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Cellular Pathways of Hereditary Spastic Paraplegia*

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Abstract

Human voluntary movement is controlled by the pyramidal motor system, a long CNS pathway comprising corticospinal and lower motor neurons. Hereditary spastic paraplegias (HSPs) are a large, genetically diverse group of inherited neurologic disorders characterized by a length-dependent distal axonopathy of the corticospinal tracts, resulting in lower limb spasticity and weakness. A range of studies are converging on alterations in the shaping of organelles, particularly the endoplasmic reticulum, as well as intracellular membrane trafficking and distribution as primary defects underlying the HSPs, with clear relevance for other long axonopathies affecting peripheral nerves and lower motor neurons.

Keywords

spasticity; lipid droplet; BMP; cytokinesis; endosome; endoplasmic reticulum

INTRODUCTION

Voluntary movement in humans relies on the pyramidal motor system, a tortuous, multisynaptic pathway in the CNS that extends from the cerebral motor cortex to neuromuscular junctions innervating skeletal muscle. This system is arranged in two main stages (Figure 1). First, axons of large pyramidal neurons originating in layer V of the cerebral motor cortex course through the medullary pyramids, where most fibers decussate in the caudal medulla before descending as lateral corticospinal tracts within the spinal cord. Although some corticospinal axons establish synapses directly with lower motor neurons in the spinal cord anterior horn, the vast majority synapse with spinal interneurons, which then establish connections with lower motor neurons. In the next stage, lower motor neurons terminate in specialized synapses at neuromuscular junctions throughout the body to regulate skeletal muscle contractility (Figure 1) (Carpenter 1991).

Distances traversed by corticospinal and lower motor neurons are among the furthest in the body; their axons extend up to 1 m in length and the axoplasm comprises >99% of total cell volume. This length has evolved to permit the very rapid relay of action potentials, enabling

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timely voluntary movement, but it comes at great expense to the neuron: Complex intracellular machineries are required for sorting and distributing proteins, lipids, mRNAs, organelles, and other molecules over such long distances. These machineries utilize an elaborate neuronal cytoskeletal scaffold along which motor proteins target and deliver components selectively throughout the cell; axonal transport machineries rely on microtubules in particular, which function as polarized tracks with their plus ends oriented toward the axon terminal. A variety of mechanoenzymes within the kinesin, dynein, and myosin protein superfamilies mediate much of the anterograde and retrograde transport specificity through selective cargo interactions. Additional specificity and regulatory control are contributed by various adaptor proteins. The interaction of intracellular cargoes with these complexes permits tightly regulated, selective allocations of organelles, proteins, lipids, and other molecules to growth cones during axonal development and to specialized axon domains such as branch points, internodal segments, and presynaptic terminals in mature neurons (Goldstein et al. 2008, Arnold 2009, Hirokawa et al. 2010).

Not surprisingly, long axons are an Achilles' heel of the nervous system; length-dependent defects in axon development and maintenance give rise to a host of neurological disorders, both acquired and inherited. Acquired disorders are numerous and highly varied, with etiologies encompassing injuries, nutritional deficiencies, endocrine and metabolic disturbances, infections, and environmental toxins, to name a few; these are not discussed here. The focus of this review is on inherited Mendelian disorders, as exemplified by the hereditary spastic paraplegias (HSPs). Although these are among the most genetically diverse of all diseases, with nearly 50 distinct loci and more than 20 gene products identified to date, they are unified by the defining, predominant clinical feature of progressive lower limb spasticity and weakness, with sparing of the upper limbs to a large extent (Fink 2006, Depienne et al. 2007, Salinas et al. 2008, Dion et al. 2009, Blackstone et al. 2011, Lang et al. 2011).

HSPs are uncommon but not rare, with a prevalence of ~3–9/100,000 in most populations, and thus likely afflict several hundred thousand individuals worldwide. Inheritance can be X-linked recessive, autosomal recessive, or autosomal dominant, and age at onset can vary widely, from early childhood to late in life. HSPs have historically been classified as pure or complicated on the basis of the absence (pure) or presence (complicated) of associated clinical features such as distal amyotrophy, cognitive dysfunction, retinopathy, ataxia, thin corpus callosum, and peripheral neuropathy (Harding 1983). Even in pure forms, urinary symptoms and mild dorsal column sensory deficits are frequently encountered. More recently, a numeric labeling scheme has taken hold, and HSPs are increasingly referred to mainly by their genetic classification, SPG1-48 (Depienne et al. 2007, Salinas et al. 2008, Dion et al. 2009, Blackstone et al. 2011).

Because most patients with HSP have a normal life span, a limited number of neuropathologic evaluations of HSPs have been published, particularly for the most instructive pure forms with a genetic diagnosis. Still, these studies have typically shown evidence of axonal degeneration, principally involving the longest ascending sensory fibers and descending corticospinal tract axons in a distal, "dying-back" manner (DeLuca et al. 2004). Because the longest corticospinal axons control the lower motor neurons innervating

muscles of the lower limbs, such findings are concordant with the cardinal clinical features of HSP; sensory manifestations tend to be clinically mild. There is usually little neuronal death even late in the disease course, especially in pure forms, so HSPs are a prototype for understanding disorders that impair axons (Soderblom & Blackstone 2006). Importantly, HSPs are fundamentally diseases of massive scale, affecting predominantly the longest neurons that are orders of magnitude larger than most other cells.

COMMON CELLULAR PATHOGENIC THEMES

The common clinical and pathological features of different HSPs prefigure a small number of common themes at the cellular level, and the genetic heterogeneity provides a significant advantage in identifying these convergent themes. Indeed, published studies have indicated that HSP disease proteins cluster within a small number of predicted cellular processes (Table 1 and Figure 2) (Soderblom & Blackstone 2006, Depienne et al. 2007, Salinas et al. 2008, Dion et al. 2009, Blackstone et al. 2011). Although we discuss HSP proteins by topic, one must remember that many of them appear to function in a number of different pathways; thus pathogenic groupings may evolve over time.

Axon Pathfinding

Among the first HSP mutations described were in the *L1CAM* gene, encoding a cell surface glycoprotein of the immunoglobulin (Ig) superfamily. Loss-of-function mutations in *L1CAM* are implicated not only in X-linked, early-onset, complicated HSP (SPG1), but also in other X-linked syndromes including MASA (for mental retardation, aphasia, shuffling gait, and adducted thumbs), hydrocephalus, and agenesis of the corpus callosum (Jouet et al. 1994, Weller & Gärtner 2001). Each of these disorders displays clinical and pathological evidence of corticospinal tract impairment; the disorders are considered together along a disease spectrum known as L1 disease or CRASH syndrome (for corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia or shuffling gait, and hydrocephalus) (Soderblom & Blackstone 2006).

The L1CAM protein is more than 1200 amino acid residues in size, with a large extracellular segment harboring 6 Ig-like domains and 5 fibronectin type III domains, a single transmembrane domain, and a short cytoplasmic tail. L1CAM participates in a complex set of extracellular and intracellular interactions, binding not only other L1CAM molecules but also a host of extracellular ligands—including other cell adhesion molecules, integrins, and proteoglycans—as well as intracellular proteins such as ankyrins. Disease mutations are found throughout the protein, and partial or complete loss of L1CAM function seems critical for the L1 disease phenotype. In *L1CAM* null mice, the corticospinal tracts are abnormal, arising from a conspicuous failure to decussate within the medulla (Dahme et al. 1997, Cohen et al. 1998).

How does this pathfinding defect occur? In the developing CNS, L1CAM associates with neuropilin-1 (Nrp1), which itself interacts with Plexin-A proteins to form the Semaphorin3A (Sema3A) receptor complex. Upon Sema3A binding to Nrp1, L1CAM and Nrp1 are cointernalized in a L1CAM-dependent manner. Sema3A is a repulsive guidance cue released from cells in the ventral spinal cord to steer corticospinal neurons away from the midline

spinal cord/medullary junction, and L1CAM mutations may affect Sema3A signaling when axons are crossing the midline by interfering with receptor internalization and signaling at growth cones (Castellani et al. 2004). In fact, the association of Nrp1 with L1CAM mediates the activation of a focal adhesion kinase-mitogen-activated protein kinase pathway controlling a critical aspect of the repulsive behavior, the disassembly of adherent zones in growth cones and their subsequent collapse (Bechara et al. 2008). This compelling role of L1CAM in axon pathfinding during development is consistent with the early onset of SPG1.

Myelination

A distinguishing feature of axons in the central and peripheral nervous systems is an insulating myelin sheath, a specialization important for increasing the speed of electrical impulse propagation. Schwann cells supply myelin for peripheral neurons, whereas oligodendrocytes myelinate axons of CNS neurons. Spastic paraplegia as a manifestation of abnormal myelination in the CNS is not uncommon; for example, this occurs in multiple sclerosis and a variety of acquired and inherited leukodystrophies. Mutations in the *PLP1* gene encoding the tetraspan integral membrane proteolipid protein (PLP) and its smaller DM20 isoform give rise to two major diseases along a clinical spectrum: a pure or complicated HSP (SPG2) and the generally much more severe Pelizaeus-Merzbacher disease (PMD) (Inoue 2005).

Although PLP and DM20 are the major protein constituents of CNS myelin (~50% of the total protein), *PLP1* duplications paradoxically cause more severe disease than do deletions, whereas complete absence of PLP/DM20 is typically associated with SPG2 or mild presentations of PMD. *Plp1* null mice in particular have been widely studied as a model for SPG2. Unexpectedly, in these mice the myelin sheath maintains its normal thickness, though with subtle anomalies of the intraperiod lines. In the underlying axons, anterograde transport is impaired, and cargoes undergoing retrograde transport become stuck at distal juxtaparanodal regions (Edgar et al. 2004, Gruenenfelder et al. 2011). It seems reasonable to postulate that oligodendrocytes modulate the activity of motor proteins involved in intracellular cargo transport via signaling cascades in the underlying axon and that this modulation is sensitive to PLP/DM20 (Gruenenfelder et al. 2011).

Mutations in a more recently identified HSP gene similarly define a disease spectrum comprising HSP and PMD-like disease where cell-cell communication is altered. The slowly progressive, complicated SPG44 is caused by homozygous mutations in the *GJC2* gene encoding connexin 47 (CX47). Connexins (typically numbered based on predicted molecular weight) are oligomeric proteins forming gap junction channels, which establish connections between apposed cell membranes to permit the intercellular diffusion of ions and small molecules (typically <1000 Da). CX47 forms connections between astrocytes and oligodendrocytes in concert with CX43. Because CX47/CX43 heterotypic channels appear essential for the maintenance of CNS myelin, alterations in CX47 that result in CX47/CX43 channel dysfunction likely underlie SPG44 (Orthmann-Murphy et al. 2009).

A third HSP with a compelling link to dysmyelination is autosomal recessive SPG35. This disorder sits along a disease spectrum spanning neurodegeneration with brain iron accumulation, leukodystrophy, and HSP and results from loss-of-function mutations in the

fatty acid-2 hydroxylase gene *FA2H* (Dick et al. 2010, Schneider & Bhatia 2010). The FA2H protein is a nicotinamide adenine dinucleotide phosphate (NADPH)–dependent monooxygenase that converts free fatty acids to 2-hydroxy fatty acids. These are incorporated into myelin galactolipids containing hydroxy fatty acid as the *N*-acyl chain, which maintains the myelin sheath. *Fa2h* null mice have been developed as a model for SPG35, and these animals exhibit significant demyelination, axon loss or enlargement, cerebellar defects, and spatial learning and memory deficits. Animals lacking *Fa2h* only in oligodendrocytes and Schwann cells do not exhibit memory deficits, indicating that some neurological manifestations may derive from a lack of FA2H in other cell types (Potter et al. 2011).

