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Hereditary Spastic Paraplegia Overview

Synonyms: Hereditary Spastic Paraparesis, Strumpell-Lorrain Syndrome

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding hereditary spastic paraplegia. The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of hereditary spastic paraplegia and recommended treatment.

Goal 2

Review the causes of hereditary spastic paraplegia.

Goal 3

Consider the differential diagnosis of hereditary spastic paraplegia.

Goal 4

Provide an evaluation strategy to identify the genetic cause of hereditary spastic paraplegia in a proband.

Goal 5

Inform genetic counseling of family members of a proband with hereditary spastic paraplegia.

1. Clinical Characteristics and Recommended Treatment: Hereditary Spastic Paraplegia

The predominant signs and symptoms of hereditary spastic paraplegia (HSP) are lower-extremity weakness and spasticity.

Neurologic examination. Individuals with HSP demonstrate the following:

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- Bilateral lower-extremity spasticity (maximal in hamstrings, quadriceps, adductors, and gastrocnemius-soleus muscles) and weakness (maximal in the iliopsoas, hamstring, and tibialis anterior muscles). Spasticity and weakness are variable. Some individuals have spasticity and no demonstrable weakness, whereas others have spasticity and weakness in approximately the same proportions.
- Lower-extremity hyperreflexia and extensor plantar responses
- Often, mildly impaired vibration sensation in the distal lower extremities

Symptom onset

- **Early onset.** When symptoms begin in very early childhood, they may be non-progressive and resemble spastic diplegic cerebral palsy.
- **Later onset.** When symptoms begin in later childhood or after they usually progress slowly and steadily. After a number of years, it is not usual for individuals with progressively worsening gait to experience a "functional plateau" (i.e., the rate of further worsening of gait impairment is similar to that attributable to age).

Classification. HSP is classified clinically as "uncomplicated" (nonsyndromic) or "complicated" (syndromic).

- **Uncomplicated (or "pure") HSP** is characterized by neurologic impairment limited to progressive lower-extremity spastic weakness, hypertonic urinary bladder disturbance, and mild diminution of lower-extremity vibration sensation [Harding 1983]. Individuals with uncomplicated HSP experience the following:
  - Difficulty walking (may either be non-progressive or worsen insidiously)
  - Often, the need for canes, walkers, or wheelchairs
  - Possible urinary urgency and lower-extremity paresthesias
  - Typically, normal strength and dexterity of the upper extremities
  - No involvement of speech, chewing, or swallowing

  Though symptoms may be disabling, life span is not shortened.

- **Complicated HSP** is characterized by the impairments present in uncomplicated HSP **plus** other system involvement or other neurologic findings including any of the following:*
  - Ataxia
  - Seizures
  - Intellectual disability
  - Dementia
  - Muscle atrophy
  - Extrapyramidal disturbance
  - Peripheral neuropathy

  * In the absence of other causes for these additional features

Treatment of Manifestations

At present, there is no specific treatment to prevent or reverse nerve degeneration in HSP. Treatments are directed at reducing symptoms and improving balance, strength, and agility. Individuals should be evaluated periodically (annually or as needed) by a neurologist and physiatrist to assess progression and develop treatment strategies to maximize walking ability and reduce symptoms.

Current recommendations:

- Daily regimen of physical therapy directed toward improving cardiovascular fitness, maintaining and improving muscle strength and gait, and reducing spasticity

- Occupational therapy, assistive walking devices, and ankle-foot orthotics as needed
- Drugs to reduce muscle spasticity (e.g., Lioresal® [oral or intrathecal], tizanidine, dantrolene, botulinum A and B toxin injections [Botox®, Dysport, Xeomin, or Myoblock]) and urinary urgency (e.g., oxybutynin, solifenacin, mirabegron, or intrabladder injections with Botox®)

2. Causes of Hereditary Spastic Paraplegia

Genetic types of hereditary spastic paraplegia (HSP). To date, more than 80 genetic types of HSP have been defined by genetic linkage analysis and identification of HSP-related gene variants. In the past, genetic loci for HSP were designated SPG (for "*sp*astic paraple*g*ia") and numbered in order of their discovery. With the identification of the causative genes at those loci, reference by clinicians and clinical labs to a specific genetic type of HSP has moved to the name of the gene rather than the locus designation. Autosomal dominant, autosomal recessive, X-linked, and maternally inherited (mitochondrial) forms of HSP have been identified.

