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Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms

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Abstract

Hereditary spastic paraplegia (HSP) is a syndrome designation describing inherited disorders in which lower extremity weakness and spasticity are the predominant symptoms. There are more than 50 genetic types of HSP. HSP affects individuals diverse ethnic groups with prevalence estimates ranging from 1.2 to 9.6 per 100,000 [39, 70, 77, 154, 185]. Symptoms may begin at any age. Gait impairment that begins after childhood usually worsens very slowly over many years. Gait impairment that begins in infancy and early childhood may not worsen significantly. *Post mortem* studies consistently identify degeneration of corticospinal tract axons (maximal in the thoracic spinal cord) and degeneration of *fasciculus gracilis* fibers (maximal in the cervico-medullary region). HSP syndromes thus appear to involve motor-sensory axon degeneration affecting predominantly (but not exclusively) the distal ends of long central nervous system (CNS) axons. In general, proteins encoded by HSP genes have diverse functions including axon transport (e.g. SPG30/KIF1A, SPG10/KIF5A and possibly SPG4/Spastin); endoplasmic reticulum morphology (e.g. SPG3A/Atlastin, SPG4/Spastin, SPG12/reticulon 2, and SPG31/REEP1, all of which interact); mitochondrial function (e.g. SPG13/chaperonin 60/heat shock protein 60, SPG7/paraplegin; and mitochondrial ATP6; 4) myelin formation (e.g. SPG2/Proteolipid protein and SPG42/Connexin 47); 5) protein folding and ER-stress response (SPG6/NIPA1, SPG8/K1AA0196 (Strumpellin), SGP17/BSCL2 (Seipin) [113-115], “mutilating sensory neuropathy with spastic paraplegia” due to CcT5 mutation and presumably SPG18/ERLIN2); 6) corticospinal tract and other neurodevelopment (e.g. SPG1/L1 cell adhesion molecule and SPG22/thyroid transporter MCT8); 7) fatty acid and phospholipid metabolism (e.g. SPG28/DDHD1, SPG35/FA2H, SPG39/NTE, SPG54/DDHD2, and SPG56/CYP2U1); and 8) endosome membrane trafficking and vesicle formation (e.g. SPG47/AP4B1, SPG48/KIAA0415, SPG50/AP4M1, SPG51/AP4E, SPG52/AP4S1, and VSPG53/VPS37A). The availability of animal models (including bovine, murine, zebrafish, *Drosophila*, and *C. elegans*) for many types of HSP permits exploration of disease mechanisms and potential treatments. This review highlights emerging concepts of this large group of clinically similar disorders. For recent review of HSP including historical descriptions, differential diagnosis, and additional references see [78].

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Introduction

"Hereditary spastic paraplegia" (HSP) is a clinical diagnostic designation for those neurologic syndromes a) in which bilateral lower extremity weakness and spasticity (each of variable degree) are the predominant (but often not only) manifestations; and b) for which gene mutation is the major causative factor. As with all classifications of clinical syndromes, it may be problematic to decide if a given disorder should be included or excluded in the category of HSP. For example, whereas paraplegin gene mutation, in which spastic paraparesis is often associated with ataxia, is recognized as a form of HSP (SPG7), Friedreich's ataxia and Charlevoix-Saguenay, syndromes in which ataxia is often associated with corticospinal tract deficits are considered forms of spinocerebellar ataxia and not forms of HSP. Although distal axon degeneration of corticospinal tracts is often reported in *post mortem* examination of HSP (discussed below), classification of a given clinico-genetic syndrome as a form of HSP is based on clinical and genetic features rather than neuropathologic features.

There are more than 50 genetic types of HSP (Table 1). Most types of HSP are designated by their genetic loci ("Spastic parapleGia" [SPG] 1 through 56) that are numbered in order of their discovery. As with other large groups of genetically heterogeneous disorders, variation in severity of the principle syndrome elements (lower extremity spasticity and weakness) together with the variable presence of additional neurologic (and occasionally systemic) abnormalities create wide clinical variation between (and within) genetic types of HSP. Nonetheless, by definition, clinical syndromes of HSP are characterized by lower extremity spasticity and weakness, each of varying degree, variable age-of-symptom onset, and variable degree of progression.

Clinical Classification

HSP syndromes are classified clinically [97] as "uncomplicated" (characterized by lower extremity spasticity and weakness and subtle lower extremity dorsal column impairment) ; and "complicated" (in which spastic paraplegia is associated with additional neurologic or systemic abnormalities including dementia, ataxia, mental retardation, neuropathy, distal wasting, loss of vision, epilepsy, or icthyosis [Sjogren-Larsson syndrome]). While some genetic types of HSP usually (but not invariantly) manifest as "uncomplicated" (e.g.SPG4 HSP due to spastin gene mutation, the single most common form of autosomal dominant HSP), other genetic types usually (but not always) manifest as "complicated HSP syndromes (such as SPG11 HSP, a common autosomal recessive form of HSP frequently associated with mental retardation and thin corpus callosum).

There is imperfect correlation between clinical classification ("uncomplicated" versus "complicated") and genetic types of HSP. Restated, many genetic types of HSP are associated with both "uncomplicated" and "complicated" HSP syndromes. For example, SPG4 HSP, initially considered to be prototypical of uncomplicated HSP, has been associated with mental retardation and dementia [46, 197, 232, 243], ataxia [169] , thin corpus callosum [174], and muscle wasting [157, 175]. Similarly, SPG3A, which usually manifests as childhood onset, uncomplicated autosomal dominant HSP, has been associated

with motor-sensory axonal neuropathy, distal wasting, and thin corpus callosum [56, 90, 116, 176]. Conversely, although autosomal recessive SPG7 (paraplegin mutation) and SPG11 (spatacsin mutation) usually manifest as “complicated HSP syndromes” (with ataxia being frequent in SPG7 HSP and mental retardation being frequent in SPG11 HSP), both of these types of HSP may also manifest as “uncomplicated” spastic paraplegia syndromes.

Some clinical variability within a given genetic type of HSP may be due to the variable consequences of discrete gene mutation (“genotype-phenotype correlation”), about which very little is known in HSP. In some cases however, both “uncomplicated” and “complicated” syndromes occur in the same family in which individuals have the identical gene mutation. These examples highlight the influence of as-yet-unidentified “modifying factors” (including genes and potentially environmental factors) in determining the phenotype.

Clinical presentation

For the vast majority of individuals, HSP presents with gait impairment due to lower extremity weakness and spasticity. Urinary urgency is common in HSP and occasionally may be an early or presenting feature. Symptoms may be first evident at any age, from early childhood through senescence. In general, subjects with “uncomplicated” HSP have normal life expectancy and do not experience loss of dexterity, strength, or coordination in the upper extremities, dysarthria or dysphagia.

Lower extremity spastic weakness (each of variable degree), combined with variable presence of one or more complicating features (discussed above) create numerous clinical HSP syndromes. The following HSP syndromes are commonly recognized (Table 2 [78]): 1) uncomplicated HSP; 2) spastic paraplegia associated with peripheral motor neuropathy and/or distal wasting; 3) spastic paraplegia associated with cognitive impairment; 4) spastic paraplegia associated with ataxia; 5) spastic paraplegia associated with neuroimaging abnormality; 6) spastic paraplegia associated with additional neurologic and systemic abnormalities. Examples of complicated HSP syndromes are summarized in Table 2.

Age of symptom onset may be quite variable even with a given genetic type of HSP. While the average age-of-symptom onset of some genetic types of HSP is much younger (e.g. childhood onset in SPG3A) than in other types (e.g. late-teenage to adult onset in SPG6 HSP), significant overlap between the range of ages at which symptoms first begin limits the ability to predict the genetic type of HSP from age of symptom onset alone.

Progression (rate and degree with which functional disability increases) in HSP is quite variable including relatively static, non-worsening disability, inexorable worsening, and, after a period of insidious decline, reaching an apparent stabilization of disability (apparent “functional plateau”). The fact that many HSP subjects seem to reach a functional plateau beyond which there is very little further disability (beyond that which is attributed to and parallels the approximate rate of normal, age-related decline) may reflect the interplay of multiple factors including a) reduced rate of neurodegeneration; and b) disease-ameliorating processes that promote recovery of damaged axons; and c) functional compensation through neuroplasticity.

