

Hereditary Spastic Paraplegias

Authors: Doctors Enza Maria Valente¹ and Marco Seri²

Creation date: January 2003

Update: April 2004

Scientific Editor: Doctor Franco Taroni

¹Neurogenetics Istituto CSS Mendel, Viale Regina Margherita 261, 00198 Roma, Italy. e.valente@css-mendel.it

²Dipartimento di Medicina Interna, Cardioangiologia ed Epatologia, Università degli studi di Bologna, Laboratorio di Genetica Medica, Policlinico S.Orsola-Malpighi, Via Massarenti 9, 40138 Bologna, Italy. <mailto:marco.seri@unibo.it>

[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Definition](#)

[Classification](#)

[Differential diagnosis](#)

[Prevalence](#)

[Clinical description](#)

[Management including treatment](#)

[Diagnostic methods](#)

[Etiology](#)

[Genetic counseling](#)

[Antenatal diagnosis](#)

[References](#)

Abstract

Hereditary spastic paraplegias (HSP) comprise a genetically and clinically heterogeneous group of neurodegenerative disorders characterized by progressive spasticity and hyperreflexia of the lower limbs. Clinically, HSPs can be divided into two main groups: pure and complex forms. Pure HSPs are characterized by slowly progressive lower extremity spasticity and weakness, often associated with hypertonic urinary disturbances, mild reduction of lower extremity vibration sense, and, occasionally, of joint position sensation. Complex HSP forms are characterized by the presence of additional neurological or non-neurological features. Pure HSP is estimated to affect 9.6 individuals in 100.000. HSP may be inherited as an autosomal dominant, autosomal recessive or X-linked recessive trait, and multiple recessive and dominant forms exist. The majority of reported families (70-80%) displays autosomal dominant inheritance, while the remaining cases follow a recessive mode of transmission. To date, 24 different loci responsible for pure and complex HSP have been mapped. Despite the large and increasing number of HSP loci mapped, only 9 autosomal and 2 X-linked genes have been so far identified, and a clear genetic basis for most forms of HSP remains to be elucidated.

Keywords

Hereditary Spastic Paraplegia (HSP), SPG loci, Strümpell-Lorrain syndrome, pure and complex forms, genetic heterogeneity.

Disease name and synonyms

Hereditary spastic paraparesis
Hereditary spastic paraplegia
Familial spastic paraplegia
Strümpell-Lorrain syndrome

Definition

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of disorders characterized by slowly progressive spasticity and weakness of lower limbs, due to a

progressive axonal degeneration mainly evident at the distal ends of the corticospinal tracts. Mild loss of the distal ends of the dorsal column fibers and of anterior horn cells may occur.

Clinically, HSPs can be divided into two main groups: pure and complex, also referred to as uncomplicated and complicated forms, respectively. Pure HSPs are characterized by slowly progressive lower extremity spasticity and weakness, often associated with hypertonic urinary disturbances, mild reduction of lower extremity vibration sense, and, occasionally, of joint position sensation. Pes cavus is sometimes present, and scoliosis may develop in some cases. Pure HSP can be highly disabling but does not shorten life span. In complex HSPs, this clinical picture is associated with other neurological or non-neurological signs and symptoms, such as seizures, dementia, deafness, amyotrophy, extrapyramidal signs, peripheral neuropathy, in the absence of other co-existing diseases (Bundey 1992; Harding 1993; Reid 1997).

Classification

Genetically, HSPs are divided by mode of inheritance (autosomal dominant, autosomal recessive and X-linked) and sub-divided by chromosomal locus or causative gene (if already identified). All genetically defined HSPs are assigned the symbol "SPG" (spastic gait) followed by a progressive number. Twenty-four SPG symbols have been assigned so far, each one identifying a different locus/gene. Considering both a clinical and genetic classifications, five HSP groups are defined:

- autosomal dominant pure (SPG3; SPG4; SPG6; SPG8; SPG10; SPG12; SPG13; SPG19),
- autosomal dominant complex (SPG9; SPG17),
- autosomal recessive pure (SPG5; SPG11; SPG24),
- autosomal recessive complex (SPG14; SPG15; SPG20; SPG21; SPG23)
- X-linked complex (SPG1/L1CAM; SPG2/PLP1; SPG16).

SPG7, due to mutations in the "*paraplegin*" gene, is an autosomal recessive form that can present either with a pure or with a complex phenotype. SPG17, also called Silver Syndrome, is usually transmitted in an autosomal dominant fashion, but can occasionally be autosomal recessive.

Differential diagnosis

Several neurological conditions must be ruled out for establishing HSP diagnosis. The following is a list of some of the most important conditions to consider in the differential diagnosis of HSP:

Structural abnormalities of the brain or the spinal cord (due to trauma, tumors, malformations etc). These can be detected by a brain and spinal cord MRI, a CT scan or other appropriate neuroimaging techniques.

