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The Hereditary Spastic Paraplegias

Nine Genes and Counting

John K. Fink, MD

The hereditary spastic paraplegias (HSPs) are inherited neurologic disorders in which the primary symptom is insidiously progressive difficulty walking due to lower extremity weakness and spasticity. There have been great strides in our knowledge of this group of disabling disorders; 20 HSP loci and 9 HSP genes have been discovered. Insights into the molecular causes of HSPs are beginning to emerge. This review summarizes these advances in HSPs' genetics. *Arch Neurol. 2003;60:1045-1049*

Hereditary spastic paraplegia (HSP) is a syndromic designation encompassing more than 30 disorders in which the predominant feature is spastic gait.[1] The HSP syndromes are classified clinically as uncomplicated (also known as pure or nonsyndromic) if symptoms are limited to progressive spastic weakness in the legs, often accompanied by urinary urgency and subtle dorsal column impairment. The HSP syndromes are classified as complicated or syndromic if the inherited disorder includes other neurologic abnormalities (eg, neuropathy, amyotrophy, ataxia, mental retardation, or thin corpus callosum) or systemic disturbances (eg, cataracts) for which alternate disorders have been excluded. Postmortem studies of uncomplicated HSP have shown axonal degeneration that is most marked in the distal terminals of corticospinal tracts and fasciculus gracilis fibers.[2]

Symptoms of HSP may begin at any age, from infancy to older than 60 years. If symptoms begin during the teenage years or later, then spastic gait disturbance usually progresses insidiously over many years. Canes, walkers, and wheelchairs may eventually be required. If symptoms begin in late infancy or early childhood, however, then there may be relatively little functional worsening, even over many years. Individuals with early-onset, apparently nonprogressive HSP may be distinguishable from those with spastic diplegic cerebral palsy only by family history (which may be absent in recessive, X-linked, or dominantly inherited HSP with variable age of symptom onset).

Autosomal dominant, autosomal recessive, and X-linked HSP are each genetically heterogeneous. Genetic mapping has identified 20 different HSP loci (**Table**) designated SPG (SPastic parapleGia) 1 through 21 in order of their discovery (*SPG18* has been identified but not published). Thus far, 10 loci for autosomal dominant HSP, 7 loci for autosomal recessive HSP, and 3 loci for X-linked HSP have been published. The occurrence of HSP in families for which known HSP loci are excluded indicates the existence of additional loci (J.K.F. and S. Rainier, PhD, unpublished observations, 2003).

Different genetic types of uncomplicated HSP usually cannot be distinguished by clinical and neuroimaging parameters alone. This reflects both the clinical similarity between different types of HSP and the phenotypic variability within a given genetic type of HSP. There may be significant clinical variability both within a given family in which all subjects have the same HSP gene mutation; between families with the same genetic type of HSP; and between families with different genetic types of HSP. For example, some families with *SPG4* HSP (due to spastin gene mutations described in the next section) include individuals with child hood-onset symptoms and individuals whose symptoms begin after age 30 years.

From the Department of Neurology, University of Michigan, and the Geriatric Research Education and Clinical Center, Ann Arbor Veterans Affairs Medical Center, Ann Arbor.

Hereditary Spastic Paraplegia (HSP)*

Spastic Gait (*SPG*) Locus	Chromosome	Gene/Protein: Function	HSP Syndrome
		Autosomal Dominant HSP	
SPG4	2p22	*SPG4*/spastin: cytosolic protein, with AAA domain that binds to microtubules	Uncomplicated
SPG13	2q24-34	Heat shock protein 60 (Hsp60), mitochondrial chaperonin (Cpn60)	Uncomplicated
SPG8	8q23-q24		Uncomplicated
SPG9	10q23.3-q24.2		Complicated: spastic paraplegia associated with cataracts, gastroesophageal reflux, and motor neuronopathy
SPG17	11q12-q14		Complicated: spastic paraplegia associated with amyotrophy of hand muscles (Silver syndrome)
SPG10	12q13	Kinesin heavy chain (KIF5A): molecular motor involved in axonal transport	Uncomplicated or complicated by distal atrophy
SPG3A	14q11-q21	*SPG3A*/atlastin: predicted to be GTPase similar to dynamins	Uncomplicated
SPG6	15q11.1	*NIPA1*: neuronal membrane protein of unknown function	Uncomplicated
SPG12	19q13		Uncomplicated
SPG19	9q33-q34		Uncomplicated
		Autosomal Recessive HSP	
SPG14	3q27-28		Complicated: spastic paraplegia associated with mental retardation and distal motor neuropathy
SPG5	8q		Uncomplicated
SPG11	15q		Uncomplicated or complicated: variably associated with HSP associated with thin corpus callosum, mental retardation, upper extremity weakness, dysarthria, and nystagmus
SPG7	16q	*SPG7*/paraplegin: mitochondrial protein	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
SPG15	14q		Complicated: spastic paraplegia associated with pigmented maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration.
SPG20	13q	*SPG20*/spartin	Complicated: spastic paraplegia associated with distal muscle wasting (Troyer syndrome)
SPG21	13q14		Childhood-onset HSP variably complicated by spastic dysarthira and pseudobulbar signs[3]
		X-linked HSP	
SPG1	Xq28	L1 cell adhesion molecule (L1CAM)	Complicated: associated with mental retardation and variably hydrocephalus, aphasia, and adducted thumbs
SPG2	Xq21	Proteolipid protein (PLP): intrinsic myelin protein	Complicated: variably associated with MRI evidence of CNS white matter abnormality
SPG16	Xq11.2		Uncomplicated Complicated: associated with motor aphasia, reduced vision, mild mental retardation, and dysfunction of the bowel and bladder

