Update on the genetics of spastic paraplegias

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Abstract

Purpose of review

Hereditary spastic paraplegias are a genetically heterogeneous group of neurological disorders. Patients present lower limb weakness and spasticity, complicated in complex forms by additional neurological signs. We review here the major steps towards understanding the molecular basis of these diseases made over the last 10 years.

Recent findings

Our perception of the intricate connections between clinical, genetic and molecular aspects of neurodegenerative disorders has radically changed in recent years, thanks to improvements in genetic approaches. This is particularly true for hereditary spastic paraplegias, for which >60 genes have been identified, highlighting (i) the considerable genetic heterogeneity of this group of clinically diverse disorders, (ii) the fuzzy border between recessive and dominant inheritance for several mutations and (iii) the overlap of these mutations with other neurological conditions in terms of their clinical effects. Several hypotheses have been put forward concerning the pathophysiological mechanisms involved, based on the genes implicated and their known function, and based on studies on patient samples and animal models. These mechanisms include mainly mitochondrial impairment, abnormal intracellular trafficking, changes to endoplasmic reticulum shaping and defects affecting lipid metabolism, lysosome physiology, autophagy, myelination and development. Several causative genes affect multiple of these functions, which are, most of the time, interconnected.

Summary

Recent major advances in our understanding of these diseases have revealed unifying pathogenic models that could be targeted in the much-needed development of new treatments.

Keywords

Hereditary spastic paraplegia, motor neuron, pyramidal syndrome, neurodegenerative diseases, intracellular trafficking, neurological diseases

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Conflict of interest

The authors have no conflict of interest to declare.

Human and animal rights and informed consent

This article is a review and reports only studies approved by editorial boards based on peer reviews. When we cited our own work, all the procedures performed in the studies involving human materials or animals were conducted in accordance with the ethical standards of our institution, with informed consent obtained from patients, and approval from ethics committees.

Introduction

Hereditary spastic paraplegias (HSPs) are a large heterogeneous group of inherited neurodegenerative diseases. Patients present progressive spasticity and weakness, predominantly affecting the lower limbs [1].

The initial symptoms are subtle. Patients generally complain of frequent falls, with stiff legs, cramps and an abnormal or unstable gait. Disease progression is usually slow, but often leads to patients requiring assistance in the form of canes, walkers or wheelchairs as their gait becomes increasingly spastic and additional signs appear. Most patients display similar clinical

features, including bilateral spasticity of the legs that is particularly marked on walking, a weakness of the muscles, leg hypertonicity, hyperreflexia and positive Babinski sign. Other frequently reported symptoms include bladder dysfunction, *pes cavus* and a loss of vibratory sensation at the ankles. The disease is considered to be uncomplicated, or pure, if these signs and symptoms are the only clinical features observed. By contrast, additional symptoms are identified in complex or complicated forms. These symptoms may be neurological or extraneurological and include cognitive/mental impairment, cerebellar ataxia, peripheral neuropathy, epilepsy, optic atrophy, retinal alterations, cataracts, dystonia and parkinsonism [2].

One of the common hallmarks of these diseases, based on the description of small numbers of pathological cases however, is axonal degeneration, which is most marked in the longest tracts. Postmortem analyses of patient tissues have revealed axonal degeneration to be most severe at the distal ends of the corticospinal tracts, *fasciculus gracilis* fibers, and spinocerebellar tracts, corresponding to the longest motor and sensory axons of the central nervous system. Observations suggesting that degeneration began at the distal end of the axons, progressing towards the cell body, led to the hypothesis that these diseases were dying-back axonopathies [3,4]. Long axons with a unique, highly polarized architecture are commonly affected, suggesting a possible role for abnormalities of cellular processes in HSP, such as axonal transport, intracellular trafficking and mitochondrial functions; this hypothesis was confirmed by the implication of genes involved in these functions in these diseases [5,6]. However, other brain structures, such as the cerebellum, cerebral cortex, basal ganglia and white matter (including the corpus callosum), may be affected in complicated forms, as shown by postmortem examinations [7] and brain imaging [8]. A simple dying back of the long axons is thus an inadequate unifying model. Other mechanisms must also be involved, to explain the degeneration of other brain structures.

Considerable genetic heterogeneity

HSP has an estimated global prevalence of 4.26/100,000, with reported values ranging from 0.9-9.6/100,000, depending on the mode of inheritance and the geographic area considered [9*]. The genetic basis of HSP is extremely diverse, with all possible classical modes of inheritance reported. Autosomal dominant (AD) forms of HSP (ADHSP) predominate in Western countries, whereas autosomal recessive (AR) forms (ARHSP) are common in inbred populations, while X-linked and maternally inherited forms are rare. However, isolated cases are often seen in clinical practice. Such cases may correspond to inherited forms that remain undiagnosed due to the *de novo* nature of the variants involved, the death of the transmitting parent before identification/clinical expression of the variant, variable expressivity and, particularly for the dominant forms, low or age-dependent penetrance of the mutation.

The observed clinical heterogeneity can be at least partly explained by the immense genetic heterogeneity. Mutations or rearrangements of at least 64 genes (the SPastic Gait/Gene or SPG genes) have been reported to date, and another 13 associated loci have been localized on chromosomal regions (Table 1) [10-13]. The study of Novarino et al. [14**] highlights this considerable heterogeneity: these authors identified 18 new genes responsible for recessive forms of HSP, through a combination of exome-sequencing, whole-genome linkage analysis, bioinformatics and the functional validation of several genes in zebrafish models. Mutations of more than 30 other genes have been shown to mimic HSP in diseases including spastic paraplegia as a clinical feature. Indeed, Novarino et al. described an “HSPome” network of 589 genes, all of which are good candidate genes for HSP, as shown by the identification of mutations of three of these genes on candidate gene screening [14**]. However, these additional genes lie beyond the scope of this review and will not be considered further here,

except for few relevant cases [10]. Several genes have been found mutated in single families only, and must therefore be considered as HSP-related genes with caution until functional studies or secondary cases are published.

Autosomal dominant forms

Twenty-two HSP loci/genes have been associated with ADHSP. Age at onset varies considerably and most cases are relatively pure. The dominant forms are mostly caused by variants or rearrangements of the *SPAST* (SPG4) gene, which account for 17-79% of all ADHSP cases. These variants cause a relatively pure form of HSP [15-18], sometimes with cognitive impairment [19,20]. Causal variants of *ATL1* (SPG3A), *REEP1* (SPG31) and *KIF5A* (SPG10) are also common. Together with the *SPAST* variants, they are responsible for the disease in about 50-60% of families with dominant forms of HSP [15-18]. *ATL1* mutations are principally associated with early onset, before the age of 10 years. Variants of *NIPA1/SPG6*, *WASHC5/SPG8*, *RTN2/SPG12*, *HSP60/SPG13*, *BSCL2/SPG17* and *CPT1C/SPG73* are much less common.

