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INVITED EDITORIAL
Is the Transportation Highway the Right Road for Hereditary Spastic Paraplegia?

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The term "hereditary spastic paraplegia" (HSP) refers to a genetically and clinically diverse group of disorders whose primary feature is progressive spasticity of the lower extremities. The condition arises because of degeneration of the longest motor and sensory axons on the spinal cord, which appear to be most sensitive to the underlying mutations. The marked genetic heterogeneity in HSP, with 20 loci chromosomally mapped and eight genes now identified, suggests that a number of defective cellular processes may be shown to result in the disease. Although previous studies have suggested a mitochondrial basis for at least one form of the disease, a mechanism common to a number of the other genes mutated in HSP has remained elusive until now. The identification of the most recent genes for the condition suggests that aberrant cellular-trafficking dynamics may be a common process responsible for the specific pattern of neurodegeneration seen in HSP.

Introduction

The term "hereditary spastic paraplegia" (or "hereditary spastic paraparesis") (HSP) is used to describe a group of clinically heterogeneous neurodegenerative disorders in which the predominant feature is progressive spasticity associated with mild weakness of the lower limbs, which may be accompanied by bladder disturbances and subtle vibratory sense impairment (McDermot et al. 2000). These disorders are classified as either "pure" (or "uncomplicated"), when the above features occur in isolation, or "complicated," in the presence of additional neurological manifestations, such as mental retardation, extrapyramidal symptoms, deafness, or optic neuropathy.

First described in the latter part of the 19th century (Seeligmuller 1876; Strumpell 1880), HSP remains a poorly understood condition. Neuropathological analysis of tissues from patients with pure forms of HSP has revealed axonal degeneration of the distal portions of the corticospinal tracts, the fasciculus gracilis, and the spinocerebellar tracts, which together constitute the longest motor and sensory axons of the CNS (Schwarz and Liu 1956; Behan and Maia 1974). A specific pattern of degeneration is seen in HSP, during which the cell bodies remain largely intact while the degeneration is principally limited to the cell axon and may be a "dying back" axonopathy, beginning distally and proceeding towards the cell body (Schwarz and Liu 1956). Despite the large and ever-increasing number of loci mapped for the various forms of HSP (table 1) and the identification of eight genes to date, a clear basis for most forms of HSP remains elusive. The identification of the causative genes and pathogenic mechanism(s) responsible for the specific patterns of neurodegeneration presents the initial challenge. In this article, we review the genes known to cause HSP and emphasize how recent discoveries suggest that defective trafficking may be a mechanism common to several forms of HSP.

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The X-Linked Genes

Two X-linked genes—L1 cell adhesion molecule (*L1CAM*) and proteolipid protein (*PLP1*)—were the first HSP genes to be identified, both of which may be mutated to produce a complicated HSP phenotype. PLP1 mutations may additionally lead to pure HSP (Jouet et al. 1994; Saugier-Veber et al. 1994). The varying complicated phenotypes associated with L1CAM mutations are often referred to as the "CRASH syndrome" (corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus) (Fransen et al. 1995). The *L1CAM* gene encodes a transmembrane glycoprotein with extracellular immunoglobulin and fibronectin type II repeats, which mediates cell adhesion and neurite growth. Neuropathological studies and the use of transgenic animal models have suggested that this molecule is