[Multiple sclerosis](#) (MS). In the first stages, this disorder may selectively involve the upper motor neurons or pyramidal tracts projecting to the lower limbs, therefore mimicking HSP. Although the clinical progression of MS is usually different, with a relapsing-remitting course, some patients may have a slowly progressive course. However, a brain and spinal cord MRI scan and laboratory testing of the cerebrospinal fluid will clarify the diagnosis.

Vitamin B12 deficiency can result in a neurological syndrome sharing some clinical features with HSP, such as leg spasticity and extensor plantar responses. The phenotype is usually complicated by sensory and motor neuropathy, with reduced tendon responses at ankles, megaloblastic anemia, gastrointestinal problems, mental retardation or encephalopathy in children, cognitive impairment in adults. Vitamin B12 levels can be assessed by measuring the serum vitamin levels and other specific metabolites, and spinal cord MRI shows typical lesions which mostly resolve after an 8 to 12 month-therapy.

[Dopa-responsive dystonia](#) has to be considered in children with progressive gait abnormalities of unknown etiology. However, the neurological examination will show a dystonic posture of lower limbs and/or parkinsonian signs instead of upper motor neuron signs, and a trial with small doses of Levodopa will lead to a massive improvement of symptoms.

[Amyotrophic lateral sclerosis](#) (ALS), [primary lateral sclerosis](#) (PLS) and infantile-onset ascending hereditary spastic paralysis (IAHSP) have to be considered in differential diagnosis, as they typically lead to an upper motor neuron degeneration. However, in ALS lower motor neuron signs are invariably present, and the disease is more rapidly progressive and mostly sporadic. PLS and IAHSP share with pure HSPs the selective involvement of upper motor neurons, but usually involve also upper extremities and bulbar muscles (speech and swallowing) as disease progresses, and there is no family history. Bladder function is also normal until late in disease.

Viral spastic paraplegia (*i.e.*, HTLV1 infection). Lower limbs spasticity can be a clinical manifestation of some viral infections of the central nervous system (CNS), and are usually part of a more complex neurological picture. These cases are usually sporadic, and a careful collection of personal history may help in

suspecting a particular viral infection and performing specific diagnostic tests.

Leukodystrophies, such as adrenomyeloneuropathy, metachromatic leukodystrophy, [Pelizaeus-Merzbacher](#) disease (etc.) can present with lower limb spasticity as part of a more complex neurological phenotype. Brain MRI will show the typical abnormalities of the white matter, which are absent in HSP. Specific laboratory and genetic testing are available for several leukodystrophies.

Prevalence

Pure HSP is estimated to affect 9.6 individuals in 100.000 (Polo *et al.* 1991).

Clinical description

In pure HSP, age of onset is widely variable, ranging from early childhood to late adulthood and the disease usually progresses slowly over the years, without exacerbations or remissions. Neurological examination shows bilateral lower limb weakness, which can be mild to severe, increased muscle tone, lower limb hyperreflexia and extensor plantar responses. In some cases, there is a decrease of joint position and vibration sense in the distal lower extremities, while other sensation modalities are normal. Strength and dexterity of the upper limbs are usually spared, although mild hyperreflexia and decreased vibration sense can be occasionally present. The bulbar district is always normal. Lower extremity paresthesias may occur.

Affected individuals experience progressive difficulty in walking and can eventually require canes, walkers or wheelchairs. Urinary symptoms are frequent and range from urinary urgency to incontinence. Most patients report that their symptoms (often referred to as "stiffness" and "rigidity" of lower limbs) are worsened by stress and anxiety.

Intra-familial phenotypic variability has been often described, especially in autosomal dominant forms. Among the eight autosomal dominant pure HSPs, the principal phenotypic difference is represented by the mean age of onset of symptoms, ranging from the first decade (as in SPG3, SPG10 and SPG12) to the fourth-fifth decade (as in SPG19). Other forms, such as SPG4, SPG8 and SPG13, are characterized by a much wider range of ages of onset, spanning several decades. Minor clinical differences concern the percentage of urinary disturbances, upper limb hyperreflexia, and the overall disability.

Other than family history, no clinical features can help distinguishing between autosomal dominant and autosomal recessive pure HSPs. One exception is SPG11, which is characterized by HSP and a thin corpus callosum in the vast

majority of families. In the single family so far described linked to SPG24, a peculiar feature was the very early onset at about 1 year of age in all affected individuals.

In complex HSP, the clinical picture is highly variable, depending on the accompanying neurological and non-neurological clinical symptoms. Among autosomal dominant complex HSPs, SPG9 is characterized by congenital bilateral cataracts, gastro-esophageal reflux with persistent vomiting and amyotrophy, while SPG17 presents with characteristic distal amyotrophy of hands and feet.