Autosomal recessive forms

ARHSP has been shown to be associated with 50 loci (Table 1), in which 45 causal genes have been identified as mutated [10]. *SPG11* is the gene most frequently mutated, accounting for about 21% of cases and causing a complex form of the disease [21]. Other frequent causes, accounting for about 20% of the ARHSP families in total, are variants of the *CYP7B1* (SPG5), *SPG7* and *ZFYVE26* (SPG15) [15-18] genes. In several countries, variants in the *SACS* gene responsible for the spastic ataxia of Charlevoix-Saguenay have also been implicated in ARHSP. In addition, *CAPN1* (SPG76) loss-of-function mutations have recently been identified in a

number of families in multiple successive publications, suggesting that their frequency in ARHSP forms are probably higher than initially thought [22-26].

X-linked and mitochondrial forms

Five X-linked loci have already been associated with HSP, and the causal gene has been identified for three of these loci: *L1CAM* (SPG1), *PLP1* (SPG2) and *SLC16A2* (SPG22). These X-linked forms remain rare in HSP cohorts, but SPG1 has been implicated in the MASA and CRASH syndromes in children, whereas SPG2 which is allelic to Pelizaeus-Merzbacher disease, can cause late-onset pure HSP in women.

MT-ATP6 is located on the mitochondrial DNA and is, therefore, maternally inherited. It has also been associated with an HSP-like phenotype in a single family [27]. It encodes one of the subunits of ATP synthase (Complex V), the final enzyme in oxidative phosphorylation (OXPHOS). As no SPG number was attributed to this gene and as the clinical description associated with variants of this gene is rare, it is not included in Table 1.

Mixed inheritance forms

One of the most intriguing findings in this field in recent years is the multiple modes of inheritance reported for variants of a number of these causal genes, including *REEP2*/SPG72, *ALDH18A1*/SPG9 and *KIF1A*/SPG30 [28*,29-31]. For SPG72, dominant mutations have a dominant-negative effect on the wild-type protein, preventing REEP2 binding to the endoplasmic reticulum (ER) membrane and resulting in a loss of function, as observed for recessive mutations in the same gene [28*]. For SPG30, dominant transmission of missense variants is based on a dominant-negative effect disrupting KIF1A binding to microtubules [32*]. In recessive HSP cases, the phenotype associated to KIF1A missense variants is less severe. The frequency of *KIF1A* mutations with an AD mode of inheritance remains unclear,

but such mutations may be common in sporadic patients of ADHSP given the high frequency of *de novo* cases.

Other forms seem to display mostly one main mode of inheritance. For example, *ATL1*/SPG3A has been reported to display mainly autosomal dominant transmission, although at least one causal variant has been shown to be recessive [33]. Other causal genes are mostly recessive, but several reports have exposed possible dominance for some variants, as demonstrated for SPG7 [34,35*] and, more recently, for *ERLIN2*/SPG18/SPG37 [36].

Sporadic forms

Most cases of spastic paraplegia are sporadic. Once other differential diagnoses, such as structural abnormalities of the brain or spinal cord, infection by human T-lymphotrophic virus type 1 [HTLV1], multiple sclerosis, dopa-responsive dystonia, amyotrophic or primary lateral sclerosis, have been excluded by MRI and biochemical analyses, mutations should be sought in genes known to be associated with or related to HSP. Such analyses have revealed that a substantial proportion of apparently sporadic cases are actually genetic. *SPAST*, *ATL1* and *SPG11* variants are frequent, as are *KIF1A* variants, for which large numbers of *de novo* cases have already been reported. Gonadal mosaicism has also been reported for SPG4 [37].

Clinical variability and overlap with other neurological conditions, phenotype-genotype correlations

Age-at-onset is variable for HSP, with the first manifestations of the disease occurring anyway between early infancy and old age. There may also be considerable variability in age at HSP onset within a given family [38]. Mutations of several ADHSP genes, including *SPAST* [39*], *REEP1* [40] and *BSCL2* [41,42], display incomplete penetrance, suggesting an effect of as yet unknown modifying factors. Two SPG4 polymorphisms (p.S44L, p.P45Q) have been suggested

to modulate or attenuate disease severity through changes in the stability of spastin (*SPAST*/SPG4 gene product) isoforms; they may act as weak mutations in association with other *SPAST* alterations [43]. Penetrance and age-at-onset have also been shown to depend on gender for SPG4 [39*].

HSP progression is also highly variable. Some patients present disabilities that progress relatively little over many years, whereas the disease rapidly worsens in others. The rate of progression may also change over time in individual patients. For example, many patients display a rapid worsening during adolescence, with slower rates of progression thereafter. The disease often eventually seems to stabilize, probably due to a number of factors, including possible functional compensation through neuroplasticity [2]. Earlier disease onset has also been reported to be associated with a less severe presentation [18].

Further variability is observed for clinical presentation, with most of the causal genes associated with both pure and complex forms of the disease. The "additional" neurological and extraneurological signs observed in complex forms are also highly variable, even within the same family. However, clinical signs of intellectual disability and ataxia are frequently reported. For example, variants of the *SACS* gene usually cause a spastic ataxia phenotype, but several patients have been identified with mutations of this gene and phenotypes at the extreme ends of the spastic ataxia spectrum: either isolated ataxia or spasticity [44,45]. It is often difficult to classify patients on this spectrum of spastic ataxia phenotypes. For example, *GBA2* mutations may cause conditions that can be classified as ataxia or HSP [46,47]. Many patients with HSP display peripheral neuropathy, highlighting the overlap with Charcot-Marie-Tooth disease. As the number of patients with each mutation increases, so does the phenotypic spectrum of each genetic entity and the overlap with other neurological conditions. There is an increasing number of genes primarily associated with other neurodegenerative disorders that are sometimes considered as differential diagnoses for HSP, such as leukodystrophies, that are

now being shown to be responsible for pure forms of spastic paraplegia. HSP and leukodystrophies have at least three causal genes in common (*PLP1*, *HSPD1*, *GJC2*), and at least eight other genes have been reported to mimic HSP in some cases (*ABCD1*, A*DAR*, *EIF2B5*, *GJA1*, *IFIH1*, *RNASEH2B*, *SAMHD1* and *TUBB4A*). This is the case, for example, for *ATP13A2* (SPG78/PARK9) which has recently been shown to be associated with HSP, but was previously associated only with Parkinson's disease [48]. Loss of function mutations in another gene possibly related to Parkinson's disease, *UCHL1* (SPG79/PARK5), has also been found in spastic ataxia patients [49]. Neurodegeneration with iron accumulation is also caused by defects of genes that have been implicated in HSP: *C9orf72* and *FA2H*. Another recent example relates to *ACO2* mutations, initially associated with infantile cerebellar-retinal degeneration combining optic atrophy, retinal degeneration, severe encephalopathy, epilepsy, and cerebellar ataxia, which have now been associated with mild to complex HSP variably associating intellectual disability, microcephaly and optic atrophy with no phenotype-genotype correlations [50,51]. Conversely, mutations of some HSP genes have also been shown to cause other diseases. For example, *SPG11* mutations are also associated with amyotrophic lateral sclerosis (ALS) and Charcot-Marie-Tooth disease [52-54], and *KIF1A* mutations have been linked to hereditary autonomic neuropathy or mental retardation [30-32,55-57].

