The Hereditary Spastic Paraplegias

Nine Genes and Counting

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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.

Hereditary spastic paraplegia (HSP) is a syndromic designation encompassing more than 30 disorders in which the predominant feature is spastic gait. The HSP syndromes are classified clinically as uncomplicated (also known as pure or non-syndromic) 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, 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.

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.
Spasins

Mutations in the SPG4 gene (spastin protein) are responsible for approximately 40% of autosomal dominant HSP cases. 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. 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 frame-shift mutations resulted in the absence of immunologically detectable spastin.

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-
ification results in 75- and 80-kDa spastin isoforms.11 Char-
vin et al11 showed spastin was present in neurons, par-
ticularly in the brain, and also in anterior horn motor 
neurons, but not within glia. Spastin contains an ATPase 
associated with diverse cellular activities (AAA) do-
main.3 It also contains a nuclear localization signal,3 and 
very recent immunofluorescent studies indicate spastin 
is a nuclear protein. The intracellular location of spastin is 
controversial because previous studies indicated that spa-
tin was distributed within the cytoplasm.12

Emerging evidence suggests that spastin may inter-
act with microtubules. Azim et al13 showed that antitu-
bulin antibodies could precipitate spastin in vitro. More 
recently, Errico et al11 showed that a spastin fusion pro-
tein colocalized with microtubules in Cos-7 and HeLa 
cells transfected with wild-type and mutant SPG4 ex-
pression vectors. Findings that spastin may interact di-
rectly with microtubules support the hypothesis that dis-
turbances in axonal cytoskeleton or transport underlie 
some forms of HSP.15

Atlastin

Autosomal dominant HSP linked to the chromosome 14q 
SPG3A locus represents approximately 10% of domi-
nantly inherited HSP cases15 and is particularly preva-
ent among those autosomal dominant HSP kindreds in 
which each affected subject developed symptoms in child-
hood.16 Zhao et al17 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, at-
lastin. 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 hydrolysis17 and is structurally ho-
omologous to guanylate binding protein 1. The func-
tional 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 re-
cycling of synaptic vesicles. Dynamins are also involved 
in the maintenance and distribution of mitochondria25 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 de-
fective synaptic vesicle recycling leading to abnormal syn-
aptic structure and impaired neurotransmission, im-
paired 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 antero-
grade and retrograde directions. KIF5A gene mutation 
was recently identified in affected subjects with HSP linked 
to the SPG10 locus.27 Subjects with KIF5A mutation ex-
hibited 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 pro-
teins, prevented stimulation of the motor ATPase by mi-
crotubule 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 distur-
bance of axonal transport.28

Heat Shock Protein 60 or Chaperonin 60

Mutation in the mitochondrial protein heat shock pro-
tein 60, also known as chaperonin 60, causes SPG13-
linked autosomal dominant HSP. SPG13 HSP is an au-
tosomal dominant form of uncomplicated HSP mapped 
to chromosome 2q24-34. Recently, Hansen et al29 iden-
tified a mutation in heat shock protein 60 in affected 
subjects from an SPG13-linked HSP kindred. The mecha-
nism 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 per-
haps the most severe forms of dominantly inherited, un-
complicated HSP.30 Chai et al31 identified nonimprinted 
Prader-Willi/Angleman (NIPA) locus genes as candi-
date’s for SPG6. Rainier et al32 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 
kinding.32 The function of NIPA1 is unknown. It is widely 
expressed, particularly in the central nervous system. The 
presence of 9 alternating hydrophobic-hydrophilic do-
 mains suggests that NIPA1 encodes a membrane pro-
tein.32 This feature makes NIPA1 unique among HSP pro-
teins. 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 al33 discovered disease-specific mutations in 
SPG7 as the cause of chromosome 16q-linked autosomal 
recessive HSP. This is a rare form of autosomal recessive

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HSP with only a few reported families affected.\textsuperscript{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.\textsuperscript{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 mitochondrial dysplasia.\textsuperscript{33}

SPG7 knockout mice exhibit signs of HSP. Ferreirinha et al\textsuperscript{35} reported preliminary studies in homozygous SPG7/paraplegin knockout mice. These animals displayed impaired performance on a rotordod 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/chaferonin 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.\textsuperscript{3,36-38}

**Spartin**

Spartin mutations cause HSP associated with distal muscle wasting (SPG20 Troyer syndrome).\textsuperscript{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.\textsuperscript{40,41} In addition, some individuals with X-linked HSP linked to the SPG2 locus on Xq22 also have PLP mutations.\textsuperscript{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.\textsuperscript{44} Although there is correlation between some of these syndromes and specific L1CAM mutations,\textsuperscript{45} X-linked hydrocephalus, MASA syndrome, and X-linked spastic paraplegia have occurred in kindreds in which affected individuals had the same L1CAM mutation.\textsuperscript{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.\textsuperscript{47-49} Dahme et al\textsuperscript{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 not to 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 chaferonin 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.


11. Charvin D, Fonknechten N, Cifuentes-Diaz C, et al. Mutations in SPG4 are re-