When HSP begins in early childhood (first evident as toe-walking by age 2 years, for example), symptoms may be relatively non-progressive even over several decades. This is "relatively non-progressive course" is typical (but not invariant) of SPG3A HSP (the most common cause of early childhood-onset, autosomal dominant HSP) but may also be seen in SPG4 HSP and other types [31, 57]. The syndrome of early childhood onset, relatively non-progressive HSP may be extremely similar to that of spastic diplegic cerebral palsy. Indeed, HSP gene mutations (including *de novo* mutation for autosomal dominant HSP) have been identified in subjects initially diagnosed as having cerebral palsy [62, 160, 171, 191]. It may be appropriate to consider the recently identified genetic loci for autosomal recessive spastic diplegic cerebral palsy as a form of very early onset HSP [153, 246].

The rate and extent of clinical worsening in HSP is quite variable. For many individuals, gait impairment worsens insidiously over many years. The rate of clinical progression may not be uniform, however. Both more rapid progression during adolescence and slower rate of worsening after 5 to 10 years of symptoms are not uncommon. As noted above, many individuals, after 5 to 10 years of worsening gait impairment, appear to reach a "functional plateau" after which the rate of worsening seems to be reduced.

There are at least four examples in which HSP gene mutations were associated with clinical syndromes other than HSP. First, SPG3A/atlastin mutation (which typically causes early childhood-onset, relatively non-progressive, uncomplicated HSP) was recently identified in a family with autosomal dominant Hereditary Sensory Neuropathy (HSN 1) rather than with the syndrome of HSP [89]. In addition to profound, early sensory loss often associated with painless injuries, impaired healing, and osteomyelitis, HSN1 may be associated with distal motor involvement in advanced cases [89].

Second, *BSCL2/Seipin* mutations, when heterozygous, cause both autosomal dominant HSP (SPG17), Charcot-Marie-Tooth type 2, and distal hereditary motor neuropathy type V. When homozygous, *BSCL2/*Seipin mutations cause, congenital generalized lipodystrophy type 2 (CGL2), manifesting as severe lipoatrophy, insulin resistance, hypertriglyceridemia, and mental retardation [114, 144].

Third, although SPG11/spatacsin mutations are a frequent cause of autosomal recessive HSP (often, but not invariably associated with thin corpus callosum and mental retardation), they have also presented as levodopa-responsive, juvenile parkinsonism [12, 158].

And finally, although mutation of the SPG20/spartin gene causes autosomal recessive HSP associated with distal muscle wasting (Troyer syndrome), hypermethylation of the SPG20/spartin promoter is an apparent biomarker of colorectal carcinoma [138].

Neurologic examination of subjects with uncomplicated HSP demonstrates variable degrees lower extremity spasticity and weakness. Spasticity is greatest in hamstring, quadriceps, adductor, and gastrocnemius-soleus muscles. Weakness is most prominent in iliopsoas, hamstring, and tibialis anterior muscles. Hypperreflexia, crossed adductor signs, extensor plantar responses are typically present (plantar responses may occasionally be absent). Vibration sensation in the toes is frequently mildly impaired. Mild upper extremity hyperreflexia, without increased muscle tone, weakness, or impaired dexterity is common in

subjects with uncomplicated HSP. Although *pes cavus* is frequent in HSP, it may be absent even in clearly affected subjects.

In addition to variable degrees of lower extremity weakness and spasticity and mild decrease in distal vibration sensation, neurologic examination of subjects with “complicated” HSP syndromes demonstrates additional neurologic or systemic abnormalities such as cognitive impairment, dementia, optic neuropathy, retinitis pigmentosa, extrapyramidal disturbance, ataxia, peripheral neuropathy, distal wasting, or cataracts.

The degree to which muscle weakness and muscle spasticity contribute to functional gait impairment is may be quite variable between individuals [97]. Some individuals have no significant weakness, with gait disturbance resulting primarily from spasticity and slowness of movements. For these individuals, medications that reduce spasticity may be beneficial. For other individuals, muscle weakness is a significant factor in gait disturbance. For individuals with significant weakness, muscle relaxing medications (including Botulinum toxin injections and intrathecal Lioresal pump) offer much less functional improvement.

Treatment

There is no effective treatment to prevent gait impairment in HSP. Spasticity may be reduced with oral or intrathecal Lioresal or oral Dantrolene or Tizanidine and selective injection of botulinum toxin (Botox). Oxybutynin is helpful in reducing urinary urgency. Physical therapy is generally recommended to improve range of motion, maintain and increase lower extremity strength, and increase cardiovascular conditioning. Toe-dragging may be reduced by ankle foot orthotics and by gait-phase dependent, transcutaneous peroneal nerve stimulation.

Genetic classification

There are dominant, recessive, X-linked forms of HSP, each of which is genetically heterogeneous. In addition, mitochondrial ATP6 mutation is an example of an spastic paraplegia syndrome that is transmitted by maternal inheritance [238]. HSP genetic loci are designated SPG (“SPastic parapleGia”) 1 through 56 in order of their discovery. There also are inherited disorders in which lower extremity spastic weakness is the primary clinical symptom that do not have “SPG” designations (e.g., SPOAN syndrome, Epsilon subunit of the cytosolic chaperonin-containing t-complex peptide-1 (Cct5), and mitochondrial ATP6 gene mutation, Table 1).

At least one form of HSP may manifest as both an autosomal recessive and autosomal dominant disorder. SPG7 HSP was originally described as an autosomal recessive disorder due to homozygous or compound heterozygous SPG7/paraplegin gene mutations. Subsequently, there are reports of complicated and uncomplicated HSP syndromes associated with heterozygous SPG7 paraplegin mutation [15, 43, 152]. Some of these individuals have similar histologic features (e.g. ragged red fibers in skeletal muscle biopsy) or biochemical evidence of mitochondrial disturbance similar to that shown in subjects with homozygous (or compound heterozygous SPG7/paraplegin mutations) [43]. It is not known whether autosomal recessive versus autosomal dominant transmission is associated with

specific SPG7 mutations. Nor is it known if other types of recessively inherited HSP may also manifest as autosomal dominant disorders. Nonetheless, the fact that SPG7 HSP may manifest as both a dominantly inherited and recessively inherited disorder has significant implications for genetic counseling.

Genetic counseling in HSP must consider the often marked phenotypic variation (including age-of-symptom onset, severity, and the presence of “complicating feature”) between (and often within) different genetic types of HSP, and even between individuals in the same family who share the identical HSP gene mutation. Genetic penetrance in autosomal dominant HSP is age-dependent, may be high (80-90% in SPG4 HSP) or as low as 70% [68]. Apparent genetic anticipation has been reported occasionally in SPG3A and SPG4 HSP [45, 170, 192, 193]. It is interesting that descriptions of apparent genetic mutation for which the causative SPG3A[160] or SPG4 HSP mutations were described did not include trinucleotide repeat (or other tandem nucleotide) expansions that have been associated with other instances of genetic anticipation (such as in Huntington's disease, myotonic dystrophy, and other disorders).

Caution must be exercised in providing genetic counseling and prognosis for many genetic types of HSP because the full phenotypic spectrum and genetic penetrance are often not fully known. This applies particularly to subjects from families for whom the genetic type is not known; and subjects with genetic types of HSP that have been described in only one or several families. With the exception of a minority of HSP types (notably SPG3A, SPG4, SPG7, and SPG11) in which dozens of affected subjects have been reported, clinical descriptions of the majority of genetic types of HSP are limited to one to several families. Moreover, very little is known about mutation-specific genetic penetrance and genotype-phenotype correlation of individual HSP gene mutations. Finally, particular caution should be used when counseling families with SPG7 HSP in light of the observation that some SPG7 may cause autosomal dominant or autosomal recessive HSP.

Neuropathology

Post mortem studies in HSP consistently report axon degeneration involving lateral corticospinal tracts that is most severe at the distal ends (in the thoracic spinal cord) and less severe in the cervical spinal cord [25, 44, 60, 96, 204, 212, 213, 245]. In addition to distal corticospinal tract degeneration, degeneration of axons in *fasciculus gracilis* fibers is observed consistently and is most prominent in the cervical spinal cord.

Spinal cord axon degeneration may be sufficient to cause mild to marked atrophy of cervical and thoracic segments [67, 100, 101, 130, 218]. In some instances, corticospinal tract degeneration has extended rostrally to include the pons, cerebral peduncles, medulla, and internal capsule. Decreased number of pyramidal (neurons (Betz cells) has been described. Demyelination of degenerating corticospinal tracts and *fasciculus gracilis* fibers is noted frequently and generally considered to be consistent with the degree of axon degeneration rather than signifying a primary demyelinating process

Caution must be used when generalizing HSP neuropathology because 1) there have been very few autopsies in HSP most of which are from subjects for whom the genetic type of

HSP is unknown (e.g. [133]). Further, there may be a bias toward performing and reporting autopsies in unusual or complicated forms of HSP, such as those in which lifespan was reduced (e.g. [148, 172]). For example, the *post mortem* findings of novel, crystalloid deposits containing oligodendroglial cytoskeletal elements (α- and β-tubulin and TPPP/p25) in a subject with apparently autosomal dominant hereditary spastic paraplegia (genetic type unknown) are of uncertain significance [252].

