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Review

Overlapping molecular pathological themes link Charcot–Marie–Tooth neuropathies and hereditary spastic paraplegias

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ABSTRACT

In this review we focus on Charcot–Marie–Tooth (CMT) neuropathies and hereditary spastic paraplegias (HSPs). Although these diseases differ in whether they primarily affect the peripheral or central nervous system, both are genetically determined, progressive, long axonopathies that affect motor and sensory pathways. This commonality suggests that there might be similarities in the molecular pathology underlying these conditions, and here we compare the molecular genetics and cellular pathology of the two groups.

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Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CMAP, compound muscle action potentials; CMT, Charcot–Marie–Tooth; CNS, central nervous system; ER, endoplasmic reticulum; HMN, hereditary motor neuropathy; HMSN, hereditary motor and sensory neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; HSP, hereditary spastic paraplegia; NCV, nerve conduction velocity; PI, phosphoinositides; PNS, peripheral nervous system; SNAP, sensory nerve action potentials.

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Introduction

In this review we focus on Charcot–Marie–Tooth (CMT) neuropathies and hereditary spastic paraplegias (HSPs). A key difference between these two groups of conditions is in the target cells that they primarily affect, with CMT neuropathies affecting the peripheral motor and sensory nerves, while the HSPs principally affect the central nervous system (CNS) axons of the corticospinal tract and dorsal columns. However, CMT neuropathies and HSPs also share many features, for example, both are genetically determined long axonopathies that affect motor and sensory pathways and which can be later-onset and are typically progressive. This commonality suggests that there might be similarities in the molecular pathology underlying these conditions, and here we compare and contrast the molecular genetics and cellular pathology of the two groups of neurodegenerative diseases.

Overview of clinical features and classification

CMT neuropathies

CMT neuropathy can be divided into demyelinating (referred as CMT1), axonal (CMT2) and intermediate clinical variants. These CMT phenotypes are grouped within the hereditary motor and sensory neuropathies (HMSN) according to clinical, electrophysiological and neuropathological criteria (Dyck et al., 2005). Other CMT related neuropathies have been classified, depending on the nerves involved, as hereditary motor neuropathies (HMN) or hereditary sensory and autonomic neuropathies (HSAN) (Dyck and Ohta, 1975; Harding and Thomas, 1980). More recently, genotype–phenotype correlation studies have revealed several more complex CMT neuropathies, involving other tissues such as the CNS, muscle, bone and skin.

The modern classification of CMT neuropathies and related disorders is based on genetics. This new era started with the discovery of the 1.4 megabase tandem duplication at chromosome 17p11.2 associated with autosomal dominant demyelinating CMT1A (Raeymaekers et al., 1991; Lupski et al., 1991; Timmerman et al., 1992). This genomic mutation is the most frequent cause of CMT disease (Nelis et al., 1996). Since then all of the Mendelian inheritance patterns have been described for CMT and 52 loci and 50 genes have been identified (Table 1). Autosomal dominant (AD) inheritance is the most frequently observed in families with CMT1, CMT2, or intermediate forms (DI-CMT). Dominant X-linked inheritance is observed in CMTX families, but some rare recessive X-linked CMT forms have also been reported. Autosomal recessive (AR) CMT accounts for less than 10% of patients, although this may be an underestimation due to the small size of sibships, and many AR-CMT patients may remain unrecognised or considered to be sporadic cases (reviewed in Timmerman et al., 2006).

Hereditary spastic paraplegias

The defining clinical feature of the HSPs is progressive lower limb spastic paraparesis. Although with increasing knowledge of the molecular genetics of HSP the distinction is becoming blurred, classically HSPs are divided into “pure” or uncomplicated forms, versus complex or complicated forms. In pure HSPs, progressive spastic paraplegia is the predominant clinical feature, and it may begin at any age, although onset in early adult life is typical. Minor additional features such as loss of vibration sense, bladder urgency or subclinical peripheral nerve involvement are relatively common. This form is the most prevalent in Northern Europe and North America. In contrast, in complex forms, other prominent neurological or non-neurological features are additionally present (Reid, 1999; Reid and Rugarli, 2010; McDermott et al., 2000; Harding, 1984; Fink, 1997).

The clinical picture of spastic paraplegia is reflected in the neuropathology of HSP, which typically shows a length-dependent ‘dying back’ axonopathy, affecting the distal ends of sensory and motor axons in the spinal cord. Strikingly, neuronal cell body loss is an infrequent finding, consistent with the main site of pathology being in the axon (reviewed in Reid and Rugarli, 2010). This length-dependent neurodegeneration is reminiscent of that seen in the peripheral nervous system (PNS) in some CMT patients.

As with CMT, the HSPs show extreme genetic heterogeneity. AD and AR inheritance patterns are found in pure and complex types of HSP, although X-linked recessive inheritance is rare. Sporadic cases are also found, and these have a number of genetic explanations, including singleton AR cases, de novo mutations and non-penetrant AD mutations in a parent. Currently nearly 50 HSP loci have been mapped and more than 20 causative genes (termed SPG — *s*pastic *p*araplegia or *sp*astic *g*ait) have been identified, leading to an expanding genetic classification of HSP disorders (Table 1).

Clinical overlaps between CMT and HSP

Peripheral neuropathy can be a feature of some types of HSP. The most obvious example is Silver syndrome, a complicated HSP caused by mutations in the Berardinelli–Seip congenital lipodystrophy 2 gene (*BSCL2*; *SPG17*). Dominant mutations in this gene present with neurological features on a spectrum ranging from HSP to CMT, with a significant subset of patients having an overlap condition termed Silver syndrome (Windpassinger et al., 2004; Irobi et al., 2004a; Auer-Grumbach et al., 2005). An axonal peripheral neuropathy may be a feature of HSP families with *atlastin-1* (*SPG3A*) mutations (Ivanova et al., 2007), and mutations in this gene also cause hereditary sensory neuropathy type I (HSN-I). Mutations in the *SPG10* gene *KIF5A* were first found in a family with pure HSP, but the phenotypic spectrum associated with mutations in this gene has expanded to include peripheral neuropathy, with the patients often having a phenotype reminiscent of Silver syndrome (Goizet et al., 2009). *REEP1* (*SPG33*) mutations are rarely accompanied by amyotrophy, peripheral nerve involvement and bulbar palsy (Hewamadduma et al., 2009). *NIPA1* (*SPG6*) and *spastin* (*SPG4*) mutation may also be associated with peripheral nerve involvement (Schulte et al., 2003; Liu et al., 2008). This clinical overlap hints at commonalities in the molecular pathology underlying the two groups of conditions, and these are discussed below.