Among autosomal recessive complex forms, patients with SPG7 can have optic atrophy, bulbar involvement, cerebellar and cortical atrophy, or simply present with a pure HSP phenotype. Mild mental retardation, neuropsychological impairment, and a distal motor neuropathy with onset around the third-fourth decade, are features suggestive of SPG14, while SPG15 generates a more complex clinical presentation with lower limb spastic paraparesis associated with distal upper limbs weakness, pigmented maculopathy, dysarthria, mental retardation and progressive intellectual decline, mild ataxia and, occasionally, dystonia, epilepsy or psychosis. Cerebellar signs, distal amyotrophy, short stature and mild developmental delay with emotional lability and onset in early childhood are found in SPG20 patients. SPG21, or MAST syndrome, is characterized by spasticity of lower limbs and often of upper limbs as well, dementia and extrapyramidal signs. Onset is usually in the late teens or twenties with slow progression, but the disease may have a later onset in the third or even fourth decade of life. MRI shows thin corpus callosum, gray matter atrophy and white matter demyelination. Spastic paraplegia with pigmentary abnormalities are the peculiar signs of SPG23, also called Lison syndrome. This complex form is in fact characterized by patchy vitiligo, areas of skin hyperpigmentation and lentigines, premature graying of body hair. The skin abnormalities can be apparent at birth, while spasticity usually has an onset in childhood. Other inconstant features may include microcephaly, facial dysmorphisms such as thin face, micro- or retrognathia, mild cognitive impairment and mild peripheral neuropathy.

All X-linked HSPs are complex forms. SPG1 is characterized by spastic paraplegia plus mental retardation and adducted thumbs, and is allelic to several other conditions such as X-linked hydrocephalus, MASA syndrome (Mental retardation, Aphasia, Shuffling gait and Adducted thumbs) and CRASH syndrome (Corpus callosum hypoplasia, Retardation,

Adducted thumbs, Spastic paraparesis and Hydrocephalus). According to the [HUGO Gene Nomenclature Committee](#), the approved locus symbol has been recently changed to L1CAM. SPG2 can give rise to a phenotype ranging from a nearly pure HSP to Pelizaeus-Merzbacher disease, a severe condition characterized by nystagmus, hypotonia, cognitive impairment, severe spasticity and ataxia, with onset in early childhood and shortened life span. According to the [HUGO Gene Nomenclature Committee](#), the approved locus symbol has been recently changed to PLP1. SPG16 also has onset in early childhood and presents with facial hypotonia, strabismus and reduced vision, bowel dysfunction, skeletal abnormalities (maxillary hypoplasia, short thick distal phalanges), mental retardation, aphasia and restlessness.

Management including treatment

There is currently no "cure" for HSP. All treatments are symptomatic.

Physical therapy and/or a regular exercise and stretching program play an important role in treating HSP symptoms. While exercise or physical therapy do not prevent or reverse the damage to the nerve fibers, it will help HSP patients in maintaining mobility, retaining or improving muscle strength, minimizing atrophy of the muscles due to disuse, increasing endurance (and reducing fatigue), preventing spasms and cramps, maintaining or improving range of motion, and providing cardiovascular conditioning. Exercise also has a positive psychological effect, helping to reduce stress and to produce feelings of well being.

Anti-spasticity drugs may improve the results of physical therapy or exercise by reducing the spasticity and allowing the weak muscles to be targeted, especially in cases where spasticity is quite severe. A limitation to the use of anti-spasticity drugs is that leg spasticity helps in some cases to overcome the problem of muscle weakness. In these patients, anti-spastic drugs may sometimes have negative rather than positive effects on walking. Side effects such as excessive sleepiness and increased weakness can also be a problem. However, if their dosage and prescription are appropriate, the anti-spasticity drugs can reduce the pain associated with spasticity, improve mobility, and increase the effectiveness of physical therapy. Baclofen, Diazepam, Tizanidine, Dantrolene Sodium and Gabapentin are among the most frequently prescribed anti-spastic drugs. Botulinum Toxin injections can greatly improve spasticity in selected muscles, and it is advised to address specific problems (*i.e.* major gait difficulties due to equinovarus foot).

Other drugs can be effective in solving urinary problems. Among these, the most important are some anticholinergic drugs (Oxybutynin chloride, Tolterodine tartrate), which inhibit bladder contractions and delay or decrease the urge to void. The most common side effect is dry mouth, other side effects include headache, dry eyes, constipation and indigestion.

The benefit of vitamins, antioxidants, creatine and Coenzyme Q10 in treating HSP have not been demonstrated.