A number of *post mortem* studies have been reported for subjects with possible or probable autosomal recessive spastic paraplegia but for whom the specific type of HSP is not known. For example Kuru *et al* [133] reported a subject with probable autosomal recessive spastic paraplegia associated with thin corpus callosum. Pathologic findings included neurodegeneration involving corticospinal tract, thalamus, cerebral white matter and substantia nigra, anterior horn, and dorsal columns of the spinal cord. There was widespread neuronal lipofuscin and eosinophilic granules; and severe gliosis in the cerebral white matter and substantia nigra. Nomura *et al* [172] reported a subject with probable autosomal recessive spastic tetraplegia, dysarthria, dementia, leading to death at age 50. Pathologic findings included severe brain atrophy, diffuse spongy changes, neuronal atrophy with lipofuscinosis, degeneration of dorsal spinocerebellar and corticospinal tracts, marked loss of anterior horn cells and nucleus gracilis neurons, and evidence of mitochondrial abnormality in skeletal muscle. Wakabayashi *et al* [240] reported a subject with probable autosomal recessive spastic paraplegia associated with thin corpus callosum, sensory disturbance, and amyotrophy. Pathologic changes included neuronal loss and gliosis in upper and lower motor neuron pathways, thalamus, lateral geniculate body, dentate nucleus, and posterior column of the spinal cord; many remaining neurons contained ubiquitinated lipofuscin granules; and reduced number of pigmented neurons in the substantia nigra. It is difficult to know the extent to which one or more *post mortem* observations from individual cases of genetically-undefined spastic paraplegia may be generalized to one or more types of spastic paraplegia of known genetic cause (genetically defined HSP).

Finally, since HSP usually does not shorten lifespan, HSP autopsies may disclose findings related to age or co-occurrence of unrelated, age-dependent disorders (such as Alzheimer's disease and Parkinsons disease). For example, *post mortem* [245] studies were reported in a subject with SPG4/spastin mutation who, in addition to progressive lower extremity spastic weakness, had dementia, facial bradykinesia and tremor. Corticospinal tract degeneration was maximal in thoracic and lumbar cord and associated with myelin pallor. In addition, neuronal loss was noted in the hippocampus and entorhinal cortex. Frequent neurofibrillary tangles that were immunoreactive for tau were present in remaining neurons. Senile plaques were not observed. Granulovacuolar degeneration and ballooned neurons that immunostained strongly for tau and α–β-crystallin were prominent in limbic areas. The substantia nigra showed moderate loss of pigmented dopaminergic neurons and frequent Lewy bodies and pale bodies. While these latter findings correlated with clinical Parkinsonism, it is not possible to determine whether the entirety of neuropathologic findings is attributable to SPG4/Spastin mutation. Murphy *et al* described an HSP subject with SPG4/spastin mutation subject who had dementia and for whom *post mortem* findings included widespread ubiquitin positivity within the neocortex and white matter [166]. These

and similar reports illustrate the caution that must be exercised in assessing which *post mortem* findings in HSP subjects are the consequence of the HSP gene mutation and which findings are attributable to the effects of age and the occurrence of unrelated, age-associated disorders (or theoretically, a combination of these factors).

The predominant distribution of axon degeneration to the distal ends of cortical spinal tracts and *fasciculus gracilis* fibers has given rise to two widely held concepts: 1) HSP reflects particular vulnerability of the longest, motor and sensory axons in the central nervous system; and 2) that the HSP represents a primary axonopathy. Each of these generalizations is incomplete in the following regards.

First, it is increasingly recognized that neuropathology in many types of HSP extends beyond the corticospinal tracts, dorsal column fibers and even the central nervous system. For example, though formerly considered to represent “uncomplicated” HSP, approximately 17% of subjects with SPG3A HSP have motor-sensory axonal peripheral neuropathy [116]. Peripheral neuropathy has been described as either a rare or common feature in more than a dozen genetic types of HSP (Table 2).

Lower motor neuron involvement, evident as distal muscle wasting is common in a many genetic types of HSP (Tables 1 and 2), notably those due to SPG10/KIF5A, SPG20/Spartin, SPG39/NTE, SPG17/BSCL2 gene mutation. In subjects with SPG39 reflects distal motor neuropathy (not motor sensory neuropathy). Lower motor neuron involvement may also occur in SPG11 HSP (many of whom conform to a clinical syndrome of juvenile ALS [173]); and is a typical feature of SPG17 (Silver syndrome) and SPG20 (Troyer syndrome). Anterior horn cell abnormalities (hyaline inclusions, altered mitochondrial distribution, and altered immunostaining for cytoskeletal proteins [nonphosphorylated neurofilament protein and β-tubulin] were also observed [244] in *post mortem* studies in SPG4 HSP (the single most common form of dominantly inherited HSP which usually manifests as an uncomplicated spastic paraplegia syndrome.

Second, neurodegeneration in many types of HSP involves neurons that are not among the longest in the CNS (such as the occurrence of dementia in SPG4 HSP, ataxia in SPG7 HSP, and optic neuropathy in SPG7 HSP). For example, *post mortem* studies in a subjects with SPG4/spastin mutation revealed variable involvement in cerebellum and basal ganglia, Clarke's column, and reduced number of anterior horn cells in some (but not all) subjects [245].

Third, myelin abnormalities are more common in HSP than previously recognized. At least two types of HSP are due to mutations in genes that are expressed not in neurons but rather in oligodendroglia (SPG2/proteolipid protein, SPG42/Connexin 47 mutation). Some mouse models of SPG2/proteolipid protein mutation HSP have axon degeneration (rather than demyelination), indicating that primary oligodendroglial abnormality may cause axonal degeneration. *Post mortem* study of a subject with late age-of-symptom onset SPG2 HSP demonstrated moderate cerebral atrophy, widespread pallor of central nervous system myelin preferentially affecting corticospinal tracts, and severe corticospinal tract axon degeneration [222].

In addition to these forms of HSP in which the causative gene mutation is expressed in oligodendroglial, white matter abnormalities have been observed in many forms of complicated HSP (e.g. due SPG5/CYPB7, SPG7/Paraplegin, SPG21/Maspardin, and SPG35/FA2H gene mutations, see Table 1) [61, 64, 131, 216, 242, 258]. It is noteworthy that homozygous mutation of the bovine spastin gene causes congenital bovine dysmyelination [228] rather than primary axonal degeneration.

Fourth, some of the abnormalities in HSP may be developmental rather than degeneration. Vassilopoulos *et al* [235] showed that the spinal canal diameter was smaller in subjects with HSP. This suggests disturbance in spinal canal development perhaps from altered induction of the developing spinal cord. Thin corpus callosum (associated most often with SPG11 but also may occur in SPG3A [176], SPG4, SPG7, SPG15, SPG21, SPG32, SPG47 , SPG49, SPG54, and SPG56 (see Table 1) is usually considered a developmental abnormality although França *et al* showed progressive corpus callosum thinning on serial brain magnetic resonance imaging [83].

Analysis of HSP genes and their encoded proteins sheds light on the molecular mechanisms underlying HSP

38 HSP genes have been identified (summarized in Table 3). Identified HSP genes are unique and, with some exceptions, do not conform to members of an extended gene or protein family. Examples of sequence-related proteins include Spastin (SPG4) and Paraplegin (SPG7) which share an AAA domain; and Spartin, whose amino-terminal region is similar to that of Spastin's. Some HSP genes (notably AP4B1 [SPG47], KIAA0415 [SPG48], AP4M1 [SPG50], AP4E1 [SPG51], AP4S1 [SPG52]), VPS37A [SPG53]) while not members of a gene family, encode related elements of a functional protein complex.

