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Review

The causes of Charcot-Marie-Tooth disease

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Abstract. Charcot-Marie-Tooth (CMT) disease serves as the summary term for the most frequent forms of inherited peripheral neuropathies that affect motor and sensory nerves. In the last 12 years, 14 genes have been identified that cause different CMT subforms. The genes found initially are predominantly responsible for demyelinating and dysmyelinating neuropathies. Genes affected in axonal and rare forms of CMT have only recently been identified. In this review, we will focus on the currently known genes that are associated with CMT syndromes with regards to their genetics and function.

Key words. Myelin; peripheral nervous system; Schwann cell; neurodegeneration; Charcot-Marie-Tooth disease; hereditary neuropathy; axon degeneration.

Introduction

Charcot-Marie-Tooth (CMT) disease is a major genetic disease in clinical neurology with a prevalence of approximately 1 in 2500 [1]. Since the first descriptions by Charcot, Marie and Tooth in 1886, the main clinical features of this syndrome were defined as distal peroneal weakness accompanied by muscular atrophy [2, 3]. More than 100 years later, the classification of CMT syndromes today has been revised and extended based on clinical features, electrophysiological, histopathological and genetic findings [4]. This development was mainly guided by progress in clinical electrophysiology and later by the advances in molecular genetics. In this review, we will predominantly concentrate on the genetic and molecular understanding of CMT. But first, we shall provide a short overview of the manifestation and biological basis of the disease.

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Classical clinical classification of CMT

The typical CMT patient is affected by slowly progressive distal muscle weakness and atrophy that primarily affects the small foot muscles, peroneal muscles and, often later, those of the hands and forearms. Foot deformities, mostly pes cavus and claw toes are common, leading to gait impairments. Although the disease is usually progressive, it rarely causes wheelchair dependence but considerably affects the quality of life.

CMT is subdivided into demyelinating (CMT1) and axonal (CMT2) forms according to clinical, electrophysiological and histopathological features. CMT1 is characterized by disease onset in the 1 or 2 decade of life, nerve conduction velocities (NCVs) less than 38 m/s, and segmental demyelination, remyelination and onion-bulb formations in nerve biopsies (fig. 1). CMT2 is associated with normal or near-normal NCVs, and nerve biopsies show loss of myelinated axons [5]. A neuropathy is called ‘axonal’ if the axon (or neuron) is affected by the primary injury. If the primary insult occurs in the myelinating Schwann cell, this is considered a ‘demyelinating

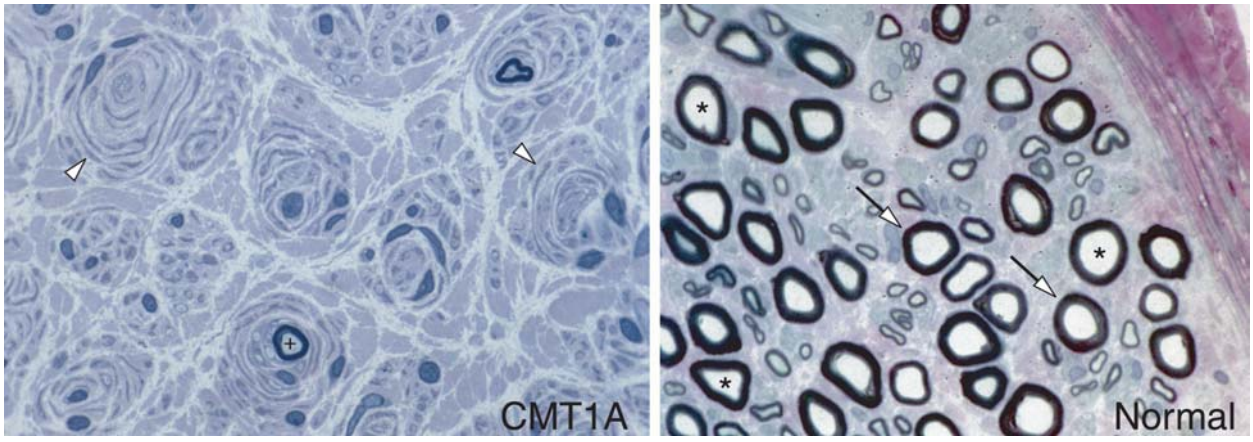

Figure 1. Histopathological comparison of a normal human sural nerve and a nerve from a CMT1A patient. Arrows indicate normally myelinated fibers; asterisks denote axons on a nerve cross-section. Open arrowheads point to onion-bulb formations consisting of supernumerary Schwann cells that surround concentrically a demyelinated axon in the diseased state. A '+' sign indicates a partially remyelinated axon (the pictures are a kind gift from Dr Steven S. Scherer, University of Pennsylvania).

neuropathy'. This distinction is based on clinical and pathological evidence. Progress in identifying the genes responsible for CMT has now revealed, however, that some of these disease genes are expressed by both cell types, neurons and Schwann cells, making the determination of the primary defect often uncertain. Furthermore, axon and Schwann cells interact intensively, leading to secondary effects that might be difficult to separate from cell-autonomous events [6]. Recent experiments on myelinated axons in the CNS suggest that the myelinating cell type may even appear morphologically completely normal and still affect the associated axon dramatically [7].