Similarities and differences in the molecular and cellular pathology of CMT neuropathies and HSPs

The spectacular advances in gene identification over the last decade have allowed functional classes of CMT and HSP genes to be identified (Fig. 1 and Table 1). In some cases, these functional classes strongly overlap, whereas other classes appear, at least so far, to be specific to one disease or the other. In the following sections we will discuss these similarities and differences.

Functional groupings that overlap in CMT and HSP

Myelination

CMT disorders. Mutations in proteins of the myelinating Schwann cells are frequently implicated in demyelinating CMT neuropathies. Peripheral myelin 22 kDa protein (PMP22) and myelin protein zero (MPZ) are structural membrane proteins of the compact myelin sheet. Connexin-32 (GJB1) is a gap junction protein present in non-compact myelin. Periaxin (PRX) is an adaptor protein and is part of a protein complex maintaining Schwann cell-axon contact. The early growth response 2 (*EGR2*) and *SOX10* genes encode essential transcription factors and drive the expression of the four myelin

genes, *PMP22*, *MPZ*, *GJB1* and *PRX*, implicated so far in CMT1 disease (reviewed in Niemann et al., 2006). In this review we will not highlight other rare CMT causing genes that have a less clear function in myelination.

Table 1
Known HSP and HMSN genes, divided into functional groups. HSP genes in red, HMSN genes in blue, genes mutated in both diseases in black.

Gene symbol	Protein name	Main phenotype	Cell biological function
Membrane traffic			
SPG3A	Atlastin–1	AD pure HSP HSNI	ER morphogenesis BMP signalling
SPG4 or SPAST	Spastin	AD pure HSP	ER morphogenesis Endosomal traffic BMP signalling Cytokinesis Cytoskeletal regulation
SPG6 or NIPA1	NIPA1	AD pure HSP	Endosomal traffic BMP signalling
SPG8 or KIAA0196	Strumpellin	AD pure HSP	Endosomal traffic Cytoskeletal regulation
SPG11	Spatacsin	AR complex HSP	Endosomal traffic DNA repair?
SPG12 or RTN2	Reticulon2	AD pure HSP	ER morphogenesis
SPG15 or ZFYVE26	Spastizin or ZFYVE26 or FYVE–CENT	AR complex HSP	Endosomal traffic Cytokinesis DNA repair?
SPG17/BSCL2	Seipin	AD complex HSP Silver syndrome	ER membrane protein Lipid droplet biogenesis
SPG20	Spartin	AR complex HSP	Endosomal traffic BMP signalling Lipid droplet biogenesis Mitochondrial?
SPG21	Maspardin	AR complex HSP	Endosomal traffic
SPG31 or REEP1	REEP1	AD pure HSP	ER morphogenesis
SPG48 or KIAA0415	KIAA0415	AR complex HSP	Endosomal traffic DNA repair?
ARHGEF10	Rho guanine–nucleotide exchange factor–10	AD CMT	Rho GTPase signalling
DNM2	Dynamin 2	AD CMT	Cytoskeleton regulation and endocytosis
FGD4	Frabin	AR CMT	Rho GTPase signalling, Phospho–inositol metabolism, Cytoskeleton regulation and endocytosis
LITAF (SIMPLE)	Lipopolysaccharide–induced TNF factor	AD CMT	Lysosomal sorting
MTMR2	Myotubularin 2	AR CMT	Phospho–inositol metabolism, Vesicle sorting
MTMR13	Myotubularin 13	AR CMT	Phospho-inositol metabolism, Vesicle sorting
RAB7	Small GTP–ase RAB7	AD CMT	Intracellular vesicle trafficking
SH3TC2	SH3 domain and tetra–tricopeptide repeats–2	AR CMT	Recycling of endosomes
Mitochondrial			
SPG13 or HSPD1	HSP60	AD pure HSP	Mitochondrial chaperone
SPG7	Paraplegin	AR complex HSP	Mitochondrial protease
GDAP1	Ganglioside–induced differentiation–associated protein–1	AR CMT	Signal transduction and mitochondrial function
MFN2	Mitofusin 2	AD CMT	Mitochondrial fusion
Myelination			
SPG2 or PLP1	PLP	XLR complex HSP	Myelin protein
SPG35 or FA2H	Fatty acid 2–hydroxylase	AR complex HSP	Hydroxylation of myelin lipids
SPG44 or GJC2	GJA12	AR complex HSP	Gap junction protein
EGR2	Early growth response–2	Complex CMT	Transcription factor
GJB1	Connexin–32	X–linked CMT	Gap junction protein
MPZ	Myelin protein zero	AD CMT	Myelin compaction
PMP22	Peripheral myelin protein–22	AD CMT	Structural myelin formation and maintenance
PRX	Periaxin	AR CMT	Schwann cell–axon contact
SOX10	SRY (sex determining region Y)–box 10	Complex CMT	Transcription factor
Cytoskeleton stability and motor proteins			
SPG10 or KIF5A	KIF5A	AD complex HSP	Microtubule-based motor protein
DCTN1	Dynactin–1	Distal HMN	Microtubule–directe motor protein
KIF1B	Kinesin–1B	AD CMT	Microtubule motor
LMNA	Laminin A/C	AR CMT	Protein of the inner nuclear envelope
NEFL	Neurofilament light chain	AD CMT	Neurofilament structure
TUBB3	Tubulin beta–3	Unspecified CMT	Neuron–specific tubulin
RNA and protein metabolism & molecular chaperones			
AARS	Alanine tRNA synthetase	AD CMT	Aminoacyl tRNA synthetase
KARS	Lysine tRNA synthetase	Complex CMT	Aminoacyl tRNA synthetase
GARS	Glycyl tRNA synthetase	AD CMT (distal HMN)	Aminoacyl tRNA synthetase
YARS	Tyrosyl tRNA synthetase	AD CMT	Aminoacyl tRNA synthetase
HSPB1 (HSP27)	Small heat shock protein B1	AD CMT (distal HMN)	Protein folding, neuronal survival, cytoskeleton dynamics
HSPB8 (HSP22)	Small heat shock protein B8	AD CMT (distal HMN)	Protein folding, neuronal survival
Miscellaneous			
SPG1 or L1CAM	L1–CAM	XLR complex HSP	Cell adhesion and signalling
SPG5 or CYP7B1	CYP7B1	AR pure HSP	Cholesterol metabolism
SPG39	Neuropathy target esterase	AR complex HSP	Phospholipid homeostasis target of organophosphates
SPG42 or SLC33A1	SLC33A1	AD pure HSP	Acetyl CoA transporter

AD = autosomal dominant, AR = autosomal recessive, XLR = X-linked recessive.