Diagnostic methods

Pure HSP is diagnosed on the basis of clinical, neurological examination (see "Clinical description"), family history and exclusion of other diagnoses (see "Differential diagnosis"), a very important criterion, as HSP is a diagnosis of exclusion in most cases.

Brain and spinal cord MRI are usually normal, even if a thinning of the spinal cord, especially in the thoracic area, has been observed in some patients. Motor evoked potentials (MEPs) are severely delayed or absent when recording from lower limbs, whereas they are generally normal in the upper limbs. MEPs can be very useful to confirm the diagnosis in mild cases or at early stages of the disease. Needle electromyography (EMG), peripheral sensory and motor neurography and somato-sensory evoked potential are usually normal.

In complex forms, as the clinical picture of pure HSP is associated with other neurological and non-neurological signs and symptoms, the diagnostic procedures will be chosen on the basis of the phenotype (*i.e.* EMG, sensory and motor nerve conduction velocities, fundus oculi examination, electroencephalography (EEG), skeletal X-ray, neuropsychological and cognitive testing, auditory test, etc).

Etiology

The genetic loci ascribed to the different HSP forms are given in the following tables:

Loci described for HSP X-linked recessive forms:

HSP form	Locus	MIM	References
SPG1/L1CAM	Xq28	312900	Kenrick <i>et al.</i> 1986
SPG2/PLP1	Xq22	312920	Keppen <i>et al.</i> 1987
SPG16	Xq11.2	300266	Steinmuller <i>et al.</i> 1997

Loci described for HSP autosomal dominant pure forms:

HSP form	Locus	MIM	References
SPG3	14q11.2-q24.3	182600	Hazan <i>et al.</i> 1993
SPG4	2p22	182601	Hazan <i>et al.</i> 1994 Hentati <i>et al.</i> 1994a
SPG6	15q11	600363	Fink <i>et al.</i> 1995
SPG8	8q23-q24	603563	Hedera <i>et al.</i> 1999 Reid <i>et al.</i> 1999b
SPG10	12q13	604187	Reid <i>et al.</i> 1999a
SPG12	19q13	604805	Reid <i>et al.</i> 2000
SPG13	2q24	605280	Fontaine <i>et al.</i> 2000
SPG19	9q33-q34	607152	Valente <i>et al.</i> 2002

Loci described for HSP autosomal recessive pure forms:

HSP form	Locus	MIM	References
SPG5	8p12-q13	270800	Hentati <i>et al.</i> 1994b
SPG7	16q24.3	602783	De Michele <i>et al.</i> 1998
SPG11	15q13-q15	604360	Martinez Murillo <i>et al.</i> 1999
SPG24	13q14	607584	Hodgkinson <i>et al.</i> 2002

Loci described for HSP autosomal dominant complex forms:

HSP form	Locus	MIM	References
SPG9	10q23.3-q24.2	601162	Seri <i>et al.</i> 1999
SPG17	11q12-q14	270685	Patel <i>et al.</i> 2001

Loci described for HSP autosomal recessive complex forms:

HSP form	Locus	MIM	References
SPG14	3q27-q28	605229	Vazza <i>et al.</i> 2000
SPG15	14q22-q24	606859	Hughes <i>et al.</i> 2001
SPG20	13q12.3	275900	Patel <i>et al.</i> 2002
SPG21	15q21-q22	248900	Simpson <i>et al.</i> 2003
SPG23	1q24-q32	270750	Blumen <i>et al.</i> 2003

Despite the large and increasing number of HSP loci mapped, only 9 autosomal and 2 X-linked

genes have been identified to date (Crosby and Proukakis 2002; Simpson *et al.* 2003; Rainier *et al.* 2003; Windpassinger *et al.* 2004), and a clear genetic basis for most HSP forms remains elusive.

Mutations in a gene encoding for paraplegin, a protein with mitochondrial localization and a chaperon-like function, have been found in both pure and complex forms of autosomal recessive HSP linked to SPG7 (Casari *et al.* 1998). This protein contains an AAA (ATPases associated with diverse cellular activities) domain, which is common to a group of molecules involved in protein degradation and trafficking, and organelle biogenesis. In particular, mitochondrial AAA proteins show chaperone-like activity ensuring the specificity of proteolysis and the activation of respiratory chain complexes (Leonhard *et al.* 1999). Muscle biopsies of SPG7 patients showing typical alteration of mitochondrial disorders (Casari *et al.* 1998) and preliminary reports of electron microscopy studies in mice lacking paraplegin (Ferreirinha *et al.* 2004) show that the paraplegin protein plays a role in mitochondrial function.

A mitochondrial involvement has also been demonstrated in a pure autosomal dominant form of HSP (SPG13) by the identification of a mutation in the heat shock protein 60 (Hsp60), a mitochondrial chaperone, in affected individuals (Hansen *et al.* 2002).