Analysis of the functions of HSP proteins indicates that a variety of primary molecular abnormalities underlie various genetic types of HSP (summarized in Figure). These include 1) axonal transport abnormality e.g. SPG30/KIF1A, SPG10/KIF5A [253] and possibly SPG4/Spastin [123]; 2) disturbance in ER morphology (e.g. SPG12/Reticulon 2, SPG3A/Atlastin, SPG4/Spastin, and SPG31/REEP1); 3) mitochondrial abnormality (e.g. SPG13/chaperonin 60/heat shock protein 60 [95], SPG7/paraplegin; and mitochondrial ATP6 [18, 48, 75, 247]; 4) primary myelin abnormality (e.g. SPG2/Proteolipid protein and SPG42/Connexin 47); 5) abnormal protein conformation leading to ER-stress response (SPG6/NIPA1, SPG8 [51, 258], SGP17/BSCL2, Seipin [113-115], and “mutilating sensory neuropathy with spastic paraplegia” due to CcT5 mutation [36]); 6) disturbance in corticospinal tract and other neurodevelopment (e.g. SPG1/L1 cell adhesion molecule and SPG22/thyroid transporter MCT8); 7) Disturbance in vesicle formation and membrane trafficking including selective uptake of proteins into vesicles (e.g. AP4B1 [SPG47], KIAA0415 [SPG48], AP4M1 [SPG50], AP4E1 [SPG51], AP4S1 [SPG52]), VPS37A [SPG53]); and 8) disturbance of lipid metabolism.

Among the molecular and cellular categories disturbed in various forms of HSP, it is notable that a subset of HSP types is caused by disturbance in phospholipid, sphingolipid, and fatty acid metabolism (reviewed in Lamari et al [134]). For example DDHD1 (SPG28) and

DDHD2 (SPG54) have phospholipase A1 activity and neuropathy target esterase (NTE, SPG39) is a phospholipase B (combined phospholipase A1 and A2 activity). In addition, mutation in a phospholipase A2 gene (PLA2G6) causes autosomal recessive infantile neuroaxonal dystrophy [125] associated with spastic tetraplegia as well as complex neurodegeneration phenotypes associated with brain iron accumulation [132, 134]. CYP2U1 (SPG56) catalyzes hydroxylation of arachidonic acid and similar long-chain fatty acids [227]. Fatty acid amide hydroxylase (FA2H, SPG35) catalyzes 2-hydroxylation of myelin galactolipids, galactosylceramine, and sulfatide. Mutations in fatty acid aldehyde dehydrogenase (FALDH, Sjogren-Larsson syndrome) and fatty acid elongase (ELOVL4) each cause autosomal recessive syndromes in which icthyosis is associated with spastic quadriplegia [9, 58]. The mechanisms (such as the roles of altered lipid-mediated signal transduction or altered membrane rigidity/fluidity) by which these fatty acid and phospholipid disturbances are pathogenic are not clear.

The functional heterogeneity of HSP genes suggests that corticospinal tract axons (and those of dorsal column fibers to a lesser extent) are vulnerable to a number of distinct molecular disturbances. Identification of many HSP proteins, increasing insights into the functions of these proteins, and functional overlap between HSP protein subsets notwithstanding, attempts to integrate functionality of HSP proteins into a single underlying pathogenic mechanism for the myriad forms of HSP is considered both premature and overly simplistic. Though knowledge of HSP is expanding rapidly, there are nearly 20 HSP genes that have been genetically mapped but not yet identified. Moreover, rather than a single, common pathogenic mechanism underlying HSP, it appears likely that disturbance in a number of different molecular processes results in a pattern of relatively selective neurodegeneration involving the corticospinal tracts predominantly. In this regard the HSPs may be similar to the amyotrophic lateral scleroses (plural), a heterogeneous group of motor neuron disorders in which a number of different underlying molecular processes (e.g. [186]) have been implicated (including excitotoxic injury, glial abnormalities, RNA processing disturbance [14], and protein misfolding, for example).

For most HSP gene mutations, the extent to which axon degeneration is “cell autonomous” (due to intrinsic disturbances only in the neurons undergoing degeneration); or “non-cell autonomous” (in which an axon's degeneration depends on its interaction with other cells including glia) is unknown. As noted above, axon degeneration in SPG2 and SPG42 are due to gene mutations that are primarily expressed in oligodendroglia (e.g. proteolipid protein and GJA12/Connexin 47). This indicates that axon degeneration in these types of HSP is “non-cell autonomous and illustrates the importance of oligodendroglia in axon maintenance.

Animal models of HSP (reviewed in [78] and, [190]) include mouse, rat, *Drosophila*, zebrafish, *C. elegans*, and cattle. The ability to produce axon degeneration and age-dependent motor impairment in animal models of HSP permits evaluation of genetic mechanisms (such as haploinsufficiency versus “dominant negative” effect) and explore pathogenic mechanisms and potential treatments. Several generalizations may be made. First, vertebrate and invertebrate animal models are useful for demonstrating “proof of concept” that an identified HSP gene mutation is pathogenic. Second, the behavioral

phenotype (locomotor impairment) in mouse models of HSP (either spontaneous mutants such as “rumpshaker” model of SPG2 or gene knock-out models), is usually much more mild than humans with the same or equivalent mutations. Preliminary observations in a transgenic rat model of SPG6 mutation suggest that rats may exhibit more severe motor impairment than mice [126]. And finally, the occurrence of congenital dysmyelination in American Brown Swiss cattle that are homozygous for bovine spastin gene mutation [228] suggests that different pathology (demyelination in cattle versus axon degeneration in humans) may be related either to species-specific effects or the nature of the gene mutation (homozygous in cattle, heterozygous in humans).

An important use of HSP animal models will be to determine the extent to which an HSP gene mutation has cell-autonomous pathogenesis. For example, does axon degeneration result when haploinsufficiency is created only in neurons (using *Cre-lox* cell-type specific gene knock-out, for example)? Studies of mouse models of ALS due to superoxide dismutase 1 (SOD1) gene mutation have highlighted the importance of glia-neuron interaction in determining the onset and rate of progression of neurodegeneration.

Conclusions

Rapid discovery of HSP genes and evaluation of their respective protein functions is reshaping our understanding of the HSPs. Nonetheless, a couple of general concepts remain. First, although lower extremity spastic weakness predominates the clinical syndrome and is the primary factor in functional disability, it is important to note that HSP for the majority of subjects is a motor-sensory disorder. Though usually subtle, dorsal column impairment is common in most types of HSP. And second, axon degeneration particularly involving distal ends of long fibers in the central nervous system is a common pathologic feature.

Beyond these concepts, much of our understanding of HSP is in a state of rapid evolution. For example, though previously considered to be a distal motor-sensory, axonopathy limited to the central nervous system, we now recognize that a majority of genetic forms of HSP involve peripheral neuropathy or other neurologic abnormalities in at least a subset of patients. The concept that HSP exclusively involves length-dependent distal axon degeneration is being modified in light of awareness that neurodegeneration may include shorter axons including those in the cerebellum and those traversing the corpus callosum. And finally, the occurrence of HSP due to mutations in genes that are expressed primarily in oligodendroglia (proteolipid protein and connexin 47) highlights the “non-cell autonomous” pathogenesis of some forms of HSP; and the importance of neuron-glial interaction in axon maintenance and degeneration. The extreme genetic heterogeneity of HSP and the diverse functions of HSP proteins indicate that corticospinal tract axons (and dorsal column axons to a lesser extent) are vulnerable to a variety of primary metabolic impairments. Rather than reflecting disturbance of a single common biochemical pathway, it appears that the common clinical features (i.e. predominated by corticospinal tract degeneration) reflect the limited phenotypic manifestations from relatively uniform degeneration elicited by diverse molecular causes. These advances and the creation of animal and *in vitro* models permit direct exploration of HSP's pathophysiology and bring us closer to developing treatments for this group of disorders.