In the late sixties, Dyck and Lambert [8] presented an initial classification based on electrophysiological changes in the peripheral nerves of CMT patients. Differentiating hallmarks were NCVs, compound motor action potentials (CMAPs), compound sensory action potentials (SNAPs), and the patterns of inheritance. Furthermore, the term 'hereditary motor and sensory neuropathy' (HMSN) was created as a synonym for CMT disease. Over time, diagnostic parameters for CMT were more and more influenced by the increasing possibilities of molecular genetics [4]. The first description of a defined genetic basis for a given CMT subtype was discovered in 1991, when a 1.5-megabase-long, intrachromosomal duplication on the short arm of chromosome 17 (17p11.2) was found to be associated with the most common subtype CMT type 1A (CMT1A) [9, 10]. Due to the fortuitous help of the analysis of two spontaneous animal models for CMT, Trembler (Tr; ([11] and Tr-J; [12]), the peripheral myelin protein 22 (PMP22) was identified as an excellent dosage-sensitive candidate gene located on the CMT1A duplication [13–16]. The final proof that *PMP22* was indeed the responsible disease gene was provided a few years later using transgenic rodents [17, 18]. This initial finding of a myelin gene as the CMT1A disease gene sparked a flurry of further investigations that led to the identification of two other genes encoding myelin components, protein zero (P0; *MPZ*) and connexin32 (Cx32; *GJB1*) as major loci for demyelinating forms of CMT, collectively termed CMT1 [19]. In the meantime, 14 genes have been found that cause different forms of CMT. Based on these recent genetic findings, a reevaluation of the existing classification may be warranted. The clinical and pathological variability of CMT, however, even when the same gene is involved, and the fact that mutations in different genes can manifest as similar phenotypes, might argue differently. A novel genetics-based categorization will be an important additional help for the clinician, but it is not likely to fully replace the traditional classification. Valuable further information for a more integrated approach to this problem will come from the detailed understanding of the pathobiological basis of CMT syndromes. The key question that needs to be answered is: How is the sequence of events defined that leads from a particular genetic alteration to biological effects that are deleterious to the proper function of peripheral nerves (for reviews: [6, 19–22])? If we are able to find the answers to this question, we will not only understand CMT disease but also learn important lessons about the basic molecular cell biology of the development and maintenance of peripheral motor and sensory nerves.

Genes mutated in CMT

For a complete and updated list of CMT genes, CMT loci and mutations, consult: http://molgen-www.uia.ac.be/CMTMutations/

Demyelinating forms of CMT

Peripheral myelin protein 22 (PMP22)

PMP22 was the first gene to be identified in the pathogenesis of the development of CMT [11–16]. Nelis and co-workers showed that the heterozygous duplication of *PMP22* is by far the most frequent mutation in CMT [23]. The reciprocal event to the duplication, the deletion of the same fragment on chromosome 17p11.2 containing *PMP22*, causes a neuropathy which is characterized by an increase in vulnerability to pressure trauma resulting in temporary nerve palsies [24]. This neuropathy, called hereditary neuropathy with liability to pressure palsies (HNPP), is associated with focal hypermyelination (tomacula). In general the clinical phenotype of HNPP is not progressive, although CMT-like symptoms may occasionally develop with age [25–27]. Some point- and frame-shifting mutations in *PMP22*, most likely causing functional null alleles, have also been identified in HNPP pedigrees [28, 29].

Most patients carrying the heterozygous CMT1A duplication show the classical demyelinating phenotype with reduced NCV below 38 m/s, associated with rather homogeneous myelin defects [30, 31]. Histopathologically, the typical changes in myelin fibers are demyelination, thin myelin sheaths and onion-bulb formation [32] (fig. 1). Axonal damage was thought to be rare and predominantly secondary to long-lasting deymelination. Extended electrophysiological studies revealed, however, that the clinical degree of handicap is correlated with axonal atrophy and loss, as indicated by the reduction of CMAP and SNAP, but not with reduced NCV [33–35]. Homozygous CMT1A duplications cause very severe dysmyelinating phenotypes [9, 36, 37].