Taken together, this subgroup of HSPs most exemplifies a noncell-autonomous disease pathogenesis. In this regard, oligodendrocytes from *Plp1* null mice were able to induce a focal axonopathy when transplanted into the dorsal columns of the myelin-deficient *shiverer* mouse (Edgar et al. 2004). Thus, HSP-associated alterations in oligodendrocyte-mediated myelination can directly cause changes in the underlying axon, impairing corticospinal tract function.

Endoplasmic Reticulum Network Morphology

Cellular organelles have diverse but characteristic morphologies that are evolutionarily conserved, indicating that the function of an organelle is fundamentally related to its form. An obvious corollary is that disruption of form can give rise to disease, and in fact, this has been shown for a number of organelles. For instance, mitochondrial morphology is shaped by the opposing processes of fission and fusion, and multiple large GTPases involved in regulating this balance are mutated in autosomal dominant neurological disorders, including optic atrophy type 1 (OPA1) and Charcot-Marie-Tooth type 2A neuropathy (MFN2) (Westermann 2010).

An analogous situation occurs in the endoplasmic reticulum (ER), and the roles of common HSP gene products in shaping the tubular ER network have indicated this may be the most common pathogenic theme (Park et al. 2010, Montenegro et al. 2012). The ER is among the most distinctive organelles because of its large size, morphological heterogeneity, and extension throughout the cell. Although it is a continuous membrane-bound luminal system, it comprises the distinct morphologies of the nuclear envelope (with thousands of specialized pores), peripheral sheet-like structures studded with polyribosomes, and a polygonal network of interconnected smooth tubules distributed widely throughout the cell. Concordant with this structural heterogeneity, the ER is a multifunctional organelle involved in the synthesis, modification, quality control, and trafficking of integral membrane and secreted proteins. It is critical as well for Ca^{2+} sequestration and release, signaling, sterol synthesis, and lipid synthesis and distribution. In neurons, the ER plays crucial roles in the massive polarized membrane expansion that occurs during axon and dendrite genesis and as an in-tracellular Ca^{2+} store integrated with pre- and postsynaptic signaling pathways (Verkhratsky 2005, Park & Blackstone 2010, Renvoisé & Blackstone 2010, Lynes & Simmen 2011).

The three most common autosomal dominant HSPs—SPG3A, SPG4, and SPG31—as well as the less common SPG12 result from mutations in proteins directly implicated in the formation of the tubular ER network, which is overwhelmingly smooth ER (Park et al. 2010, Montenegro et al. 2012). Mutations in the SPG3A gene *ATL1* are the second most common cause of HSP and are the most common cause of early-onset disease. The SPG3A protein atlastin-1 is a member of a family of large oligomeric GTPases related to the dynamin superfamily. Atlastin-1 is one of three homologous proteins in mammals (atlastin-1, -2 and -3) thought to be paralogs, but it is the only form expressed highly in the CNS (Zhu et al. 2003, Rismanchi et al. 2008). Atlastin-related GTPases are found in all eukaryotic cells and include Sey1p in *Saccharomyces cerevisiae* and root hair defective 3 (RHD3) in *Arabidopsis* (Hu et al. 2009). In contrast with mammals, species such as *S. cerevisiae* and *Drosophila melanogaster* have only a single atlastin ortholog. Across species, the atlastins can diverge considerably at the sequence level, but all share a similar domain organization: a large cytoplasmic N-terminal domain containing a tripartite GTP-binding domain, two very closely spaced hydrophobic segments, and a small cytoplasmic C-terminal tail (Figure 3). These multimeric, integral membrane GTPases localize predominantly to the tubular ER but are also found in the ER-Golgi intermediate compartment and in the *cis*-Golgi apparatus in some cell types (Zhu et al. 2003, 2006; Rismanchi et al. 2008).

Atlastin GTPase activity is required for the formation of the three-way junctions in ER tubules in a wide range of species by directly mediating homotypic fusion of ER tubules (Rismanchi et al. 2008, Hu et al. 2009, Orso et al. 2009, Bian et al. 2011, Byrnes & Sondermann 2011, Chen et al. 2011, Moss et al. 2011). Consistent with this role, atlastins localize to discrete sites along ER tubules, including at three-way junctions. Depletion of atlastin-1 by shRNA in cultured cortical neurons inhibits axon elongation (Zhu et al. 2006), and there is a link between proper ER morphology and the formation and maintenance of long cellular processes such as axons and plant root hairs (see sidebar, ER Shaping: Plant Roots to Axons).

Mammalian atlastins and yeast Sey1p (synthetic enhancement of *yop1*) interact directly with the reticulon and Yop1p/DP1/REEP families of ER-shaping proteins in the tubular ER (Hu et al. 2009, Park et al. 2010). Members of these families each have two long hydrophobic stretches that form intramembrane hairpin domains predicted to partially span the lipid bilayer, inducing and/or stabilizing high-curvature ER tubules via hydrophobic wedging (Voeltz et al. 2006, Hu et al. 2008, Shibata et al. 2009, West et al. 2011). Mutations in *REEP1* cause an autosomal dominant, pure HSP known as SPG31. REEP1 belongs to a family of related proteins (REEP1–6 in mammals) and was originally identified on the basis of its ability to promote trafficking of olfactory receptors to the plasma membrane surface (Saito et al. 2004). REEP1 localizes to the tubular ER and interacts with atlastin-1 via its predicted hydrophobic hairpin motifs. Some members (REEP1–4) also have an extended C-terminal domain (relative to REEP5–6) that binds microtubules, establishing REEP1 as a member of a subfamily of REEPs (REEP1–4) involved not only in ER shaping but also in interactions of ER tubules with the microtubule cytoskeleton (Park et al. 2010, Blackstone et al. 2011). Very recently, mutations in the *RTN2* gene encoding the ER-shaping protein reticulon 2 have been identified in families with autosomal dominant SPG12 (Montenegro et al. 2012).

The fundamental link between the tubular ER and microtubules has been appreciated for decades (Terasaki et al. 1986), and although the microtubule cytoskeleton is not absolutely required for ER network formation (Shibata et al. 2009), microtubule-based ER motility is key for the proper organization and distribution of ER tubules. This is achieved through a variety of mechanisms: membrane sliding, in which ER tubules slide along microtubules using motor activity; microtubule movement, in which ER tubules latch on to moving microtubules; and the tip attachment complex, in which ER attaches to growing microtubule plus ends (Waterman-Storer & Salmon 1998).

Impairment of this relationship between ER tubules and the microtubule cytoskeleton as a pathogenic mechanism for HSPs is supported further by the fact that the SPG4 protein spastin, a microtubule-interacting and severing AAA ATPase, binds atlastin-1 and REEP1 as well as the ER-shaping protein reticulon 1 (Evans et al. 2006, Mannan et al. 2006, Sanderson et al. 2006, Connell et al. 2009, Park et al. 2010). Spastin occurs as two main isoforms generated by differential use of AUG start codons: a 60-kDa form and a 67-kDa form (Mancuso & Rugarli 2008). The larger iso-form has an additional 86 amino acid stretch at the N-terminus containing a hydrophobic segment predicted to insert in the ER membrane as a partially membrane-spanning hairpin (Park et al. 2010). Interactions of M1 spastin with REEP1 and atlastin-1 appear to be mediated largely through this hairpin, though flank-ing regions may also participate (Evans et al. 2006, Sanderson et al. 2006). The larger spastin isoform is particularly enriched in the spinal cord, and a dysfunctional M1 spastin polypeptide, but not one representing the shorter M87 form (M85 in rodents), was deleterious to axon growth in cultured neurons (Solowska et al. 2008), strengthening the evidence linking M1 spastin to HSP pathogenesis. By comparison, M87 spastin appears involved in cytokinesis, secretion, and possibly endocytosis through its interactions linking microtubule dynamics to membrane modeling in these compartments (Yang et al. 2008, Connell et al. 2009). In sum, there appear to be strong physical and functional links between M1 spastin, atlastin-1, reticulon 2, and REEP1 involved in shaping the tubular ER network in concert with the microtubule cytoskeleton. Even so, the ER has a large number of functions, and it remains unclear which are most pathogenically relevant for HSPs.

Because several other HSP proteins also localize to the ER, understanding these may clarify the role of ER in HSP pathogenesis. Mutations in the Berardinelli-Seip congenital lipodystrophy protein 2 gene *BSCL2*, which encodes an integral membrane of the ER known as BSCL2/seipin, cause two distinct diseases. Heterozygous gain-of-function mutations in an *N*-linked glycosylation site give rise to a disease spectrum encompassing autosomal dominant SPG17 (Silver syndrome), with distal amyotrophy as a significant feature in addition to spastic paraparesis, and distal hereditary motor neuropathy type V, characterized by more prominent distal spinal muscular atrophy (Windpassinger et al. 2004). In contrast, auto-somal recessive loss-of-function mutations give rise to Berardinelli-Seip congenital lipodys-trophy, without spasticity or amyotrophy. The seipin protein and its yeast ortholog, Fld1p (few lipid droplets 1), regulate the size of lipid droplets (LDs), explaining the loss-of-function lipodystrophy presentation (Cui et al. 2011; Fei et al. 2011a,b; Tian et al. 2011). The missense changes underlying SPG17 have resulted in misfolding of seipin, forming aggregates and triggering ER stress (Ito & Suzuki 2009, Yagi et al. 2011), which may play a role in HSP pathogenesis. LDs accumulate under various cellular stress conditions, and a

number of unfolded protein response pathways have been implicated in LD formation (Hapala et al. 2011). However, it will be important to investigate any effects of misfolded seipin on other aspects of ER structure and function.

Recently, the gene for the complicated, autosomal recessive SPG18 was identified in a consanguinous Saudi family as *ERLIN2* (Alazami et al. 2011). A second study independently identified loss-of-function *ERLIN2* mutations in a family with motor dysfunction, joint contractures, and intellectual disability (Yıldırım et al. 2011). The erlin2 protein resides in the ER and contains a SPFH domain—named for its presence in stomatin, prohibitin, flotillin, and HflC/K. SPHF domain–containing proteins share the ability to assemble into large oligomers, and they localize preferentially to cholesterol-rich domains, including lipid rafts (Browman et al. 2006). Erlin2 has been functionally linked to ER-associated degradation (ERAD), a multistep degradative pathway encompassing ubiquitin-proteosome-mediated degradation of ER proteins, thereby regulating levels of proteins such as the inosi-tol trisphosphate receptor (Pearce et al. 2009). Also, erlin2 binds gp78, a membrane-bound ubiquitin ligase similar to HRD1 that mediates sterol-accelerated ERAD of 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase, a key enzyme in the biosynthesis of cholesterol (Jo et al. 2011).