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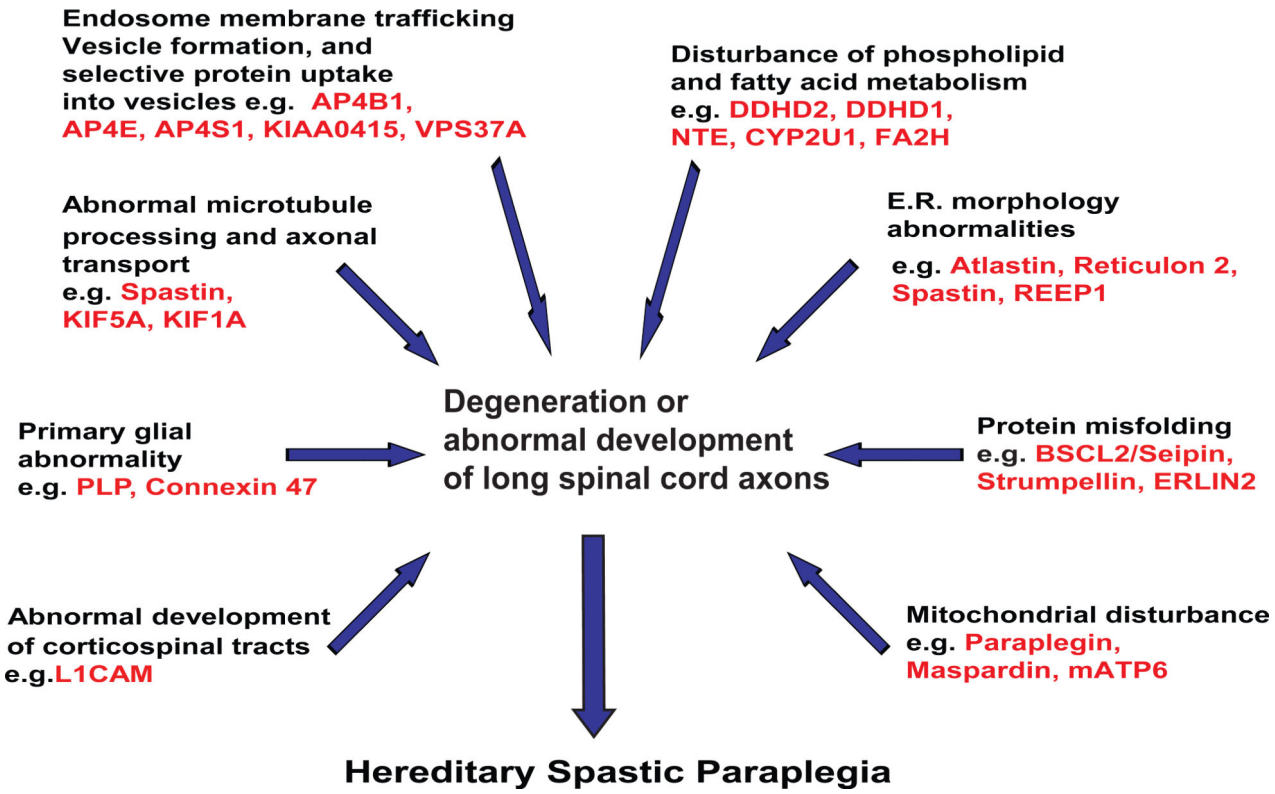

Emerging molecular pathogenesis of the Hereditary Spastic Paraplegias*

* Some HSP proteins participate in more than one process. In addition, a primary HSP protein abnormality (causative gene mutation) may disturb multiple other cellular and molecular processes.

Table 1

Genetic types of HSP (updated from [79]) (updated from [78])

Spastic gait (SPG) locus	Protein	Clinical Syndrome	References
Autosomal dominant HSP			
SPG3A (14q11-q21)	Atlastin	Uncomplicated HSP: symptoms usually begin in childhood (and may be non-progressive); symptoms may also begin in adolescence or adulthood and worsen insidiously. Genetic non-penetrance reported. *De novo* mutation reported presenting as spastic diplegic cerebral palsy.	[99, 184, 259]
SPG4 (chr.2p22)	Spastin	Uncomplicated HSP, symptom onset in infancy through senescence, single most common cause of autosomal dominant HSP (~40%); some subjects have late onset cognitive impairment.	[49, 72, 98, 104, 201]
SPG6 (15q11.1)	Not imprinted in Prader Willi/ Angelman 1 (NIPA1)	Uncomplicated HSP: prototypical late-adolescent, early-adult onset, slowly progressive uncomplicated HSP. Rarely complicated by epilepsy or variable peripheral neuropathy. One subject with uncomplicated HSP later died from amyotrophic lateral sclerosis.	[50, 65, 80, 81, 148, 189, 223]
SPG8 (8q23-q24)	KIAA0196 (Strumpellin)	Uncomplicated HSP	[29, 100, 102, 195, 233]
SPG9 (10q23.3-q24.2)	Unknown	Complicated: spastic paraplegia associated with cataracts, gastroesophageal reflux, and motor neuronopathy	[155, 214]
SPG10 (12q13)	Kinesin heavy chain (KIF5A)	Uncomplicated HSP or complicated by distal muscle atrophy	[76, 196]
SPG12 (19q13)	Reticulon 2 (RTN2)	Uncomplicated HSP	[195] [162]
SPG13 (2q24-34)	Chaperonin 60 (heat shock protein 60, HSP60)	Uncomplicated HSP: adolescent and adult onset	[82, 95] [41]
SPG17 (11q12-q14)	BSCL2/seipin	Complicated: spastic paraplegia associated with amyotrophy of hand muscles (Silver Syndrome)	[19, 183, 249]
SPG19 (9q33-q34)	Unknown	Uncomplicated HSP	[234]
SPG29 (1p31.1-21.1)	Unknown	Complicated: spastic paraplegia associated with hearing impairment; persistent vomiting due to hiatal hernia inherited	[16]
SPG31 (2p12)	Receptor expression enhancing protein 1 (REEP1	Uncomplicated HSP or occasionally associated with peripheral neuropathy	[24, 263, 264]
SPG33 (10q24.2)	ZFYVE27/protrudin}	Uncomplicated HSP	[146]
SPG36 (12q23-24)	Unknown	Onset age 14 to 28 years, associated with motor sensory neuropathy	[210]
SPG37 (8p21.1-q13.3)	Unknown	Uncomplicated HSP	[91]
SPG38 (4p16-p15)	Unknown	One family, 5 affected subjects, onset age 16-21 years. Subjects had atrophy of intrinsic hand muscles (severe in one subject at age 58)	[177]
SPG40 (locus unknown)	Unknown	Uncomplicated spastic paraplegia, onset after age 35, known autosomal dominant HSP loci excluded	[221]
SPG41 (11p14.1-p11.2	Unknown	Single Chinese family with adolescent onset, spastic paraplegia associated with mild weakness of intrinsic hand muscles	[257]

Spastic gait (SPG) locus	Protein	Clinical Syndrome	References
SPG42 (3q24-q26)	Acetyl CoA transporter (SLC33A1)	Uncomplicated spastic paraplegia reported in single kindred, onset age 4-40 years, possibly one instance of incomplete penetrance.	[136, 137, 209]
Autosomal recessive HSP			
SPG5 (8p)	CYP7B1	Uncomplicated or complicated by axonal neuropathy, distal or generalized muscle atrophy, and white matter abnormalities on MRI	[30, 53, 103, 165, 225, 230, 247]
SPG7 (16q)	Paraplegin	Uncomplicated or complicated: variably associated with mitochondrial abnormalities on skeletal muscle biopsy and dysarthria, dysphagia, optic disc pallor, axonal neuropathy, and evidence of “vascular lesions”, cerebellar atrophy, or cerebral atrophy on cranial MRI	[61, 85]
SPG11 (15q)	Spatacsin (KIAA1840)	Uncomplicated or complicated: spastic paraplegia variably associated with thin corpus callosum, mental retardation, upper extremity weakness, dysarthria, and nystagmus; may have “Kjellin syndrome”: childhood-onset, progressive spastic paraplegia accompanied by pigmentary retinopathy, mental retardation, dysarthria, dementia, and distal muscle atrophy; juvenile, slowly progressive ALS reported in subjects with SPG11 HSP; 50% of autosomal recessive HSP is considered to be SPG11	[149, 250]
SPG14 (3q27-28)	Unknown	Single consanguineous Italian family, 3 affected subjects, onset age ~30 years; Complicated spastic paraplegia with mental retardation and distal motor neuropathy (sural nerve biopsy was normal)	[236]
SPG15 (14q)	Spastizin/ZFYVE26	Complicated: spastic paraplegia variably associated with associated with pigmented maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration (Kjellin syndrome).	[92, 111]
SPG18 (8p12-p11.21)	Endoplasmic reticulum, lipid raft associated protein 2 (ERLIN2)	Two families described with spastic paraplegia complicated by mental retardation and thin corpus callosum. ERLIN2 mutations also identified in subjects with juvenile primary lateral sclerosis	[7, 8] [5]
SPG20 (13q)	Spartin	Complicated: spastic paraplegia associated with distal muscle wasting (Troyer syndrome)	[54, 55, 140, 182, 187]
SPG21 (15q21-q22)	Maspardin	Complicated: spastic paraplegia associated with dementia, cerebellar and extrapyramidal signs, thin corpus callosum, and white matter abnormalities (Mast syndrome)	[216]
SPG23 (1q24-q32)	Unknown	Complicated: childhood onset HSP associated with skin pigment abnormality (vitiligo), premature graying, characteristic facies; Lison syndrome	[33]
SPG24 (13q14)	Unknown	Complicated: childhood onset HSP variably complicated by spastic dysarthira and pseudobulbar signs	[108]
SPG25 (6q23-q24.1)	Unknown	Consanguineous Italian family, four subjects with adult (30-46 years) onset back and neck pain related to disk herniation and spastic paraplegia; surgical correction of disk herniation ameliorated pain and reduced spastic paraplegia. Peripheral neuropathy also present.	[262]
SPG26 (12p11.1–12q14)	Unknown	Single consanguineous Bedouin family with five affected subjects. Complicated: childhood onset (between 7 and 8 years), progressive spastic paraparesis with dysarthria and distal amyotrophy in both upper and lower limbs, nerve conduction studies were normal; mild intellectual impairment, normal brain MRI	[248]
SPG27 (10q22.1-q24.1)	Unknown	Complicated or uncomplicated HSP. Two families described. In one family (7 affected subjects) uncomplicated spastic paraplegia began between ages 25 and 45 years. In the second family (three subjects described) the disorder began in childhood and included spastic paraplegia, ataxia, dysarthria; mental retardation, sensorimotor polyneuropathy, facial dysmorphism and short stature.	[155],[198]