Besides gene duplications and deletions, a number of point mutations in *PMP22* have been described [38]. Some of them appear to be heterozygous null alleles and lead to HNPP, as described above. Very few mutations are recessively inherited [39, 40]. The vast majority, however, are associated with membrane-associated domains of the PMP22 protein and are dominantly inherited. In general, this last group of mutations causes a more severe CMT1 phenotype than duplication, and some have been classified as Déjérine-Sottas syndrome (DSS) [41, 42].

How does this pletora of mutations affect *PMP22* and cause the different phenotypes? The answer to this intriguing question is far from clear, but appropriate animal models mimicking the different genetic situations have been generated. They will help to shed light on this interesting problem [43]. This includes *Pmp22* null mice [44–46], mice and rats carrying additional copies of the PMP22 gene [17, 18, 47–49], mice with an internal *Pmp22* deletion [50] and *Pmp22* point mutations [11, 12, 51, 52].

Clearly, the key to understanding the disease phenotypes is knowledge of the detailed function of the PMP22 protein. This polypeptide comprises 160 amino acids and is membrane associated [53]. It is most abundant in peripheral nerves, and mainly expressed by myelinating Schwann cells [54–56]. PMP22 plays a crucial role in the development and maintenance of compact myelin, as is well established by the disease phenotypes of CMT1A and HNPP patients as well as animal models [38]. Additional in vitro data suggest that PMP22 may regulate cell proliferation [57–59], cell death [59–61], cell differentiation [61–64] and membrane traffic [65]. Furthermore, a function of PMP22 as a constituent of intercellular junctions in epithelia has been suggested [66]. The significance of the latter finding in the etiology of CMT, although intriguing, remains to be elucidated. Such a function might rather be related to the fact that PMP22 is also expressed outside of the nervous system [55], shows distant similarities to the tight junction components of the claudin protein family [67] and belongs to the closely related PMP22/EMP gene family [68].

How do altered levels of PMP22 produce their phenotypes in HNPP and CMT1A? It has been suggested that PMP22 is part of a stoichiometric complex with P0, the major adhesion protein of peripheral myelin and evidence for direct interaction of the two proteins has been presented [69] but is also debated [70]. However, the possibility that a reduced PMP22/P0 ratio (in HNPP) or the opposite situation (in CMT1A) may affect myelin stability remains an interesting hypothesis. Alternatively, or in addition, Schwann cell proliferation and differentiation might be affected [71, 72]. Importantly, from the point of developing future treatment, the effects of PMP22 overexpression in Schwann cells in a CMT1A animal model appear to be reversible, at least with regard to myelination [73]. Whether neuronal deficiencies that correlate with the disease-associated handicaps can also be reversed remains open [6, 33–35, 74, 75].

How do dominant PMP22 point mutations cause the disease? At least some of them appear to produce a gain-of-abnormal function, since most PMP22 point mutations in human and animal models have more severe phenotypes compared with HNPP and heterozygous PMP22 knockout mice. One disesease mechanism has been elucidated in that some PMP22 mutant proteins are retained intracellularly, in the endoplasmic reticulum (ER) and/or the intermediate compartment [38, 61, 64, 69, 76–80]. In addition, the mutant proteins encoded by the Tr (G150D) and Tr-J alleles (L16P) aggregate abnormally in transfected fibroblasts [70], although such aggregates have been suggested to be even protective in PMP22 point mutation-based peripheral neuropathies [52]. Since PMP22 forms dimers and multimers, mutant PMP22 retained in the ER and/or intermediate compartment may prevent the efficient transport of wild-type PMP22 to the cell membrane in the form of a classical dominant-negative effect [38, 70, 80]. However, genetic evidence shows that at

least the Tr mutation causes also a toxic gain of function in the absence of wild-type PMP22. Heterozygous Tr mice have a more pronounced phenotype than heterozygous PMP22 knockout mice (and HNPP patients with a heterozygous PMP22 deletion). In addition, mice carrying a PMP22 null allele and the Tr allele as a compound heterozygote display a much worse neuropathy than heterozygous or homozygous PMP22 knockout animals [46].