The recent identification of new HSP genes suggests that other different pathogenetic mechanisms could be responsible for HSP. In particular, aberrant intracellular-trafficking dynamics has been postulated to represent a common process for the specific pattern of neurodegeneration observed in HSP phenotypes (Crosby and Proukakis 2002).

The gene responsible for the autosomal dominant SPG4-linked HSP encodes a protein named spastin, which is a member of the AAA protein family (Hazan *et al.* 1999). A recent study has shown that wild-type spastin interacts transiently with microtubules and probably is involved in microtubules dynamics (Errico *et al.* 2002) since its overexpression results in a microtubule-disassembly phenotype. In contrast, spastin mutants are able to bind constitutively to microtubules and recent data indicate the N-terminal region of spastin as responsible for microtubule binding (Errico *et al.* 2002). No functional domains have been identified in this portion with the exception of an ESP domain localized close to the N-terminal region of spastin.

Interestingly, an ESP domain is also present in the N-terminal portion of the spartin protein, which is responsible for a complex autosomal recessive form of HSP (SPG20; Troyer

syndrome) (Patel *et al.* 2002). This domain, present in endosomal trafficking molecules, indicates that altered intracellular protein trafficking (Crosby and Proukakis 2002) could play a pivotal role in the pathogenesis of different HSP phenotypes.

Additional evidence that defective trafficking could be responsible for some forms of HSP is provided by the identification of mutations in the *atlastin* gene in a pure autosomal dominant HSP form (SPG3) (Zhao 2001). *Atlastin* is a GTPase gene sharing no homology with *spartin* or *spastin*. In contrast, its gene product shows structural homology with members of the dynamin family. Dynamins play essential roles in a wide variety of vesicle trafficking events that are important for the action of neurotrophic factors and during neurotransmission (McNiven *et al.* 2000).

The identification of the *kinesin heavy chain* gene (*KIF5A* gene) as responsible for a pure autosomal dominant HSP form (SPG10) (Reid *et al.* 2002) provides new support for defective trafficking in some HSP forms. *KIF5A* is part of a heterotetrameric motor protein complex involved in the transport of cargoes along microtubules in an anterograde direction (Goldstein and Yang 2000). Several studies analysing *kinesin* mutants have clearly demonstrated a role in defective microtubule-mediated trafficking, leading to axonal degeneration in the peripheral as well as in the CNS (Crosby and Proukakis 2002).

The gene responsible for MAST syndrome (SPG21) has recently been identified and encodes ACP33 (Acidic Cluster Protein 33Kd), also called Maspardin (MAst syndrome, Spastic Paraplegia, Autosomal Recessive, with Dementia). Although the function of Maspardin is still unclear, preliminary functional studies suggest a role of this protein in vesicle-mediated trafficking and protein sorting within the cytoplasm (Simpson *et al.* 2003).

A mutation in a novel gene *NIPA1* (nonimprinted in Prader-Willi/Angelman loci 1) has been recently described in the original family linked to SPG6 on chromosome 15q11-q13 and in an additional unrelated kindred with autosomal dominant HSP. *NIPA1* is highly expressed in neuronal tissues and although the function of the *NIPA1* protein is not known, the clear prediction based on hydrophobicity analysis of an integral membrane-associated protein (Chai *et al.* 2003) suggests that this protein functions as a membrane transporter or receptor (Rainier *et al.* 2003).

The gene responsible for Silver syndrome, the rare autosomal dominant form of hereditary spastic paraparesis complicated by amyotrophy of the hands and occasionally also of the lower

limbs (SPG17), has been recently identified (Windpassinger *et al.* 2004). Heterozygous missense mutations in the *BSC2* gene have been described in patients affected with Silver syndrome as well as in patients with autosomal dominant distal hereditary motor neuropathy (dHMN). Null mutations in the *BSC2* gene were previously reported to cause autosomal recessive Berardinelli-Seip congenital lipodystrophy type 2, a disorder clinically unrelated to dHMN and Silver syndrome. The *BSC2* gene encodes the protein seipin, an integral membrane protein of the endoplasmic reticulum (Windpassinger *et al.* 2004). The missense mutations identified in Silver syndrome and in dHMN patients affect glycosylation of seipin and result in aggregate formation leading to neurodegeneration (Windpassinger *et al.* 2004).