These wide spectra for age-at-onset, progression and symptoms, together with their clinical overlap with other neurological diseases and the high degree of genetic heterogeneity, make it difficult to establish phenotype–genotype correlations. The various presentations of the disease are sometimes associated with different modes of inheritance. For example, heterozygous variants of *HSPD1* are associated with HSP, whereas homozygous missense variants are responsible for hypomyelinating leukodystrophy type 4 [58]. Another illustration is provided by TFG, for which a heterozygous variant in the P/Q-rich domain causes autosomal dominant hereditary motor and sensory neuropathy [59], whereas homozygous variants of the coiled-coil

and PB1 domains have been linked to HSP [60,61], suggesting that different pathogenic mechanisms may be involved. Similarly, the nature, location and zygosity of *KIF1A* mutations explain the phenotype: hereditary autonomic neuropathy results from a complete loss of function [56], whereas homozygous missense mutations cause a relatively pure HSP phenotype [30,57], and heterozygous missense mutations in the motor domain result in dominant negative effects on the kinesin protein, accounting for early-onset complex HSP [32*]. For SPG7, the p.A510V mutation is more often associated with ataxia than with spastic paraplegia [62*]. By contrast, mutations of *PNPLA6* and *ALDH18A1* underlie multiple phenotypes and/or are transmitted by multiple modes of inheritance, sometimes without spasticity, and with no clustering according to the nature or location of the mutations [63*,29].

Pathogenic mechanisms

We still know little about the mechanisms underlying the degeneration of distal portions of the corticospinal tracts, and of other brain structures in complex forms. However, the identification of a number of causal genes and determination of the functions of their products have suggested that alterations to intracellular trafficking may be a common element. The affected functions include active axonal transport, the activities of the endolysosomal system, organelle shaping, and lipid metabolism. In some clinicogenetic forms, effects on myelination, mitochondrial functions and axon guidance have also been observed. Several HSP-related proteins are known to be involved in multiple of these pathways, which may well be interconnected. It is, therefore, often difficult to determine which dysfunction is the principal cause of the neurodegeneration for a given gene/protein.

Intracellular active transport

Three HSP proteins perfectly illustrate the requirement of intracellular trafficking for the maintenance of long axons. Mutations of *KIF5A* (SPG10) result in a lower affinity of the kinesin-1 motor protein encoded by this gene for microtubules and a decrease in the gliding velocity of microtubule-dependent anterograde axonal transport [64]. The SPG30 and SPG58 forms are caused by mutations of the genes encoding the KIF1A and KIF1C proteins, respectively. Both dominant and recessive mutations have been described for SPG30, with a dominant negative effect disrupting KIF1A binding to microtubules underlying dominant transmission [32*]. For SPG58, all the mutations identified to date affect the ATPase and the microtubule-binding domains of KIF1C and minor or subclinical signs can be observed in heterozygous parents of homozygous patients [65]. A spontaneous mutation of KIF1C in Charolais cattle has been shown to cause a frequent spastic ataxia with severe demyelination in the brain [66*].

Many other HSP proteins may be involved in intracellular trafficking. Spastin (*SPAST/SPG4*), an adenosine triphosphatase (ATPase), has three domains with different cellular activities: a microtubule-interacting domain, a microtubule-interacting and endosomal trafficking domain (MIT) and an ATPase (AAA) domain with microtubule-severing activity [67]. Spastin exists in two main isoforms: M1, which is mostly associated with the ER, and M87, which is cytoplasmic [68,69]. *SPAST* knockout mice have focal swellings of the spinal cord axons, with abnormal accumulations of organelles and cytoskeletal components, suggesting an impairment of axonal transport associated with mild late motor impairment with no detectable neuron loss [70]. These defects occur close to growth cones, in regions of transition between stable and dynamic microtubules. Spastin localizes to areas of the cytoplasm important for microtubule dynamics [71], and the overproduction of this protein results in microtubule depletion in cultures of mammalian cells [72] and disruption of the microtubule network in *Drosophila melanogaster* [73,74] and *Caenorhabditis elegans* [75]. These findings

led to suggestions that the axon degeneration observed in spastic paraplegia was due to defective axonal microtubule organization. Spastin has several other functions (some of which will be discussed below). In particular, it interacts with CHMP1B [76], which is associated with the endosomal sorting complex of the ESCRT transport machinery. This complex is involved in several pathways, and plays a role in the completion of cell division. The M87 isoform is required for cytokinesis and the microtubule disruption that normally occurs during this process is impaired in its absence [68,77]. Truncating and missense mutations of Spastin are thought to result in a loss of function through haploinsufficiency or dominant negative effects.

Spastin interacts with Atlastin-1 (*SPG3A*) [78,79], a transmembrane dynamin/guanylate-binding protein. Its subcellular distribution (ER, *cis*-Golgi, vesicular structures in axonal growth cones, varicosities and axonal branch points) [80,81] suggests a functional role in both intracellular trafficking and axonal development, consistent with the early onset of disease in SPG3A patients. Some atlastin-1 mutations affect the GTPase activity of the protein [81]. These mutations have been reported to affect the budding of vesicles from the ER, or their targeting to the Golgi apparatus, possibly due to impairment of the interaction of Atlastin-1 with p24, a protein of the p24/emp/gp25L protein family [82].

Another HSP protein, Spartin (*SPG20*), has been implicated in epidermal growth factor receptor [EGFR] endocytosis and transport [83]. It is found in synapse-like structures, neurites and the *trans*-Golgi network of differentiated neurons [84]. Maspardin (*SPG21*) is found in endosomes and *trans*-Golgi vesicles and is thought to be involved in membrane sorting [85]. The NIPA1 protein (*SPG6*) is a transmembrane protein specific to neurons, present in the early endosomal compartment and on the plasma membrane, where it is thought to transport magnesium [86]. Pathogenic missense mutations of the gene encoding this protein prevent its transfer from endosomes to the plasma membrane. This effect probably results from a dominant-negative gain of function, because large gene deletions do not cause HSP in humans.

NIPA1 ortholog in *Drosophila* (Spict) interacts with bone morphogenetic protein (BMP) receptors, promoting their internalization [87]. BMP signaling is required for normal assembly of the microtubule cytoskeleton, so *NIPA1* mutations may also interfere with axonal transport.