Table 1

Summary of the Known HSP Loci and Genes

Symbol/Locus	Cytogenetic Location	Inheritance	Protein	OMIM Number	HSP Syndrome(s)
L1CAM (SPG1)	Xq28	X-linked	L1CAM	MIM 312900	Complicated
PLP1 (SPG2)	Xq28	X-linked	PLP1	MIM 312920	Complicated (rarely pure)
SPG3A	14q11-q21	Autosomal dominant	Atlastin	MIM 182600	Pure
SPG4	2p22	Autosomal dominant	Spastin	MIM 182601	Mainly pure
SPG5A	8q	Autosomal recessive		MIM 270800	Pure
SPG6	15q11.1	Autosomal dominant		MIM 600363	Pure
SPG7	16q24.3	Autosomal recessive	Paraplegin	MIM 600146	Pure and complicated
SPG8	8q23-q24	Autosomal dominant		MIM 603563	Pure
SPG9	10q23.3-q24.2	Autosomal dominant		MIM 601162	Complicated
SPG10	12q13	Autosomal dominant	KIF5A	MIM 604187	Pure
SPG11	15q13-q15	Autosomal recessive		MIM 604360	Pure
SPG12	19q13	Autosomal dominant		MIM 604805	Pure
SPG13	2q24-q34	Autosomal dominant	HSP60	MIM 605280	Pure
SPG14	3q27-q28	Autosomal recessive		MIM 605229	Complicated
SPG15	14q22-q24	Autosomal recessive		MIM 606859	Complicated
SPG16	Xq11.2	X-linked		MIM 300266	Complicated
SPG17 (Silver syndrome)	11q12-q14	Autosomal dominant		MIM 270685	Complicated
SPG19	9q33-q34	Autosomal dominant		MIM 607152	Pure
SPG20 (Troyer syndrome)	13q12.3	Autosomal recessive	Spartin	MIM 275900	Complicated

NOTE.—Data taken from the HUGO Gene Nomenclature Committee database, where SPG3A, SPG5B, and SPG18 are listed as "reserved."

required for normal development of the corticospinal tract (reviewed by Casari and Rugarli 2001), and recent data suggest a function for L1CAM in potentiation of neuronal migration (Thelen et al. 2002).

PLP1 encodes one of the major components of myelin and is mutated in complicated and (rarely) in pure forms of HSP. Mutations in *PLP1* are also responsible for Pelizaeus-Merzbacher disease (Saugier-Veber et al. 1994), which is characterized by significant hypomyelination of the CNS with a reduced number of mature oligodendrocytes. An understanding of the pathogenic mechanisms underlying these conditions has been provided by the generation of knockout mice lacking PLP1. Perhaps surprisingly, these animals have essentially normal CNS function but assemble compact myelin sheaths and ultimately develop widespread axonal swelling and degeneration (Griffiths et al. 1998). Consequently, a lack of PLP1 protein does not cause the dysmyelination seen in PMD, and the axonal defect is best explained by a deficiency in oligodendroglial function. The fact that this is associated with the accumulation of membranous dense bodies and mitochondria suggests that axonal transport is impaired (Griffiths et al. 1998).

The Mitochondrial Story

A different mechanism of action has been proposed for the paraplegin gene (*SPG7*), the third HSP gene to be identified, which is mutated to produce both complicated and pure forms of autosomal recessive HSP (Casari et al. 1998). Paraplegin is a mitochondrial metalloprotease with strong homology to the yeast mitochondrial ATPases afg3, rca1, and yme1. It contains an AAA (ATPases associated with diverse cellular activities) domain common to the AAA proteins (Patel and Latterich 1998), a group of molecules possessing a range of functions that include protein degradation and trafficking and organelle biogenesis. Mitochondrial AAA proteins display chaperone-like activity in functions such as ensuring the specificity of proteolysis and the activation of respiratory chain complexes (Leonhard et al. 1999). Consistent with a role for paraplegin in mitochondrial function, muscle biopsies obtained from some patients with paraplegin mutations show typical signs of mitochondrial disease (Casari et al. 1998). These include ragged-red fibers, intense succinate-dehydrogenase–stained areas, and cytochrome-oxidase–negative fibers. Furthermore, the degree of mitochondrial abnormality correlates with the severity of the disease. Taken together, these findings suggest that a mitochondrial-based mechanism underlies this form of the disorder. Very recent preliminary reports of electron microscopy studies in mice lacking paraplegin reveal that, long before degeneration, the axons are filled with abnormal mitochondria. Subsequently, swollen axons containing accumulated organelles and neurofilaments are seen, which suggests that mitochondrial dysfunction may lead to axonal degeneration by impairing axonal transport (Ferreirinha et al. 2001).