As mentioned before, the most common CMT mutation is the "CMT1A duplication", in which duplication of a 1.4 megabase region on chromosome 17p12 occurs via an unequal crossing-over event between proximal and distal low copy repeats (LCR). The CMT1A duplication represents 70% of AD CMT1. Interestingly, the reciprocal deletion of the same CMT1A region results in another neuropathy, hereditary neuropathy with liability to pressure palsies (HNPP). Both the CMT1A duplication and the HNPP deletion frequently occur de novo and are then transmitted within the family in an AD pattern. As the entire regulatory and coding region of the *PMP22* gene maps within the CMT1A/HNPP region, clinical phenotypes associated with *PMP22* are dosage sensitive; three copies of *PMP22* cause the demyelinating CMT1A neuropathy, while one copy of *PMP22* causes the HNPP neuropathy. However, point mutations within the *PMP22* gene itself or genomic rearrangements involving regulatory regions can also cause HNPP or variants of CMT1, but these mutations are uncommon (Timmerman and Lupski, 2006; Zhang et al., 2010). Several PMP22 transgenic rodent models have been developed to mimic these CMT1A/HNPP dosage effects, and were used to develop

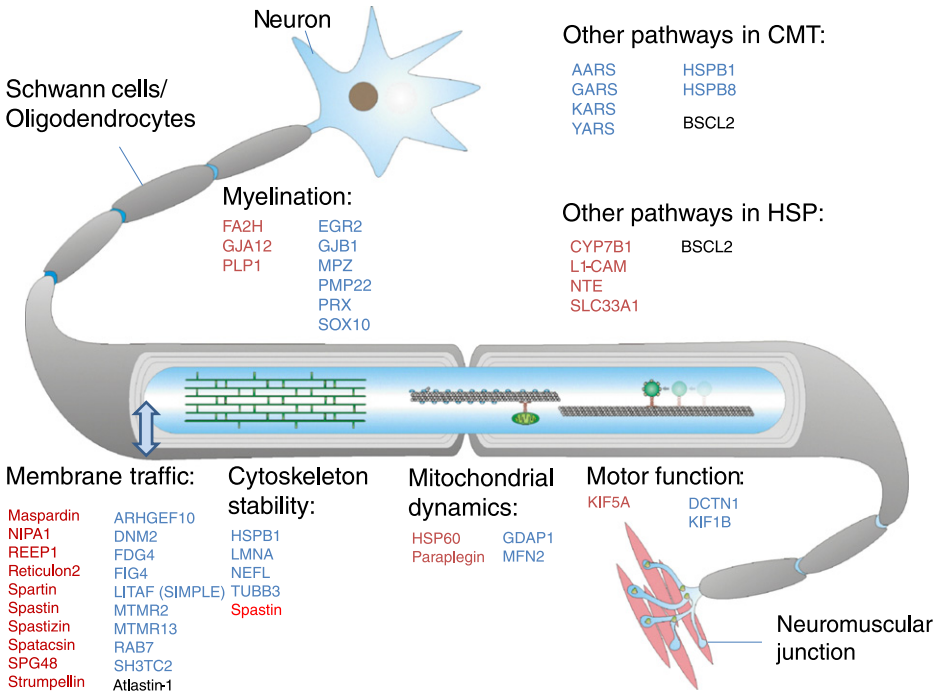

Fig. 1. Similarities and differences in the molecular pathology of CMT and HSP. The HSP associated genes are indicated in red and the CMT neuropathy associated genes are in blue. Genes involved in both HSP and CMT diseases are in black.

therapeutic approaches for the demyelinating CMT1 neuropathy (reviewed in Nave et al., 2007).

The AD inherited CMT1B type is caused by mutations in the *MPZ* gene, which encodes P0, the most abundant protein in myelin (Hayasaka et al., 1993). More than 100 different point mutations, most missense mutations, have been described in this gene, representing a mutation frequency of approximately 5% of CMT1. Interestingly, genotype/phenotype correlations have shown that *MPZ* mutations targeting specific amino acid changes in the P0 protein can also cause an axonal type of CMT or rarely congenital hypomyelination. Pathological studies in peripheral nerve biopsies demonstrate that specific mutations can cause a decompaction of the myelin sheet (myelinopathy), clusters of regenerating axons (axonopathy), or a mixed phenotype (Shy et al., 2004). Specific *MPZ* mutations have been modelled in the mouse and revealed a dominant negative effect of the mutant P0 protein or cause a pathogenic effect in the unfolded protein response (Fratta et al., 2011).

Mutations in *GJB1* cause the X-linked variant of CMT (CMTX) (Bergoffen et al., 1993). *GBJ1* mutations cause approximately 12% of CMT1 cases and can target almost every codon of the gene. In addition, some rare *GBJ1* promoter variants have been shown to be pathogenic. In general patients with connexin 32 protein mutations usually have a homogeneous clinical CMT disease course, with a demyelinating phenotype, but they might also have an axonopathy (reviewed in Kleopa and Scherer, 2006).

Loss-of-function mutations in the *PRX* gene cause an early onset AR-CMT, known as CMT4F (Boerkoel et al., 2001). Patients with *periaxin* mutations have demyelination with focal thickening of the myelin, and abnormal paranodes that lack septate-like junctions. Periaxin is part of the dystroglycan–dystrophin-related protein-2 complex, which links the Schwann cell cytoskeleton to the extracellular matrix. *Periaxin*-null mice develop a demyelinating peripheral neuropathy later in life. Their peripheral nerves can remyelinate, but show abnormal myelin thickness (Court et al., 2008). Mutations in the EGR2 and SOX10 transcription factors usually cause more complex CMT phenotypes, ranging from severe congenital hypomyelination to a classical CMT1 neuropathy in the case of EGR2, and to CMT plus Waardenburg–Hirschsprung syndrome in the case of SOX10 (Warner et al., 1998; Inoue et al., 1999).