Abnormal trafficking has also been implicated in several other disorders closely related to HSP, such as Charcot-Marie-Tooth disease, in which patients present neuropathies affecting the long axons of the peripheral nervous system, and ALS. For example, truncating mutations of *ALS2*, which encodes Alsin, have been implicated in various lower and upper motor neuron disorders with different clinical presentations [88,89]. The knockout of Alsin in mouse leads to distal axonopathy [90] and abnormal trophic factor (IGF1, BDNF) receptor transport [91]. *ALS2* missense variants are associated with Alsin delocalization from the endosomes and greater susceptibility to induced apoptotic stress *in vitro* [92].

Together, these observations suggest that alterations to intracellular trafficking are particularly deleterious for long axons.

Endoplasmic reticulum shaping

The ER is a membrane-bound organelle consisting of the nuclear envelope, sheets forming the rough ER and a tubular network connected to other organelles throughout the cell. It has many different functions (protein and lipid synthesis, calcium homeostasis regulation and exchange of molecules with other organelles), depending on its morphology. Long-axon neurons appear to be particularly dependent on the formation and maintenance of the ER, as several HSP proteins are involved in these processes. Indeed, the three most frequent autosomal dominant HSPs are caused by mutations of the *SPG3A*, *SPAST*/SPG4 and *REEP1*/SPG31 genes, encoding Atlastin-1, Spastin and REEP1, respectively. These proteins insert their hairpin loop domains into the membrane of the tubular ER, thereby contributing to the shaping of this structure.

Atlastin-1 mediates homotypic fusions of ER tubules, generating the three-way junctions between ER tubules that shape the characteristic morphology of the ER in the periphery of the cell. Atlastin-1 loss results in changes to the morphology of the ER [93-95]. Spastin M1 interacts with Atlastin-1 and REEP1, and links the microtubule cytoskeleton to the ER tubule network [96]. The REEP1 and REEP 2-4 proteins also interact with microtubules [97,98], and these interactions are believed to underlie the formation and stabilization of the ER tubular network. REEP1 depletion decreases the number of ER three-way junctions [69], and losses of REEP2 function cause ER sheet expansion [28*]. Other HSP-related proteins, such as ARL6IP1 (SPG61), RAB3GAP2 (SPG69) and Reticulon 2 (SPG12), are also involved in ER shaping. Depletion of the *Drosophila* ortholog of Reticulon 1, Rtnl1, leads to ER sheet expansion and a loss of tubular ER markers from distal motor axons [99]. Axonal continuity and the correct axonal transport of ER tubules were recently shown to require ER shaping genes, such as *Rtnl1*, in *Drosophila* [100*].

These findings suggest that long axons are highly sensitive to changes in the morphology of the ER tubular network. However, the ER has many functions and it remains unclear which are the most relevant to the pathophysiology of HSP. Changes in the morphology of the ER have recently been shown to lead to a loss of contact between the ER and other organelles, consistent with the probable impairment of the functions of membranous contact sites in several HSPs [101*]. Changes in ER shaping may also underlie defects of lipid synthesis and metabolism, as the ER plays a crucial role in these functions.

Lipid metabolism

Many *in vitro* and *in vivo* models of HSP display alterations to lipid metabolism. Indeed, several HSP-related proteins have been implicated in regulating the number and size of lipid droplets (LDs). These organelles are the site of lipid storage within the cell. The changes to

LDs dynamics in HSP may reflect the changes in ER shaping, as LDs are formed from the ER [102]. The modulation of Atlastin-1, Spastin or REEP1 expression has consistently been shown to lead to changes in the number or size of LDs [103-105]. Spastin M1 downregulation (or the expression of a dominant-negative variant) results in the presence of smaller numbers of LDs in nerves, skeletal muscles and fat bodies in a *Drosophila* model [105**]. Conversely, the co-overproduction of REEP1 and Atlastin-1 in mammalian cells results in the presence of very large LDs [104], and REEP1 has been shown to play a role in regulating LDs both *in vitro* and *in vivo* [103,106]. Furthermore, postmortem analyses of the brains of SPG54 patients with *DDHD2* mutations have revealed the accumulation of large LDs in cells [107], and the absence of Spartin (SPG20) has been shown to be associated with the presence of larger numbers of LDs in the adipose tissue of female KO mice [108]. Finally, Seipin (SPG17) is an integral ER protein involved in LD biogenesis. Alterations to the LDs in axons may, therefore, contribute to the pathophysiology of HSP.

Some cases of HSP are caused by mutations of genes encoding proteins directly involved in lipid metabolism. SPG26 is caused by mutations of *B4GALNT1* [109], which encodes an enzyme involved in ganglioside synthesis. A loss of the function of this enzyme leads to GM3 ganglioside accumulation in cells [110]. Loss-of-function mutations affecting the GBA2 glucocerebrosidase enzyme (SPG46) [46,47] lead to glucosylceramide accumulation, resulting in changes to cytoskeletal dynamics in animal models [111]. SPG5 is caused by mutations of the gene encoding an enzyme involved in cholesterol metabolism, CYP7B1, and affected patients have high levels of oxysterol substrates in the plasma membrane and cerebrospinal fluid [112]. Finally, losses of function of the fatty acid hydroxylases PNPLA6, FA2H, DDHD1 and DDHD2 also lead to HSP, but the reasons for this are less well understood.

Overall, these findings suggest that the correct regulation of lipid metabolism is crucial for the neurons affected in HSP.

Endolysosomal trafficking pathway

Endolysosomal dysfunctions have been reported in various HSP models in recent years. Such dysfunctions may be associated with changes to lipid metabolism, as in lysosomal storage diseases (LSD), a group of diseases in which lipids and other materials accumulate in lysosomes due to a primary dysfunction of these organelles [113]. An accumulation of undigested materials reminiscent of that observed in LSD has been reported in some HSP models. This finding is of particular interest because patients with LSD sometimes display spasticity, which can lead to a misdiagnosis of HSP [114]. Electron microscopy analyses of the fibroblasts of SPG48 patients have revealed an accumulation of membrane material in the endolysosomes [115]. The gene mutated in SPG48 encodes AP5Z1, a subunit of the AP-5 complex involved in vesicular-mediated trafficking of cargoes. This protein interacts with Spatacsin (SPG11) and Spastizin (SPG15) [115]. The SPG11 and SPG15 HSP subforms are clinically indistinguishable. The loss of either of these proteins impairs the autophagic lysosome reformation (ALR) process [116]. Material has been shown to accumulate in the endolysosomal pathways of both SPG11 and SPG15 mice [117-119]. This material was recently identified as simple gangliosides in SPG11 mice, and its accumulation results from the impairment of lysosome reformation due to the loss of Spatacsin [120**]. The prevention of ganglioside accumulation prevented neuronal cell death *in vitro* and corrected the motor phenotype of a zebrafish model of the SPG11 disease, demonstrating the deleterious effects on neurons of ganglioside accumulation in lysosomes. Such an accumulation is also observed in various LSDs characterized by neurodegeneration and in more common neurodegenerative diseases, such as Alzheimer's disease [121,122].