Autosomal dominant HSP is the most common type of HSP, found in 75%-80% of affected individuals.

- SPG4, caused by a pathogenic variant in *SPAST*, is the most common type, accounting for approximately 40% of all autosomal dominant HSP.
- SPG3A, caused by a pathogenic variant in *ATL1*, is the second most common type of autosomal dominant HSP, accounting for approximately 10%-15% of all autosomal dominant HSP. SPG3A is the main cause of autosomal dominant HSP with early onset (occurs in >75% of individuals in this category).
- SPG30 (caused by a pathogenic variant in *KIF1A*) and SPG31 (caused by a pathogenic variant in *REEP1*) are both relatively common, each accounting for about 5% of all autosomal dominant HSP.
- Other types of autosomal dominant HSP with a predominantly adult onset are relatively rare and most of them account for 1% or less of all autosomal dominant HSP.

Autosomal recessive HSP is very heterogeneous, with an ever-growing list of newly identified genes. Many new causes of autosomal recessive HSP are very rare and may be limited to a single family or even a single individual. The frequency is increased in populations with a higher degree of consanguinity. AR HSP is found in an estimated 25%-30% of all individuals with HSP.

Most common types of autosomal recessive HSP are encountered in the general population:

- SPG5A, caused by pathogenic variants in *CYP7B1*, accounts for 7.3% of all autosomal recessive HSP and 3% of apparently sporadic pure spastic paraplegia.
- SPG7, caused by pathogenic variants in *SPG7*, may account for approximately 5% of all autosomal recessive HSP.
- SPG11, caused by pathogenic variants in *SPG11*, accounts for 3%-5% of all autosomal recessive HSP but is found in 75% of individuals with all types of HSP who have radiologic signs of thin or absent corpus callosum.

X-linked HSP and mitochondrial HSP are the rarest genetic forms of HSP, accounting for fewer than 1%-2% of all individuals affected with HSP.

Other. Several types of HSP (e.g., those associated with pathogenic variants in *ATL1* [Khan et al 2014], *SPG7* [McDermott et al 2001], and *ALDH18A1* [Coutelier et al 2015]) may be inherited as either autosomal recessive or autosomal dominant disorders.

Table 1. Hereditary Spastic Paraplegia: Genes and Distinguishing Clinical Features – Autosomal Dominant Inheritance

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
ADAR	Not assigned	Uncomplicated	Early childhood	Abnormal pattern of interferon expression determined by reverse transcription PCR assay	Reported in a single Hispanic individual		Crow et al [2014]
ALDH18A1	SPG9A	Complicated	Adolescence to adulthood (1 subject w/infantile onset)	• Cataracts • Gastroesophageal reflux • Motor neuronopathy Variably present: • Dysarthria • Ataxia • Cognitive impairment	• Rare • Allelic w/AR HSP (SPG9B)	OMIM 601162	Coutelier et al [2015]
ATAD3A	Not assigned	Complicated	Early onset	• Amyotrophy • Hyperkinetic movements • May be confused w/hyperkinetic cerebral palsy	Rare		Cooper et al [2017]
ATL1	SPG3A	Uncomplicated	Infantile to childhood (rarely adult onset)	• Progression may be minimal w/ static course. • May present as spastic diplegic cerebral palsy • Complicated phenotype w/ peripheral neuropathy or autonomic failure reported	• 80% of early-onset AD HSP • 10%-15% of all AD HSP	Spastic Paraplegia 3A	Zhao et al [2001], Namekawa et al [2006], Rainier et al [2006], Ivanova et al [2007]
BICD2	Not assigned	Complicated	Childhood or adult	• Infantile onset assoc w/SMA w/ variable upper motor signs & contractures • Adult onset assoc w/mild amyotrophy	Rare		Oates et al [2013]