Lipid Synthesis and Metabolism

These latter two HSP proteins, erlin2 and seipin, present compelling insights into how defects in ER shaping and distribution might cause HSP. A key function of the ER is the synthesis, metabolism, and distribution of lipids and sterols, employing both vesicular and nonvesicular mechanisms, and other HSP proteins fit into this pathogenic theme. The complicated, autosomal recessive HSP Troyer syndrome (SPG20) is caused by mutations resulting in a loss of spartin protein (Bakowska et al. 2008). Spartin localizes to a variety of cellular structures and has been implicated in a number of functions, including cytokinesis and epidermal growth factor (EGF) receptor trafficking (Robay et al. 2006, Bakowska et al. 2007, Renvoisé et al. 2010, Lind et al. 2011). Spartin also regulates LD biogenesis by promoting atrophin-1 interacting protein 4 (AIP4)-mediated ubiquitination of LD proteins (Eastman et al. 2009, Edwards et al. 2009, Hooper et al. 2010) and by recruiting PKC-ζ via the PKC-ζ-interacting proteins ZIP1 (p62/sequestosome) and ZIP3 to LDs (Urbanczyk & Enz 2011). Little is known about any roles for LDs in axons. However, because the SPG17 protein seipin regulates LD formation, alterations in LD biogenesis or turnover could affect lipid distribution, organelle shaping, or signaling pathways important for axonal health.

Although not directly implicated in LD biogenesis, other HSP proteins are enzymes involved in related lipid and cholesterol biosynthetic pathways. SPG42 is caused by mutations in the *SLC33A1* gene encoding the acetyl-CoA transporter. In animals, acetyl-CoA is essential for maintaining the balance between carbohydrate and fat metabolism. Under normal circumstances, acetyl-CoA from fatty acid metabolism enters the citric acid cycle, contributing to the energy supply of the cell. SLC33A1 transports acetyl-CoA into the Golgi apparatus lumen and has been directly linked to the growth of axons because knock down of *slc33a1* in zebrafish causes defective outgrowth from the spinal cord (Lin et al. 2008).

Last, neuropathy target esterase (NTE) is an integral membrane protein of neuronal ER that is mutated in autosomal recessive SPG39, a complicated HSP with prominent amyotrophy. NTE deacylates the major membrane phospholipid, phosphatidylcholine. Mutation of the NTE gene *PNPLA2* or chemical inhibition of NTE with organophosphates alters membrane composition and causes distal degeneration of long spinal axons in mice and man (Rainier et al. 2008, Read et al. 2009). Another HSP protein, cytochrome P450-7B1 (CYP7B1), is mutated in autosomal recessive SPG5 (Tsaousidou et al. 2008) and functions in cholesterol metabolism; in patients with SPG5 there is a dramatic increase in oxysterol substrates in plasma and cerebrospinal fluid (Schüle et al. 2010). Given the fundamental roles played by lipids and sterols in neuronal functions, it seems very likely that more genes will be identified within this category.

Endosomal Dynamics

Although changes in ER morphology encompass proteins altered in the majority of patients with HSP, more HSP proteins have been implicated in endosomal dynamics; however, an immediate caveat is that the cell seems to coopt some of these proteins and machineries for other functions (Blackstone et al. 2011). As noted earlier, the SPG20 protein spartin functions in LD turnover, but it is also required for efficient EGF receptor degradation and likely regulates EGF signaling (Bakowska et al. 2007). Spartin may also regulate a variety of signaling pathways via ubiquitin modification through its interactions with E3 ubiquitin ligases such as AIP4 and AIP5. Spartin harbors an MIT domain as well and interacts selectively with IST1, a component of the ESCRT-III complex. ESCRT comprises a series of cytosolic protein complexes, ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III, and the sequential activities of these complexes are required to recognize and sort ubiquitin-modified proteins into internal vesicles of multivesicular bodies (Hurley & Hanson 2010). More recently, ESCRT proteins have been implicated in other cellular functions, including viral budding and cytokinesis, and spartin has been shown to participate in cytokinesis (Renvoisé et al. 2010, Lind et al. 2011).

This link to ESCRT-III is shared by the SPG4 protein spastin. Although discussed earlier in the context of its interactions with REEP1 and atlastin-1 to coordinate ER membrane modeling and microtubule interactions (Park et al. 2010), spastin harbors an MIT domain that binds the ESCRT-III subunits CHMP1B and IST1 to couple the severing of microtubules with membrane scission. These ESCRT interactions are crucial for spastin's role in severing microtubules to complete the abscission phase of cytokinesis (Yang et al. 2008, Connell et al. 2009, Guizetti et al. 2011). ESCRT proteins are also involved in centrosome stability (Morita et al. 2010), raising the possibility that axon genesis and regulation by centrosomes could be a function of these proteins. Other possibilities include roles for the ESCRT-III interactions with spastin and spartin in the delivery and downregulation of cell surface receptors to regulate signaling in axons.

Mutations in the KIAA1096 (SPG8) gene that encodes strumpellin cause a severe, pure HSP (Valdmanis et al. 2007). Strumpellin contains few motifs or domains of identified function, aside from a region of putative spectrin repeats. The main clues to its possible endosomal functions stem from its identification as a subunit of the WASH complex (Derivery &

Gautreau 2010). This complex, comprising seven subunits (five core components), connects tubular endosomes of retrograde cargo sorting to the cytoskeleton, and it associates with endosomes via an interaction with vacuolar protein sorting–associated protein 35 (VPS35) (Harbour et al. 2010). Along with VPS26 and VPS29, VPS35 is a component of retromer, an endosomal complex responsible for sorting cargoes from endosomes to the *trans*-Golgi network (Bonifacino & Hurley 2008). Depletion of members of the WASH complex cause increased tubulation at early endosomes, impairing trafficking through early endosomal compartments (Derivery et al. 2009, Gomez & Billadeau 2009, Jia et al. 2010). Several members of the complex—WASH1, FAM21 (family with sequence similarity 21), and actin-capping protein—regulate actin dynamics. The WASH complex helps generate an actin network on early endosomes, for instance by activating the Arp2/3 complex to nucleate new actin filaments branching off extant filaments. The increased tubulation associated with WASH-complex depletion may reflect a lack of actin-mediated forces that are required for fission of tubular transport intermediates from the endosome (Campellone & Welch 2010). Thus, the WASH complex (containing strumpellin) exemplifies another HSP protein functioning in coordinating membrane modeling and cytoskeletal organization. Strumpellin interacts with valosin-containing protein (VCP/p97), an AAA ATPase mutated in frontotemporal dementia with Paget's disease of bone and inclusion body myopathy (Clemen et al. 2010), and *VPS35* is mutated in a number of families with autosomal dominant, late-onset Parkinson disease (Vilariño-Güell et al. 2011, Zimprich et al. 2011). A causative mutation in the WASH subunit SWIP has recently been identified for autosomal recessive intellectual disability (Ropers et al. 2011). Thus, roles of the WASH-retromer axis in neurological disease clearly extend beyond the HSPs and represent a very important area for investigation.

Another emerging HSP-related complex related to endocytic trafficking comprises the SPG15 protein spastizin/FYVE-CENT, the SPG11 protein spatacsin, and the SPG48 protein KIAA0415. Clinically, SPG11 and SPG15 share a number of characteristics; both are frequently associated with thin corpus callosum, and both can present with juvenile parkinsonism. Spastizin and spatacsin colocalize in cytoplasmic structures and were identified as proteins that coprecipitate with the SPG48 protein KIAA0415 (Slabicki et al. 2010, Murmu et al. 2011). KIAA0415 was originally proposed as a DNA helicase on the basis of sequence predictions (Slabicki et al. 2010), but a very recent study provides compelling evidence that it is a subunit of a new adaptor protein complex, AP-5, involved in endosomal dynamics (Hirst et al. 2011). Spastizin/FYVE-CENT contains a FYVE domain and binds the lipid PI(3)P, functioning along with ESCRT proteins in cytokinesis (Sagona et al. 2010). Along these lines, mutations in multiple proteins of the AP-4 complex, which is involved in trafficking of amyloid precursor protein from the *trans*-Golgi to endosomes (Burgos et al. 2010), cause autosomal recessive syndromes with prominent clinical features ranging from intellectual disability to progressive spastic paraplegia (Abou Jamra et al. 2011, Moreno-De-Luca et al. 2011). Thus, these adaptor protein complexes appear highly relevant for pathogenesis of HSPs and other neurological diseases.

Together, the expanding number of HSP genes implicated in endosome dynamics are already revealing new relationships among protein complexes, with implications that extend beyond the primary HSPs. Indeed, a number of patients with familial amyotrophic lateral sclerosis

(ALS) resulting from an autosomal recessive mutation in the *ALS2* gene encoding the alsin protein, a guanine nucleotide exchange factor (GEF) for the small GTPases Rab5 and Rac1, have a disease presentation more similar to the HSPs than to ALS. Examination of *Als2* null mice revealed motor impairments and a distal axonopathy of the corticospinal tract. Rab5-dependent endosomal fusion is impaired in neurons from these mice, whereas alsin overexpression in neurons stimulates Rab5-dependent endosomal fusion, resulting in enlarged endosomes (Devon et al. 2006, Deng et al. 2007, Hadano et al. 2007).

Motor-Based Transport

The identification of mutations in the *KIF5A* gene encoding kinesin heavy chain 5A (known also as kinesin-1A) in families with SPG10, a pure or complicated HSP, has provided direct evidence for motor-based transport impairments underlying HSPs (Reid et al. 2002, Goizet et al. 2009). KIF5 proteins are ATP-dependent motors that move cargoes in the anterograde direction along axons, and most mutations are missense changes in the motor domain. *Drosophila* harboring mutations in the *KIF5* ortholog *Khc* have posterior paralysis, with organelle-filled axon swellings jammed with cargoes (Hurd & Saxton 1996). In mammals, the KIF5A motor protein shuttles neurofilament subunits along axons and possibly other anterograde cargoes such as vesicles. KIF5 also regulates transport of cargoes in den-drites and has roles in a number of membrane traffic pathways. The efficiency of cargo transport to the distal axon is thought to be affected either because the mutated KIF5A are slower motors or because they have reduced micro-tubule binding affinity and act in a dominant-negative manner by competing with wild-type motors for cargo binding (Ebbing et al. 2008).

Mitochondrial Function

Mitochondrial dysfunction has been implicated in a host of developmental and degenerative neurological disorders, manifesting clinically as peripheral neuropathies, movement disorders, visual disturbances, and cognitive disability (Di-Mauro & Schon 2008). Given this fundamental link to neurological disease, it is surprising that so few HSP genes encode mitochondrial proteins. Two resident mitochondrial proteins mutated in HSPs are paraplegin (autosomal recessive SPG7) and HSP60 (autosomal dominant SPG13). Paraplegin is an *m*-AAA metalloprotease of the inner mitochondrial membrane, where it functions in ribosomal assembly and protein quality control. Muscle tissue from SPG7 patients exhibits defects in oxidative phosphorylation and *Spg7* null mice have axonal swellings with accumulated mitochondria and neurofilaments, indicating that both mitochondrial function and axonal transport are impaired (Ferreirinha et al. 2004). SPG13 is typically a late-onset, pure HSP, and a causative missense mutation (p.V98I) impairs HSP60 chaperonin activity, leading to impaired mitochondrial quality contol (Bross et al. 2008).