It was recently suggested that defective endosome fission due to a loss of contact between the ER and endosomes might disturb the trafficking of lysosomal enzymes, accounting for the

lysosomal dysfunctions observed in many forms of HSP [101*]. Lysosomal dysfunctions may be associated with a decrease in degradation capacity.

Thus, lysosomal functions appear to be crucial for neurons, and lysosomal dysfunction may impair a number of pathways in which these organelles are involved, including autophagy. These changes would also contribute to alterations to lipid metabolism and the shaping of organelles, such as the ER, showing then the links between these cellular functions altered in HSPs

Other functions

A few of the identified HSP genes encode proteins associated with mitochondrial functions. These genes include *HSPD1 (*HSP60), *ACO2* and *SPG7*. Missense mutations of the gene encoding mitochondrial HSP60 cause SPG13, through the disruption of HSP60 activity and mitochondrial quality control [123]. The gene mutated in SPG7 encodes Paraplegin, a member of the mitochondrial AAA protease family. Paraplegin-deficient mice present an abnormal accumulation of mitochondria in axons, leading to motor deficits, followed by axon swelling and neurodegeneration [124]. *ACO2* mutations impair the Krebs cycle through a reduction of the aconitase enzyme activity and a subsequent impaired mitochondrial respiration in lymphoblastoid cell lines of patients [50,51].

The association of the microtubule-associated protein Spartin (SPG20) with mitochondria is also lost following mutation of the corresponding gene [125], which suggests that Troyer syndrome (SPG20) may result from a defect of microtubule-mediated mitochondrion transport. Finally, SPG77 is caused by mutations of *FARS2*, which encodes a mitochondrial phenylalanyl tRNA synthetase (mtPheRS) [126].

Mitochondrial functions may also be altered indirectly in other HSPs. In patients with mutations affecting REEP1, the interactions between REEP1 and mitochondrial PGAM5 are abnormal, resulting in alterations to mitochondrial morphology [127*].

Abnormal development is clearly observed in two clinically different X-linked forms of HSP: SPG1 and SPG2. The cell surface glycoprotein L1-CAM, which is mutated in SPG1, plays a crucial role in the migration and differentiation of neurons. Alterations to this protein in patients and knockout mice are associated with developmental phenotypes (e.g., corpus callosum hypoplasia, adducted thumbs, psychomotor retardation, hydrocephalus, a small corticospinal tract and poor associations of non-myelinating Schwann cells) due to a lack of axonal guidance [128]. Mutations of *PLP1*, encoding an integral protein of myelin and involved in the maturation of oligodendrocytes, account for the occurrence of dysmyelination and axonal degeneration in the central nervous system of SPG2 patients and of cases with the allelic Pelizaeus-Merzbacher disease. *PLP1* loss-of-function mutations in mice is associated with abnormal oligodendroglial dynamics, inflammation and degeneration of long axons at later stages [129].

Mutations of other HSP genes may result in developmental defects as well. This might be the case in HSP entities with early age at onset and/or clinical presentations combining spasticity with early cognitive deficiencies. Overt motor or brain developmental defects have been reported for knockdowns of *SPAST* (SPG4), *SPG3A*, *SPG11*, *SPG15* and *GBA2* (SPG46) in zebrafish, regardless of their known implication in neurodevelopment [130**,131,46].

Conclusions

The growing use of next-generation sequencing is improving diagnosis, but also leading to the continual identification of new causal genes for HSP. The increasing number of HSP genes

identified up to now highlights the extreme genetic heterogeneity of these disorders and their clinical and functional overlap with other neurological conditions. The challenge facing us in the genetics of HSP is explaining the clinical variability between patients carrying identical mutations, some of whom may develop a complex HSP, whereas others develop another neurological condition in which spasticity is no more than a minor element, if present at all.

There is still no specific treatment for preventing or slowing neuronal degeneration or dysfunction. Only symptomatic treatments based on antispasticity drugs, botulinum toxin or physiotherapy can help to improve the patient's quality of life [2]. Several studies in animal models have identified compounds or strategies that may improve phenotypes [132-136], but their transfer into patient care will require further characterization of their effects and the identification of useful biomarkers for demonstrating their beneficial activity, a process currently underway for SPG5 [137**,138*]. Finally, several HSP models display a number of different cellular dysfunctions, complicating identification of the primary dysfunction, or the dysfunction of greatest relevance to the disease. However, several common pathways relating to intracellular membrane dynamics (Figure 1) are affected in multiple HSPs, suggesting that it may be possible to develop therapies targeting these common elements in the future.

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Figure Legend

Figure 1: Overview of the main altered/known functions of proteins involved in HSP.