How could a toxic gain of function be generated by impaired PMP22 trafficking? In analogy to the involvement of the unfolded protein response in modulation of disease severity in Pelizaeus-Merzbacher disease due to proteolipid protein mutations [81], accumulation of mutant PMP22 may trigger a similar effect. However, there is no experimental evidence to support such a mechanism. Another ER chaperone, calnexin, may be involved by getting sequestered away by mutant PMP22 and contributing to the resulting neuropathy [77]. Furthermore, inefficient proteasome function could be toxic to the cell and may add to the potential disease mechanism [82, 83]. Finally, PMP22 accumulates in lysosomes of (de)myelinating Schwann cells of Tr-J mice, potentially related to a role of the endosomal/lysosomal degradation pathway in the pathogenesis of demyelination [79, 82, 83]. This is of special interest considering that a lyosomal protein of unknown function, LITAF/SIMPLE, was recently identified as being mutated in the dominant demyelinating CMT1C disease [84].

P0, *MPZ*

In 1981, the first genetic linkage data suggested a gene located on chromosome 1 to be associated with an autosomal dominant demyelinating CMT syndrome [85]. This was classified later as CMT1B [5], and the mutations responsible were found in *MPZ* [86–89]. P0/*MPZ* is a major PNS myelin component that belongs to the immunoglobulin superfamily [90] and plays a major role in compaction of the myelin sheath as a homophilic adhesion protein [91–95]. Structural analysis of the P0 extracellular domain suggests that four molecules form a tetramer in cis that interacts homophilically in trans with tetramers in the opposing membrane [96, 97]. Similar to mutations in PMP22, the clinical, electrophysiological and histopathological findings turned out to be heterogeneous for *MPZ* mutations [89]. These range from autosomal dominant CMT1B to severe forms classified as DSS. Furthermore, the same mutation can cause different degrees of disease severity in different patients [98]. Close to a hundred *MPZ* mutations have been described up to now. The main phenotype is a demyelinating neuropathy that is clinically and by electrophysiological means indistinguishable from CMT1A. Less frequently, patients are very severely affected [5, 89]. As expected from the function of P0, transfection studies in cultured cells revealed that some CMT1B mutations in the P0 extracellular domain [99] and cytoplasmic mutants of a protein kinase C (PKC) phosphorylation site [100] reduced adhesion. The latter finding is particularly interesting since it may imply that loss of P0 signaling function (which is largely unknown) is part of the disease mechanism.

A second set of dominant mutations in *MPZ* is associated with CMT2 [98, 101–106]. The mechanism of how these mutations in a gene that is exclusively expressed by Schwann cells but not neurons are causing axonal neuropathy is unclear. The answer to this question will require the construction of precise mouse models mimicking these mutations, and their detailed analysis. Such efforts have begun, and they have revealed potential mutation-specific effects [94, 107, 108]. However, further refinements are needed before more definitive statements can be made.

Lipopolysaccharide-induced tumor necrosis factor α factor LITAF/SIMPLE

Mutations in *LITAF/SIMPLE* cause the dominant inherited demyelinating CMT1C disease [84]. In the three families described so far, the phenotype cannot be distinguished from other forms of CMT1. Little is known about the biological function of LITAF/SIMPLE. The corresponding messenger RNA (mRNA) is found in the sciatic nerve, but in contrast to the other genes causing CMT1, its expression level is not altered after nerve injury. Originally described as a transcription factor involved in tumor necrosis factor α (TNF-α) gene regulation (hence the name; [109]), further analysis indicates that LITAF/SIMPLE encodes a small integral membrane protein of lysosomes/late endosomes [110]. It has been speculated that altered lysosomal function and protein degradation may have an impact on myelin development and maintenance based on upregulation of this pathway in Tr-J [79]. If correct, mutated LITAF/SIMPLE may exert its effect in a similar way [84].

Early growth response gene (EGR2/Krox20)

Based on theoretical considerations, transcriptional regulators of the myelin-associated CMT genes are likely candidates to cause CMT1-like phenotypes [111]. Indeed, mutations in SOX10, a key regulator of myelin genes, lead to syndromes including peripheral neuropathies [112–114]. Similarly, several dominant mutations in the zinc-finger transcription factor *EGR2*/Krox20 have been found in patients suffering from severe forms of demyelinating CMT (CMT1D and DSS) [115, 116]. An additional mutation results in the syndrome congenital hypomyelination (CH; [116]), which shows absence of peripheral nervous system (PNS) myelin from birth.

EGR2/Krox20 is a zinc-finger transcription factor with a crucial role in the regulation of PNS myelination, since Krox20-deficient mice show a complete lack of myelin (amyelination) [117]. Overexpression of EGR2/Krox20 in Schwann cells strongly increased the expression of MPZ, PMP22, GJB1/Cx32, periaxin (PRX) and other myelin-related genes [118]. Furthermore, EGR2/Krox20 can activate the MPZ promoter in cotransfected Schwann cells [119]. *EGR2*/Krox20 mutations are likely to act through gain of function, since heterozygous Krox20-null mice are not affected. Some of the mutant proteins show reduced DNA binding and transactivation in in vitro assays [120], and a dominant-negative effect on myelin gene expression has been suggested [118]. The pathogenesis seems to consist of a combination of (partial) loss-of-function and gain-of-abnormal-function mechanisms that require further clarification.