The two SPG1 and SPG2 X-linked forms have been shown to be caused by mutations in the genes for L1 cell adhesion molecule (*L1CAM*) and the proteolipidic protein (*PLP1*), respectively (Jouet *et al.* 1994; Saugier-Verber *et al.* 1994). They represent the first genes demonstrated to be responsible for HSP phenotypes. *L1CAM* is a transmembrane glycoprotein with extracellular immunoglobulin and fibronectin type III repeat (Casari and Rugarli, 2001). It is expressed during development on the surface of long axons and growth cones, including those of the corticospinal tract. Furthermore, *L1* mediates cell adhesion and neurite growth. Neuropathological studies and the analysis of transgenic animals have suggested that this molecule is required for normal development of corticospinal tract (Casari and Rugarli, 2001). Conversely, the *PLP1* gene encodes one of the major components of myelin and mutations in this gene are also responsible for Pelizaeus-Merzbacher disease, a genetic disorder characterized by significant hypomyelination of the CNS with a reduced number of mature oligodendrocytes. An important step in understanding the pathogenesis of HSP caused by *PLP1* mutations has been the generation of the knockout animals that do not express any PLP. Surprisingly these animals have normal CNS function but assemble compact myelin sheaths and subsequently develop widespread axonal swelling and degeneration, most likely secondary to impaired axonal transport (Casari and Rugarli, 2001).

Genetic counseling

Many HSPs cases are referred annually to the outpatient Genetic Clinics for genetic counseling. Due to the wide heterogeneity, the genetic classification of the different HSP patients remains difficult. As mentioned in the "clinical

description" section, the age of onset in some patients as well as the presence of additional features specific for several complex forms could help in the classification of affected individuals and families.

In most familial cases, segregation analysis is sufficient to establish the pattern of inheritance and to calculate an accurate risk of recurrence. Sometimes, in such pedigrees linkage analysis could be useful in order to confirm the segregation of the disease phenotype with a previously mapped HSP locus. Sporadic cases represent the majority of HSP patients in genetic counseling. They could represent recessive cases with a risk of recurrence for their parents of 25%, but without risk with an extremely low risk of recurrence for their children. Conversely, they could correspond to autosomal dominant cases due to a *de novo* mutation in a HSP gene. In this case, their parents do not show specific risks for other pregnancies but they do have a risk of 50% to transmit the disorder. Sporadic HSP male patients could be due to mutations in X-linked HSP genes suggesting that their mothers could be carriers with a risk of 50% to have an additional affected son. Finally, similar to other neurodegenerative disorders such as Parkinson disease, amyotrophic lateral sclerosis, or Alzheimer's disease, sporadic HSP cases may represent multifactorial/multigenic phenocopies of the monogenic diseases. In such cases, recurrence risk is expected to be extremely low.

The identification of a mutation in sporadic patients by direct sequencing of the identified HSP genes could clarify the pattern of inheritance and the risk of recurrence.

Antenatal diagnosis

Due to the late onset of the disorder and to the wide clinical and genetic heterogeneity, prenatal diagnosis of HSP cases has to be discussed in specific cases.

References

Blumen SC, Bevan S, Abu-Mouch S, Negus D, Kahana M, Inzelberg R *et al* (2003) A locus for complicated hereditary spastic paraplegia maps to chromosome 1q24-q32. *Ann Neurol* 54:796-803

Bunday S (ed) (1992) *Genetics and neurology*. Edinburgh: Churchill Livingstone

Casari G, De Fusco M, Ciarmatori S, Zeviani M, Mora M, Fernandez P, De Michele G *et al* (1998) Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. *Cell* 93:973-983

Casari G, Rugarli E (2001) Molecular basis of inherited spastic paraplegias. *Curr Opin Genet Dev* 11:336-342

Chai JH, Locke DP, Grealley JM, Knoll JH, Ohta T, Dunai J, Yavor A, Eichler EE, Nicholls RD. (2003) Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. *Am J Hum Genet*. 73:898-925

Crosby AH, Proukakis C (2002) Is the Transportation Highway the Right Road for Hereditary Spastic Paraplegia? *Am J Hum Genet* 71:1009-1016.

De Michele G, De Fusco M, Cavalcanti F, Filla A, Marconi R, Volpe G, Monticelli A *et al* (1998) A new locus for autosomal recessive hereditary spastic paraplegia maps to chromosome 16q24.3. *Am J Hum Genet* 63:135-139

Errico A, Ballabio A, Rugarli EI (2002) Spastin, the protein mutated in autosomal dominant hereditary spastic paraplegia, is involved in microtubule dynamics. *Hum Mol Genet* 11:153-163

Ferreirinha F, Quattrini A, Pirozzi M, Valsecchi V, dina G, Broccoli V, Auricchio A, Piemonte F, Tozzi G, Gaeta L, Casari G, Ballabio A, Rugarli EI (2004) Axonal degeneration in paraplegin-deficient mice is associated with abnormal mitochondria and impairment of axonal transport.