RELATED DISORDERS

We have discussed the convergent pathways of many proteins mutated in HSPs, but it has become increasing clear that the HSP presentation is often part of a broader disease spectrum; thus it is important to consider related disorders that may share pathogenic themes. Indeed, the importance of organelle morphology and distribution in maintaining axons is also emphasized by other inherited axonopathies, particularly peripheral nerve

disorders such as the Charcot-Marie-Tooth (CMT) neuropathies and hereditary sensory and autonomic neuropathies (HSAN). Mutations in the *FAM134B* gene were identified in some patients with HSAN II. The FAM134B protein is a member of the FAM134 protein family, each of which contains a pair of long hydrophobic segments reminiscent of those in ER-shaping reticulon and Yop1p/DP1/REEP proteins. FAM134B is enriched in the *cis*-Golgi apparatus, and its depletion causes prominent changes in Golgi morphology in neurons (Kurth et al. 2009). More recently, homozygous loss-of-function *KIF1A* mutations were identified in an Afghan family with HSAN II (Rivière et al. 2011), and the KIF1A protein is a motor involved in axonal transport of synaptic vesicles. A family has also been recently identified with hereditary spastic paraplegia caused by homozygous mutation in the KIF1A motor domain (Erlich et al. 2011), indicating that HSP and HSANs may, in at least some cases, fall along a phenotypic spectrum. In fact, dominant missense mutations in the SPG3A protein atlastin-1 have been recently reported in hereditary sensory neuropathy (HSN) I (Guelly et al. 2011). More generally, these disorders highlight the implications of morphological defects in the ER and the early secretory pathway as well as distribution defects in the pathogenesis of length-dependent axonopathies.

Pathogenic studies of CMT peripheral neuropathies are also instructive. CMT1 is composed of demyelination disorders, and CMT2 is composed of those that cause axonopathies. Axonal forms of CMT in particular can be caused by mutations in genes that encode proteins that function in organelle morphogenesis and trafficking. CMT2A results from mutations in the gene encoding mitofusin2 (*MFN2*), which regulates mitochondrial morphology by mediating mitochondrial fusion and has also been implicated in mitochondrial connections with the ER (de Brito et al. 2010). The CMT2B protein Rab7, a small GTPase that regulates endosomal vesicle trafficking, interacts with the SPG21 protein maspardin, another HSP-associated protein that localizes to endosomes (Hanna & Blackstone 2009, McCray et al. 2010, Soderblom et al. 2010). Very recently, a large CMT2 pedigree was reported with autosomal dominant mutation in *DYNC1H1*, which codes for the dynein heavy chain 1 involved in retrograde axonal transport (Weedon et al. 2011).

Finally, ER shaping mechanisms may have roles in related neurologic disorders such as familial ALS, in which both corticospinal and lower motor neurons are affected. In the superoxide dismutase 1 (SOD1) G93A transgenic mouse model for ALS, overexpression of the ER-shaping protein reticulon-4A selectively redistributed the ER chaperone protein disulfide isomerase and protected against neurodegeneration. Conversely, loss of reticulon-4A increased disease severity (Yang et al. 2009). Further supporting a role for aberrant ER morphogenesis in neurologic disorders, a mutant variant of vesicle-associated membrane protein–associated protein B (VAP-B) that underlies another familial ALS (ALS8) is associated with the production of a novel form of organized smooth ER (Fasana et al. 2010).

E PLURIBUS UNUM?

These divisions as discussed above are, of necessity, somewhat arbitrary because cellular pathways show a great deal of interdependence, and a number of HSPs can fit into several

pathogenic themes. For instance, the shaping phenomenon crosses over a number of categories, from ER to endosomes. A natural question is, then, can these be unified further?

Bone Morphogenetic Protein Signaling

One compelling candidate that crosses HSP categories and is widely implicated in neurodegenerative diseases is bone morphogenetic protein (BMP) signaling (Bayat et al. 2011). HSP-associated mutations are found in at least four proteins—atlastin-1, NIPA1 (nonim-printed in Prader-Willi/Angelman syndrome 1; SPG6), spastin, and spartin—that function as inhibitors of BMP signaling. In *Drosophila* and mammals, BMP signaling functions in regulating axonal growth and synaptic function, and impairment of BMP signaling in *Drosophila* leads to axon transport defects (Wang et al. 2007). In rodents, BMP signaling is upregulated following lesioning of the corticospinal tract, and suppression of this upregulation can promote regrowth of axons (Matsuura et al. 2008).

Of the HSP proteins known to inhibit BMP signaling, the best characterized mechanistically is NIPA1, an integral membrane protein with 9 predicted TMDs that localizes to endo-somes and the plasma membrane and functions in Mg^{2+} transport (Goytain et al. 2007). *Drosophila* larvae lacking spichthyin (NIPA1 or-tholog) have increased synaptic boutons at neu-romuscular junctions and increased phosphorylated MAD (mothers against decapentaplegic), a downstream messenger of BMP signaling. These changes can be suppressed with genetic alterations that inhibit BMP signaling (Wang et al. 2007). NIPA1/spichthyin is thought to inhibit BMP signaling by promoting the internalization of BMP type II receptors and their subsequent lysosomal degradation, and NIPA1 missense changes found in SPG6 patients interfere with this process, upregulating signaling. Similarly, depletion of spartin or spastin, which both localize partially to endosomes, upregulates BMP signaling (Tsang et al. 2009).

Dysregulated BMP signaling linked to axonal abnormalities has also been demonstrated for atlastin. Depletion of atlastin-1 in zebrafish resulted in abnormal spinal motor axon morphology, with increased branching and decreased larval mobility. BMP signaling was up-regulated in these larvae, and pharmacological or genetic inhibition of BMP signaling rescued the *atl1* null phenotype (Fassier et al. 2010). In sum, these results suggest that abnormal BMP signaling, probably caused by abnormal BMP receptor trafficking in many cases, could be a unifying mechanism for some classes of HSP, including the two most common, SPG4 and SPG3A, which comprise almost 50% of patients. Investigating relevant HSP animal models will be critical to determine whether inhibition of BMP signaling using small-molecule inhibitors, several of which are available, can rescue disease phenotypes.

Interorganelle Contacts and Communication

Another possibility for linking HSP themes further is via interorganelle contacts. The ER is distributed promiscuously throughout the cell, and to mediate its many functions, it interacts with other organelles at specialized contact sites. Such interactions occur with the plasma membrane, mitochondria, and lysosomes/endosomes. The importance of these connections for functions such as interorganelle exchange of lipids/sterols, signal transduction, and mobilization of Ca^{2+} stores is increasingly appreciated (Carrasco & Meyer 2011, Toulmay &

Prinz 2011). In particular, ER-mitochondrial contacts have been intensively studied recently, with MFN2 in mammals and an ER-mitochondrial encounter structure (ERMES) in yeast playing crucial roles (de Brito et al. 2010, Kornmann & Walter 2010). In a model of pulmonary arterial hypertension, there was decreased ER-to-mitochondria phospholipid transfer and intramitochondrial Ca^{2+} (Sutendra et al. 2011). The contacts between mitochondria and ER were disrupted in a manner dependent on increased expression of an ER-shaping protein of the reticulon family, Nogo-B, linking changes in an ER-shaping protein to mitochondrial dysfunction.

CONCLUDING REMARKS

The HSPs have recently been called a “paradigmatic” example of how a disease can foster insights into fundamental cellular processes, particularly with regard to formation of the tubular ER network (De Matteis & Luini 2011). Ongoing studies investigating how the ER network is shaped in neurons using electron microscopy reconstruction or super-resolution confocal microscopy will improve our understanding of the appearance, contacts, and dynamics of ER in axons. With the increasing throughput and falling cost of next-generation sequencing technologies, more genes for HSPs and related disorders will assuredly be uncovered, likely many more. Important insights into endocytic trafficking pathways in particular seem sure to follow.

With some compelling cellular mechanisms already identified, pharmacologic manipulation of these pathways and evaluations in cellular and animal models will be increasingly important. Pathways such as BMP signaling and micro-tubule stability (Orso et al. 2005, Yu et al. 2008) currently seem to be particularly attractive targets because they would likely relate to a significant percentage of HSP patients and seem amenable to regulation by small molecules, which could ultimately lead to therapies.

Animal models may be a particular challenge for HSPs because successfully modeling a disease of 1 m axons in small rodents is not a given. The slow, variable rates of progression in HSP patients will be challenges for assessing the efficacy of therapies, but emerging noninvasive stimulation (triple stimulation technique) and imaging modalites such as diffusion tensor imaging (Duning et al. 2010, Unrath et al. 2010) might be useful biomarkers, particularly because they can detect changes in patients with known HSP mutations at a presymptomatic phase, when disease-modifying therapies would be most useful (Duning et al. 2010). The past several years have yielded remarkable advancements in our understanding of the pathogenesis underlying the HSPs; with increasing interest in the fascinating biology of HSP proteins and technological advances in genetics and imaging moving rapidly, the future is hopeful for those afflicted.

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Glossary

HSP
hereditary spastic paraplegia

Spasticity
increase in muscle tone associated with hyperactive tendon stretch reflexes

Corpus callosum
arched bridge of nerve fibers connecting the left and right cerebral hemispheres

Intraperiod lines
fused outer leaflets of contiguous plasma membranes in the myelin sheath

Dynamin superfamily
large, multimeric GTPases involved in membrane fission or fusion

Root hairs
long, thin, tubular outgrowths of plant root epidermal cells that absorb water and minerals from soil

Hydrophobic wedging
partitioning the bulk of intramembrane hydrophobic domains within one leaflet of a phospholipid bilayer, generating membrane curvature

Lipid droplet (LD)
dynamic cytoplasmic organelle consisting of a phospholipid monolayer surrounding a neutral lipid core; proteins are found within the monolayer and decorating its surface

MIT domain
conserved domain comprising three α-helices present in microtubule-interacting and trafficking proteins

ESCRT
endosomal sorting complex required for transport

WASH complex
Wiscott-Aldrich syndrome protein and SCAR (suppressor of cAMP receptor) homolog complex

Tubular transport intermediate
small, cigar-shaped organelles that traffic from one membrane compartment to another

Amyotrophic lateral sclerosis (ALS)
a degenerative disorder affecting corticospinal and lower motor neurons

Bone morphogenetic protein (BMP)
a member of the transforming growth factor-βsuperfamily

LITERATURE CITED

Abou Jamra R, Philippe O, Raas-Rothschild A, Eck SH, Graf E, et al. Adaptor protein complex 4 deficiency causes severe autosomal-recessive intellectual disability, progressive spastic paraplegia, shy character, and short stature. Am J Hum Genet. 2011; 88(6):788–95. [PubMed: 21620353]

Alazami AM, Adly N, Al Dhalaan H, Alkuraya FS. A nullimorphic *ERLIN2* mutation defines a complicated hereditary spastic paraplegia locus (SPG18). Neurogenetics. 2011; 12(4):333–36. [PubMed: 21796390]

Arnold DB. Actin and microtubule-based cytoskeletal cues direct polarized targeting of proteins in neurons. Sci Signal. 2009; 2(83):pe49. [PubMed: 19671926]

Bakowska JC, Jupille H, Fatheddin P, Puertollano R, Blackstone C. Troyer syndrome protein spartin is mono-ubiquitinated and functions in EGF receptor trafficking. Mol Biol Cell. 2007; 18(5):1683–92. [PubMed: 17332501]

Bakowska JC, Wang H, Xin B, Sumner CJ, Blackstone C. Lack of spartin protein in Troyer syndrome: a loss-of-function disease mechanism? Arch Neurol. 2008; 65(4):520–24. [PubMed: 18413476]

Bayat V, Jaiswal M, Bellen HJ. The BMP signaling pathway at the *Drosophila* neuromuscular junction and its links to neurodegenerative diseases. Curr Opin Neurobiol. 2011; 21(1):182–88. [PubMed: 20832291]

Bechara A, Nawabi H, Moret F, Yaron A, Weaver E, et al. FAK-MAPK-dependent adhesion disassembly downstream of L1 contributes to semaphorin3A-induced collapse. EMBO J. 2008; 27(11):1549–62. [PubMed: 18464795]