ER: endoplasmic reticulum

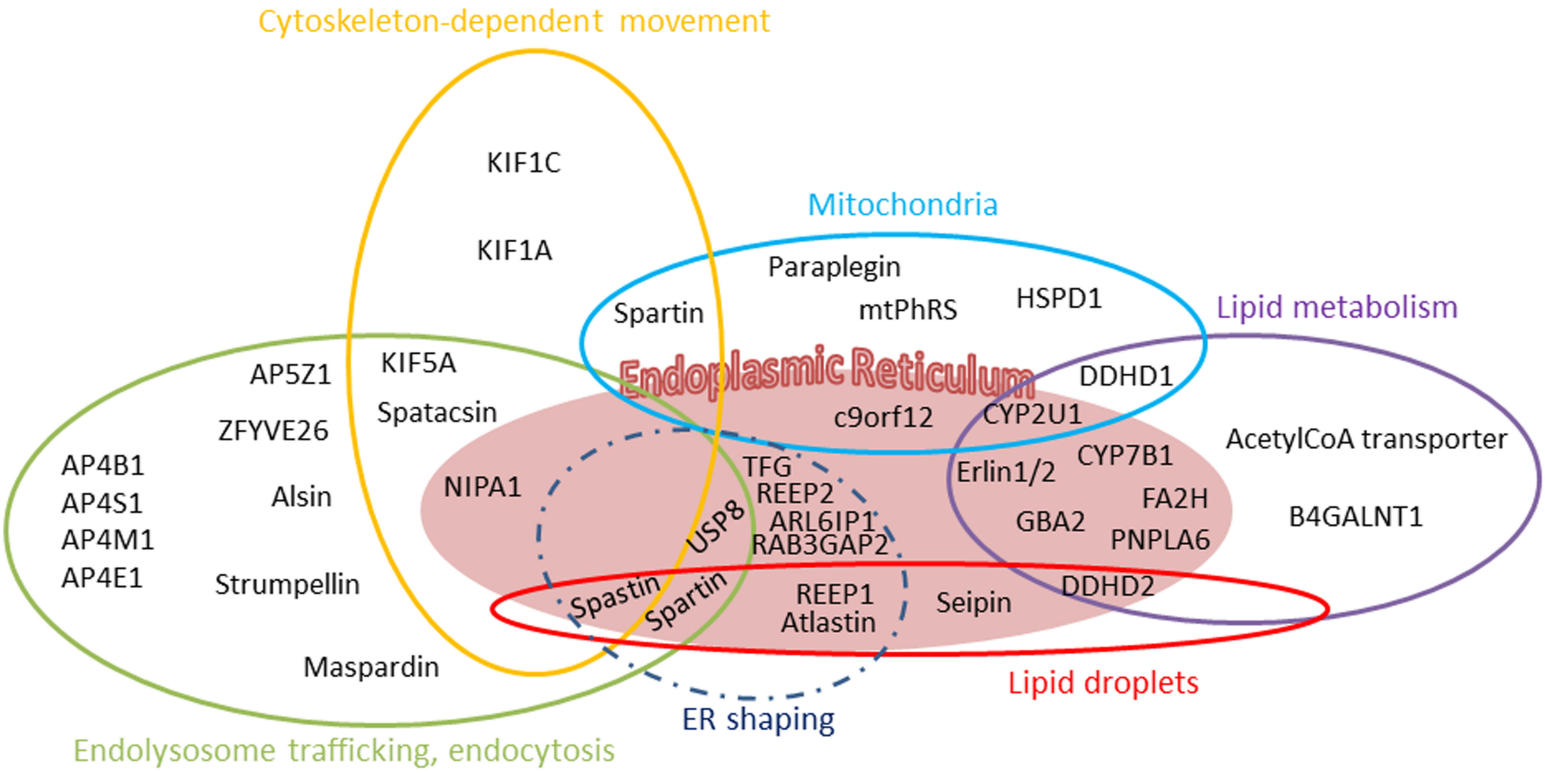
Cytoskeleton-dependent movement
KIF1C
KIF1A
Mitochondria
Paraplegin
Spartin
mtPhRS
HSPD1
Lipid metabolism
AP5Z1
KIF5A
Endoplasmic Reticulum
DDHD1
ZFYVE26
Spatacsin
c9orf12
CYP2U1
AcetylCoA transporter
AP4B1
AP4S1
AP4M1
AP4E1
NIPA1
TFG
REEP2
ARL6IP1
RAB3GAP2
USP8
Alsin
Erlin1/2
CYP7B1
FA2H
GBA2
PNPLA6
B4GALNT1
Strumpellin
Spastin
Spartin
REEP1
Atlastin
Seipin
DDHD2
Maspardin
Lipid droplets
ER shaping
Endolysosome trafficking, endocytosis

Table 1. Loci and genes implicated in spastic paraplegias, the proteins they encode and the associated clinical features in patients

ARHSP—autosomal recessive hereditary spastic paraplegia; ATPase—adenosine triphosphatase; CMT 4D—Charcot-Marie-Tooth subtype 4D; ER—endoplasmic reticulum; FR—frameshift; GTPase—guanosine triphosphatase; IFD—in-frame deletion or duplication; LL—lower limbs; MIM—Mendelian inheritance in man; MS—missense; NS—nonsense; RG—rearrangements; SPG—spastic gait gene; SPL—splice site mutations; TCC—thin corpus callosum; UL—upper limbs; UTR—untranslated region; WMH—white matter hyperintensities.

Locus (MIM)	Chromosome	Gene (protein)	Putative roles of the protein	Mutations	Frequency	Age at onset, *y*	Phenotype in patients
Autosomal dominant forms							
SPG4 (182601)	2p22.3	*SPAST* (spastin)	Microtubule-severing activity, early secretory pathway, BMP signaling	MS, NS, FR, SPL, RG	40% of dominant forms (9%–18% of sporadic cases)	Variable (0-74)	Pure, but sometimes cognitive deficits, with incomplete penetrance
SPG6 (600363)	15q11.1	*NIPA1*	Mg^{2+} transporter, endosomal trafficking, BMP signaling	MS (hot spot at c.316)	Rare	8–40	Pure or rarely with seizures, memory impairment or neuropathy
SPG8 (603563)	8q24.13	*WASHC5* (strumpellin)	Endosomal trafficking	MS, RG	Rare	18–60	Pure or atrophy of shins
SPG10 (604187)	12q13	*KIF5A*	Motor protein (axonal transport)	MS, NS, IFD, SPL	3%	2–51	Pure or neuropathy, amyotrophy, parkinsonism
SPG12 (604805)	19q13.32	RTN2 (Reticulon 2)	ER-shaping protein	FR, RG	Rare	5–36	Pure
SPG13 (605280)	2q33.1	*HSPD1*	Mitochondrial chaperone	MS	2 families	17-68	Pure
SPG17 (270685)	11q13	*BSCL2* (seipin)	ER protein, lipid metabolism	MS	Rare	8-40	Silver syndrome: severe distal wasting

SPG19 (607152)	9q33-q34	Unknown	–	–	1 family	36–55	Pure
SPG29 (609727)	1p31.1-p21.1	Unknown	–	–	1 family	Childhood through early adulthood	Sensorineural hearing impairment, neonatal hyperbilirubinemia without kernicterus, hiatal hernia
SPG31 (610250)	2p11.2	*REEP1*	ER-shaping protein, ER-microtubule interaction, mitochondrial function	MS, NS, FR, SPL, 3' UTR	4.5%	Variable	Pure or with amyotrophy, distal sensory loss
SPG36 (613096)	12q23-q24	Unknown	–	–	1 family	14-33	Demyelinating sensorimotor neuropathy
SPG38 (612335)	4p16-p15	Unknown	–	–	1 family	16-19	Amyotrophy
SPG41 (613364)	11p14.1-p11.2	Unknown	–	–	1 family	mean 16.6±3.0	Pure
SPG42 (612539)	3q25.31	SLC33A1	ER membrane transporter, BMP signaling, autophagy	MS	Rare	4-42	Pure
SPG73 (616282)	19q13.33	CPT1C	Lipid metabolism	MS	1 family	19-48	Muscle atrophy, Delayed central sensory evoked potentials
Autosomal recessive forms							
SPG5A (270800)	8q21.3	*CYP7B1*	Cholesterol and neurosteroid metabolism	MS, NS, SPL and FR	7%	1–47	Pure or with cerebellar signs, cognitive impairment, nystagmus
SPG11 (604360)	15q21.1	*SPG11* (spatacsin)	Lysosome shaping, autophagy	NS, MS, FR, SPL, IFD, RG	21% (59% of ARHSP-TCC)	Childhood through adulthood	Pure or mostly complex with cognitive impairment, TCC, neuropathy, amyotrophy, WMH, mild cerebellar signs, cerebral atrophy
SPG14 (605229)	3q27-q28	Unknown	–	–	1 family	Adulthood	Distal motor neuropathy, cognitive impairment, visual agnosia
SPG15 (270700)	14q24.1	*ZFYVE26* (spastizin)	Endosomal trafficking, autophagy, cytokinesis	NS, MS, FR, SPL, RG	4%	5–23	Pure or mostly complex with cognitive impairment, cerebellar signs, TCC, WMH, neuropathy, amyotrophy, retinopathy (Kjellin syndrome)