A single missense mutation (V72I) in heat shock protein 60 (Hsp60, also known as "chaperonin"), a mitochondrial chaperone not structurally related to paraplegin, has recently been identified in a dominant form of HSP (SPG13; Hansen et al. 2002). The *Escherichia coli* HSP60

orthologue GroEL is essential for growth under a variety of conditions (Fayet et al. 1989). Through use of a complementation assay, wild-type HSP60, but not HSP60 (V72I), was shown to support growth of strains of *E. coli* in which the endogenous orthologous genes had been deleted (Hansen et al. 2002). The mechanism of action of this mutation is unclear. The dominant inheritance of this form of HSP may arise through haploinsufficiency caused by a lowering of overall chaperonin activity. Alternatively, mutant subunits may perturb the allosteric coupling of wild-type molecules, thus exerting a dominant negative effect. Because of the discovery of mutations within genes encoding chaperones and their action as phenotype modulators, a role for chaperones is increasingly recognized in a range of neurodegenerative conditions, including autosomal recessive spastic ataxia of Charlevoix-Seguenay (MIM 270550) and amyotrophic lateral sclerosis (Slavotinek and Biesecker 2001), which have some similarities with HSP.

Transport Mechanisms in Axons: an Overview

It is of particular interest that the axonal degeneration in HSP is maximal in the longest tracts. Because of the length of their axons and their highly polarized architecture, neurons are highly dependent on an intricate system of transport designed to ensure correct targeted delivery of cell components (reviewed by Almenar-Queralt and Goldstein 2001). Important components of the cytoskeleton, along which different motor proteins move their cargoes at different rates, include polarized microtubules, utilized for long-range transport, and actin, utilized for short-range transport (reviewed by Apodaca 2001). Fast and slow axonal transport occurs along microtubules. Slow axonal transport, by which many cytoskeletal proteins move, is thought to occur only in the anterograde direction (i.e., towards the plus end of the microtubule). Fast anterograde transport, powered by kinesin motor proteins, is used for the transport of vesicles, membranes, and membranous organelles such as mitochondria. Fast retrograde transport (i.e., towards the minus end of the microtubule) is powered by dynein motor proteins and delivers endosomes, other organelles, and neurotrophic signals back to the cell bodies. Endosomes function as a central sorting site for both the biosynthetic and degradative pathways. Endocytosed substances move from early endosomes either to tubular recycling endosomes along the actin cytoskeleton, or via endosomal carrier vesicles/multivesicular bodies to late endosomes and then to lysosomes along the microtubule cytoskeleton (Matteoni and Kreis 1987; Gruenberg 2001). Newly synthesized lysosomal proteins also pass through an endosomal intermediate en route from the *trans*-Golgi to the lysosome (Babst et al. 1998). Studies of rat hippocampal neurons have allowed the clear identification of two apparently distinct classes of endosomes in axons: stationary round-oval endosomes and highly mobile tubulovesicular endosomes, which move along microtubules in both directions (Prekeris et al. 1999).

Spartin and Endosomal Trafficking

Until recently, there was little evidence to link the functions of any of the known HSP genes. However the recent identification of *spartin* (spastic paraplegia autosomal recessive Troyer syndrome), mutated in Troyer syndrome (TRS; SPG20), has suggested that the biochemical roles of some genes mutated to result in HSP may be related (Patel et al. 2002). TRS is an autosomal recessive complicated form of HSP associated with dysarthria and distal amyotrophy, present at high frequency in the Amish population of the United States (Cross and McKusick 1967). We have now identified >25 cases of TRS in the Amish community, all of which can be linked together to produce a single extensive pedigree. A single homozygous base pair deletion (1110delA) in exon 4 of *spartin,* located on chromosome 13q12.3, accounts for all cases of TRS within this population (Patel et al. 2002). Multiple sequence alignment reveals that spartin contains three novel domains, two of which are located in the C-terminal portion and are present in plants (data not shown). At present, the only functional information reported for these domains concerns their expression under stress conditions such as dehydration and senescence.