Spastic gait (SPG) locus	Protein	Clinical Syndrome	References
SPG28 (14q21.3-q22.3)	DDHD1	Uncomplicated: pure spastic paraplegia, onset in infancy, childhood, or adolescence, either as an uncomplicated spastic paraplegia syndrome; or variable associated with axonal neuropathy, distal sensory loss, and cerebellar eye movement disturbance	[40] [227]
SPG29 (14q)	Unknown	Uncomplicated HSP, childhood onset	
SPG30 (2q37.3)	KIF1A	Complicated: spastic paraplegia, distal wasting, saccadic ocular pursuit, peripheral neuropathy, mild cerebellar signs	[127]
SPG32 (14q12-q21)	Unknown	Mild mental retardation, brainstem dysraphia, clinically asymptomatic cerebellar atrophy	
SPG35 (16q21-q23)	Fatty acid 2-hydroxylase (FA2H)	Childhood onset (6 -11 years), spastic paraplegia with extrapyramidal features, progressive dysarthria, dementia, seizures. Brain white matter abnormalities and brain iron accumulation; an Omani and a Pakistani kindred reported.	[63, 64, 131]
SPG39 (19p13)	Neuropathy target esterase (NTE)	Complicated: spastic paraplegia associated with wasting of distal upper and lower extremity muscles	[188]
SPG43 (19p13.11-q12)	C19orf12	Two sisters from Mali, symptom onset 7 and 12 years, progressive spastic paraplegia with atrophy of intrinsic hand muscles and dysarthria (one sister)	[156]
SPG44 (1q41)	Gap junction protein GJA12/ GJC2, also known as connexin47 (Cx47)	Allelic with “Pelizeaus-Merzbacher-like disease” (PMLD, early onset dysmyelinating disorder with nystagmus, psychomotor delay, progressive spasticity, ataxia). GJA/GJC2 mutation I33M causes a milder phenotype: late-onset (first and second decades), cognitive impairment, slowly progressive, spastic paraplegia, dysarthria, and upper extremity involvement. MRI and MR spectroscopy imaging consistent with a hypomyelinating leukoencephalopathy	[178]
SPG45 (10q24.3-q25.1)	Unknown	Single consanguineous kindred from Turkey, five subjects described: affected subjects had mental retardation, infantile onset lower extremity spasticity and contractures, one subject with optic atrophy, two subjects with pendular nystagmus; MRI in one subject was normal.	[69]
SPG46 (9p21.2-q21.12)	Unknown	Dementia, congenital cataract, ataxia, thin corpus callosum	[38]
SPG47 (1p13.2-1p12)	AB4B1	Two affected siblings from consanguineous Arabic family with early childhood onset slowly progressive spastic paraparesis, mental retardation, and seizures; one subject had ventriculomegaly; the other subject had thin corpus callosum and periventricular white matter abnormalities	[34]
SPG48 (7p22.1)	KIAA0415	Analysis of KIAA0415 gene in 166 unrelated spastic paraplegia subjects (38 recessive, 64 dominant, 64 “apparently sporadic”) and control subjects revealed homozygous mutation in two siblings with late onset (6th decade) uncomplicated spastic paraplegia; and heterozygous mutation in one subject with apparently sporadic spastic paraplegia.	[217]
SPG49 (14q32.31)	TECPR2	5 subjects from three apparently unrelated families (Jewish Bukharian ancestry) had infantile onset hypotonia, developmental delay with severe cognitive impairment, dysmorphic features (short stature, brady-microcephaly, oral, facial, dental, nuchal abnormalities). Spastic, ataxic, rigid gait developed in childhood; additional features included gastroesophageal reflux, recurrent apneic episodes, mild dysmorphic features. Two subjects had epilepsy and MRI of two subjects showed thin corpus callosum and cerebellar atrophy.	[179]
SPG50 (7q22.1)	AP4M1	Five subjects from one consanguineous Moroccan family exhibited infantile onset, nonprogressive spastic quadriplegic with severe cognitive impairment; variably associated with adducted thumbs. Ventriculomegaly, white matter abnormalities and variable cerebellar atrophy noted on neuroimaging. Neuroaxonal abnormalities, gliosis, and reduced myelin noted on post mortem examination.	[167, 237]

Spastic gait (SPG) locus	Protein	Clinical Syndrome	References
SPG51 15q21.2	AP4E1	Two siblings from a consanguineous Palestinian Jordanian family and two siblings from a consanguineous Syrian family exhibited microcephaly, hypotonia, psychomotor delay, spastic tetraplegia, marked cognitive impairment with severe language impairment, facial dysmorphic features, abnormal brain MRI showed (including atrophy and diffuse white matter loss). Seizures were variably present.	[2, 163, 167]
SPG52 (14q12)	AP4S1	5 affected subjects from consanguineous Syrian family exhibited neonatal hypotonia and severe cognitive impairment and progressive, early childhood onset, spastic paraplegia, microcephaly, short stature, facial dysmorphism	[2]
SPG52 (14q12)	AP4S1	Five subjects from a consanguineous Syrian kindred exhibited delayed motor development, and severe cognitive impairment. Neonatal hypotonia was followed by progressive spastic gait with contractures. Dysmorphic features included short stature, microcephaly, and facial abnormalities	[1, 59, 107]
SPG53 (8p22)	VSP37A	9 subjects from two Arab Moslem families exhibited developmental delay, progressive lower extremity spasticity, and subsequently progressive upper extremity involvement; associated with skeletal dysmorphism (kyphosis and *pectus carinatum*); mild to moderate cognitive impairment; and variable hypertrichosis and impaired vibration sensation.	[261]
SPG54 (8p11.23)	DDHD2	Affected subjects reported from four unrelated families exhibited psychomotor delay, cognitive impairment, progressive spasticity (onset before age 2 years), thin corpus callosum, periventricular white matter abnormalities. Additional clinical features include foot contractures, dysarthria, dysphagia, strabismus, optic hypoplasia	[6, 211]
SPG55	C12ORF65	2 Japanese brothers from consanguineous parents exhibited early onset spastic paraplegia variably associated with reduced visual acuity (with central scotoma and optic atrophy), reduced upper extremity strength and dexterity, lower extremity muscle atrophy, and motor sensory neuropathy.	[215] [13]
SPG56 4q25	CYP2U1	5 unrelated families were reported with early childhood onset spastic paraplegia, variable upper extremity involvement, upper extremity dystonia, cognitive impairment, thin corpus callosum, brain white matter disturbance, axonal neuropathy, basal ganglia calcifications	[227]
2q31.1	GAD1	Four siblings in consanguineous Pakistani family with spastic cerebral palsy, and moderate to severe mental retardation	[161] [153] [141]
“SPOAN” syndrome (11q23)	Unknown	Complicated spastic paraplegia associated with optic atrophy, neuropathy (SPOAN)	[142]
5p15.31-14.1 No SPG designation	Epsilon subunit of the cytosolic chaperonin-containing t-complex peptide-1 (Cct5)	Complicated spastic paraplegia associated with mutilating sensory neuropathy.	[36, 37]
X-linked HSP			
SPG1 (Xq28)	L1 cell adhesion molecule (L1CAM)	Complicated: associated with mental retardation, and variably, hydrocephalus, aphasia, and adducted thumbs	[122]
SPG2 (Xq28)	Proteolipid protein	Complicated: variably associated with MRI evidence of CNS white matter abnormality; may have peripheral neuropathy	[47, 110, 129, 208]
SPG16 (Xq11.2-q23)	Unknown	Uncomplicated; or complicated: associated with motor aphasia, reduced vision, nystagmus, mild mental retardation, and dysfunction of the bowel and bladder	[220, 224]
SPG22 (Xq21)	Monocarboxylate transport 8 (MCT8)	Complicated (Allan-Herndon-Dudley syndrome): congenital onset, neck muscle hypotonia in infancy, mental retardation, dysarthria, ataxia, spastic paraplegia, abnormal facies	[10, 28, 150]
SPG34		Uncomplicated, onset 12 to 25 years	[143]