SPG20 (275900)	13q12.3	*SPART* (spartin)	Endosomal trafficking, microtubule interaction, lipid droplet turnover, BMP signaling, mitochondrial function	MS, SPL, FR	Rare	Early childhood	Troyer syndrome: developmental delay and short stature, cognitive impairment, cerebellar signs, distal amyotrophy
SPG21 (248900)	15q22.31	*SPG21* (maspardin)	Endosomal/*trans*-Golgi trafficking	MS, FR	Rare	20-60	Cognitive decline and apraxia (Japanese family) or Mast syndrome: cognitive decline, extrapyramidal syndrome, dementia, dysarthria, TCC, WMH, cerebellar signs, neuropathy.
SPG23 (270750)	1q32.1	DSTYK	Dual serine/threonine and tyrosine protein kinase	RG	3 families	Childhood	Lison syndrome: pigmentary abnormalities, cognitive impairment, peripheral neuropathy
SPG24 (607584)	13q14	Unknown	–	–	1 family	Early childhood	Pure
SPG25 (608220)	6q23-24.1	Unknown	–	–	1 family	30–46	Mild sensorimotor neuropathy, spinal disc herniation, spondylosis
SPG26 (609195)	12p13.3	*B4GALNT1*	Biosynthesis of complex gangliosides	MS, NS, SPL, IFD, FR	Rare	First or second decades of life	Cognitive impairment, distal amyotrophy, dysarthria, cerebellar signs, cortical atrophy, ataxia, neuropathy, cataracts
SPG27 (609041)	10q22.1-q24.1	Unknown	–	–	2 families	25-45 (P), 2-7 (C)	Pure or with sensorimotor polyneuropathy, 1 case with cognitive impairment and skeletal abnormalities
SPG28 (609340)	14q22.1	*DDHD1*	Lipid metabolism, mitochondrial function	NS, SPL, FR	Rare	6–16	Pure or with distal sensory impairment, neuropathy or oculomotor disturbances
SPG32 (611252)	14q12-q21	Unknown	–	–	1 family	Childhood	Cognitive impairment, TCC, cortical and cerebellar atrophy, pontine dysraphia
SPG35 (612319)	16q23.1	FA2H	Myelination, fatty acid metabolism	MS,NS, SPL, FR	Rare	2-17, 1 family with adult onset	Spastic quadriparesis, cognitive impairment, ataxia, optic atrophy, seizures, TCC, cerebellar atrophy, leukodystrophy, WMH

SPG39 (612020)	19p13.2	PNPLA6	Lipid metabolism, axonal integrity	MS, FR, RG	Rare	Variable	Distal muscle atrophy, axonal motor neuropathy
SPG43 (615043)	19q12	C19orf12	Unknown	MS	3 families	Childhood	Distal muscle atrophy, distal sensory impairment, motor neuropathy
SPG44 (613206)	1q42.13	GJC2	Myelination, oligodendrocyte homeostasis	MS, FR	1 family	First or second decades of life	Cerebellar ataxia, dysarthria, cognitive impairment, TCC
SPG45/ SPG65 (613162)	10q24.33	NT5C2	Purine/pyrimidine nucleotide metabolism	MS, NS, SPL, FR, RG	Rare	Infancy	Cognitive impairment, delayed motor development TCC, WMH
SPG46 (614409)	9p13.3	GBA2	Lipid metabolism	MS, NS, SPL, FR	Rare	1-16	Cognitive impairment, cerebellar ataxia, dysarthria, nystagmus, male infertility, cerebral and cerebellar atrophy, TCC, polyneuropathy
SPG47 (614066)	1p13.2	AP4B1	Vesicle formation and trafficking	FR	Rare	Birth	Severe cognitive impairment, microcephaly, seizures, dystonia, dysarthria, TCC, WMH
SPG48 (613647)	7p22.1	AP5Z1	Vesicle trafficking, endosomal dynamics, DNA repair	MS, NS, FR	Rare	Mostly adult-onset (2-60)	Cognitive impairment, ataxia, parkinsonism, neuropathy, TCC, WMH
SPG49 (615031)	14q32.31	TECPR2	Autophagy	FR	Rare	Infancy	Hypotonia, microcephaly, ataxia, dysarthria, areflexia, intellectual disability, cerebral atrophy, TCC, breathing abnormalities
SPG50 (612936)	7q22.1	AP4M1	Vesicle formation and trafficking	MS, NS, FR	Rare	Birth	Severe cognitive impairment, microcephaly, seizures, cerebellar atrophy, strabismus, TCC, WMH
SPG51 (613744)	15q21.2	AP4E1	Vesicle formation and trafficking	NS, FR, RG	Rare	Birth	Severe cognitive impairment, microcephaly, seizures, cortical and cerebellar atrophy, hypotonia, nystagmus
SPG52 (614067)	14q12	AP4S1	Vesicle formation and trafficking	NS, FR	Rare	Birth	Severe cognitive impairment, microcephaly, axial hypotonia, TCC

SPG53 (614898)	8p22	VPS37A	Vesicle trafficking	MS	2 families	Infancy	Delayed psychomotor development, cognitive impairment, kyphosis
SPG54 (615033)	8p11.23	DDHD2	Lipid metabolism, membrane trafficking	MS, NS, SPL, FR, RG	Rare	Infancy	Cognitive impairment, developmental delay, dysarthria, strabismus, TCC, WMH
SPG55 (615035)	12q24.31	C12orf65	Mitochondrial matrix protein	NS, SPL, FR	Rare	First or second decades of life	Optic atrophy, strabismus, distal muscle atrophy and weakness, cognitive impairment, neuropathy
SPG56 (615030)	4q25	CYP2U1	Lipid metabolism	MS, NS, SPL, FR	1.5%	0 (Birth) - 8	Pure or with delayed motor development, axonal neuropathy, dystonia, cognitive impairment, TCC and WMH (rare)
SPG57 (615658)	3q12.2	TFG	ER morphogenesis, vesicle trafficking	MS	5 families	Infancy	Pure or with optic atrophy, axonal and demyelinating sensorimotor neuropathy
SPG58 (611302)	17p13.2	KIF1C	Motor protein (axonal transport)	MS, NS, SPL, RG	Rare	2-30	Pure or mostly complex with ataxia, dysarthria, distal muscle atrophy, cerebellar atrophy
SPG59 (603158)	15q21.2	USP8	Endosomal morphology, membrane trafficking	MS	1 family	20 months	Nystagmus, borderline intelligence
SPG60 (612167)	3p22.2	WDR48	DNA damage repair, lysosomal trafficking	FR	1 family	1 year	Nystagmus, peripheral neuropathy, mild learning disability
SPG61 (615685)	16p12.3	ARL6IP1	ER morphogenesis, protein transport	NS, FR	3 families	Birth to infancy	Sensorimotor neuropathy, acromutilation, intellectual disability, developmental delay, brain atrophy
SPG62 (615681)	10q24.31	ERLIN1	ER-associated degradation, cholesterol homeostasis	MS, ND, IFD	3 families	1-13	Pure
SPG63 (615686)	1p13.3	AMPD2	Purine nucleotide metabolism	MS, FR	2 families	Infancy	Amyotrophy, short stature, TCC, WMH
SPG64 (615683)	10q24.1	ENTPD1	Purine nucleotide metabolism	MS, NS	2 families	3-22	Dysarthria, cerebellar signs, amyotrophy, intellectual disability, delayed puberty, microcephaly, WMH