The N-terminal portion contains a recently described ESP domain, so named because it was identified in three molecules: End13/Vps4, SNX15 (sorting nexin 15), and PalB (Phillips et al. 2001). The N-terminal portion of the ESP domain has similarity to the tetratricopeptide repeat homology consensus sequence (Phillips et al. 2001), which mediates protein-protein interactions (Blatch and Lassle 1999). Our multiple alignment studies reveal that the length of the ESP domain can be slightly extended from that previously described and that it is present in a range of other molecules, many of which have a well-defined and consistent biochemical role (fig. 1). The sorting nexins are a family of mammalian proteins whose yeast orthologues have been identified as essential components in intracellular protein trafficking. Sorting nexin 15 (SNX15) is a recently discovered SNX that, on the basis of morphological and biochemical data, is also thought to play a crucial role in trafficking through the endocytic pathway, although no obvious orthologue in yeast or *Caenorhabditis elegans* has been found (Barr et al. 2000; Phillips et al. 2001). Immunofluorescence staining in COS7 cells has revealed that, although predicted to be soluble, SNX15 is found both within the cytosol and on membranes (Barr et al. 2000). Immunofluorescence staining of endogenous SNX15 showed that it resides within small puncta that partially colocalize with proteins that mark

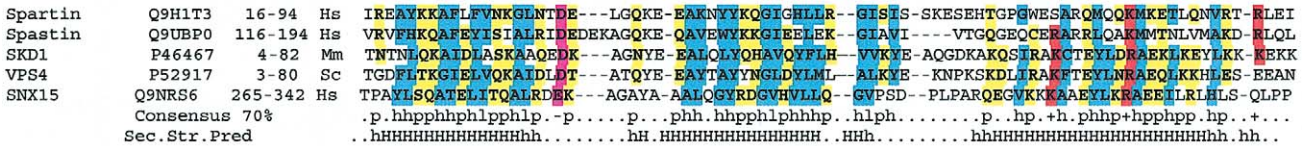

Figure 1 Multiple sequence alignment of selected members of the ESP (MIT) domain–containing proteins. Sequences are indicated using their database accession number followed by the starting and the ending residues of the domain and by the species. The consensus present in ⩾70% of the sequences is given below the alignment; residues and colors are as follows: h (hydrophobic, *blue*), l (aliphatic, *blue*), K (lysine), p (polar, *yellow*), and R (arginine). Plus signs (+) indicate conserved, positively charged residues (lysine and arginine), which are colored in red in the alignment; minus signs (−) indicate conserved, negatively charged residues, which are indicated in pink. The secondary structure prediction ("Sec.Str.Pred.") at the bottom of the alignment is derived from the alignment (H = helix predicted with expected average accuracy >82%; h = helix predicted with expected average accuracy <82%). Abbreviations: Hs, *Homo sapiens;* Mm, *Mus musculus;* and Sc, *Saccharomyces cerevisiae*.

or cycle through early endosomes. Overexpression of recombinant SNX15 in several cell types resulted in the appearance of abnormal structures, disrupting the organization of endosomes and leading to the formation of abnormal membrane-limited structures containing markers from early endosomes, late endosomes, and lysosomes. Taken together, these data suggest that SNX15 may normally reside on a subpopulation of early endosomes and that its overexpression causes abnormal trafficking of proteins from the plasma membrane to the *trans*-Golgi network or to recycling endosomes (Barr et al. 2000; Phillips et al. 2001). The overexpression of SNX15 also slowed the internalization of transferrin and furin, proteins endocytosed through clathrin-coated pits, indicating that SNX15 may affect clathrin-mediated endocytosis (Barr et al. 2000).