Spastic gait (SPG) locus	Protein	Clinical Syndrome	References
Maternal (mitochondrial) inheritance HSP			
No SPG designation	Mitochondrial ATP6 gene	Adult onset, progressive spastic paraplegia, mild to severe symptoms, variably associated with axonal neuropathy, late-onset dementia, and cardiomyopathy.	[238]

Table 2

Examples of complicated HSP syndromes[*#] (from [78])

Spastic paraplegia and peripheral neuropathy
HSP types SPG2, 3A, 5, 6, 7, 10, 25, 27, 30, 31, 55, 56, SPOAN, Cct5 (epsilon subunit), mutation), mitochondrial ATP6 gene mutation
Spastic paraplegia and distal amyotrophy
HSP types SPG3A (rare feature of), 4 (rare feature of), 5, 10, 14, 15, 17, 20, 26, 30, 38, 39, 41, 43, 55
Spastic paraplegia and mental retardation
HSP types SPG 1, 11, 14, 16,18, 20, 22, 26, 27, 32, 44, 45, 47, 49, 50, 51, 52, 53, 54, 56, GAD1 mutation
Spastic paraplegia with dementia
SPG4, 15, 21, 35, 46, and Mitochondrial ATP6 gene mutation
Spastic paraplegia and vision impairment (including blindness)
HSP types SPG15, 16, 45, 46, 54, 55, and SPOAN syndrome
Spastic paraplegia and deafness
SPG29
Spastic paraplegia with skeletal abnormalities or dysmorphic features
HSP types SPG25, 49, 50, 51, 52, 53
Spastic paraplegia and extrapyramidal movement disorder
HSP types SPG21, 35, 56
Spastic paraplegia and epilepsy
HSP types SPG6, 35, 47, 51
Spastic paraplegia, short stature, seizures, retinal degeneration, ichthyosiform skin changes (Sjogren-Larsson syndrome); autosomal recessive[117], [118]
Spastic paraplegia and dysarthria
HSP types SPG7, 15, 22, 24, 27, 35, 43, 44, 54
Spastic paraplegia and ataxia
HSP types SPG7, 21, 22, 27, 30, 32, 46, 49
Spastic paraplegia and hematologic abnormality
Spastic paraplegia and May-Hegglin anomaly: cytoplasmic inclusions in leukocytes, giant platelets, and thrombocytopenia; autosomal dominant[84]
Spastic paraparesis and Evan's syndrome (Coombs-positive hemolytic anemia and immune thrombocytopenia without a known underlying etiology); probably autosomal recessive[4]
Spastic paraplegia and MRI brain abnormalities

HSP types SPG1, 2, 5, 7 (variably abnormal), 11, 15, 18, 21, 32, 35, 44, 46, 47, 49, 50, 54, 56
Spastic paraplegia and skin abnormalities
Spastic paraplegia with short stature: seizures, retinal degeneration, ichthyosiform skin changes (Sjogren Larsson syndrome); autosomal recessive[117], [118]
SPG23 HSP: Childhood onset spastic paraplegia associated with skin pigment abnormality; autosomal recessive[33]
Spastic paraplegia and endocrine disturbance
Spastic paraplegia and Kallman syndrome (hypogonadotrophic hypogonadism and anosmia)[231]

*Note that the “complicating feature” may be frequently or infrequently associated with a specific genetic type of HSP.

#see Table 1 for reference

Table 3

HSP proteins (updated from[78])

HSP gene/protein	Functions	References
SPG1/L1CAM	Integral membrane glycoprotein, cell adhesion molecule in the immunoglobulin superfamily; mediates cell-to-cell and cell-to-matrix attachment; functions include guidance of neurite outgrowth during development, neuronal cell migration, and neuronal cell survival. *Interacts with Bone morphogenic protein (affects L1CAM gene regulation)*	[22, 124, 256]
SPG2/PLP1	Proteolipid protein (PLP1) is an integral myelin protein expressed in oligodendroglia and Schwann cells but not in neurons	[219]
SPG3A/atlastin	Dynamin family GTPase, interacts with HSP proteins spastin, NIPA1, and REEP1; involved in membrane fusion and severing; contributes to endoplasmic reticulum morphology. *Interacts with SPG4/spastin, REEP1, NIPA1, DP1/Yop1p and reticulon families of ER-shaping proteins, HPK/GCK-like kinase (HGK) (a protein kinase in the c-Jun N-terminal kinase signaling pathway; Inhibits BMP signaling in Zebrafish model*	[21, 35, 52, 71, 73, 180, 181, 200, 205, 260]
SPG4/spastin	Cytosolic (and possibly nuclear) protein with AAA domain; (AAA domain is also present in paraplegin); interacts with microtubules and has microtubule severing properties; interacts with atlastin and REEP1 and contributes to endoplasmic reticulum morphology; mutations affect axonal transport. *Interacts with:SPG3A/Atlastin, SPG31/REEP1, SPG33/ZFYVE27, ESCRT-II complex associated CHMP1B, Reticulon 1 (endoplasmic reticulum protein), Reticulon 3, CREL5, COPS5, Tubulin; inhibits bone morphogenic protein signaling*	[11, 146, 181, 194, 202, 205, 229]
SPG5/CYP7B1	Cytochrome P450-7B1 (CYP7B1) provides primary metabolic route for cholesterol derivatives dehydroepiandrosterone (DHEA) and related hydroxysteroids via 7α-hydroxylation; and that in the liver; and an alternative route for cholesterol metabolism.	[230]
SPG6/NIPA1	"Not imprinted in Prader Willi/Angelman 1" (NIPA1): 9 alternating hydrophobic-hydrophilic domains predicts integral membrane localization; NIPA1 binds to BMP-II receptor to inhibit BMP signaling; NIPA1 transcription is induced by low extracellular Mg^{++}; NIPA1 expression causes inwardly directly Mg^{++} conductance. *Interacts with Type II bone morphogenic protein (BMP) receptor 2 (BMPRII) to inhibit BMP signaling and SPG3A/atlastin*	[229]
SPG7/paraplegin	Mitochondrial metalloprotease, involved as protein chaperone in mitochondrial protein quality control. *Interacts with AFG3L2 (mutations cause spinocerebellar ataxia type 28)*	[145, 203]
SPG8/Strumpellin (KIAA0196)	KIAA0196/Strumpellin, mutations may be pathogenic through protein aggregation: Strumpellin binds to valosin-containing protein (VCP; also known as p97, TER ATPase and Cdc48p); VCP-positive inclusions occur in a wide variety of neurodegenerative disorders including Parkinson's disease, Lewy body disease, Huntington's disease, amyotrophic lateral sclerosis and spinocerebellar ataxia type III (Machado-Joseph disease); Strumpellin may also regulate actin dynamics through its interaction with WASH; *interacts with Valosin-containing protein (VCP; also known as p97, TER ATPase and Cdc48p); WASH, a Wiskott-Aldrich syndrome protein (WASP) family member, via SWIP (Strumpellin and WASH interacting protein (WASH localizes to endosomal subdomains and regulates endocytic vesicle scission in an Arp2/3-dependent manner).*	[119]
SPG10/KIF5A	Kinesin heavy chain (KIF5A) a molecular motor subunit that participates in the intracellular movement of organelles and macromolecules.	[253]
SPG11/Spatacsin	Unknown function; spatacsin is a component of a protein complex that includes two other HSP proteins, SPG15/ZFYVE26 and SPG48/KIAA0415 [217] suggesting that these forms of HSP may share similar molecular pathogenesis. *Interacts with SPG48/KIAA0415, SPG15/ZfyVe26, C200RF29, DKFZp761E198*	[217]
SPG12/RTN2	RTN2 gene encodes reticulon 2, an ER-shaping protein. *Reticulon interacts with SPG4/spastin.*	[162]
SPG13/ HSPD1	HSPD1 gene encodes Chaperonin 60 (also known as heat shock protein 60, HSP60), the large subunit of the mitochondrial Hsp60/Hsp10 chaperonin complex; functions in mitochondrial protein quality control (binding and sequestration, and refolding of unfolded proteins)	[94]
SPG15/Spastizin (ZFYVE26)	FYVE-domain proteins have diverse functions including membrane trafficking, signal transduction, regulating the cytoskeleton, and serving as phosphatidylinositol 3-phosphate (PtdIns3P) phosphatases. Spastizin colocalizes with ER and endosome markers and is a component of a protein complex that includes two other HSP proteins, SPG11/spatacsin and SPG48/KIAA0415. *Interacts with SPG11/Spatacsin and SPG48/KIAA0415*	[92, 164, 217]