SPG66 (610009)	5q32	ARSI	Hormone biosynthesis, cell signaling	FR	1 family	Infancy	Amyotrophy, severe sensorimotor polyneuropathy, corpus callosum and cerebellar hypoplasia, colpocephaly
SPG67 (611655)	2q33.1	PGAP1	GPI biosynthesis, ER-to-Golgi transport of GPI-anchor proteins	SPL	1 family	Infancy	Amyotrophy, cerebellar signs, corpus callosum agenesis, vermis hypoplasia, defective myelination
SPG68 (604806)	11q13.1	FLRT1	Cell adhesion, receptor signaling	Nonstop	1 family	Infancy	Nystagmus, optic atrophy, amyotrophy, peripheral neuropathy
SPG69 (609275)	1q41	RAB3GAP2	ER morphogenesis, exocytosis of neurotransmitters and hormones	NS	1 family	Infancy	Global developmental delay, dysarthria, intellectual disability, deafness, cataract
SPG70 (156560)	12q13.3	MARS	Cytosolic methionyl-tRNA synthetase	MS	1 family	Infancy	Amyotrophy, bilateral achilles contracture
SPG71 (615635)	5p13.3	ZFR	Unknown	MS	1 family	Infancy	TCC
SPG74 (616451)	1q42.13	IBA57	Mitochondrial function	SPL	1 family	First decade	Optic atrophy, distal leg muscle atrophy, axonal peripheral neuropathy
SPG75 (616680)	19q13.12	MAG	Myelination	MS	2 families	Early childhood	Optic atrophy, distal muscle atrophy, cognitive impairment, peripheral neuropathy, nystagmus, cerebellar atrophy
SPG76 (616907)	11q13.1	CAPN1	Axon maturation and maintenance	MS, NS, SPL, FR	10 families	19-39, 1 case with congenital-onset	Pure or with dysarthria, ataxia, sensory axonal neuropathy, hyperreflexia
SPG77 (611592)	6p25.1	FARS2	Mitochondrial function	MS, IFD	3 families	Birth to Infancy	Pure or with lower limb amyotrophy, developmental delay, cerebellar atrophy, seizures
SPG78 (617225)	1p36.13	ATP13A2	Autophagy, membrane trafficking, mitochondrial function	MS, NS, IFD	5 families	Adulthood	Cognitive impairment, parkinsonism, ataxia, dysarthria, cerebellar and cortical atrophy, axonal sensorimotor peripheral neuropathy

SPG79 (615491)	4p13	UCHL1	DNA damage response	MS	2 families	Childhood	Optic atrophy, nystagmus, cerebellar ataxia, axonal sensorimotor neuropathy
SPOAN (609541)	11q13,2	KLC2	Motor protein (axonal transport)	RG	47 sibships, endemic to Brazil	Infancy	Congenital optic atrophy, dysarthria, neuropathy, acoustic startle
X-linked forms							
SPG1 (303350)	Xq28	*L1CAM*	Cell adhesion, neurite outgrowth, myelination	MS, NS, FR, RG, SPL	Rare with spasticity	Infancy	TCC, cognitive impairment, adducted thumbs, hydrocephalus
SPG2 (312920)	Xq22.2	*PLP1* (proteolipid protein 1)	Primary constituent of myelin	MS, NS, FR, RG, SPL	Rare with spasticity	Infancy to childhood	Congenital nystagmus, cognitive impairment, ataxia, seizures, allelic to Pelizaeus-Merzbacher
SPG16 (300266)	Xq11.2	Unknown	–	–	2 families	Infancy	Pure or with mild cognitive impairment, motor aphasia, vision loss
SPG22 (300523)	Xq13.2	SLC16A2	Thyroid hormone transporter	MS, NS, FR, RG, SPL, IFD	Rare in HSP cohorts	Congenital	Allan-Herndon-Dudley syndrome: cognitive impairment, spastic quadriplegia, hypotonia, dystonia, ataxia, leukodystrophy
SPG34 (300750)	Xq24-q25	Unknown	–	–	1 family	12-25	Pure
Autosomal dominant and recessive forms							
SPG3A (182600)	14q22.1	*ATL1*(atlastin-1)	GTPase, ER-to-Golgi transfer, spastin partner, BMP signaling	MS, NS, FR, SPL, IFD, RG	10% (39% of young patients) - AD form; 1 family reported - AR form	Mostly early onset (< 10)	Pure but sometimes neuropathy, with incomplete penetrance
SPG7 (607259)	16q24.3	*SPG7* (paraplegin)	Mitochondrial ATPase	MS, NS, FR, SPL, IFD, RG	7% of AR families	11–42	Pure or with neuropathy, optic atrophy and cerebellar atrophy, ataxic gait, pyramidal signs
SPG9 (601162/ 616586)	10q24.1	*ALDH18A1*	P5CS pathway	MS	7 AD families, 2 AR families	13-59 (AD), 1-7 (AR)	Pure or with cataracts, skeletal abnormalities, gastroesophageal reflux, amyotrophy, intellectual disability

SPG18 (611225) & SPG37 (611945)	8p11.2	ERLIN2	ER-associated degradation (ERAD) pathway, lipid metabolism	MS, SPL, RG	5 AR families; 2 AD families	1-19	AR: complex with contractures, cognitive impairment and sometimes seizures; AD: pure form
SPG30 (610357)	2q37.3	*KIF1A*	Motor protein (axonal transport)	MS, FR	Rare	1–30	AR:pure or with neuropathy, cerebellar signs, ataxia, cognitive impairment; AD: complex with cerebellar atrophy, TCC, motor and intellectual retardation
SPG72 (615625)	5q31.2	*REEP2*	ER morphogenesis	MS, SPL	2 families - AD, 2 families - AR	Infancy to childhood	Pure or with amyotrophy, mild dysarthria