Table 1. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
BSCL2 [2]	SPG17	Complicated	Adulthood	• Distal amyotrophy affecting hands & feet • Motor neuropathy • Can be indistinguishable from ALS	Rare	*BSCL2*-Related Neurologic Disorders/ Seipinopathy	Windpassinger et al [2004], Musacchio et al [2017]
CPT1C	SPG73	Uncomplicated	Early adulthood	Foot deformity may be present.	Single family	OMIM 616282	Rinaldi et al [2015]
DNM2 [3]	Not assigned	Complicated	Before age 20 yrs	• Axonal polyneuropathy may be present. • Mild distal amyotrophy in feet	Single family		Sambuughin et al [2015]
ERLIN2	SPG18 [4]	Uncomplicated	Juvenile to adulthood	None	• Single family • Most pathogenic variants assoc w/AR HSP (See Table 2.)		Rydning et al [2018]
HSPD1	SPG13	Uncomplicated	Adulthood	Mild distal amyotrophy	Rare	OMIM 605280	Hansen et al [2002]
KIF1A	SPG30	Uncomplicated (for AD inheritance)	Juvenile to adulthood	• Some individuals have mild ID. • Optic nerve atrophy, epilepsy can be rarely seen in AD SPG30.	5%-6% of all AD HSP	OMIM 610357	Roda et al [2017], Pennings et al [2020]
KIF5A [4]	SPG10	Complicated	Juvenile or adulthood	• Polyneuropathy • Pes cavus	• 1%-2% of all AD HSP • 5%-8% of all complicated AD HSP	OMIM 604187	Reid et al [2002], Blair et al [2006], Liu et al [2014]

Table 1. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
NIPA1	SPG6	Uncomplicated	Adulthood (infantile onset rare)	• Severe weakness & spasticity • Rapidly progressive • Rarely, complicated by epilepsy or variable peripheral neuropathy	Rare (~1% of AD HSP)	OMIM 600363	Rainier et al [2003], Du et al [2011], Svenstrup et al [2011], Hedera [2013]
ATP2B4 (*PMCA4*)	Not assigned	Uncomplicated	Adulthood	None	Single family		Li et al [2014]
REEP1	SPG31	Uncomplicated	Variable from 2nd to 7th decades	Mild amyotrophy variably present.	Common, 4%-6% of all AD HSP	OMIM 610250	Züchner et al [2006], Hewamadduma et al [2009]
REEP2	SPG72	Uncomplicated	Very early, average age 4 yrs	• Musculoskeletal problems • Mild postural tremor	• Rare • Inheritance can be dominant or recessive	OMIM 615625	Esteves et al [2014]
RTN2	SPG12	Uncomplicated	Before age 20 yrs	None	5% of early-onset AD HSP but overall rare	OMIM 604805	Montenegro et al [2012]
SLC33A1	SPG42	Uncomplicated	Early adulthood	• Slowly progressive • Mild pes cavus	Single family known	OMIM 612539	Lin et al [2008]
SPAST	SPG4	Uncomplicated	Variable from infancy to 7th decade	• Cognitive decline & dementia common • Distal amyotrophy variably present • Complicated phenotype w/ ataxia variably present	40% of AD HSP	Spastic Paraplegia 4	Hazan et al [1999], Fonknechten et al [2000], Nielsen et al [2004], Murphy et al [2009]
SPG7	SPG7	Uncomplicated or complicated	Juvenile or adulthood	• Dysarthria • Ataxia • Optic atrophy • Supranuclear palsy • Mitochondrial abnormalities on skeletal muscle biopsy	AD inheritance suggested for some pathogenic variants, but overall this is rare	Spastic Paraplegia 7	McDermott et al [2001]

Table 1. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
WASHC5	SPG8	Uncomplicated	Adulthood (rare infantile onset reported)	Severe motor deficit in some individuals	Rare (~1% of AD HSP)	Spastic Paraplegia 8	Hedera et al [1999], Valdmanis et al [2007]
TUBB4A [5]	Not assigned	Complicated	Juvenile	• Cerebellar ataxia • MRI evidence of hypomyelination	Rare		Kancheva et al [2015]
ZFYVE27	SPG33	Uncomplicated	Adulthood	Mild pes cavus	Single family known	OMIM 610244	Mannan et al [2006]

AD = autosomal dominant; AR = autosomal recessive; ALS = amyotrophic lateral sclerosis; CMT = Charcot-Marie-Tooth neuropathy; DI-CMT = dominant intermediate Charcot-Marie-Tooth neuropathy; HMN = hereditary motor neuropathy; HSP = hereditary spastic paraplegia; ID = intelectual disability; SMA = spinal muscular atrophy