Bian X, Klemm RW, Liu TY, Zhang M, Sun S, et al. Structures of the atlastin GTPase provide insight into homotypic fusion of endoplasmic reticulum membranes. Proc Natl Acad Sci USA. 2011; 108(10):3976–81. [PubMed: 21368113]

Blackstone C, O'Kane CJ, Reid E. Hereditary spastic paraplegias: membrane traffic and the motor pathway. Nat Rev Neurosci. 2011; 12(1):31–42. [PubMed: 21139634]

Bonifacino JS, Hurley JH. Retromer. Curr Opin Cell Biol. 2008; 20(4):427–36. [PubMed: 18472259]

Bross P, Naundrup S, Hansen J, Nielsen MN, Christensen JH, et al. The Hsp60-(p. V98I) mutation associated with hereditary spastic paraplegia SPG13 compromises chaperonin function both in vitro and in vivo. J Biol Chem. 2008; 283(23):15694–700. [PubMed: 18400758]

Browman DT, Resek ME, Zajchowski LD, Robbins SM. Erlin-1 and erlin-2 are novel members of the prohibitin family of proteins that define lipid-raft-like domains of the ER. J Cell Sci. 2006; 119(Pt 15):3149–60. [PubMed: 16835267]

Burgos PV, Mardones GA, Rojas AL, daSilva LLP, Prabhu Y, et al. Sorting of the Alzheimer's disease amyloid precursor protein mediated by the AP-4 complex. Dev Cell. 2010; 18(3):425–36. [PubMed: 20230749]

Byrnes LJ, Sondermann H. Structural basis for the nucleotide-dependent dimerization of the large G protein atlastin-1/SPG3A. Proc Natl Acad Sci USA. 2011; 108(6):2216–21. [PubMed: 21220294]

Campellone KG, Welch MD. A nucleator arms race: cellular control of actin assembly. Nat Rev Mol Cell Biol. 2010; 11(4):237–51. [PubMed: 20237478]

Carpenter, MB. Core Text of Neuroanatomy. 4. Baltimore, MD: Wilkins & Wilkins; 1991.

Carrasco S, Meyer T. STIM proteins and the endoplasmic reticulum-plasma membrane junctions. Annu Rev Biochem. 2011; 80:973–1000. [PubMed: 21548779]

Castellani V, Falk J, Rougon G. Semaphorin3A-induced receptor endocytosis during axon guidance responses is mediated by L1 CAM. Mol Cell Neurosci. 2004; 26(1):89–100. [PubMed: 15121181]

Chen J, Stefano G, Brandizzi F, Zheng H. *Arabidopsis* RHD3 mediates the generation of the tubular ER network and is required for Golgi distribution and motility in plant cells. J Cell Sci. 2011; 124(Pt 13):2241–52. [PubMed: 21652628]

Clemen CS, Tangavelou K, Strucksberg K-H, Just S, Gaertner L, et al. Strumpellin is a novel valosin-containing protein binding partner linking hereditary spastic paraplegia to protein aggregation diseases. Brain. 2010; 133(10):2920–41. [PubMed: 20833645]

Cohen NR, Taylor JSH, Scott LB, Guillery RW, Soriano P, Furley AJW. Errors in corticospinal axon guidance in mice lacking the neural cell adhesion molecule L1. Curr Biol. 1998; 8(1):26–33. [PubMed: 9427628]

Connell JW, Lindon C, Luzio JP, Reid E. Spastin couples microtubule severing to membrane traffic in completion of cytokinesis and secretion. Traffic. 2009; 10(1):42–56. [PubMed: 19000169]

Cui X, Wang Y, Tang Y, Liu Y, Zhao L, et al. Seipin ablation in mice results in severe generalized lipodystrophy. Hum Mol Genet. 2011; 20(15):3022–30. [PubMed: 21551454]

Dahme M, Bartsch U, Martini R, Anliker B, Schachner M, Mantei N. Disruption of the mouse *L1* gene leads to malformations of the nervous system. Nat Genet. 1997; 17(3):346–49. [PubMed: 9354804]

de Brito OM, Scorrano L. An intimate liaison: spatial organization of the endoplasmic reticulum–mitochondria relationship. EMBO J. 2010; 29(16):2715–23. [PubMed: 20717141]

De Matteis MA, Luini A. Mendelian disorders of membrane trafficking. N Engl J Med. 2011; 365(10): 927–38. [PubMed: 21899453]

DeLuca GC, Ebers GC, Esiri MM. The extent of axonal loss in the long tracts in hereditary spastic paraplegia. Neuropathol Appl Neurobiol. 2004; 30(6):576–84. [PubMed: 15540998]

Deng H-X, Zhai H, Fu R, Shi Y, Gorrie GH, et al. Distal axonopathy in an alsin-deficient mouse model. Hum Mol Genet. 2007; 16(23):2911–20. [PubMed: 17855450]

Depienne C, Stevanin G, Brice A, Durr A. Hereditary spastic paraplegias: an update. Curr Opin Neurol. 2007; 20(6):674–80. [PubMed: 17992088]

Derivery E, Gautreau A. Evolutionary conservation of the WASH complex, an actin polymerization machine involved in endosomal fission. Commun Integr Biol. 2010; 3(3):227–30. [PubMed: 20714399]

Derivery E, Sousa C, Gautier JJ, Lombard B, Loew D, Gautreau A. The Arp2/3 activator WASH controls the fission of endosomes through a large multiprotein complex. Dev Cell. 2009; 17(5): 712–23. [PubMed: 19922875]

Devon RS, Orban PC, Gerrow K, Barbieri MA, Schwab C, et al. *Als2*-deficient mice exhibit disturbances in endosome trafficking associated with motor behavioral abnormalities. Proc Natl Acad Sci USA. 2006; 103(25):9595–600. [PubMed: 16769894]

Dick KJ, Eckhardt M, Paisán-Ruiz C, Alshehhi AA, Proukakis C, et al. Mutation of FA2H underlies a complicated form of hereditary spastic paraplegia (SPG35). Hum Mutat. 2010; 31(4):E1251–60. [PubMed: 20104589]

DiMauro S, Schon EA. Mitochondrial disorders in the nervous system. Annu Rev Neurosci. 2008; 31:91–123. [PubMed: 18333761]

Dion PA, Daoud H, Rouleau GA. Genetics of motor neuron disorders: new insights into pathogenic mechanisms. Nat Rev Genet. 2009; 10(11):769–82. [PubMed: 19823194]

Duning T, Warnecke T, Schirmacher A, Schiffbauer H, Lohmann H, et al. Specific pattern of early white-matter changes in pure hereditary spastic paraplegia. Mov Disord. 2010; 25(12):1986–92. [PubMed: 20669295]

Eastman SW, Yassaee M, Bieniasz PD. A role for ubiquitin ligases and Spartin/SPG20 in lipid droplet turnover. J Cell Biol. 2009; 184(6):881–94. [PubMed: 19307600]

Ebbing B, Mann K, Starosta A, Jaud J, Schöls L, et al. Effect of spastic paraplegia mutations in KIF5A kinesin on transport activity. Hum Mol Genet. 2008; 17(9):1245–52. [PubMed: 18203753]

Edgar JM, McLaughlin M, Yool D, Zhang S-C, Fowler JH, et al. Oligodendroglial modulation of fast axonal transport in a mouse model of hereditary spastic paraplegia. J Cell Biol. 2004; 166(1):121–31. [PubMed: 15226307]

Edwards TL, Clowes VE, Tsang HTH, Connell JW, Sanderson CM, et al. Endogenous spartin (SPG20) is recruited to endosomes and lipid droplets and interacts with the ubiquitin E3 ligases AIP4 and AIP5. Biochem J. 2009; 423(1):31–39. [PubMed: 19580544]

Erlich Y, Edvardson S, Hodges E, Zenvirt S, Thekkat P, et al. Exome sequencing and disease-network analysis of a single family implicate a mutation in *KIF1A* in hereditary spastic paraparesis. Genome Res. 2011; 21(5):658–64. [PubMed: 21487076]

Evans K, Keller C, Pavur K, Glasgow K, Conn B, Lauring B. Interaction of two hereditary spastic paraplegia gene products, spastin and atlastin, suggests a common pathway for axonal maintenance. Proc Natl Acad Sci USA. 2006; 103(28):10666–71. [PubMed: 16815977]

Fasana E, Fossati M, Ruggiano A, Brambillasca S, Hoogenraad CC, et al. A VAPB mutant linked to amyotrophic lateral sclerosis generates a novel form of organized smooth endoplasmic reticulum. FASEB J. 2010; 24(5):1419–30. [PubMed: 20008544]

Fassier C, Hutt JA, Scholpp S, Lumsden A, Giros B, et al. Zebrafish atlastin controls motility and spinal motor axon architecture via inhibition of the BMP pathway. Nat Neurosci. 2010; 13(11): 1380–87. [PubMed: 20935645]

Fei W, Du X, Yang H. Seipin, adipogenesis and lipid droplets. Trends Endocrinol Metab. 2011a; 22(6): 204–10. [PubMed: 21497513]

Fei W, Shui G, Zhang Y, Krahmer N, Ferguson C, et al. A role for phosphatidic acid in the formation of "supersized" lipid droplets. PLoS Genet. 2011b; 7(7):e1002201. [PubMed: 21829381]

Ferreirinha F, Quattrini A, Pirozzi M, Valsecchi V, Dina G, et al. Axonal degeneration in paraplegin-deficient mice is associated with abnormal mitochondria and impairment of axonal transport. J Clin Invest. 2004; 113(2):231–42. [PubMed: 14722615]

Fink JK. Hereditary spastic paraplegia. Curr Neurol Neurosci Rep. 2006; 6(1):65–76. [PubMed: 16469273]

Goizet C, Boukhris A, Mundwiller E, Tallaksen C, Forlani S, et al. Complicated forms of autosomal dominant hereditary spastic paraplegia are frequent in SPG10. Hum Mutat. 2009; 30(2):E376–85. [PubMed: 18853458]

Goldstein AYN, Wang X, Schwarz TL. Axonal transport and the delivery of pre-synaptic components. Curr Opin Neurobiol. 2008; 18(5):495–503. [PubMed: 18950710]

Gomez TS, Billadeau DD. A FAM21-containing WASH complex regulates retromer-dependent sorting. Dev Cell. 2009; 17(5):699–711. [PubMed: 19922874]

Goytain A, Hines RM, El-Husseini A, Quamme GA. *NIPA1*(*SPG6*), the basis for autosomal dominant form of hereditary spastic paraplegia, encodes a functional Mg^{2+} transporter. J Biol Chem. 2007; 282(11):8060–68. [PubMed: 17166836]

Gruenenfelder FI, Thomson G, Penderis J, Edgar JM. Axon-glial interaction in the CNS: what we have learned from mouse models of Pelizaeus-Merzbacher disease. J Anat. 2011; 219(1):33–43. [PubMed: 21401588]

Guelly C, Zhu P-P, Leonardis L, Papić L, Zidar J, et al. Targeted high-throughput sequencing identifies mutations in *atlastin-1* as a cause of hereditary sensory neuropathy type I. Am J Hum Genet. 2011; 88(1):99–105. [PubMed: 21194679]

Guizetti J, Schermelleh L, Mántler J, Maar S, Poser I, et al. Cortical constriction during abscission involves helices of ESCRT-III-dependent filaments. Science. 2011; 331(6024):1616–20. [PubMed: 21310966]