HSP gene/protein	Functions	References
SPG17/BSCL2	BSCL2/seipin: Endoplasmic reticulum transmembrane protein; mutations appear pathogenic through induction of endoplasmic reticulum stress-mediated apoptosis.	[113-115]
SPG18/ERLIN2	ERLIN2 is a component of lipid rafts that localize to ER and nuclear membranes. ERLIN2 is a mediator of ER stress response to protein misfolding.	[42, 241]
SPG20/Spartin	Spartin: N-terminal region similar to spastin; homologous to proteins involved in the morphology and trafficking of endosomes; also localizes to mitochondria; interacts with Eps 15, a protein known to be involved in endocytosis and the control of cell proliferation, suggesting that spartin may be involved in endocytosis, vesicle trafficking, or mitogenic activity; spartin promoter hypermethylation is associated with cytokinesis arrest in colorectal carcinoma. *Interacts with GRP78, GRP75, ubiquitin, and the E3 ubiquitin-protein ligases AIP4/Itch and AIP5/WWP1, and; nucleolar protein "nucleolin"; inhibits BMP signaling.*	[20, 109, 138, 140, 159, 229]
SPG21/Maspardin	Appears to be a cytosolic protein partitioned between the cytosol and vesicles of the endosomal/*trans*-Golgi network; may play a role in endosomal trafficking; may be similar to a noncatalytic α/β hydrolase protein NDRG1, mutations in which cause peripheral neuropathy with early axonal involvement. *Interacts with Aldehyde dehyrogenase ALDH16A1*	[93, 216]
SPG22/MCT8	Monocarboxylate transport 8 (MCT8) is a thyroid hormone transporter, results in elevated serum triiodothyronine (T3) levels	[147]
SPG28/DDHD1	DDHD1 is a phosphatidic acid-preferring phospholipase A1 (PA-PIA1). There is evidence that DDHD1 is involved in stimulus-dependent formation of arachidonic acid-containing lysophosphatidyl inositol which plays a role in signal transduction including that of GPR55, a G-protein coupled, putative canabinoid receptor.	[254]
SPG30/KIF1A	Microtubule-dependent motor protein (in kinesin-3 family) with apparent role as primary anterograde motor protein for axonal transport of dense-core vesicles	[128, 139]
SPG31/REEP1	Receptor expression enhancing protein 1 (REEP1), structurally related to the DP1/Yop1p family of endoplasmic reticulum -shaping proteins; required for ER network formation in vitro; forms complexes with atlastin and spastin within endoplasmic reticulum; also binds to microtubules and promotes ER alignment along the microtubule cytoskeleton *in vitro. Interacts with PG3A/Atlastin and SPG4/Spastin*	[181]
SPG33/ZFYVE27	ZFYVE27/protrudin has a role in Rab-11-mediated membrane trafficking and promotes neurite outgrowth. *Interacts with SPG4/Spastin and RAB11*	[32, 146]
SPG35/FA2H	Fatty acid 2-hydroxylase (FA2H) in oligodendroglia catalyzes the 2-hydroxylation of myelin galactolipids, galactosylceramine, and sulfatide; and therefore, helps determine myelin lipid content.	[86]
SPG39/NTE	Neuropathy target esterase (NTE) is a phospholipase B localized to ER membranes; may reduce cytotoxic lysophosphatidylcholine; implicated in toxic organophosphorus compound induced delayed neurodegeneration (OPIDN); may function to regulate cyclic AMP-dependent protein kinase. *Interacts with Cyclic AMP-dependent protein kinase (in Drosophila)*	[3, 17, 27, 66, 87, 88, 120, 121, 199, 239, 251, 255]
SPG42/SLC33A1	SLC33A1 is an acetyl CoA transporter that moves acetyl-CoA into the Golgi apparatus where it may be transferred to sialyl residues of gangliosides and glycoproteins	[136]
SPG43/C19orf12	Membrane protein of uncertain function	
SPG44/GJA12/GJC2	Gap junction protein (GJA12/GJC2) also known as connexin47 (Cx47); important factor in formation of specialized channels ("gap junctions") between cells that allow selective movement of ions and metabolites between adjacent intracellular compartments.	[74, 178, 206]
SPG47/AP4B1	Adaptor protein complexes (AP1, AP2, AP3, and AP4) are widely expressed, evolutionarily conserved complexes that participate in vesicle formation and selective inclusion of specific proteins for these vesicles. Homozygous mutations in three AP4 proteins (AP4B1, AP4E1, AP4M1, AP4S1) were identified in subjects with somewhat diverse, autosomal recessive neurologic disorders that share neonatal hypotonia, spastic tetraplegia, marked cognitive impairment associated, and thin corpus callosum.	[1, 23, 59, 106, 107, 237]
SPG48/KIAA0415	KIAA0415 encodes a putative helicase involved in DNA repair; Interacts with SPG11/Spatacsin, SPG15/ZFYVE26, C20ORF29, DKFZp761E198. KIAA0415's function as a subunit for adapter protein 5 (AP-5) suggests a role in endosome membrane dynamics.	[105, 106, 217]

HSP gene/protein	Functions	References
SPG49/TECPR2	Tectonin beta propeller repeat containing protein 2 (TECPR2) appears to participate in autophagy. TECPR2 binds to homologues of autophagy related proteins (Atg8) including MAP1LC3; and upregulates autophagosome accumulation *in vitro*.	[26, 179]
SPG50/ AP4M1	(see AP4B1)	[1, 23, 59, 107, 237]
SPG51/AP4E1	(see AP4B1)	
SPG52/AP4S1	(see AP4B1)	[59, 107]
SPG53/VPS37A	Vacuolar protein sorting 37A encodes a subunit of endosomal sorting complex required for transport (ESCRT-I) complex. ESCRTs regulate trafficking of proteins from endosomes to lysosomes and other vesicles and participate in many other diverse cellular processes including autophagy, membrane scission, and microRNA function.	[135, 261]
SPG54/DDHD2	DDHD2 (DDHD-domain-containing 2) is an intracellular phospholipase A_1 ($iPLA_1$). DDHD2 and related proteins (DDHD1 and SEC23IP) also appear to be involved organelle biogenesis and membrane trafficking.	[6, 112, 168, 168, 207, 211, 226]
SPG56/CYP2U1	CYP2U1 can catalyze hydroxylation of arachidonic acid, eicosopentanoic acid, docoshexanoic acid and related long-chain fatty acids that mediate signal transduction pathways.	[227]
CcT5	Epsilon subunit of the cytosolic chaperonin-containing t-complex peptide-1 (Cct5); contributes to the protein folding and assembly of a wide variety of cytosolic proteins including actin and tubulin	[36]
Mitochondrial ATP6 gene	Synthesis of ATP (from ADP) in mitochondria is coupled to translocation of protons from the mitochondrial matrix to specific intermembrane sites. Mitochondrial ATP6 forms a channel through which protons flow back from intermembrane sites into the mitochondrial matrix; and is thus an important factor in mitochondrial ATP production.	[151, 238]

Table 5

Animal models of hereditary spastic paraplegia (see[78] for references)

HSP Genetic Type	Protein name	Mouse	*Drosophila*	Zebrafish	*C. elegans*	Other
SPG1	L1 cell adhesion molecule (L1CAM)	+			+	
SPG2	Proteolipid protein	+				
SPG3A	Atlastin	+	+	+		
SPG4	Spastin	+	+	+	+	Cattle [228]
SPG5 (8p)	CYP7B1	+				
SPG6	“Not imprinted in Prader Willi/Angelman 1” (NIPA1		+		+	Rat [126]
SPG7 (16q)	Paraplegin	+				
SPG8	KIAA0196/Strumpellin,		+	+		
SPG10	Kinesin heavy chain (KIF5A	+				
SPG11 (15q)	Spatacsin (KIAA1840)			+		
SPG13	HSPD1 gene encodes Chaperonin 60 (also known as heat shock protein 60, HSP60	+				
SPG21 (15q21-q22)	Maspardin	+				
SPG30 (2q37.3)	KIF1A	+			+	
SPG39 (19p13)	Neuropathy target esterase (NTE)	+	+			
SPG42 (3q24-q26)	Acetyl CoA transporter (SLC33A1)			+		
SPG53	Vesicle protein sorting 37A (VPS37A)			+		
SPG54	DDHS2		+			