In addition to the above molecules, we have identified the ESP domain in yeast vacuolar protein sorting factor 4 (Vps4p), in its mammalian orthologues VPS4 and SKD1, and in spastin (commonly mutated in HSP; see below), which are all closely related ATPases belonging to subfamily 7 of the AAA group of proteins (Babst et al. 1997; Beyer 1997; Hazan et al. 1999; Yoshimori et al. 2000). Yeast Vps4p is an essential component of the intracellular protein transport machinery, in which it is required for the efficient transport of newly synthesized carboxy-peptidase Y from the Golgi network to the vacuole, the yeast counterpart of the animal lysosome (Babst et al. 1998). Mutant cells exhibit defects in several intracellular trafficking routes. Through use of a mutated form of Vps4p that is unable to bind to or hydrolyze ATP, it was shown that Vps4p associates transiently with an endosomal compartment in an ATP-dependent process (Babst et al. 1998). The ATP-hydrolysis–deficient Vps4p is directed to the class E compartment, thought to be an aberrant endosomal structure containing material from both the endocytic and biosynthetic pathways (Babst et al. 1998). Vps4p ATPase may therefore catalyze the "uncoating" of a protein complex associated with the cytoplasmic face of the endosomal membrane, in a process that is required for normal endosomal morphology and sorting (Babst et al. 1998). Like SNX15, Vps4p shows no obvious membrane-binding regions. It does, however, contain a putative 34–amino acid coiled-coil motif (Scheuring et al. 2001) that corresponds almost exactly to the terminal portion of the ESP domain. Deletion of a region including this coiled-coil motif abolishes the membrane association, thus implicating the ESP domain in the process of binding to endosomal membranes (Babst et al. 1998).

Numerous lines of evidence point to a similar role for the mammalian orthologues of Vps4p in protein trafficking and the regulation of endosomal morphology. Humans harbor two nonallelic Vps4p orthologues (VPS4-A and VPS4-B) that share a high degree of sequence similarity throughout the polypeptides (Scheuring et al. 2001). Heterologous expression of the human genes in Vps4p mutant yeast leads to suppression of the temperature-sensitive growth defect. Moreover, both human proteins associate with endosomal compartments in yeast when mutated to the ATPase-defective state (Scheuring et al. 2001). However, unlike yeast Vps4p, which binds exclusively to the class E perivacuolar compartment, ATPase-defective mammalian VPS4-A binds to multiple endosomal compartments (Bishop and Woodman 2000). SKD1, a mouse orthologue of VPS4 that most closely resembles human VPS4-B (Scheuring et al. 2001), is also involved in this process and is believed to associate transiently with membranes. Overexpression of mutant *SKD1* in cultured mammalian cells results in the defective uptake of transferrin and low-density lipoprotein, due to a loss of their respective cell surface receptors (Yoshimori et al. 2000). Electron microscopy reveals exaggerated multivesicular vacuoles with numerous tubulovesicular extensions, suggesting that *SKD1* is likely to be involved in the regulation of endosome morphology and transport. Very recent data suggest that the specific stage of endosomal trafficking for which SKD1 is required is the formation of autolysosomes in the late stages of the autophagic pathway (Nara et al. 2002). Finally, the ESP domain is also contained within

the recently identified human RPK118, found to colocalize with early endosomes (Hayashi et al. 2002).

Spastin and Microtubules

Notably, the ESP domain present within the endosomal trafficking molecules was also detected in the N-terminus of spastin (SPG4), the gene most commonly mutated in autosomal dominant HSP (Hazan et al. 1999). A recent study has shown that wild-type spastin interacts transiently with microtubules and is likely to be involved in microtubule dynamics (Errico et al. 2002). Overexpression of spastin in COS-7 and HeLa cells results in a microtubule-disassembly phenotype. These changes are not seen in cells transfected with mutant spastin and are specific to microtubules. However, spastin mutants, including most disease-causing AAA cassette missense mutants and a protein lacking the entire AAA cassette, are able to constitutively bind to microtubules, leading to a redistribution of the microtubule array. This suggests that spastin microtubule binding is ATPase-dependent, a finding analogous to the Vps4/SKD1 studies in which transient binding to membranes is also dependent on ATPase function. Although missense and truncating mutations have been shown to cause similar phenotypes, implying that haploinsufficiency is the pathogenic mechanism (Fonknechten et al. 2000), the finding that spastin mutants are able to constitutively bind microtubules raises the possibility of a dominant negative effect asserted by at least some spastin mutations. However, an important issue is the apparent instability of aberrant mRNA in truncating mutations (Svenson et al. 2001), which argues against such a dominant negative effect.