One recessive mutation in the R1 domain of EGR2/Krox20 preventing interactions with the NAB corepressor has been classified as CMT4E [116]. It probably results in the deregulation of EGR2 by increasing its activity on myelin genes. The recessive nature of this mutation may be due to a threshold effect in which increased levels of expression of a target gene have to be reached for causing a phenotype [120]. This hypothesis appears plausible in the context of the dosage sensitivity of the PMP22 [17, 18] and P0 [107] genes.

Gap junction protein beta 1 (GJB1/Cx32)

Mutations affecting *GJB1* cause CMT1X. Linked to the X-chromosome and thus inherited without male-to-male transmission, this is the second most common form of demyelinating CMT, accounting for 10–15% of all cases. CMT1X is considered to be an X-linked dominant trait because it affects female carriers with variable clinical involvement due to random X-chromosome inactivation [121]. Males are uniformly affected, and the clinical manifestations are indistinguishable from those in patients with CMT1A or CMT1B. In comparison to CMT1A and CMT1B biopsies, less demyelination and remyelination and more axonal degeneration/regeneration are observed in CMT1X [122–124].

More than 200 mutations have been found in *GJB1* since the original CMT1X gene was identified [125]. Despite this genetic heterogeneity, the disease severity caused by *GJB1* mutations is similar in affected men [122, 126, 127]. Notably in contrast to the other CMT1 genes, some particular *GJB1* mutations show signs of central nervous system (CNS) involvement [128–131].

GJB1/Cx32 is a four-transmembrane protein of the connexin family, components of gap junctions that permit the exchange of small signaling molecules across the membranes of cells. In PNS nerves, Cx32 is found in incisures and paranodal loops of myelinating Schwann cells [132]. It has been suggested that Cx32 may form gap junctions between adjacent layers of the myelin sheath to establish a short radial pathway, and convincing experimental evidence has been obtained [133]. However, the pathway and rate of diffusion of 5,6-carboxyfluorescein in *Gjb1* knockout mice were not altered compared with wild-type mice. Since other connexins such as Cx29 (human homologue, Cx31.3) are also present in inscisures [134, 135], they may partially substitute for the lack of Cx32. One would then hypothesize that unknown peculiar features of Cx32-containing channels are the basis for more specific disruptions of the radial pathway by *GJB1/Gjb1* mutations that cause demyelination in humans and mice [121, 136].

The consequences of the molecular alterations of CMT1X-associated Cx32 mutants have been analyzed by expression studies in heterologous cells in culture and *Xenopus* oocytes [137]. These experiments revealed that many mutants are not able to form functional channels. Others build up channels but with altered biophysical characteristics. As also observed for PMP22 mutant proteins, a number of altered Cx32 proteins show defects in intracellular trafficking [138]. Some are completely blocked in the ER. Others reach the cell membrane but with an increased accumulation in the Golgi apparatus when compared with wild-type Cx32. The detailed functional consequences of these findings remain to be determined and appear to be complex [139, 140]. In particular, the situation has to be assessed in myelinating Schwann cells, since it is likely to differ considerably from the settings in cultured nonmyelinating cells [141].

Some Cx32 mutants may have additional toxic gain-of-function effects, in particular when associated with unusually severe phenotypes. Since connexins assemble into hexamers, dominant-negative affects appear likely. Cx32 mutants, however, cannot interact with themselves since *GJB1* is subject to X-chromosome inactivation [121]. They may interact, however, with other connexins expressed by myelinating Schwann cells (or if CNS abnormalities have been observed, with connexins expressed by cells in the CNS).

Ganglioside-induced differentiation-associated protein-1 (GDAP1)

Mutations in *GDAP1* are associated with a severe recessive form of CMT termed CMT4A [142–146]. Patients have strongly reduced NCV with a clinical onset early in childhood, often progressing to strong clinical impairment. On nerve biopsies, severe hypomyelination, basal lamina onion bulbs (possibly indicating Schwann cell death) and loss of large myelinated axons are observed. In contrast, a second set of *GDAP1* mutations shows a recessive CMT2-like phenotype with normal NCV and loss of myelinated fibers without signs of demyelination. Vo-

cal cord paresis was noted as additional feature [146]. Recent data suggest that patients carrying mutations in *GDAP1* can exhibit a definitive demyelinating neuropathy, an axonal form or an intermediate peripheral neuropathy with both features [147, 148].