Abbreviations: AAA, ATPase associated with diverse cellular activities; CNS, central nervous system; MRI, magnetic resonance imaging.
*The table is modified from Fink.[4]

FIVE AUTOSOMAL DOMINANT HSP GENES

Spastin

Mutations in the *SPG4* gene (spastin protein) are responsible for approximately 40% of autosomal dominant HSP cases.[4] Hereditary spastic paraplegia due to *SPG4* gene mutation is the single most common form of autosomal dominant HSP, and possibly the single most common form of any type of HSP. At this stage, we know very little about the function of spastin, the encoded protein of *SPG4*, and the mechanisms by which spastin abnormalities lead to axonal degeneration in HSP. It is widely held that most, if not all, *SPG4* mutations are pathogenic because of haploinsufficiency (ie, decreased abundance of functionally normal spastin) rather than a dominant negative mechanism.[5-10] This conclusion is based on (1) the fact that many mutations reduce the abundance of full-length, sequence-normal spastin, such as mutations that cause premature translation termination, insertions, or deletions that lead to nonsense transcripts and mutations that cause aberrant messenger RNA splicing, and (2) recent studies in which expression of *SPG4* bearing nonsense or frameshift mutations resulted in the absence of immunologically detectable spastin.[11]

SPG4 is expressed widely and undergoes alternate splicing variable inclusion of exon 4. Thus far, none of the more than 80 reported HSP-specific *SPG4* mutations have occurred in exon 4. In addition to variable splicing, there is also evidence that tissue-specific posttranslational modi-

fication results in 75- and 80-kDa spastin isoforms.[11] Charvin et al[11] showed spastin was present in neurons, particularly in the brain, and also in anterior horn motor neurons, but not within glia. Spastin contains an ATPase associated with diverse cellular activities (AAA) domain.[5] It also contains a nuclear localization signal,[5] and very recent immunofluorescent studies indicate spastin is a nuclear protein. The intracellular location of spastin is controversial because previous studies indicated that spastin was distributed within the cytoplasm.[12]

Emerging evidence suggests that spastin may interact with microtubules. Azim et al[13] showed that antitubulin antibodies could precipitate spastin in vitro. More recently, Errico et al[11] showed that a spastin fusion protein colocalized with microtubules in Cos-7 and HeLa cells transfected with wild-type and mutant *SPG4* expression vectors. Findings that spastin may interact directly with microtubules support the hypothesis that disturbances in axonal cytoskeleton or transport underlie some forms of HSP.[14]

Atlastin

Autosomal dominant HSP linked to the chromosome 14q *SPG3A* locus represents approximately 10% of dominantly inherited HSP cases[15] and is particularly prevalent among those autosomal dominant HSP kindreds in which each affected subject developed symptoms in childhood.[16] Zhao et al[17] identified mutations in a novel gene (*SPG3A*) as the cause of this form of HSP. At this stage, insight into the possible function of *SPG3A* comes only from analysis of the sequence of its encoded protein, atlastin. Atlastin does not contain an AAA motif and is not homologous to spastin or other proteins implicated in HSP. In contrast, atlastin contains conserved motifs for GTPase binding and hydrolysis[17] and is structurally homologous to guanylate binding protein 1. The functional importance of atlastin's GTPase motif is indicated by a recently identified HSP mutation that disrupted a conserved GTPase domain.[18]

Guanylate binding protein 1, to which atlastin shows homology, is a member of the dynamin family of large GTPases. Dynamins play essential roles in a wide variety of vesicle trafficking events.[19-24] Dynamins play essential roles in the action of many neurotrophic factors and are critical elements in the rapid and efficient process of recycling of synaptic vesicles. Dynamins are also involved in the maintenance and distribution of mitochondria[25] and, through their association with actin and microtubules, have been implicated in maintenance of the cytoskeleton.[26] The important and diverse functions of dynamins raise many interesting possibilities by which atlastin mutations could cause axonal degeneration. These possibilities include defective synaptic vesicle recycling leading to abnormal synaptic structure and impaired neurotransmission, impaired activation of selected neurotrophic factors, and impaired mitochondrial distribution.