HSP disorders. Mutations in three myelin genes, *proteolipid protein1 (PLP1)*, *fatty acid 2-hydroxylase (FA2H)* and *GJA12/GJC2* can cause hereditary spastic paraplegia. Using alternative splicing, the *PLP1* gene encodes two myelin protein isoforms, proteolipid protein (PLP) and DM20, which together are the most abundant proteins of CNS myelin. Mutations in *PLP1* cause a spectrum of disorders, ranging from a severe leukodystrophy called Pelizaeus–Merzbacher disease, to a much milder spastic paraplegia (*SPG2*). The SPG2 phenotype tends to be associated with whole gene deletions, or with truncating mutations, or missense mutations that alter non-conserved amino acids. Mutations that affect only the PLP isoform have also been suggested to be associated with the milder SPG2 phenotype. The *PLP1* knockout mice, which are a model of *SPG2*, have only subtle abnormalities of the CNS myelin sheath (reviewed in Gruenenfelder et al., 2011). However, axonal transport of mitochondria and other organelles in these mice is significantly impaired, consistent with the view that the oligodendrocyte plays a role in supporting the axon that requires the *PLP1* encoded proteins, distinct from their role in myelination (Edgar et al., 2004).

As well as being a cause of CMT (see above), mutations in gap junction proteins may also underlie HSP. The *GJA12/GJC2 (SPG44)* gene encodes the gap junction protein connexin 47. Gap junction channels incorporating connexin 47 are essential for proper myelin formation. AR mutations in this gene cause a Pelizaeus–Merzbacher like disease, although a mutation has also been described in a family with complicated HSP (Orthmann-Murphy et al., 2009; Uhlenberg et al., 2004). Thus, like the *PLP1* gene, mutations in this gene appear to cause a spectrum of disorders ranging from severe leukodystrophy to a much milder spastic paraplegia.

Mutations in *FA2H* (*SPG35*) cause an AR complicated spastic paraplegia in which white matter abnormalities are a prominent feature (Edvardson et al., 2008; Dick et al., 2010). FA2H catalyses the hydroxylation of sphingolipid components of myelin, including galactosylceramide, and pathogenic mutations cause deficient enzymatic activity

(Dick et al., 2010). Mutations in this gene also cause a form of neurodegeneration with brain iron accumulation (Kruer et al., 2010). Although many of the clinical features associated with FA2H deficiency are probably caused by abnormality of the protein's function in oligodendrocytes, not all are, as additional phenotypes are seen in mice constitutively lacking *FA2H*, versus those in which the gene is conditionally lost only in oligodendrocytes (Potter et al., 2011).

Membrane traffic

Membrane traffic refers to the targeted movement of small membrane-bound vesicular or tubular transport intermediates between intracellular membrane compartments. A typical membrane traffic process involves cargo concentration co-ordinated with vesicle formation and budding, a transport step, driven by molecular motors acting on the cytoskeleton, followed by target recognition and fusion with the target membrane. These steps are frequently regulated by RAB GTPases, which in turn are often recruited, together with other effector proteins, to membranes by interactions with membrane phosphoinositides (PIs).

CMT disorders. Several genes implicated in intracellular membrane traffic processes are mutated in CMT neuropathies. Here we focus on mutations in *SIMPLE* (*LITAF*), *DNM2*, *RAB7* and *SH3TC2*. We will also highlight genes that have a role in the endosomal PI phosphate metabolism of the myelinating Schwann cells, namely two myotubularin-related phosphatases (*MTMR2* and *MTMR13*) and the *FIG4* phosphatase. Furthermore, mutations in *frabin* (*FGD4*) and the *ARHGEF10* guanine-nucleotide-exchange-factor, highlight the role of cytoskeletal regulation by Rho GTPase family signalling in Schwann cell biology.

Mutations in the gene encoding the endocytic protein dynamin 2 (*DNM2*) are associated with a dominant intermediate CMT subtype (DI-CMTB) (Zuchner et al., 2005). However, *DNM2* mutations can also cause an AD centronuclear myopathy (Bitoun et al., 2005). Patients with DI-CMTB have a classic, mild to moderately severe CMT phenotype. The DNM2 protein belongs to the dynamin family of ubiquitously expressed GTPases, which are implicated in many cellular functions, including cytoskeleton regulation and endocytosis. The dynamins can bind to actin and other cytoskeletal proteins, and their main cellular role is in catalysing fission of endosomes. How *DNM2* mutations cause a peripheral nerve disease remains an enigma (Claeys et al., 2009).

CMT2B is an axonal form of CMT in which axonal degeneration, leading to progressive axonal loss, is the primary defect. CMT2B is also characterised by a prominent sensory loss, often complicated by severe ulcero-mutilations of toes and fingers. The clinical phenotype closely resembles the HSN type I, making its classification within the CMT neuropathies difficult (Auer-Grumbach et al., 2003). Mutations in the gene encoding the small GTPase RAB7 are associated with CMT2B (Verhoeven et al., 2003a). The RAB7 protein belongs to the RAB family of small GTPases, members of which have a major role in intracellular vesicle trafficking, controlling vesicle budding, transport, tethering and fusion (Spinosa et al., 2008). CMT4C is an AR demyelinating form of CMT caused by mutations in *SH3TC2* (Senderek et al., 2003). The SH3TC2 protein is recruited to recycling endosomes by interacting with the active GTP-bound form of RAB11. Disease-associated mutations cause loss of this interaction, with resulting mistargeting of the protein away from endosomes (Stendel et al., 2010).

CMT1C is caused by mutations in the gene encoding the small integral membrane protein of the lysosome/late endosome (*SIMPLE*), also known as the lipopolysaccharide-induced TNF factor (LITAF) (Bennett et al., 2004). CMT1C patients have a classical HMSN or demyelinating CMT phenotype, clinically resembling the CMT1A and CMT1B subtypes. SIMPLE/LITAF interacts with proteins of the lysosomal degradation pathway, and was proposed to interfere with protein degradation. Although it plays a role in lysosomal sorting of plasma membrane proteins, much of its function and its involvement in peripheral nerve degeneration is unknown (Shirk et al., 2005).