GDAP1 encodes a protein with two predicted transmembrane domains and a glutathione *S*-transferase domain. The gene was originally identified due to its high expression in differentiated Neuro2a cells induced by GD3 synthase overexpression and in retinoic acid-induced neural-differentiated mouse embryonic carcinoma P19 cells [149]. GDAP1 is expressed in the brain and in peripheral nerve [146], but no data are yet available at cellular resolution. One might only speculate at this time whether cell-automomous or non-cell-autonomous mechanisms related to specific *GDAP1* mutations are responsible for the observed peculiar Schwann cell and/or axonal phenotypes. The glutathione *S*-transferase domain indicates some function of GDAP1 in detoxification and protection against reactive oxygen species. Such processes are implicated in motor neuron death in amyotrophic lateral sclerosis and other neurodegenerative diseases [150]. Similar mechanisms are also likely to be involved in Schwann cell death in diabetic neuropathies. Thus, the function of GDAP1 might be a key element in defining potential common disease mechanisms of various neuropathies.

Myotubularin-related protein-2 (MTMR2)

Mutations affecting *MTMR2* are the cause of a severe autosomal recessive, demyelinating form of CMT that has been named CMT4B1 [151, 152]. CMT4B1 has its clinical onset in early childhood and leads progressively to wheelchair dependence [153]. NCV is strongly reduced. Nerve biopsies show a peculiar feature with the presence of focally infolded and redundant loops of myelin sheets. These characteristics suggest a primary insult to the myelinating Schwann cell. MTMR2 is, however, also expressed by peripheral neurons [154, 155], and the contribution of the different cell types remains to be determined.

MTMR2 belongs to a family of myotubularin-related proteins that is named after the founding member myotubularin (MTM), the mutated culprit gene in X-linked myotubular myopathy [156]. MTMR2 contains a pleckstrin homology-GRAM (glucosyltransferase, Rab-like GTPase activator and myotubularin) domain, a phosphatase domain, a coiled-coil domain and a PDZ-binding motif [156]. The membrane phospholipids phosphatidylinositol-3-phosphate [PI(3)P] and phosphatidylinositol-3,5-phosphate [PI(3,5)P2] are dephosphorylated by MTM, MTMR2, MTMR3 and MTMR6 [155, 157–160]. Since phosphoinositides regulate intracellular membrane trafficking [161], the demyelinating neuropathy CMT4B1 might be triggered by the malfunction of neural membrane recycling, and/or endocytic or exocytotic processes, and/or disturbed membrane-mediated transport pathways. This may include autophagy, the process that targets cytosolic proteins and organelles to lysosomes for hydrolase-mediated degradation [162]. If this pathway is indeed disturbed, other proteins involved in the same process might be good candidates for other forms of CMT. Altered lysosomal function can cause demyelinating peripheral neuropathies as revealed by mice deficient in the lysosomal membrane protein LIMP-2/LGP85 [163]. In addition, the disease mechanisms in CMT1C (LITAF/SIMPLE) and possibly of some PMP22 point mutations [79] might be related. Furthermore, recent observations that overexpression of PMP22 affects membrane trafficking and the finding of vesicles resembling autophagic vacuoles in PMP22 overexpressing cells might hint toward some kind of functional connection [65, 77].

The known *MTMR2* mutations show a complex pattern [152, 154, 164], but loss of phosphatase activity appears to be frequent [155].

Myotubularin-related protein-13/Set binding factor 2 (MTMR13/SBF2)

Based on the finding of mutations in *MTMR2* in CMT4B1, related genes that show similar pathological features have been analyzed. As a result, mutations in *MTMR13/SBF2* have been identified in this recessive demyelinating CMT subtype [165, 166]. In one family, the disease was also associated with glaucoma [166]. *MTMR13/SBF2* encodes a homologue of *MTMR2* but without a functional phosphatase domain. Loss of phosphatase activity was previously shown to be associated with disease-causing mutations of MTMR2 [155]. A potential disease mechanism that would reconcile these findings may be that the two MTMRs that cause CMT4B, MTMR13/SBF2 as phospatase-inactive adaptor and MTMR2 as catalytic subunit interact as a complex together to regulate the levels of PI(3), PI(5) and PI(3,5) phosphatidylinositol and/or the subcellular localization of the complex. Such a role for MTMR-like pseudophosphatases was proposed earlier [167]. Furthermore, at least some monomeric myotubularins appear to be catalytically inactive, and binding of substrate phosphoinositides and the allosteric activator PI(5) triggers oligomerization and activation [157]. How pseudophosphatases may affect this regulatory circuit is an exciting open question.