Hadano S, Kunita R, Otomo A, Suzuki-Utsunomiya K, Ikeda J-E. Molecular and cellular function of ALS2/alsin: implication of membrane dynamics in neuronal development and degeneration. Neurochem Int. 2007; 51(2–4):74–84. [PubMed: 17566607]

Hanna MC, Blackstone C. Interaction of the *SPG21* protein ACP33/maspardin with the aldehyde dehydrogenase ALDH16A1. Neurogenetics. 2009; 10(3):217–28. [PubMed: 19184135]

Hapala I, Marza E, Ferreira T. Is fat so bad? Modulation of endoplasmic reticulum stress by lipid droplet formation. Biol Cell. 2011; 103(6):271–85. [PubMed: 21729000]

Harbour ME, Breusegem SYA, Antrobus R, Freeman C, Reid E, Seaman MNJ. The cargo-selective retromer complex is a recruiting hub for protein complexes that regulate endosomal tubule dynamics. J Cell Sci. 2010; 123(Pt 21):3703–17. [PubMed: 20923837]

Harding AE. Classification of the hereditary ataxias and paraplegias. Lancet. 1983; 1(8334):1151–55. [PubMed: 6133167]

Hirokawa N, Niwa S, Tanaka Y. Molecular motors in neurons: transport mechanisms and roles in brain function, development, and disease. Neuron. 2010; 68(4):610–38. [PubMed: 21092854]

Hirst J, Barlow LD, Francisco GC, Sahlender DA, Seaman MNJ, et al. The fifth adaptor protein complex. PLoS Biol. 2011; 9(10):e1001170. [PubMed: 22022230]

Hooper C, Puttamadappa SS, Loring Z, Shekhtman A, Bakowska JC. Spartin activates atrophin-1-interacting protein 4 (AIP4) E3 ubiquitin ligase and promotes ubiquitination of adipophilin on lipid droplets. BMC Biol. 2010; 8:72. [PubMed: 20504295]

Hu J, Shibata Y, Voss C, Shemesh T, Li Z, et al. Membrane proteins of the endoplasmic reticulum induce high-curvature tubules. Science. 2008; 319(5867):1247–50. [PubMed: 18309084]

Hu J, Shibata Y, Zhu P-P, Voss C, Rismanchi N, et al. A class of dynamin-like GTPases involved in the generation of the tubular ER network. Cell. 2009; 138(3):549–61. [PubMed: 19665976]

Hurd DD, Saxton WM. Kinesin mutations cause motor neuron disease phenotypes by disrupting fast axonal transport in Drosophila. Genetics. 1996; 144(3):1075–85. [PubMed: 8913751]

Hurley JH, Hanson PI. Membrane budding and scission by the ESCRT machinery: It's all in the neck. Nat Rev Mol Cell Biol. 2010; 11(8):556–66. [PubMed: 20588296]

Inoue K. *PLP1*-related inherited dysmyelinating disorders: Pelizaeus-Merzbacher disease and spastic paraplegia type 2. Neurogenetics. 2005; 6(1):1–16. [PubMed: 15627202]

Ito D, Suzuki N. Seipinopathy: a novel endoplasmic reticulum stress-associated disease. Brain. 2009; 132(Pt 1):8–15. [PubMed: 18790819]

Jia D, Gomez TS, Metlagel Z, Umetani J, Otwinowski Z, et al. WASH and WAVE actin regulators of the Wiskott-Aldrich syndrome protein (WASP) family are controlled by analogous structurally related complexes. Proc Natl Acad Sci USA. 2010; 107(23):10442–47. [PubMed: 20498093]

Jo Y, Sguigna PV, DeBose-Boyd RA. Membrane-associated ubiquitin ligase complex containing gp78 mediates sterol-accelerated degradation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. J Biol Chem. 2011; 286(17):15022–31. [PubMed: 21343306]

Jouet M, Rosenthal A, Armstrong G, MacFarlane J, Stevenson R, et al. X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the *L1* gene. Nat Genet. 1994; 7(3):402–7. [PubMed: 7920659]

Kornmann B, Walter P. ERMES-mediated ER-mitochondria contacts: molecular hubs for the regulation of mitochondrial biology. J Cell Sci. 2010; 123(Pt 9):1389–93. [PubMed: 20410371]

Kurth I, Pamminger T, Hennings JC, Soehendra D, Huebner AK, et al. Mutations in *FAM134B*, encoding a newly identified Golgi protein, cause severe sensory and autonomic neuropathy. Nat Genet. 2009; 41(11):1179–81. [PubMed: 19838196]

Lang N, Optenhoefel T, Deuschl G, Klebe S. Axonal integrity of corticospinal projections to the upper limbs in patients with pure hereditary spastic paraplegia. Clin Neurophysiol. 2011; 122(7):1417–20. [PubMed: 21195663]

Lin P, Li J, Liu Q, Mao F, Li J, et al. A missense mutation in *SLC33A1*, which encodes the acetyl-CoA transporter, causes autosomal-dominant spastic paraplegia (*SPG42*). Am J Hum Genet. 2008; 83(6):752–59. [PubMed: 19061983]

Lind GE, Raiborg C, Danielsen SA, Rognum TO, Thiis-Evensen E, et al. *SPG20*, a novel biomarker for early detection of colorectal cancer, encodes a regulator of cytokinesis. Oncogene. 2011; 30(37):3967–78. [PubMed: 21499309]

Lynes EM, Simmen T. Urban planning of the endoplasmic reticulum (ER): how diverse mechanisms segregate the many functions of the ER. Biochim Biophys Acta. 2011; 1813(10):1893–905. [PubMed: 21756943]

Mancuso G, Rugarli EI. A cryptic promoter in the first exon of the *SPG4* gene directs the synthesis of the 60-kDa spastin isoform. BMC Biol. 2008; 6:31. [PubMed: 18613979]

Mannan AU, Boehm J, Sauter SM, Rauber A, Byrne PC, et al. Spastin, the most commonly mutated protein in hereditary spastic paraplegia interacts with Reticulon 1 an endoplasmic reticulum protein. Neurogenetics. 2006; 7(2):93–103. [PubMed: 16602018]

Matsuura I, Taniguchi J, Hata K, Saeki N, Yamashita T. BMP inhibition enhances axonal growth and functional recovery after spinal cord injury. J Neurochem. 2008; 105(4):1471–79. [PubMed: 18221366]

McCray BA, Skordalakes E, Taylor JP. Disease mutations in Rab7 result in unregulated nucleotide exchange and inappropriate activation. Hum Mol Genet. 2010; 19(6):1033–47. [PubMed: 20028791]

Montenegro G, Rebelo AP, Connell J, Allison R, Babalini C, et al. Mutations in the ER-shaping protein reticulon 2 cause the axon-degenerative disorder hereditary spastic paraplegia type 12. J Clin Invest. 2012; 122(2):538–44. [PubMed: 22232211]

Moreno-De-Luca A, Helmers SL, Mao H, Burns TG, Melton AMA, et al. Adaptor protein complex-4 (AP-4) deficiency causes a novel autosomal recessive cerebral palsy syndrome with microcephaly and intellectual disability. J Med Genet. 2011; 48(2):141–44. [PubMed: 20972249]

Morita E, Colf LA, Karren MA, Sandrin V, Rodesch CK, Sundquist WI. Human ESCRT-III and VPS4 proteins are required for centrosome and spindle maintenance. Proc Natl Acad Sci USA. 2010; 107(29):12889–94. [PubMed: 20616062]

Moss TJ, Andreazza C, Verma A, Daga A, McNew JA. Membrane fusion by the GTPase atlastin requires a conserved C-terminal cytoplasmic tail and dimerization through the middle domain. Proc Natl Acad Sci USA. 2011; 108(27):11133–38. [PubMed: 21690399]

Murmu RP, Martin E, Rastetter A, Esteves T, Muriel M-P, et al. Cellular distribution and subcellular localization of spatacsin and spastizin, two proteins involved in hereditary spastic paraplegia. Mol Cell Neurosci. 2011; 47(3):191–202. [PubMed: 21545838]

Orso G, Martinuzzi A, Rossetto MG, Sartori E, Feany M, Daga A. Disease-related phenotypes in a *Drosophila* model of hereditary spastic paraplegia are ameliorated by treatment with vinblastine. J Clin Invest. 2005; 115(11):3026–34. [PubMed: 16276413]

Orso G, Pendin D, Liu S, Tosetto J, Moss TJ, et al. Homotypic fusion of ER membranes requires the dynamin-like GTPase atlastin. Nature. 2009; 460(7258):978–83. [PubMed: 19633650]

Orthmann-Murphy JL, Salsano E, Abrams CK, Bizzi A, Uziel G, et al. Hereditary spastic paraplegia is a novel phenotype for *GJA12/GJC2* mutations. Brain. 2009; 132(Pt 2):426–38. [PubMed: 19056803]

Park SH, Blackstone C. Further assembly required: construction and dynamics of the endoplasmic reticulum network. EMBO Rep. 2010; 11(7):515–21. [PubMed: 20559323]

Park SH, Zhu P-P, Parker RL, Blackstone C. Hereditary spastic paraplegia proteins REEP1, spastin, and atlastin-1 coordinate microtubule interactions with the tubular ER network. J Clin Invest. 2010; 120(4):1097–110. [PubMed: 20200447]

Pearce MMP, Wormer DB, Wilkens S, Wojcikiewicz RJH. An endoplasmic reticulum (ER) membrane complex composed of SPFH1 and SPFH2 mediates the ER-associated degradation of inositol 1,4,5-trisphosphate receptors. J Biol Chem. 2009; 284(16):10433–45. [PubMed: 19240031]

Potter KA, Kern MJ, Fullbright G, Bielawski J, Scherer SS, et al. Central nervous system dysfunction in a mouse model of Fa2h deficiency. Glia. 2011; 59(7):1009–21. [PubMed: 21491498]

Rainier S, Bui M, Mark E, Thomas D, Tokarz D, et al. Neuropathy target esterase gene mutations cause motor neuron disease. Am J Hum Genet. 2008; 82(3):780–85. [PubMed: 18313024]

Read DJ, Li Y, Chao MV, Cavanagh JB, Glynn P. Neuropathy target esterase is required for adult vertebrate axon maintenance. J Neurosci. 2009; 29(37):11594–600. [PubMed: 19759306]

Reid E, Kloos M, Ashley-Koch A, Hughes L, Bevan S, et al. A kinesin heavy chain (*KIF5A*) mutation in hereditary spastic paraplegia (SPG10). Am J Hum Genet. 2002; 71(5):1189–94. [PubMed: 12355402]

Renvoisé B, Blackstone C. Emerging themes of ER organization in the development and maintenance of axons. Curr Opin Neurobiol. 2010; 20(5):531–37. [PubMed: 20678923]

Renvoisé B, Parker RL, Yang D, Bakowska JC, Hurley JH, Blackstone C. SPG20 protein spartin is recruited to midbodies by ESCRT-III protein Ist1 and participates in cytokinesis. Mol Biol Cell. 2010; 21(19):3293–303. [PubMed: 20719964]

Rismanchi N, Soderblom C, Stadler J, Zhu P-P, Blackstone C. Atlastin GTPases are required for Golgi apparatus and ER morphogenesis. Hum Mol Genet. 2008; 17(11):1591–604. [PubMed: 18270207]