Studies using artificial spastin mutants indicate that the microtubule-binding capability of this molecule resides within its N-terminal region, although no functional domains in this region have been identified (Errico et al. 2002). Since the ESP domain lies within the N-terminal portion of spastin and no other domains in this region have been discovered, it seems possible that ESP provides the structural framework for microtubule interaction. However, the domain is also present within the Vps4p orthologues, as well as within SNX15 and RPK118, which have not been linked to microtubules but are involved in endosome modulation. Because the term "ESP" does not relate to its function and given its presence in the endosome-associating molecules and the microtubule-binding spastin, we propose the alternative descriptive term "MIT" for this domain (contained within microtubule-interacting and endosomal trafficking molecules).

Atlastin and the Dynamins

Additional support for defective trafficking as the basis for some forms of HSP is provided by the identification of three different mutations in atlastin (SPG3A) that result in dominantly inherited early-onset HSP (Zhao et al. 2001*b;* Muglia et al. 2002). Although the atlastin gene shares no homology with spartin or spastin, it encodes a product possessing structural homology with members of the dynamin family of large GTPases and has been tentatively assigned to this group. Dynamins play essential roles in a wide variety of vesicle trafficking events that are important for the action of neurotrophic factors and during neurotransmission (reviewed by McNiven et al. 2000). Seminal in vitro studies have shown that, under the correct conditions, dynamin self-assembles to form stacks of helical ring structures resembling the necks of invaginated coated pits, supporting a role for dynamin in the constriction and scission of budding vesicles (Hinshaw and Schmid 1995). Moreover, dynamin has been implicated in multiple clathrin-dependent and -independent vesicle-mediated processes, in both endocytic and secretory pathways (reviewed by McNiven et al. 2000). In addition to its involvement in the early stages of endocytic vesicle formation, dynamin is also thought to play a role in the later stages of membrane trafficking and may participate in the formation and liberation of coated vesicles from secretory compartments.

Kinesin Mutation Found in HSP

New support for defective trafficking in some forms of HSP is provided by the most recently identified causative gene. In the study by Reid et al. (2002 [in this issue]), a mutation in a kinesin heavy chain gene, *KIF5A,* has been identified in a family with chromosome 12q–linked HSP (SPG10). KIF5A, which does not contain the MIT (ESP) domain, forms part of a heterotetrameric protein motor complex that transports cargoes along microtubules in an anterograde direction (Goldstein and Yang 2000). The mutation identified in this family occurs in an invariant asparagine residue (N256S) located within the motor domain of the molecule, which has been previously identified as crucial to motor function in biochemical studies of kinesin proteins. Biochemical properties of a yeast mutant with a substitution in the homologous amino acid position (N650K) suggest that the human mutation may result in a dominant-negative version of the neuronal kinase-I motor (Hoyt et al. 1993).

Loss-of-function mutations in kinesin heavy chain genes associated with neurological disorders have been identified in a range of species (Reid et al. 2002). In particular, disruption of the murine gene encoding kinesin motor protein Kif1bβ results in a "staggering gait" phenotype in adult heterozygous animals (Zhao et al. 2001*a*) with reduced synaptic vesicle precursors. *KIF1B*β mutations in humans result in Charcot-Marie-Tooth type 2A (MIM 118210), a common inherited peripheral neuropathy characterized by weakness and atrophy of distal

muscles, depressed tendon reflexes, and mild sensory loss (Zhao et al. 2001*a*). The Q98L mutation identified in *KIF1Bβ* was shown to disrupt the motor function of the protein. Consequently the levels of synaptic vesicle protein cargoes, such as synaptotagmin and SV2, were specifically decreased in the peripheral axons of *Kif1B* heterozygous mice. Neurophysiological studies of *Kif1B* heterozygous mice showed the pathology to be an axonopathy rather than demyelination (Zhao et al. 2001*a*). In addition to the mutations in the kinesin heavy chain genes, mouse kinesin light chain (KLC) mutants exhibit overt movement defects and small size (Rahman et al. 1999). Their sensory and motor neurons display alterations in the intracellular location of various cellular components. Thus, kinesin mutation studies clearly support a role for defective microtubule-mediated trafficking leading to axonal degeneration in the peripheral as well as the central nervous system, highlighting the universal need of long axons for intact transport systems.