AR mutations in *MTMR2* and *MTMR13* cause respectively CMT4B1 and CMT4B2 (Bolino et al., 2000; Azzedine et al., 2003). Patients with these demyelinating CMT subtypes have characteristic focally folded myelin sheets upon nerve biopsies. Both enzymes are functionally associated proteins and are respectively inactive or active PI 3-phosphatases. They play important roles in vesicle sorting, by influencing the PI content of membrane compartments, and in modulation of the intracellular molecular signalling (Berger et al., 2002). *Mtmr13*-deficient mice develop a peripheral neuropathy characterised by reduced nerve conduction velocity (NCV), myelin out- and infoldings (Tersar et al., 2007). In the rodent, this dysmyelination worsens throughout life and the neuropathy clinically resembles CMT4B2 in human. Similarly, the *Mtmr2*-null mouse also shows myelin outfoldings and mimics CMT4B1 neuropathy (Bolis et al., 2005). In Schwann cells, Mtmr2 interacts with Discs large 1 (Dlg1), a scaffold involved in polarised trafficking and membrane addition, whose localization in *Mtmr2*-null nerves is altered (Bolis et al., 2009). Thus in CMT4B neuropathies, myelin outfoldings probably result from a loss of negative control of membrane production during peripheral nerve myelination (Bolis et al., 2007).

Recessive mutations in *FIG4* have been reported to cause a severe HMSN phenotype (CMT4J) (Chow et al., 2007; Nicholson et al., 2011). The Fig4 protein is also involved in PI metabolism, since it is a lipid phosphatase for PI(3,5) phosphate. The best characterised role for this protein is in endosome–lysosome function. The *Fig4*-null mouse develops a multi-system disorder with degeneration of the CNS, peripheral neuropathy and reduced fur pigmentation. The neonatal degeneration in the *Fig4*-null mice affects sensory and autonomic ganglia followed by loss of neurons in the cerebral cortex and other brain regions. The peripheral nerve shows fewer large calibre axons, slowed NCVs and reduced compound muscle action potentials (CMAP) (Chow et al., 2007).

Mutations in genes related to Rho GTPase function are also implicated in CMT. Rho GTPases control many cellular functions, often by influencing the actin cytoskeleton. These GTPases are regulated by a variety of guanine nucleotide exchange factors (GEFs), activating proteins (GAPs) and dissociation inhibitors (GDIs). Recessive mutations in the *FGD4* gene encoding the frabin protein, a GEF for the Rho family member Cdc42, were reported in consanguineous CMT4H families (Stendel et al., 2007; Delague et al., 2007). Affected patients develop an early onset, severely disabling neuropathy with deforming scoliosis. They also show myelin outfoldings in their peripheral nerve biopsies, very similar to patients with *MTMR2* and *MTMR13* mutations (Fabrizi et al., 2009). Little is known on the cellular role of frabin, but it induces Cdc42-mediated cell-shape changes in transfected Schwann cells, suggesting that the Rho GTPase signalling is essential for proper myelination of the PNS. Mutation of *ARHGEF10* causes a very mild phenotype with only slowed NCV and thinly myelinated sheets. Only one dominant mutation is reported in *ARHGEF10* so far (Verhoeven et al., 2003b). The encoded protein is a GEF that regulates the activity of RhoGTPases by catalyzing the exchange of bound GDP by GTP. The mouse orthologue Gef10 is highly expressed in the PNS, and might play a signalling role in the developmental myelination of peripheral nerves.

HSP disorders. The largest subgroup of HSP genes encode proteins involved in membrane traffic processes. A well-characterised example is a group of four HSP proteins, reticulon2, spastin, atlastin-1 and REEP1, that act to shape the morphology of the endoplasmic reticulum (ER) (Montenegro et al., in press reviewed in Blackstone et al., 2011$). Mutations in the genes encoding these proteins all cause AD pure HSP (Hazan et al., 1999; Zhao et al., 2001; Zuchner et al., 2006). An important sequence feature of these proteins is the

presence of at least one predicted "hairpin loop" membrane domain that partially inserts into the membrane lipid bilayer. The proteins participate in an interaction network, mediated by interactions that require the hairpin loop. Such hairpin loops are believed to generate or sense membrane curvature, and these sets of proteins are involved in shaping the tubular ER (Hu et al., 2009; Park et al., 2010). Thus, for example, atlastin-1 mediates homotypic fusion of ER tubules and is required for the formation of 3 way junctions in the honeycomb network of the tubular ER (Hu et al., 2009; Orso et al., 2009), while expression of ATPase-defective spastin (see below) in cultured cells causes a profound tubulation of the ER along abnormal microtubule bundles (Sanderson et al., 2006). Interestingly, a recent study demonstrated that mutations in *atlastin-1* also cause a rare form of HSAN (HSN type I). This axonal neuropathy is characterised by a prominent sensory loss, resulting in delayed wound healing and osteomyelitis often necessitating distal amputations of limbs. This finding demonstrated that HSN I and SPG3A are allelic disorders and suggested a role for atlastin-1 in sensory neuronal function within the peripheral nervous system. The abnormal atlastin-1 protein causing HSN type I showed a reduced GTPase activity and caused a disruption of ER morphology, highlighting a potential role for abnormal ER shaping in peripheral neuropathy, as well as HSP (Guelly et al., 2011).

As well as being involved in membrane shaping at the ER, HSP proteins are involved in membrane shaping at the endosome. The *SPG8* gene encodes strumpellin, which is part of a multiprotein complex called the WASH complex. Depletion of components of this complex, including strumpellin, enhances early endosomal tubulation, resulting in impaired trafficking of receptors that transit in tubular transport intermediates. Fission of these endosomal tubules requires an actin network on the endosome, which is believed to allow generation of an actin-dependent force that helps separate the tubular transport compartment from the endosomal body. This fission process also requires dynamin, providing a possible relationship to CMT (see above) (Derivery et al., 2009; Gomez and Billadeau, 2009; Harbour et al., 2010).