J Clin Invest 113:231-242

Fink JK, Wu CB, Jones SM, Sharp GB, Lange BM, Lesicki A, Reinglass T *et al* (1995) Autosomal dominant familial spastic paraplegia: tight linkage to chromosome 15q. *Am J Hum Genet* 56:188-192

Fontaine B, Davoine CS, Durr A, Paternotte C, Feki I, Weissenbach J, Hazan J *et al* (2000) A new locus for autosomal dominant pure spastic paraplegia, on chromosome 2q24-q34. *Am J Hum Genet* 66:702-707

Goldstein LSB, Yang Z (2000) Microtubule-based transport systems in neurons: the role of kinesins and dynamins. *Annu Rev Neurosci* 23:39-71

Hansen JJ, Durr A, Cournu-Rebeix I, Georgopoulos C, Ang D, Nielsen MN, Davoine CS *et al*. (2002) Hereditary spastic paraplegia SPG13 is associated with a mutation in the gene encoding the mitochondrial chaperonin Hsp60. *Am J Hum Genet* 70:1328-1332

Harding AE (1993) Hereditary spastic paraplegias. *Semin Neurol* 13:333-336

Hazan J, Lamy C, Melki J, Munnich A, de Recondo J, Weissenbach J (1993) Autosomal dominant familial spastic paraplegia is genetically heterogeneous and one locus maps to chromosome 14q. *Nature Genet* 5:163-167

- Hazan J**, Fontaine B, Bruyn RPM, Lamy C, van Deutekom JCT, Rime CS, Dürr A *et al* (1994) Linkage of a new locus for autosomal dominant familial spastic paraplegia to chromosome 2p21-p24. *Hum Mol Genet* 3:1569-1573
- Hazan J**, Fonknechten N, Mavel D, Paternotte C, Samson D, Artiguenave F, Davoine CS *et al* (1999) Spastin, a new AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. *Nature Genet* 23:296-303
- Hedera P**, Rainier S, Alvarado D, Zhao X, Williamson J, Otterud B, Leppert M, Fink JK (1999) Novel Locus for Autosomal Dominant Hereditary Spastic Paraplegia on Chromosome 8q. *Am J Hum Genet* 64:563-569
- Hentati A**, Pericak-Vance MA, Lennon F, Wasserman B, Hentati F, Juneja T, Angrist MH *et al* (1994a) Linkage of a locus for autosomal dominant familial spastic paraplegia to chromosome 2p markers. *Hum Mol Genet* 3:1867-1871
- Hentati A**, Pericak-Vance MA, Hung WY, Belal S, Laing N, Boustany RM, Hentati F *et al* (1994b) Linkage of "pure" autosomal recessive familial spastic paraplegia to chromosome 8 markers and evidence of genetic locus heterogeneity. *Hum Mol Genet* 3:1263-1267
- Hodgkinson, C. A.; Bohlega, S.; Abu-Amero, S. N.; Cupler, E.; Kambouris, M.; Meyer, B. F.; Bharucha, V. A. (2002) A novel form of autosomal recessive pure hereditary spastic paraplegia maps to chromosome 13q14 *Neurology* 59: 1905-1909
- Hughes CA**, Byrne PC, Webb S, McMonagle P, Patterson V, Hutchinson M, Parfrey NA (2001) SPG15, a new locus for autosomal recessive complicated HSP on chromosome 14q. *Neurology* 56:1230-1233
- Jouet M**, Rosenthal A, Armstrong G, MacFarlane J, Stevenson R, Paterson J, Metzenberg A *et al* (1994) X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. *Nature Genet* 7:402-407
- Kenwrick S**, Ionasescu V, Ionasescu G, Searby C, King A, Dubowitz M, Davies KE (1986) Linkage studies of X-linked recessive spastic paraplegia using DNA probes. *Hum Genet* 73:264-266
- Keppen LD**, Leppert MF, O'Connell P, Nakamura Y, Stauffer D, Lathrop M, Lalouel JM *et al* (1987) Etiological heterogeneity in X-linked spastic paraplegia. *Am J Hum Genet* 41:933-943
- Leonhard K**, Stiegler A, Neupert W, Langer T (1999) Chaperone-like activity of the AAA domain of the yeast Yme1 AAA protease. *Nature* 398:348-351.
- Lison M**, Kornbrut B, Feinstein A, Hiss Y, Boichis H, Goodman RM (1981) Progressive spastic paraparesis, vitiligo, premature graying, and distinct facial appearance: a new genetic syndrome in 3 sibs. *Am J Med Genet* 9:351-357
- Martinez Murillo F**, Kobayashi H, Pegoraro E, Galluzzi G, Creel G, Mariani C, Farina E *et al* (1999) Genetic localization of a new locus for recessive familial spastic paraparesis to 15q13-q15. *Neurology* 53:50-56
- McNiven MA**, Cao H, Pitts KR, Yoon Y (2000) The dynamin family of mechanoenzymes: pinching in new places. *Trends Biochem Sci* 25:115-120
- Patel H**, Hart PE, Warner TT, Houlston RS, Patton MA, Jeffery S, Crosby AH (2001) The Silver syndrome variant of hereditary spastic paraplegia maps to chromosome 11q12-q14, with evidence for genetic heterogeneity within this subtype. *Am J Hum Genet* 69:209-215
- Patel H**, Cross H, Proukakis C, Hershberger R, Bork P, Ciccarelli FD, Patton MA *et al* (2002) SPG20 is mutated in Troyer syndrome, an hereditary spastic paraplegia. *Nature Genet* 31:347-348
- Polo JM**, Calleja J, Combarros O, Berciano J (1991) Hereditary ataxias and paraplegias in Cantabria, Spain. An epidemiological and clinical study. *Brain* 114 (Pt 2):855-66
- Rainier, S.**; Chai, J.-H.; Tokarz, D.; Nicholls, R. D.; Fink, J. K. (2003) NIPA1 gene mutations cause autosomal dominant hereditary spastic paraplegia (SPG6). *Am. J. Hum. Genet.* 73: 967-971
- Reid E** (1997) Pure hereditary spastic paraplegia. *J Med Genet* 34:499-503
- Reid E**, Dearlove AM, Rhodes M, Rubinsztein DC (1999a) A new locus for autosomal dominant "pure" hereditary spastic paraplegia mapping to chromosome 12q13, and evidence for further genetic heterogeneity. *Am J Hum Genet* 65:757-763
- Reid E**, Dearlove AM, Whiteford ML, Rhodes M, Rubinsztein DC (1999b) Autosomal dominant spastic paraplegia: refined SPG8 locus and further genetic heterogeneity. *Neurology* 53:1844-1849
- Reid E**, Dearlove AM, Osborn O, Rogers MT, Rubinsztein DC (2000) A locus for autosomal dominant "pure" hereditary spastic paraplegia maps to chromosome 19q13. *Am J Hum Genet* 66:728-732
- Reid E**, Kloos M, Ashley-Koch A, Hughes L, Bevan S, Svenson IK, Graham FL *et al* (2002) A Kinesin Heavy Chain (KIF5A) mutation in Hereditary Spastic Paraplegia (SPG10). *Am J Hum Genet* 71:1189-1194
- Saugier-veber P**, Munnich A, Bonneau D, Rozet J-M, Le Merrer M, Gil R, Boespflug-Tanguy O (1994) X-linked spastic paraplegia and Pelizaeus-Merzbacher disease are allelic disorders at the proteolipid protein locus. *Nature Genet* 6:257-262