Crude expression analysis of *MTMR13/SBF2* revealed mRNA in multiple tissues, especially in brain, spinal cord and sciatic nerve. Cellular resolution combined with functional experiments in the protein-expressing cell types will be required to elucidate the tantalizing cell biology of the CMT4B diseases. Such analyses will also help to understand why the disease is affecting only pe-

ripheral nerves or, in the case of the glaucoma-associated mutation, also other cell types [166].

N-*myc*-downstream regulated gene 1 (*NDRG1*)

Mutations in *NDRG1* are responsible for CMT4D (also called HMSN-Lom; [168, 169]). This is a rare recessive demyelinating syndrome that also includes hearing loss and dysmorphic features caused by a protein-truncating nonsense mutation. Onset of disease is early in life with fast progression leading to severe handicaps. *NDRG1* is widely expressed, but its function is unknown [170, 171]. Recent computer-aided modeling suggests that NDRG1 belongs in the α/β hydrolase superfamily, but it is predicted not to be enzymatically active [172]. If it associates with other hydrolases, this may hint toward a function in degradation processes that have been implicated in other types of demyelinating CMT. Alternatively, NDRG1 might be involved in the cellular stress response and the regulation of cell growth [173].

PRX

PRX was identified as a potential candidate for CMT based on the phenotype of *Prx*-deficient mice [174]. These animals showed PNS myelin outfoldings (tomacula, focal hypermyelination), followed by demyelination similar to *Pmp22*-deficient mice, but with a delayed onset [45]. In addition, *Prx*-deficient mice displayed the unique feature among myelin mutants of neuropathic pain [174]. Prominent sensory impairments were also observed in CMT4F patients carrying *PRX* mutations [175–177]. Recessive mutations in *PRX* were initially identified in patients presenting with a severe form of demyelinating DSS. However, *PRX* mutations can cause a broad spectrum of demyelinating neuropathies [178].

PRX is a PDZ domain-containing protein that is exclusively expressed by myelinating Schwann cells [179, 180]. In the adult myelinated fibers, PRX is connected to the dystroglycan complex by dystrophin related protein-2 (DRP-2) linking the basal lamina to the cytoskeleton of the Schwann cell, thus allowing potential signal transduction [181]. During development, PRX is found in the adaxonal membrane of the myelinating Schwann cell and may have some additional function [180]. Furthermore, an isoform of PRX is targeted to the nucleus of embryonic Schwann cells, suggesting that this protein can shuttle between the nucleus and cortical signaling/adherence complexes [182].

Axonal forms of CMT

Kinesin1B (KIF1B)

A single mutation in the kinesin superfamily motor protein *KIF1B* has been identified up to now in dominant CMT2A [183]. The mutant allele leads to loss of function in the motor domain and indicates that defects in axonal transport due to a mutated motor protein can be responsible for axonal peripheral neuropathy. Heterozygous *Kif1B* null mice develop a peripheral neuropathy similar to humans, supporting haploinsufficiency as the underlying genetic mechanism [183]. It is currently debated, however, which of the two isoforms generated by differential splicing of *KIF1B*, KIF1Bα and/or KIF1Bβ, is defective in CMT2A [183, 184].

The kinesin superfamily (KIF) motors are responsible for microtubule-dependent transport of a variety of organelles and vesicles [185]. KIF1Bα mediates the transport of mitochondria [186]. KIF1Bβ associates with synaptic vesicles containing synaptophysin, synaptotagmin, and SV2 [183]. If, indeed, the transport of mitochondria is affected, the resulting phenotype may be caused by a similar mechanism as suggested for neurofilament mutations associated with CMT4E (see below; [187]). In any case, motor and sensory neurons possess very long axons and might be particularly sensitive to altered transport of various loads. Such disturbed transport mechanisms were suggested earlier to be a potential common denominator in several peripheral neuropathies, since axonal impairment, also in demyelinting forms of CMT, appears to start almost always distally and is associated with defects in the cytoskeleton [21].

Small GTP-ase late endosomal protein gene 7 (RAB7)

CMT2B is characterized by marked distal muscle weakness and wasting, high frequency of foot ulcers, and amputations of the toes due to recurrent infections [188–190]. Two missense mutations have been found in *RAB7* as the underlying genetic defect [191].

RAB7 encodes a member of the Rab family of ras-related GTPases that are involved in intracellular membrane trafficking [191]. *RAB7* is widely expressed, but its function in the nervous system remains to be determined. In particular, it will be an important task to elucidate why particular RAB7 mutations manifest themselves exclusively in the peripheral nervous system.