Troyer syndrome is a complex AR-HSP caused by mutation of the *SPG20* gene, which encodes spartin (Patel et al., 2002). This protein has a complex subcellular distribution, being predominantly cytosolic at steady state, but also being recruited under certain circumstances onto endosomes, the cytokinetic midbody and lipid droplets (Eastman et al., 2009; Edwards et al., 2009; Renvoise et al., 2006; Robay et al., 2006). A localisation on mitochondria has also been reported (Joshi and Bakowska, 2011; Lu et al., 2006). With regard to its endosomal function, spartin regulates lysosomal degradation of the epidermal growth factor receptor (EGFR), a well-characterised endocytic cargo that, when stimulated by ligand, is trafficked to lysosomes for degradation (Bakowska et al., 2007). Spartin can also be recruited to lipid droplets, where it regulates lipid droplet biogenesis. It binds to a number of E3 ubiquitin ligases which are active at both endosomes and on lipid droplets, and it appears to function by activating these enzymes (Eastman et al., 2009; Edwards et al., 2009; Hooper et al., 2010). Interestingly, the Silver syndrome protein seipin also has a role in lipid droplet formation. AD mutations in the Berardinelli–Seip congenital lipodystrophy (*BSCL2*) gene, that encodes seipin, cause a range of neuropathies including CMT, distal HMN or Silver syndrome (see above). Null mutations in the *BSCL2* gene were identified in an AR form of Berardinelli–Seip congenital lipodystrophy (congenital generalized lipodystrophy type 2) (Boutet et al., 2009; Payne et al., 2008; Szymanski et al., 2007). However, this role of seipin may not be related to the pathogenesis of Silver syndrome. Silver syndrome mutations probably lead to impaired folding of the protein in the ER, causing the unfolded protein response and ER stress, and it has been suggested that this gain of function may cause the disease (Ito and Suzuki, 2009; Daisuke and Norihiro, 2007).

The *SPG6* gene encodes NIPA1, a polytopic integral membrane protein that localises to the plasma membrane and to endosomes, and possibly also to the Golgi apparatus (Goytain et al., 2007; Liao et al., 2008). The protein is a magnesium transporter (Goytain et al., 2007). Disease causing mutations in this protein cause it to be trapped in the ER and it has been suggested that this could cause the disease via a gain-of-function induction of ER stress (Zhao et al., 2008). Alternatively, NIPA1 regulates bone morphogenic protein (BMP) receptor traffic and signalling, and it has been proposed that dysregulation of this causes the disease. This hypothesis is based on observations on mammalian and *Drosophila* NIPA1, which both regulate traffic of the type II BMP receptor at endosomes (Tsang et al., 2009; Wang et al., 2007). Intriguingly, two other HSP proteins that can localise to endosomes, spastin and spartin, are also inhibitors of BMP signalling, while abnormal BMP signalling has also been described in association with atlastin-HSP models, suggesting that abnormal BMP signalling could be a unifying mechanism in a group of HSPs (Tsang et al., 2009; Fassier et al., 2010).

Several other HSP proteins may localise to endosomes, although their function is relatively poorly characterised. The *SPG21* gene, which is mutated in Mast syndrome, an AR complex HSP, encodes the endosomal protein maspardin (Simpson et al., 2003). Maspardin binds to the cytoplasmic tail of the CD4 immune receptor and regulates its signalling activity, although it is unlikely that this function is relevant to the protein's role in causing HSP (Zeitlmann et al., 2001). Maspardin has been suggested to bind to RAB7 (McCray et al., 2010), the gene involved in CMT2B (Verhoeven et al., 2003a). Although spastizin (encoded by *SPG15*), spatacsin (encoded by *SPG11*) and the protein encoded by *SPG48* have been described as having a role in DNA repair (Slabicki et al., 2010), very recent data also suggests that these proteins have a role at endosomes, since they form part of a novel endosomal adaptor protein complex termed AP5 (Hirst et al., 2011). Interestingly, mutations in both SPG11 and SPG15 cause a type of complex HSP with thin corpus callosum.

Cytoskeleton stability and motor proteins

CMT disorders. Neurofilaments are the major intermediate filaments of neurons and are categorised into NEFL (light), NEFM (medium) and NEFH (heavy) subtypes. Aberrant neurofilament assembly and transport can induce neurodegenerative disease and cause defective neurofilament metabolism. Clinical and electrophysiological studies revealed that CMT patients with NEFL mutations develop a mixed axonal and demyelinating neuropathy. This mixed HMSN phenotype has been subdivided into CMT2E and CMT1E types, respectively (Mersiyanova et al., 2000; De Jonghe et al., 2001). A transgenic mouse model expressing a NEFL mutation under the tet-off tetracycline regulated system showed hind limb clasping and gait anomalies, as well as sensorimotor deficits resembling the human CMT2E pathology (Dequen et al., 2010).

Homozygosity mapping in inbred families with AR axonal CMT (AR-CMT2A) resulted in the identification of homozygous mutations in *LMNA* (De Sandre-Giovannoli et al., 2002). This gene encodes lamin A/C, a filamentous component of the inner nuclear envelope. Sciatic nerves of *Lmna*-null mice reveal a strong reduction in axon density, enlarged axons and unmyelinated axons, similar to the phenotypes of the human peripheral axonopathy. Interestingly, a number of other diseases have been associated with lamin mutations, including muscular dystrophies, cardiomyopathies and progeria (reviewed in Bernard et al., 2006).

Mutations in the neuron-specific tubulin βIII gene *TUBB3* have been found in patients with a congenital fibrosis of the extraocular muscles (Levin et al., 2010). In this context it is worth to note that some of these patients presented with a peripheral neuropathy and were initially diagnosed as CMT patients. These *TUBB3* mutations result in the stabilization of microtubules.

Mutations in motor-associated proteins may also cause CMT. A rare missense mutation was discovered in the *dynactin-1* gene (*DCTN1*)

(Puls et al., 2003). The dynactin complex is an adaptor for and activator of the microtubule minus end-directed motor protein dynein. Dynein has many cellular functions, and is essential for retrograde axonal transport. The disease phenotype caused by the *DCTN1* mutation is characterised by vocal cord paralysis leading to breathing difficulties, progressive facial weakness, and weakness and atrophy in the hands. This phenotype is a spinal form of CMT, better known as distal hereditary motor neuropathy (distal HMN type V). The mutation affects the p150 subunit of dynactin, disturbs the dynactin-microtubule-binding and enhances dynein and dynactin aggregation. Transgenic mice overexpressing the p150 subunit of dynactin develop a late onset progressive motor neuron degeneration mimicking the human disease (Laird et al., 2008).

HSP disorders. Mutations in the gene encoding the microtubule severing protein spastin constitute the most common cause of HSP. The C-terminal of spastin contains an AAA ATPase domain, which catalyses microtubule severing, and a microtubule binding domain (MTBD). Domains in the N-terminal region target spastin to specific sites of action, by binding to adaptor proteins (reviewed in Blackstone et al., 2011; Reid and Rugarli, 2010). Spastin has a number of cellular functions, including regulation of ER morphology and participation in the abscission stage of cytokinesis. It is also dynamically recruited to endosomes where it interacts with members of a complex required for endosomal sorting and degradation (Yang et al., 2008; Sanderson et al., 2006; Reid et al., 2005; Connell et al., 2009). Some of these functions are discussed in more detail above. Mice lacking spastin have abnormal axonal swellings, and defective anterograde and retrograde axonal transport (Tarrade et al., 2006).