Overview

Our aim in this review has been to highlight common ground between the likely functions of the genes mutated in HSP. The involvement of aberrant mitochondrial processes in neurodegenerative diseases is well established (Orth and Schapira 2001), and paraplegin and HSP60 mutations offer evidence for the involvement of this mechanism in HSP. The preferential degeneration of long axons may be explained by their high energy requirements and may arise as a result of inadequate fueling of axonal transport. With the recent identification of new genes underlying different forms of HSP, evidence is accumulating to link defective trafficking dynamics with the neurodegeneration seen in the disease. A mutated kinesin, part of the anterograde transport machinery, provides the most direct evidence. Spastin, the first dominant HSP gene identified, binds microtubules, which are the key to axonal transport. A potential role of endosomal trafficking is highlighted by the discovery of the MIT (ESP) domain, present in endosomal-associated molecules, in the recently identified spartin. The presence of the MIT (ESP) domain in spastin suggests that the function of these two proteins is related to some extent. Atlastin, the second dominant HSP gene identified, may well have a function in vesicular transport. Notably, it is interesting that mice lacking paraplegin, a mitochondrial protein, or PLP1, a myelin component, also display defects in axonal transport.

Defective trafficking has also been implicated in other neurodegenerative diseases. Alsin is mutated in amyotrophic lateral sclerosis 2 (MIM 205100), which has a number of features in common with HSP, and is thought to be involved in membrane-proximity activities of small GTPases that modulate microtubule assembly, membrane organization, and trafficking in neuronal cells (Yang et al. 2001). The genes for chorea-acanthocytosis, an autosomal recessive disorder characterized by hyperkinetic movements and abnormal erythrocyte morphology (caused by mutations in *CHAC* [MIM 200150]), and Niemann-Pick type C1, a fatal neurovisceral disorder caused by mutations in *NPC1* (MIM 257220), are also thought to be involved in this mechanism (Rampoldi et al. 2001; Zhang et al. 2001).

Until recently, the wide range of possible functions for the limited number of genes known to underlie HSP seemed at loggerheads with the specific pattern of neuronal damage seen in this condition. However, these preliminary studies are beginning to provide a functional link between different forms of the condition. Trafficking along microtubules is a vital process by which the cell transfers a wide range of constituents from one region to another, and long axons may be particularly susceptible to its disruption. This could explain why mutations in widely expressed genes, such as spastin and spartin, lead to degeneration of very specific cell types. In simple terms, it would appear that mutations in genes involved in these processes may result in road blocks that prevent essential cargoes from reaching their correct cellular destination. Additional functional studies are now required to explore the biochemical roles of these molecules in more detail, in order to confirm or refute the defective transportation hypothesis. The rapid pace of this research, which now includes the production of animal models of the disease and the ability to study transport in living cells, offers real hope that confirmation of the biochemical pathophysiology of HSP may soon be at hand. With the number of HSP genes identified now increasing, new diagnostic tools are becoming available to substantiate the clinical diagnosis of HSP, and a molecular-based reclassification of this group of conditions may ultimately be appropriate. In years to come, additional studies of the pathogenic mechanisms will open the possibility for creating treatments for this group of conditions.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

HUGO Gene Nomenclature Committee, http://www.gene.ucl.ac.uk/nomenclature/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SPG1 [MIM 312900], SPG2 [MIM 312920], SPG3A [MIM 182600], SPG4 [MIM 182601], SPG5A [MIM 270800], SPG6 [MIM 600363], SPG7 [MIM 600146], SPG8 [MIM 603563], SPG9 [MIM 601162], SPG10 [MIM 604187], SPG11 [MIM 604360], SPG12 [MIM 604805], SPG13 [MIM 605280], SPG14 [MIM 605229], SPG15 [MIM 606859], SPG16 [MIM 300266], SPG17 [MIM 270685], SPG19 [MIM 607152], SPG20 [MIM 275900], autosomal recessive spastic ataxia of Charlevoix-Seguenay [MIM 270550], Charcot-Marie-Tooth type 2A [MIM 118210], amyotrophic lateral sclerosis 2 [MIM 205100], CHAC [MIM 200150], and NPC1 [MIM 257220])

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