Kinesin Heavy Chain

Kinesin heavy chain (KIF5A) is a molecular motor that participates in the intracellular movement of organelles and macromolecules along microtubules in both anterograde and retrograde directions. KIF5A gene mutation was recently identified in affected subjects with HSP linked to the *SPG10* locus.[27] Subjects with KIF5A mutation exhibited either uncomplicated HSP or HSP associated with distal muscle atrophy.[27] The HSP-specific KIF5A mutation disrupted an invariant asparagine residue that, when mutated in orthologous kinesin heavy chain motor proteins, prevented stimulation of the motor ATPase by microtubule binding.[27] Finding KIF5A mutations in *SPG10* HSP suggests that degeneration of distal axons in this and possibly of other forms of HSP may be related to disturbance of axonal transport.[28]

Heat Shock Protein 60 or Chaperonin 60

Mutation in the mitochondrial protein heat shock protein 60, also known as chaperonin 60, causes *SPG13*-linked autosomal dominant HSP. *SPG13* HSP is an autosomal dominant form of uncomplicated HSP mapped to chromosome 2q24-34. Recently, Hansen et al[29] identified a mutation in heat shock protein 60 in affected subjects from an *SPG13*-linked HSP kindred. The mechanism by which heat shock protein 60 mutations cause HSP are not yet known. It is intriguing however, that 2 HSP genes, heat shot protein 60 or chaperonin 60 and *SPG7* or paraplegin, encode mitochondrial proteins.

NIPA1

NIPA1 gene mutations cause autosomal dominant HSP linked to chromosome 15q (*SPG6* HSP). *SPG6* HSP is a prototypical example of adolescent or adult-onset, slowly progressive, uncomplicated HSP. *SPG6* and *SPG8* are perhaps the most severe forms of dominantly inherited, uncomplicated HSP.[30] Chai et al[31] identified nonimprinted Prader-Willi/Angleman (NIPA) locus genes as candidate's for *SPG6*. Rainier et al[32] identified a disease-specific mutation in a novel gene (*NIPA1*) in an *SPG6*-linked HSP kindred and in an unrelated kindred that was too small for linkage analysis. Precisely the same *NIPA1* gene mutation (T45R) was discovered in 2 unrelated kindreds.[32] The function of *NIPA1* is unknown. It is widely expressed, particularly in the central nervous system. The presence of 9 alternating hydrophobic-hydrophilic domains suggests that *NIPA1* encodes a membrane protein.[32] This feature makes *NIPA1* unique among HSP proteins. The NIPA1 mutation T45R appears to act through a "dominant negative" gain of function. This prediction is based on the observation that subjects who are missing one *NIPA1* gene entirely (eg, subjects with Prader-Willi and Angleman syndromes who have deletions involving this region of chromosome 15q) do not develop HSP.

TWO AUTOSOMAL RECESSIVE HSP GENES

Paraplegin

SPG7 encodes a mitochondrial protein (paraplegin). De Michele et al[33] discovered disease-specific mutations in *SPG7* as the cause of chromosome 16q–linked autosomal recessive HSP. This is a rare form of autosomal recessive

HSP with only a few reported families affected.[33,34] Within these families, some individuals had pure HSP, and others had HSP complicated by dysarthria, dysphagia, optic disc pallor, axonal neuropathy, and evidence of vascular lesions, cerebellar atrophy, or cerebral atrophy on cranial magnetic resonance imaging. Paraplegin is highly homologous to the yeast mitochondrial ATPases AFG3, RCA1, and YME1, which have both proteolytic and chaperone-like activities at the inner mitochondrial membrane. Paraplegin is also localized to mitochondria.[33] Muscle biopsy specimens from some, but not all, HSP patients with *SPG7* gene mutations showed ragged-red and cytochrome-oxidase–negative fibers and abnormal mitochondrial structure typical of mitochondriopathy.[33]

SPG7 knockout mice exhibit signs of HSP. Ferreirinha et al[35] reported preliminary studies in homozygous *SPG7*/paraplegin knockout mice. These animals displayed impaired performance on a rotorod apparatus that started at age 6 months and worsened with age. Histological analysis of the spinal cord showed axonal swelling, particularly in the lateral columns of the lumbar spinal cord, consistent with a retrograde axonopathy. The changes were progressive with signs of axonal degeneration becoming prominent at age 12 months.

