arg941Leu (R941L) amino acid substitution (*119*, *131*, *132*). Heterozygous R941L patient fibroblasts exhibit elongated mitochondria, indicating impaired mitochondrial fission through a dominant-negative effect (*119*).

CMT resulting from mutations in *MYH14* is classified as CMT type 2 (CTM2) (*2*). Patients with MYH14-associated CMT present clinically with axonal loss and foot deformities, along with atrophy and weakness in the distal muscles of the lower limb (*119*, *129*, *131*, *132*). Additionally, there is a high rate of hearing loss in these patients, that is not typically observed in other forms of CMT (*119*, *129*, *131*, *132*). Currently, there is no therapy for MYH14-associated CMT. Recent research has attempted to increase MYH14 activity to limit metastasis in carcinomas, establishing the small molecule 4-hydroxyacetophenone as means of activating MYH14 (*127*, *128*). However, the effectiveness of 4-hydroxyacetophenone in correcting MYH14-associated CMT is questionable, due to the molecule's apparent inability to alter *MYH14* gene expression and the dominant negative effect of the R941L substitution (*119*, *127*, *128*).

Conclusion

Mitochondrial fusion and fission are essential in development, metabolism, growth, survival, and death. Failure for mitochondria to divide limits cell growth, while complete loss of the ability to fuse is embryonic lethal (*133*). Impairments in a cells ability to perform these fusion and fission events are associated with a multitude of human diseases (*39*).

Charcot-Marie-Tooth disease is the most common hereditary peripheral neuropathy, that manifests from mutations in a multitude of genes (*2*). Within CMT exists pathogenically implicated genes that regulate mitochondrial fusion and fission in the peripheral neurons (*9*). Unfortunately, there is no cure for any form of CMT and most treatment options can only offer symptom management. However, with recent developments allowing for greater accessibility to genome sequencing and gene editing biotechnologies, there is promise in understanding therapeutic targets and for the development of curative therapies.

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