1. Genes are listed alphabetically.

2. Allelic with distal hereditary motor neuropathy type V (dHMN-V) and variants of Charcot-Marie-Tooth disease type 2

3. Allelic with CMT2M; DI-CMTB, centronuclear myopathy; & lethal congenital contractures syndrome type 5

4. Allelic with Charcot-Marie-Tooth disease axonal CMT2A and ALS25 (susceptibility to ALS)

5. Allelic with hypomyelinating leukodystrophy type 6 and autosomal dominant dystonia type 4

Table 2. Hereditary Spastic Paraplegia: Genes and Distinguishing Clinical Features – Autosomal Recessive Inheritance

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
SPG21 (*ACP33*)	SPG21	Complicated	Childhood	• Ataxia • Adult-onset dementia & parkinsonism • Polyneuropathy • Akinetic mutism seen in advanced cases	• Rare, first described in Old Order Amish population (later identified in various ethnic groups) • Also known as Mast syndrome	OMIM 248900	Cross & McKusick [1967a], Simpson et al [2003], Ishiura et al [2014]
ALDH18A1	SPG9B	Complicated	Adolescence to adulthood (one subject w/ infantile onset)	• Cataracts • Gastroesophageal reflux • Motor neuronopathy Variably present: • Dysarthria • Ataxia • Cognitive impairment	• Rare • Allelic w/AD HSP (SPG9A)	OMIM 616586	Coutelier et al [2015]
ALDH3A2	Not assigned	Complicated	Childhood	• Congenital ichthyosis • Macular dystrophy • Leukodystrophy • Seizures in ~40% of patients	• Rare • Most common in people of Swedish ancestry • Known as Sjögren-Larsson syndrome		Rizzo et al [1999], Gordon [2007]
AMPD2 [2]	SPG63	Complicated	Infancy	• Short stature • Thin corpus callosum • White matter changes	Rare	OMIM 615686	Novarino et al [2014], Kortüm et al [2018]
AP4B1	SPG47	Complicated	Infancy	• Severe ID • Facial dysmorphism • Seizures • Stereotypic laughter w/ tongue protrusion	Rare	OMIM 614066	Abou Jamra et al [2011], Bauer et al [2012]

Table 2. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
AP4E1	SPG51	Complicated	Infancy	• Severe ID • Facial dysmorphism • Seizures • Stereotypic laughter w/ tongue protrusion	Rare	OMIM 613744	Abou Jamra et al [2011], Moreno-De-Luca et al [2011]
AP4M1	SPG50	Complicated	Infancy	• Severe ID • Facial dysmorphism • Seizures • Stereotypic laughter w/ tongue protrusion	Rare	OMIM 612936	Verkerk et al [2009]
AP4S1	SPG52	Complicated	Infancy	• Severe ID • Facial dysmorphism • Seizures • Stereotypic laughter w/ tongue protrusion	Rare	OMIM 614067	Abou Jamra et al [2011], Hardies et al [2015]
AP5Z1	SPG48	Uncomplicated	Typically adulthood; rarely infancy	• Urinary incontinence • Parkinsonism • Dystonia • Thin corpus callosum • Leukodystrophy • Severe DD in infantile onset	Single family	OMIM 613647	Słabicki et al [2010], Pensato et al [2014]
ATL1	SPG3A	Uncomplicated	Infantile to childhood (rarely adult onset)	• Progression may be minimal w/static course • May present as spastic diplegic cerebral palsy • Complicated phenotype w/ peripheral neuropathy or autonomic failure reported	AR inheritance is very rare.	Spastic Paraplegia 3A	Khan et al [2014]
B4GALNT1	SPG26	Complicated	Juvenile	• Amyotrophy • Dysarthria • Ataxia • DD • Dystonia	Rare	OMIM 609195	Boukhris et al [2013], Harlalka et al [2013]