KIF5A is a kinesin motor protein that moves cargo towards the microtubule plus end, which in the axon is towards the distal end. KIF5 has essential roles in axonal transport and has been characterised as a motor for neurofilaments, although the full range of cargoes specifically transported by KIF5A is not known (Xia et al., 2003). Mutations in KIF5A cause AD-HSP and typically affect the motor function of the protein, so it is likely that they reduce cargo delivery to the axon (Ebbing et al., 2008; Reid et al., 2002).

Mitochondrial dynamics

CMT disorders. Two proteins targeted to mitochondria are associated with CMT neuropathies; ganglioside-induced differentiation associated protein 1 (GDAP1) and mitofusin 2 (MFN2). Both proteins are encoded by nuclear genes, and are involved in mitochondrial fusion, fission and fragmentation. CMT associated mutations in these genes suggest that perturbed mitochondrial dynamics leads to peripheral nerve dysfunction, perhaps by slowing of the axonal transport mechanism (reviewed in Palau et al., 2009).

Dominant mutations in *MFN2* are responsible for ~20% of axonal CMT patients (CMT2A) (Zuchner et al., 2004). Patients with *MFN2* mutations present a classical but rather severe CMT phenotype. Neurophysiological examination usually shows normal to slightly reduced NCV with often severely reduced CMAP and sensory nerve action potentials (SNAP). The few documented nerve biopsies show loss of large myelinated fibres and degenerative mitochondrial changes (Verhoeven et al., 2006). Mitofusins are outer mitochondrial membrane proteins involved in regulating mitochondrial dynamics. Cellular models of CMT2A mutations have demonstrated alteration of mitochondrial transport, providing important insights into the molecular mechanisms of axonal degeneration in CMT2A (Baloh et al., 2007).

Mutations in *GDAP1* are predominantly associated with recessive demyelinating or axonal CMT (CMT4A) (Baxter et al., 2002; Cuesta et al., 2002), however recent studies demonstrated that dominant *GDAP1* mutations can also occur (Zimon et al., 2011). Patients with recessive mutations usually have a severe neuropathy with onset in early childhood. In contrast, patients with dominant *GDAP1* mutations usually have a mild axonal neuropathy with later onset and slower disease progression. Cellular studies have shown that recessive *GDAP1* mutations are associated with reduced mitochondrial fission activity, while dominant mutations impair mitochondrial fusion and cause mitochondrial damage. Thus, different cellular mechanisms disturbing mitochondrial dynamics underlie similar clinical manifestations. These alterations may lead to axonal transport defects and impaired energy production (Niemann et al., 2009).

HSP disorders. Two genes mutated in HSP, *paraplegin* (SPG7) and *HSPD1 (SPG13)* have mitochondrial functions. Patients with AR *paraplegin* mutations can have pure HSP, but more typically have a complex HSP associated with ocular and cerebellar abnormalities (Casari et al., 1998). Muscle biopsies may show histological or biochemical evidence of oxidative phosphorylation defects (Arnoldi et al., 2008; Casari et al., 1998; Wilkinson et al., 2004). The paraplegin protein is an AAA ATPase that participates in a complex (with a related protein AFG3L2) at the inner mitochondrial membrane, termed the matrix-AAA protease. This complex has been thoroughly studied in yeast, where it participates in protein quality control at the inner membrane, selectively cleaving misfolded inner membrane proteins (Arlt et al., 1996; Arlt et al., 1998). It is also involved in the proteolytic processing and maturation of certain proteins, most importantly of a mitochondrial ribosomal component, thereby regulating ribosomal protein synthesis (Nolden et al., 2005). Paraplegin also has a role in processing OPA1, a GTPase involved in inner membrane fusion (Ehses et al., 2009; Ishihara et al., 2006). Mice lacking paraplegin develop an axonopathy, the appearance of which correlates with the development of morphologically abnormal mitochondria. This is followed by jamming of the axons with accumulated organelles, suggesting a defect in axonal transport (Ferreirinha et al., 2004).

Rare AD pure HSP families have been described with mutations in *HSPD1*, the gene which encodes the mitochondrial chaperone HSP60 (Hansen et al., 2002). HSP60 is required for proper folding of a subset of mitochondrial proteins. Interestingly, AR mutations in the same gene can cause Pelizaeus–Merzbacker like disease, providing another example of different mutations in the same gene causing leukodystrophy or HSP (Magen et al., 2008).

Disease-specific groups of genes

Other pathways involved in CMT

The identification of mutations in genes coding for aminoacyl-tRNA synthetases and for small heat shock proteins came as a surprise to the CMT research field. So far no mutations in this group of ubiquitously expressed genes have been associated with HSP. The first mutations were found in the *GARS* gene, coding for glycyl aminoacyl-tRNA synthetase, in families affected by a dominant axonal CMT (CMT2D) or a neuropathy with more prominent motor involvement (distal HMN) (Antonellis et al., 2003). Soon after, mutations were reported in the *tyrosyl aminoacyl-tRNA synthetase* gene (*YARS*) in patients with dominant intermediate CMT type C (DI-CMTC) (Jordanova et al., 2006). More recently, a dominant mutation was found in *alanine aminoacyl-tRNA synthetase* (*AARS*) in a family with axonal CMT (CMT2N) (McLaughlin et al., 2012; Latour et al., 2009); and a compound heterozygous mutation was detected in *lysine aminoacyl-tRNA synthetase* (*KARS*) in a CMT patient presenting with a Schwannoma, self-abusive behaviour and dysmorphic features (McLaughlin et al., 2010). A mouse model for mutant GARS (Seburn et al., 2006) and a fly model for mutant YARS (Storkebaum et al., 2009) recapitulate the respective CMT disease phenotypes. However, the reason why peripheral nerves alone are vulnerable to mutations in genes coding for *aminoacyl-tRNA synthetases* remains unclear.