Rivière J-B, Ramalingam S, Lavastre V, Shekarabi M, Holbert S, et al. *KIF1A*, an axonal transporter of synaptic vesicles, is mutated in hereditary sensory and autonomic neuropathy Type 2. Am J Hum Genet. 2011; 89(2):219–30. [PubMed: 21820098]

Robay D, Patel H, Simpson MA, Brown NA, Crosby AH. Endogenous spartin, mutated in hereditary spastic paraplegia, has a complex subcellular localization suggesting diverse roles in neurons. Exp Cell Res. 2006; 312(15):2764–77. [PubMed: 16781711]

Ropers F, Derivery E, Hu H, Garshasbi M, Karbasiyan M, et al. Identification of a novel candidate gene for non-syndromic autosomal recessive intellectual disability: the WASH complex member SWIP. Hum Mol Genet. 2011; 20(13):2585–90. [PubMed: 21498477]

Sagona AP, Nezis IP, Pedersen NM, Liestøl K, Poulton J, et al. PtdIns(3)P controls cytokinesis through KIF13A-mediated recruitment of FYVE-CENT to the midbody. Nat Cell Biol. 2010; 12(4):362–71. [PubMed: 20208530]

Saito H, Kubota M, Roberts RW, Chi Q, Matsunami H. RTP family members induce functional expression of mammalian odorant receptors. Cell. 2004; 119(5):679–91. [PubMed: 15550249]

Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. Lancet Neurol. 2008; 7(12):1127–38. [PubMed: 19007737]

Sanderson CM, Connell JW, Edwards TL, Bright NA, Duley S, et al. Spastin and atlastin, two proteins mutated in autosomal-dominant hereditary spastic paraplegia, are binding partners. Hum Mol Genet. 2006; 15(2):307–18. [PubMed: 16339213]

Schneider SA, Bhatia KP. Three faces of the same gene: *FA2H* links neurodegeneration with brain iron accumulation, leukodystrophies, and hereditary spastic paraplegias. Ann Neurol. 2010; 68(5): 575–77. [PubMed: 21031573]

Schüle R, Siddique T, Deng H-X, Yang Y, Donkervoort S, et al. Marked accumulation of 27-hydroxycholesterol in SPG5 patients with hereditary spastic paresis. J Lipid Res. 2010; 51(4): 819–23. [PubMed: 19812052]

Shibata Y, Hu J, Kozlov MM, Rapoport TA. Mechanisms shaping the membranes of cellular organelles. Annu Rev Cell Dev Biol. 2009; 25:329–54. [PubMed: 19575675]

Sieberer BJ, Ketelaar T, Esseling JJ, Emons AMC. Microtubules guide root hair tip growth. New Phytol. 2005; 167(3):711–19. [PubMed: 16101908]

Słabicki M, Theis M, Krastev DB, Samsonov S, Mundwiller E, et al. A genome-scale DNA repair RNAi screen identifies SPG48 as a novel gene associated with hereditary spastic paraplegia. PLoS Biol. 2010; 8(6):e1000408. [PubMed: 20613862]

Soderblom C, Blackstone C. Traffic accidents: molecular genetic insights into the pathogenesis of the hereditary spastic paraplegias. Pharmacol Ther. 2006; 109(1–2):42–56. [PubMed: 16005518]

Soderblom C, Stadler J, Jupille H, Blackstone C, Shupliakov O, Hanna MC. Targeted disruption of the Mast syndrome gene *SPG21* in mice impairs hind limb function and alters axon branching in cultured cortical neurons. Neurogenetics. 2010; 11(4):369–78. [PubMed: 20661613]

Solowska JM, Morfini G, Falnikar A, Himes BT, Brady ST, et al. Quantitative and functional analyses of spastin in the nervous system: implications for hereditary spastic paraplegia. J Neurosci. 2008; 28(9):2147–57. [PubMed: 18305248]

Sparkes I, Hawes C, Frigerio L. FrontiERs: movers and shapers of the higher plant cortical endoplasmic reticulum. Curr Opin Plant Biol. 2011; 14(6):658–65. [PubMed: 21831697]

Sutendra G, Dromparis P, Wright P, Bonnet S, Haromy A, et al. The role of Nogo and the mitochondria-endoplasmic reticulum unit in pulmonary hypertension. Sci Transl Med. 2011; 3(88):88ra55.

Terasaki M, Chen LB, Fujiwara K. Microtubules and the endoplasmic reticulum are highly interdependent structures. J Cell Biol. 1986; 103(4):1557–68. [PubMed: 3533956]

Tian Y, Bi J, Shui G, Liu Z, Xiang Y, et al. Tissue-autonomous function of *Drosophila Seipin* in preventing ectopic lipid droplet formation. PLoS Genet. 2011; 7(4):e1001364. [PubMed: 21533227]

Toulmay A, Prinz WA. Lipid transfer and signaling at organelle contact sites: the tip of the iceberg. Curr Opin Cell Biol. 2011; 23(4):458–63. [PubMed: 21555211]

Tsang HTH, Edwards TL, Wang X, Connell JW, Davies RJ, et al. The hereditary spastic paraplegia proteins NIPA1, spastin and spartin are inhibitors of mammalian BMP signalling. Hum Mol Genet. 2009; 18(20):3805–21. [PubMed: 19620182]

Tsaousidou MK, Ouahchi K, Warner TT, Yang Y, Simpson MA, et al. Sequence alterations within CYP7B1 implicate defective cholesterol homeostasis in motor-neuron degeneration. Am J Hum Genet. 2008; 82(2):510–15. [PubMed: 18252231]

Unrath A, Müller H-P, Riecker A, Ludolph AC, Sperfeld A-D, Kassubek J. Whole brain-based analysis of regional white matter tract alterations in rare motor neuron diseases by diffusion tensor imaging. Hum Brain Mapp. 2010; 31(11):1727–40. [PubMed: 20336652]

Urbanczyk A, Enz R. Spartin recruits PKC-ζ via the PKC-ζ-interacting proteins ZIP1 and ZIP3 to lipid droplets. J Neurochem. 2011; 118(5):737–48. [PubMed: 21707618]

Valdmanis PN, Meijer IA, Reynolds A, Lei A, MacLeod P, et al. Mutations in the *KIAA0196* gene at the *SPG8* locus cause hereditary spastic paraplegia. Am J Hum Genet. 2007; 80(1):152–61. [PubMed: 17160902]

Verkhratsky A. Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. Physiol Rev. 2005; 85(1):201–79. [PubMed: 15618481]

Vilariño-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, et al. *VPS35* mutations in Parkinson disease. Am J Hum Genet. 2011; 89(1):162–67. [PubMed: 21763482]

Voeltz GK, Prinz WA, Shibata Y, Rist JM, Rapoport TA. A class of membrane proteins shaping the tubular endoplasmic reticulum. Cell. 2006; 124(3):573–86. [PubMed: 16469703]

Wang H, Lockwood SK, Hoeltzel MF, Schiefelbein JW. The *ROOT HAIR DEFECTIVE3* gene encodes an evolutionarily conserved protein with GTP-binding motifs and is required for regulated cell enlargement in *Arabidopsis*. Genes Dev. 1997; 11(6):799–811. [PubMed: 9087433]

Wang X, Shaw WR, Tsang HTH, Reid E, O'Kane CJ. *Drosophila* spichthyin inhibits BMP signaling and regulates synaptic growth and axonal microtubules. Nat Neurosci. 2007; 10(2):177–85. [PubMed: 17220882]

Waterman-Storer CM, Salmon ED. Endoplasmic reticulum membrane tubules are distributed by microtubules in living cells using three distinct mechanisms. Curr Biol. 1998; 8(14):798–806. [PubMed: 9663388]

Weedon MN, Hastings R, Caswell R, Xie W, Paszkiewicz K, et al. Exome sequencing identifies a *DYNC1H1* mutation in a large pedigree with dominant axonal Charcot-Marie-Tooth disease. Am J Hum Genet. 2011; 89(2):308–12. [PubMed: 21820100]

Weller S, Gärtner J. Genetic and clinical aspects of X-linked hydrocephalus (L1 disease): mutations in the *L1CAM* gene. Hum Mutat. 2001; 18(1):1–12. [PubMed: 11438988]

West M, Zurek N, Hoenger A, Voeltz GK. A 3D analysis of yeast ER structure reveals how ER domains are organized by membrane curvature. J Cell Biol. 2011; 193(2):333–46. [PubMed: 21502358]

Westermann B. Mitochondrial fusion and fission in cell life and death. Nat Rev Mol Cell Biol. 2010; 11(12):872–84. [PubMed: 21102612]

Windpassinger C, Auer-Grumbach M, Irobi J, Patel H, Petek E, et al. Heterozygous missense mutations in *BSCL2* are associated with distal hereditary motor neuropathy and Silver syndrome. Nat Genet. 2004; 36(3):271–76. [PubMed: 14981520]

Yagi T, Ito D, Nihei Y, Ishihara T, Suzuki N. N88S seipin mutant transgenic mice develop features of seipinopathy/BSCL2-related motor neuron disease via endoplasmic reticulum stress. Hum Mol Genet. 2011; 20(19):3831–40. [PubMed: 21750110]

Yang D, Rismanchi N, Renvoisé B, Lippincott-Schwartz J, Blackstone C, Hurley JH. Structural basis for midbody targeting of spastin by the ESCRT-III protein CHMP1B. Nat Struct Mol Biol. 2008; 15(12):1278–86. [PubMed: 18997780]

Yang YS, Harel NY, Strittmatter SM. Reticulon-4A (Nogo-A) redistributes protein disulfide isomerase to protect mice from SOD1-dependent amyotrophic lateral sclerosis. J Neurosci. 2009; 29(44): 13850–59. [PubMed: 19889996]

Yıldırım Y, Orhan EK, Iseri SAU, Serdaroglu-Oflazer P, Kara B, et al. A frameshift mutation of *ERLIN2* in recessive intellectual disability, motor dysfunction and multiple joint contractures. Hum Mol Genet. 2011; 20(10):1886–92. [PubMed: 21330303]

Yu PB, Hong CC, Sachidanandan C, Babitt JL, Deng DY, et al. Dorsomorphin inhibits BMP signals required for embryogenesis and iron metabolism. Nat Chem Biol. 2008; 4(1):33–41. [PubMed: 18026094]

Zhu P-P, Patterson A, Lavoie B, Stadler J, Shoeb M, et al. Cellular localization, oligomerization, and membrane association of the hereditary spastic paraplegia 3A (SPG3A) protein atlastin. J Biol Chem. 2003; 278(49):49063–71. [PubMed: 14506257]

Zhu P-P, Soderblom C, Tao-Cheng J-H, Stadler J, Blackstone C. SPG3A protein atlastin-1 is enriched in growth cones and promotes axon elongation during neuronal development. Hum Mol Genet. 2006; 15(8):1343–53. [PubMed: 16537571]

Zimprich A, Benet-Pagés A, Struhal W, Graf E, Eck SH, et al. A mutation in *VPS35*, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet. 2011; 89(1):168–75. [PubMed: 21763483]

RELATED RESOURCES

Neuromuscul. Dis. Cent. Web page. Familial spinal cord syndromes. http://neuromuscular.wustl.edu/spinal/fsp.html. A comprehensive, frequently updated resource for information on all types of HSPs and related disorders

Reid, E., Rugarli, EI. Hereditary spastic paraplegias. In: Valle, D.Beaudet, AL.Vogelstein, B.Kinzler, KW.Antonarakis, SE., et al., editors. The Online Metabolic and Molecular Bases of Inherited Diseases. Vol. Ch 228.1. New York: McGraw Hill; 2010. http://dx.doi.org/10.1036/ommbid.266

Spastic Paraplegia Found. Web page. http://www.sp-foundation.org. Valuable information on research efforts focusing on the HSPs.