Seri M, Cusano R, Forabosco P, Cinti R, Caroli F, Picco P, Bini R *et al* (1999) Genetic mapping to 10q23.3-q24.2, in a large Italian pedigree, of a new syndrome showing bilateral cataracts, gastroesophageal reflux and spastic paraparesis with amyotrophy. *Am J Hum Genet* 64:586-593

Simpson MA, Cross H, Proukakis C, Pryde A, Hershberger R, Chatonnet A *et al* (2003) Maspardin is mutated in Mast syndrome, a complicated form of Hereditary Spastic Paraplegia associated with dementia. *Am J Hum Genet* 73:1147-1156

Steinmuller R, Lantigua-Cruz A, Garcia-Garcia R, Kostrzewa M, Steinberger D, Muller U (1997) Evidence of a third locus in X-linked recessive spastic paraplegia. *Hum Genet* 100:287-289

Valente EM, Brancati F, Caputo V, Bertini E, Patrono C, Costanti D, Dallapiccola B (2002) Novel locus for autosomal dominant pure hereditary spastic paraplegia (SPG19) maps to chromosome 9q33-q34. *Ann Neurol* 51:681-685

Vazza G, Zortea M, Boaretto F, Micaglio GF, Sartori V, Mostacciolo ML (2000) A new locus for autosomal recessive spastic paraplegia associated with mental retardation and distal motor neuropathy, SPG14, maps to chromosome 3q27-q28. *Am J Hum Genet* 67:504-509

Windpassinger C, Auer-Grumbach A, Irobi J, Patel H, Petek E, Horl G *et al* (2004) Heterozygous missense mutations in BSCL2 are associated with distal hereditary motor neuropathy and Silver syndrome. *Nature Genet* 36:271-276

Zhao X, Alvarado D, Rainier S, Lemons R, Hedera P, Weber CH, Tükel T, Apak M, Heiman-Patterson T, Ming L, Bui M, Fink J K (2001) Mutations in a newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. *Nature Genet* 29:326-331