Table 2. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
BICD2	Not assigned	Complicated	Childhood	• Amyotrophy • Contractures	Rare		Oates et al [2013]
MTRFR (*C12orf65*)	SPG55	Complicated	Childhood	• DD • Visual loss • Polyneuropathy • Arthrogryposis • Signs of mitochondrial encephalomyopathy, some classified as Leigh's syndrome	Rare	OMIM 615035	Shimazaki et al [2012]
C19orf12	SPG43	Complicated	Childhood	• Amyotrophy • Dysarthria • Multiple contractures • Neurodegeneration w/brain iron accumulation in some	Rare	OMIM 615043	Landouré et al [2013], Schubert et al [2016]
CYP2U1	SPG56	Complicated	Infancy	• Severe DD • Dystonia • Polyneuropathy • Calcification of basal ganglia	Rare	OMIM 615030	Tesson et al [2012]
CYP7B1	SPG5A	Uncomplicated or complicated	Juvenile to early adulthood	• Ataxia • Polyneuropathy • Extrapyramidal signs • MRI signs of leukodystrophy	SPG5A was diagnosed in 9 of 172 families w/ histories consistent w/AR inheritance of HSP. [3]	OMIM 270800	Tsaousidou et al [2008], Goizet et al [2009]
DDHD1	SPG28	Uncomplicated	Childhood	Scoliosis	Rare	OMIM 609340	Tesson et al [2012]
DDHD2	SPG54	Complicated	Infancy	• Severe DD • Optic atrophy • Thin corpus callosum • Leukodystrophy	Rare	OMIM 615033	Schuurs-Hoeijmakers et al [2012]
ENTPD1	SPG64	Complicated	Infancy	• Mild cognitive disability • Behavioral disturbances • White matter changes	Rare	*ENTPD1*-Related Neurodevelopmental Disorder	Novarino et al [2014]

Table 2. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
ERLIN1	SPG62	Complicated	Childhood	• Amyotrophy • Ataxia • Phenotype consistent w/ juvenile onset of ALS reported	Rare	OMIM 615681	Novarino et al [2014], Tunca et al [2018]
ERLIN2	SPG18	Complicated (rarely pure AR HSP reported)	Childhood	• DD • Seizures • Contractures • Juvenile primary lateral sclerosis phenotype reported • Allelic w/AD pure HSP	Rare	OMIM 611225	Alazami et al [2011], Yıldırım et al [2011], Al-Saif et al [2012]
FA2H [4]	SPG35	Complicated	Childhood	• Seizures • Dystonia • Parkinsonism w/iron accumulation in basal ganglia	Rare	OMIM 612319	Edvardson et al [2008], Dick et al [2010], Pensato et al [2014]
GAD1	Not assigned	Complicated	Childhood	• Moderate to severe ID • Single reported family was described as having AR cerebral palsy	Rare (single family reported)		Lynex et al [2004]
GBA2	SPG46	Complicated	Childhood	• DD • Ataxia • Hearing loss • Polyneuropathy	Rare	OMIM 614409	Hammer et al [2013], Coarelli et al [2018]
GJC2 [5]	SPG44	Complicated	Childhood	• Febrile seizures • Deafness • Episodic spasms • Variable degree of leukodystrophy	Rare	OMIM 613206	Uhlenberg et al [2004], Orthmann-Murphy et al [2009]
GRID2 [6]	Not assigned	Complicated	Childhood	• Amyotrophy • Ataxia	Rare		Utine et al [2013], Maier et al [2014]
IBA57 [7]	SPG74	Complicated	Childhood	• Optic atrophy • Peripheral neuropathy	Rare	OMIM 616451	Lossos et al [2015], Torraco et al [2017]

Table 2. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
KIF1A [8]	SPG30	Complicated	Childhood	• Spastic ataxia • Polyneuropathy	Rare	OMIM 610357	Hamdan et al [2011], Rivière et al [2011], Klebe et al [2012]
KIF1C	SPG58	Complicated	Childhood	• Spastic ataxia • Dystonia	Rare		Caballero Oteyza et al [2014], Dor et al [2014]
KLC2	Not assigned	Complicated	Childhood	• Optic atrophy • Neuropathy • Contractures in later stages • Cognition remains intact	• Rare • Also known as spastic paraplegia optic atrophy, & neuropathy (SPOAN)	OMIM 609541	Melo et al [2015]
KLC4	Not assigned	Complicated	Childhood	• Ataxia • Multiple contractures • Variable degree of leukodystrophy	Rare		Bayrakli et al [2015]
MARS1 [9]	SPG70	Complicated	Infancy	• Nephrotic syndrome, polyneuropathy • Mild ID • Late onset of CMT2 (axonal) type also reported	Rare		Gonzalez et al [2013], Novarino et al [2014]
NT5C2	SPG45	Complicated	Childhood	• Optic atrophy • Nystagmus • Strabismus • ID • Hypoplastic corpus callosum	Rare	OMIM 613162	Novarino et al [2014], Elsaid et al [2017]
PGAP1 [10]	SPG67	Complicated	Infancy	• Severe DD • Tremor • Agenesis of corpus callosum • Hypomyelination	Rare		Murakami et al [2014], Novarino et al [2014]