ER SHAPING: PLANT ROOTS TO AXONS

In the flowering plant Arabidopsis, root hairs are long processes emanating from root epidermal cells. Like axon growth, root hair tip growth is an extreme form of polarized cell expansion regulated by signaling molecules, Ca^{2+} flux, cytoskeletal dynamics, GTPases of the Rab, Arf, and Rho/Rac families, and reactive oxygen species. Loss-of-function mutations in the atlastin/SPG3A ortholog RHD3 have highlighted the importance of proper ER morphology in Arabidopsis root hair formation (Wang et al. 1997, Chen et al. 2011). rhd3 mutant plants have abnormal tubular ER bundles within short, wavy root hairs and an unusually large number of vesicles in subapical (rather than apical) hair regions. This defective polarized expansion may reflect decreased or misplaced deposition of secretory vesicles during root hair elongation. Although ER tubules in plants are oriented mostly along actin fibers, root hair tip growth depends on microtubules also, and ER morphology changes during root hair elongation (Sieberer et al. 2005). Given the speed and adaptability of Arabidopsis genetics and conservation of atlastin/RHD3 GTPases as well as ER-shaping reticulon/REEP proteins (Sparkes et al. 2011), continued studies of root hair elongation will likely provide insights into the functions of ER in axon growth and maintenance.

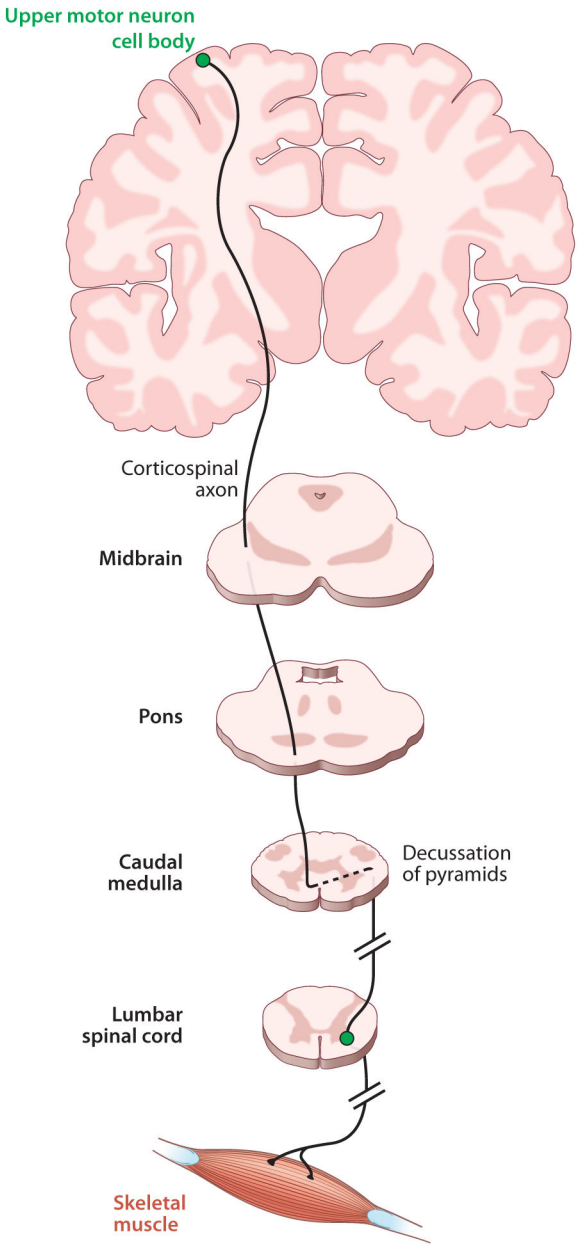

Figure 1.

Schematic diagram of the corticospinal tract emphasizing its descent through the CNS. Although most fibers decussate in the caudal medulla, a minority of fibers descend uncrossed as the ventral corticospinal tract (not shown).

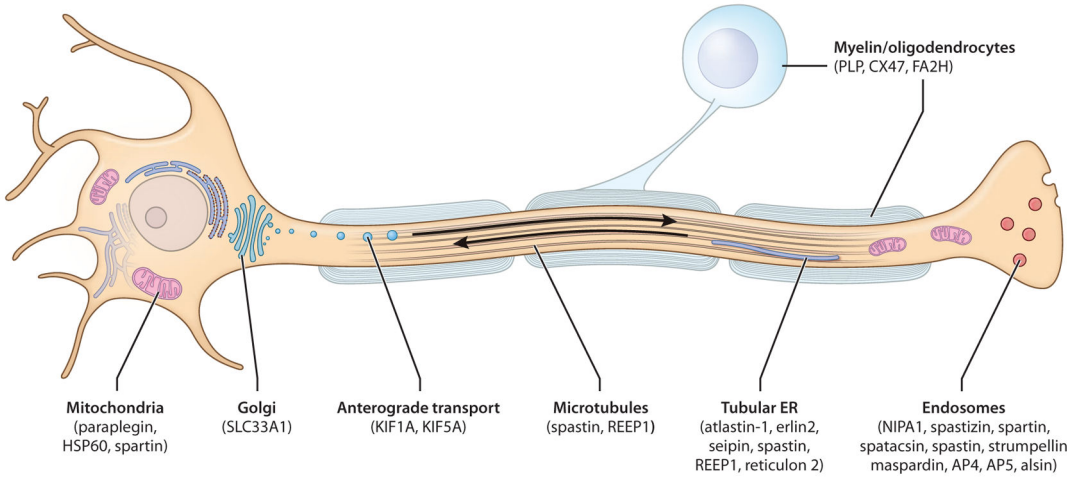

Figure 2.

Common pathogenic themes in the HSPs. This schematic representation of a corticospinal motor neuron emphasizes where HSP gene products as listed in Table 1 are proposed to function. L1CAM is an integral membrane protein localized to the plasma membrane. CYP7B1 and NTE distributions are not shown, pending more detailed studies of their sites of action.

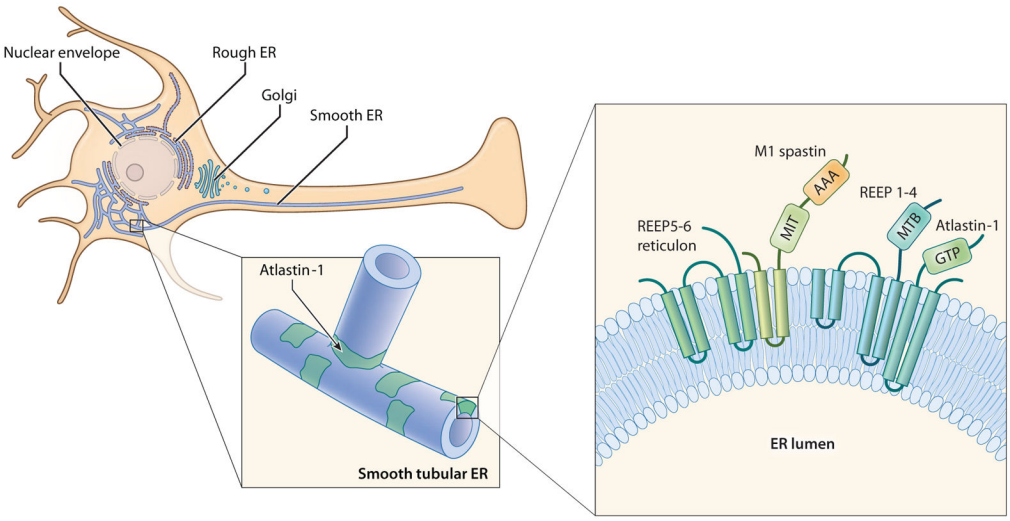

Figure 3.

Spastin, atlastin, REEP, and reticulon proteins interact and shape the endoplasmic reticulum (ER) network. (*Left*) Schematic diagram of a neuron showing the distribution of different ER domains. Below this schematic is an enlargement of a three-way tubular ER junction. REEP and reticulon proteins form large oligomers to shape the tubular ER. Atlastin proteins are enriched in puncta along the tubules, including at three-way junctions. (*Right*) Proposed membrane topologies for protein families involved in generating the tubular ER network. GTP, atlastin GTPase domain; MTB, microtubule-binding domain.

Table 1

Identified HSP genes, grouped functionally[a,b]

Disease/gene[b]	Protein name	Inheritance	Cellular functions
	Membrane traffic and organelle shaping		
SPG3A/*ATL1*	Atlastin-1	AD	ER morphogenesis BMP signaling
SPG4/*SPAST*	Spastin (M1 and M87 isoforms)	AD	Microtubule severing ER morphogenesis Endosomal traffic BMP signaling Cytokinesis
SPG6/*NIPA1*	NIPA1	AD	Endosomal traffic Mg^{2+} transport BMP signaling
SPG8/*KIAA0196*	Strumpellin	AD	Endosomal traffic Cytoskeletal (actin) regulation
SPG10/*KIF5A*	KIF5A	AD	Microtubule-based motor protein
SPG11	Spatacsin	AR	Endosomal traffic
SPG12/*RTN2*	Reticulon 2	AD	ER morphogenesis
SPG15/*ZFYVE26*	Spastizin/ ZFYVE26/ FYVE-CENT	AR	Endosomal traffic Cytokinesis Autophagy
SPG17/*BSCL2*	Seipin/BSCL2	AD	Lipid droplet biogenesis at ER
SPG18/*ERLIN2*	Erlin2	AR	ER-associated degradation Lipid raft-associated
SPG20	Spartin	AR	Endosomal traffic BMP signaling Cytokinesis Lipid droplet turnover Mitochondrial regulation
SPG21	Maspardin	AR	Endosomal traffic
SPG31/*REEP1*	REEP1	AD	ER morphogenesis ER-microtubule interaction
SPG48/*KIAA0415*	KIAA0415 (AP-5 subunit)	AR	Endocytic adaptor protein complex

Disease/gene[b]	Protein name	Inheritance	Cellular functions
AP-4 deficiency/*AP4S1, AP4B1, AP4E1*	AP-4 S1, B1, and E1 subunits	AR	Endocytic adaptor protein complex
JPLS/*ALS2*	Alsin	AR	Endosomal traffic
	Mitochondrial regulation		
SPG7	Paraplegin	AR	Mitochondrial *m*-AAA ATPase
SPG13/*HSPD1*	HSP60	AD	Mitochondrial chaperonin
	Myelination and lipid/sterol modification		
SPG2/*PLP1*	Proteolipid protein	X-linked	Major myelin protein
SPG5/*CYP7B*	CYP7B1	AR	Cholesterol metabolism
SPG35/*FA2H*	Fatty acid 2-hydroxylase	AR	Myelin lipid hydroxylation
SPG39/*PNPLA2*	Neuropathy target esterase	AR	Phospholipid homeostasis
SPG42/*SLC33A1*	SLC33A1	AD	Acetyl-CoA transporter
SPG44/*GJC2*	Connexin-47	AR	Intercellular gap junction channel
	Axon Pathfinding		
SPG1/*L1CAM*	L1CAM	X-linked	Cell adhesion and signaling

[a] Abbreviations: AD, autosomal dominant; AR, autosomal recessive; BMP, bone morphogenetic protein; ER, endoplasmic reticulum.

[b] When different from disease name.