The small heat shock proteins HSPB1 (*HSP27*) and HSPB8 (*HSP22*) are widely expressed molecular chaperones with essential cellular

function. They protect cells from stress situations by refolding and protecting other proteins and cellular components. Point mutations in *HSPB1* and *HSPB8* have been identified in patients with axonal CMT or distal HMN (Irobi et al., 2004b; Evgrafov et al., 2004). Mutant small heat shock proteins may interfere with neuronal pathways by the formation of protein aggregates, which could disrupt axonal cargo transport, affect neuronal cell survival or hamper their chaperone function. Interestingly the motor neurons seem to be particularly vulnerable to mutations in these genes (Irobi et al., 2010). Furthermore, specific mutations in *HSPB1* result in a higher in vivo chaperone activity when compared to the wild-type protein (Almeida-Souza et al., 2010). This enhanced activity is accompanied by an increased binding of HSPB1 to tubulin and stabilization of the microtubule network (Almeida-Souza et al., 2011). Furthermore, tubulin was less acetylated in transgenic mice overexpressing the mutant HSPB1 protein. Treatment with histone deacetylase (HDAC6) inhibitors corrected the axonal transport defects in this mouse model (Almeida-Souza et al., 2011). Other cellular studies demonstrated that destabilization and aggregation of the neurofilament-light protein (NEFL) are induced by mutant *HSBP1* (Evgrafov et al., 2004; Ackerley et al., 2006), perhaps providing a link with the mechanism of CMT associated with *NEFL* mutation (see above).

Other pathways involved in HSPs

Several additional biochemical pathways have been implicated in HSP. Mutations in CYP7B1 cause AR HSP. *CYP7B1* (SPG5) encodes a 7α-hydroxylase involved in the formation of primary bile acids from cholesterol. In the brain this enzyme is involved in cholesterol metabolism and in formation of a neuroprotective neurosteroid (Tsaousidou et al., 2008). *SLC33A1* (SPG42) encodes an acetyl CoA transporter of the Golgi apparatus. Mutations in this gene cause autosomal dominant pure HSP. In zebrafish this gene is required for normal axonal outgrowth (Lin et al., 2008). The *neuropathy target esterase* (*NTE*) gene product is involved in organophosphate (OP)-induced delayed neuropathy (OPIDN), in which there is peripheral and central long motor axonopathy. This gene is mutated in a complex HSP that resembles Troyer syndrome (Rainier et al., 2008). NTE is an ER membrane phospholipase that regulates membrane phospholipid metabolism (Muhlig-Versen et al., 2005; Quistad et al., 2003), although the mechanism by which mutations in this gene cause HSP is not clearly understood.

Conclusions and future directions

The CMTs and HSPs are unified by the fact that both involve progressive loss of long axons. Both groups of disorders show an extreme degree of genetic heterogeneity. This genetic heterogeneity provides numerous avenues for us to explore the range of cellular processes that are important in axonal maintenance and degeneration.

It is clear that the molecular pathological causes of CMT and HSP overlap at a number of different levels. Firstly, in some cases either a CMT neuropathy phenotype or an HSP phenotype may be caused by mutations in the same gene, with obvious examples including *BSCL2* and *atlastin-1*. Secondly, many of the genes implicated in CMT and HSP seem to be involved in similar cellular processes. These can be divided into a few broad classes; myelination, membrane traffic and axonal transport, cytoskeletal organisation and mitochondrial function (Fig. 1). Within these broad overlaps, there are specific examples where mutations in members of the same gene family (e.g. *GJB1* and *GJA12*), or in genes encoding proteins involved in closely related biochemical pathways (e.g. in endosomal functions) can cause either disease. There are also examples where HSP and CMT-related proteins may directly interact with each other or be directly functionally related, for example, the interaction between maspardin and RAB7.

There are other areas in which there does not yet appear to be any overlap. However, it must be stressed that many CMT and HSP genes have yet to be identified; although nearly 50 HSP loci have been mapped, only 20 genes have been identified at the time of writing. For CMT and related disorders we know so far 50 causative genes. Thus it is likely that additional areas of overlap between HSP and CMT will emerge upon the discovery of novel genes, and as our knowledge of the cell biology of the pathways involved becomes more complete.

An interesting feature of these axonopathies is that the genes involved are often widely expressed, in both non-neuronal and neuronal tissues. Why then do they cause such specific disease? Although a variety of answers to this question are possible, we speculate that key factors are the highly polarised nature of the neuron and the extreme length (up to 1 m) of the axons involved. These features necessitate complex machineries to sort appropriate cargoes into and out of the axon, to transport them appropriately in anterograde and retrograde directions, and to provide the energy for these processes. This may explain the large number of causal genes involved in membrane traffic and axonal transport processes, and mitochondrial function, which are mutated in HSP or CMT. A related question is why mutation of some genes causes an HSP phenotype, whereas others are associated with a CMT phenotype? Clearly there are biological differences between PNS and CNS neurons, for example in myelination, which is controlled by Schwann cells in the PNS and oligodendrocytes in the CNS, and in the capacity to regenerate after injury, which is much greater in the PNS. Thus the context of the gene abnormality is not identical in the CNS and PNS, so factors such as differential protein redundancy or the presence or absence of critical compensatory pathways could be important.

A number of CMT and HSP genes encode proteins involved in myelination, highlighting the fact that Schwann cells in the PNS or oligodendrocytes in the CNS may be the primary site of pathology. However, even in this situation, an axonopathy is also found, and in some cases this is associated with axonal transport defects, suggesting that axonal–glial interactions are important for this process. The HSP genes involved in myelination appear to be a clinically distinct subset, since they are all associated with leukodystrophy, which is generally absent in other types of HSP. Perhaps these genes might be analogous to the subset of genes that cause demyelinating CMT.

Although the large number of genes involved in HSP and CMT gives enormous opportunities for understanding the cell biology of these conditions, at the clinical level this presents great difficulty in identifying the causative gene in the individual case, after the most common few genes are excluded. However, this situation is set to change in the very near future, with the advent of high throughput sequencing technologies that will allow sequencing of all known HSP/CMT genes in a single analysis. We also expect that these new methodologies will lead to the rapid identification of all of the remaining HSP/CMT genes that have yet to be found, giving further crucial insights into the cell biology of these conditions. In the future, high throughput sequencing may also allow the identification of genes that modify the disease phenotypes (e.g. age at onset, rate of progression), although this will rely on the availability of large cohorts of mutation-defined patients.

In conclusion, we have highlighted the most relevant pathways involved in CMT and HSP. Knowledge of the causative genes and their associated biochemical functions is allowing us to begin to understand the connections between these two groups of disorders. Although targeting these pathways therapeutically will be very challenging, the emergence of common molecular pathological themes holds the promise of treatments that may not be limited to individual subtypes of these diseases.

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