Lamin A/C (LMNA)

Recessive mutations affecting *LMNA* are the cause of the axonal neuropathy CMT2B1 [192, 193]. The onset of this CMT disease form is usually in the 2 decade with rapid progression involving upper limbs and proximal muscles, leading to severe handicaps. Motor NCVs are normal or slightly slowed, and biopsies reveal a reduction of myelinated axons and clusters of regenerated axons. Similar pathological features have been observed in sciatic nerves of *Lmna*-deficient mice [193]. Particular *LMNA* mutations are associated with a number of other inherited

diseases, including limb-girdle muscular dystrophy type 1B, autosomal dominant Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy type 1A and autosomal dominant partial lipodystrophy. This suggests the existence of distinct functional domains in lamin A/C that are essential for different cell types.

LMNA encodes the nuclear components lamins A/C. These proteins are thought to be the evolutionary progenitors of intermediate filament proteins of the cytoskeleton and may have dual functions as building blocks as well as transcriptional regulators [194]. Knowledge of the structure-function relationship of lamins A/C will undoubtedly provide the key to understanding how specific mutations in *LMNA* lead to the observed multitude of genetic diseases.

Neurofilament light chain (*NEFL*)

NEFL encodes an intermediate filament protein that is a major cytoskeleton component of neurons. The first patients identified as carriers of dominant *NEFL* mutations showed the clinical picture of axonal CMT with additional hyperkeratosis, classified as CMT2E with early onset and slightly reduced NCVs [195, 196]. Later, additional mutations were reported with significant slowing of NCVs [197], some with the more severe DSS phenotype [198]. The nerve biopsy of one patient showed dysmyelination, loss of myelinated fibers, onion bulbs and clusters of regenerating axons. Thus, the phenotype of *NFEL* mutations appears to be heterogeneous, with different degrees of severity of axonal neuropathy and/or occasional features of severe demyelinating CMT [198].

NEFL is mainly expressed by neurons, although some expression has also been found in Schwann cells deprived of axonal contact [199]. *Nefl* null mice do not develop a CMT2-like neuropathy [200], but a point mutation that disrupts the assembly of neurofilaments causes severe peripheral neuropathy and massive motor neuron death in transgenic mice [201]. Since CMT2E is autosomal dominantly inherited, these data suggest that *NEFL* mutations associated with CMT2E act by gain of function rather than haploinsufficiency. This hypothesis is further supported by recent findings that some CMT2E-NEFL proteins disrupt assembly and axonal transport of neurofilaments as well as mitochondria localization in various transfected cells, including sensory neurons [187, 202, 203].

Closing remarks

Recent progress in the genetics of CMT has been remarkable, and 14 genes have been described so far in the pathogenetics of the different forms of the disease. For some of the disease-causing proteins, we have a rather clear picture about their function. For others, we are just at the beginning of determining their role in myelinated nerves. With regard to disease mechanisms, the crucial interplay between neurons (axons) and myelinating Schwann cells has turned into a prominent factor [6]. This has become particularly obvious with the finding that the disability in most if not all inherited neuropathies, axonal and demyelinating forms, is correlated with axonal loss [33, 35, 74, 204]. Myelin deficiency also leads to a decrease in axonal caliber, axonal transport, and affects neurofilaments and microtubules [205]. However, the signals that mediate this cell-to-cell communication are largely unknown. Loss of trophic support by damaged Schwann cells may contribute, and recent data suggest that inflammation is involved [206].

Further work will focus on the identification of other genes that can cause CMT. Modern molecular methods are expected to lead to fast progress on this issue by high-throughput transcriptomics [118, 207] and proteomics in conjunction with simplified chromosomal mapping, made possible due to the advances in the Human Genome Project. Deciphering the exact role of the different mutated CMT proteins in neurons and/or Schwann cells and elucidating the underlying disease mechanisms will continue to be a formidable task. This will include elucidation of the specific contributions of the affected proteins in Schwann cells and/or neurons to the disease phenotype (primary and secondary insults). On the cellular level, aberrant regulation of intracellular transport of proteins and lipids (membranes) in conjunction with altered intracellular degradation mechanisms, together with impaired axonal transport, have emerged as novel potentially important contributors to the various CMT phenotypes.

Clinical neurologists, pathologists, geneticists, cell biologists and molecular biologists will be required to work closely together to meet the challenge of understanding CMT. This endeavor should not only bring us closer to the development of potential treatment strategies, but we will also learn important lessons about the biology of the peripheral nerve.

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