Although 2 HSP genes (*SPG7*/paraplegin and *SPG13*/chaperonin 60) are mitochondrial proteins, it does not appear that all types of HSP are due to mitochondrial dysfunction. Biochemical and histological evidence of mitochondrial abnormalities has been sought but has not been observed in *SPG4* (spastin), *SPG3A* (atlastin), *SPG8*, and *SPG6* autosomal dominant HSP.[5,36-38]

Spartin

Spartin mutations cause HSP associated with distal muscle wasting (*SPG20* Troyer syndrome).[39] This gene is designated "spartin" (spastin-related autosomal recessive Troyer protein) because its amino-terminal region is similar to that of spastin, mutations in which cause *SPG4* HSP. Spartin is also homologous to proteins involved in endosome morphology and membrane trafficking.

TWO X-LINKED HSP GENES

Proteolipid Protein

Proteolipid protein (PLP) is an intrinsic myelin protein. PLP gene duplications and point mutations cause Pelizaeus-Merzbacher disease, an infantile-onset, progressive leukodystrophy, and are responsible for dysmyelination in jimpy mice.[40,41] In addition, some individuals with X-linked HSP linked to the *SPG2* locus on Xq22 also have PLP mutations.[42,43] Although some of these patients have clinical features consistent with uncomplicated HSP, others have abnormal-appearing white matter on brain magnetic resonance imaging scans or evidence of peripheral neuropathy. Leukodystrophy is not a feature of other forms of uncomplicated HSP.

Some of the phenotypic variation of PLP mutation syndromes (infantile-onset leukodystrophy vs childhood-onset slowly progressive spastic paraparesis) can be attributed to different mutations in the PLP gene. However, both syndromes have occurred in the same family in individuals who share the same PLP gene mutation (F. Cambi, MD, PhD, J.K.F., unpublished observation, 2001). This observation indicates that, in some cases, the neurologic consequences of PLP gene mutation are influenced by modifying factors that presumably include additional genes and possibly environmental factors.

L1 Cell Adhesion Molecule

Neuronal cell adhesion molecule L1 (L1CAM) gene mutations cause a variety of X-linked neurologic disorders, including complicated spastic paraplegia, hydrocephalus, and mental retardation aphasia, shuffling gait, and adducted thumbs (MASA) syndrome.[44] Although there is correlation between some of these syndromes and specific L1CAM mutations,[45] X-linked hydrocephalus, MASA syndrome, and X-linked spastic paraplegia have occurred in kindreds in which affected individuals had the same L1CAM mutation.[46] L1CAM is an integral membrane glycoprotein and a member of the immunoglobulin superfamily of cell adhesion molecules that mediate cell-to-cell attachment. L1CAM is found primarily in the nervous system, and its functions include guidance of neurite outgrowth during development, neuronal cell migration, and neuronal cell survival.[47,48] Dahme et al[49] used gene targeting to create transgenic mice in which the L1CAM gene was disrupted. These animals exhibited weak hind limbs and reduced size of corticospinal tracts.

CONCLUSIONS

The very recent discovery of many HSP genes is rapidly shaping new concepts of the pathophysiologic mechanisms of HSP. Whereas the uniform clinical appearance of uncomplicated HSPs initially suggested that a common biochemical disturbance underlies most types of HSP, this appears to not be the case. Rather, it appears that very long central nervous system axons (ie, corticospinal tracts and dorsal column fibers) are particularly vulnerable to a number of distinct biochemical disturbances and that the highly similar clinical features of genetically diverse types of uncomplicated HSP reflect the limited repertoire of symptoms from corticospinal tract and, to a lesser extent, dorsal column fiber disturbance.

Based on the diversity of the HSP genes discovered, a biochemical classification of HSP is emerging. For example, one can consider (1) HSP due to mitochondrial abnormality (including *SPG13* due to chaperonin 60 mutation and *SPG7* due to paraplegin mutation); (2) HSP due to axonal transport abnormality (including *SPG10* due to kinesin heavy chain mutation and possibly *SPG3A* due to atlastin mutation and *SPG4* due to spastin mutation; (3) HSP due to primary myelin disturbance (*SPG2* due to PLP mutation); and (4) HSP due to embryonic development of corticospinal tract neurons (*SPG1* due to L1CAM mutation). Whether these disparate primary biochemical disturbances converge into one or more common pathways remains to be determined. Each HSP gene discovery permits direct exploration of the molecular mechanisms that underlie HSP, insights that bring us one step closer to developing real treatment.

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Corresponding author and reprints: John K. Fink, MD, 5214 Cancer Geriatrics Center Bldg, Box 0940, 1500 E Medical Center Dr, Ann Arbor, MI 48109 (e-mail: jkfink@umich.edu).

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