Table 2. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
PNPLA6 [11]	SPG39	Complicated	Childhood	• Amyotrophy • Endocrine abnormalities w/ short stature or hypogonadotropic hypogonadism • Chorioretinal dystrophy	Rare	*PNPLA6*-Related Disorders	Rainier et al [2008], Synofzik et al [2014], Hufnagel et al [2015]
REEP2	SPG72	Uncomplicated	Early childhood	• Musculoskeletal problems • Mild postural tremor	• Rare • Inheritance can be dominant or recessive.	OMIM 615625	Esteves et al [2014]
SPART	SPG20	Complicated	Juvenile	• Distal amyotrophy • Short stature • Kyphoscoliosis • Multiple limb contractures	• Rare • Mostly seen among Old Order Amish	Troyer Syndrome	Cross & McKusick, [1967b], Patel et al [2002]
SPG7	SPG7	Uncomplicated or complicated	Juvenile or adulthood	• Dysarthria • Ataxia • Optic atrophy • Supranuclear palsy • Mitochondrial abnormalities on skeletal muscle biopsy	• 5%-12% of AR HSP • AD inheritance suggested for some pathogenic variants; this remains controversial	Spastic Paraplegia 7	Casari et al [1998], McDermott et al [2001], Arnoldi et al [2008], Brugman et al [2008]
SPG11	SPG11	Complicated	Childhood or early adulthood	• DD • Optic atrophy • Ataxia • Pseudobulbar signs • Polyneuropathy • Levodopa-responsive parkinsonism • Hypoplastic or absent corpus callosum	• 5% of AR HSP • 75% of HSP w/DD & hypoplasia of corpus callosum	Spastic Paraplegia 11	Stevanin et al [2007], Paisan-Ruiz et al [2008], Riverol et al [2009], Guidubaldi et al [2011]
TECPR2	SPG49	Complicated	Childhood	• Central apnea • Severe DD • Microcephaly • Dysmorphic features	Rare	*TECPR2*-HSAN with ID	Oz-Levi et al [2012]

Table 2. continued from previous page.

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
TFG	SPG57	Complicated	Childhood	• Optic atrophy • Severe polyneuropathy	Rare	OMIM 615658	Beetz et al [2013]
USP8	SPG59	Uncomplicated	Childhood	None	Rare		Novarino et al [2014]
WDR48	SPG60	Complicated	Infancy	• Polyneuropathy • DD	Rare		Novarino et al [2014]
ZFYVE26	SPG15	Complicated	Childhood or early adulthood	• DD • Optic atrophy • Ataxia • Central retinal degeneration • Polyneuropathy	1%-2% of AR HSP	Spastic Paraplegia 15	Hanein et al [2008], Pensato et al [2014]

AD = autosomal dominant; AR = autosomal recessive; ALS = amyotrophic lateral sclerosis; DD = developmental delay; HSP = hereditary spastic paraplegia; ID = intellectual disability; *TECPR2*-HSAN with ID = *TECPR2*-related hereditary sensory and autonomic neuropathy with intellectual disability

1. Genes are listed alphabetically.

2. Allelic with pontocerebellar hypoplasia type 9

3. Goizet et al [2009]

4. Allelic with fatty acid hydroxylase-associated neurodegeneration and leukodystrophy

5. Allelic with Pelizaeus-Merzbacher-like disease 1 and hereditary lymphedema type IC

6. Allelic with autosomal recessive spinocerebellar ataxia 18 (See Hereditary Ataxia Overview.)

7. Allelic with multiple mitochondrial dysfunctions syndrome 3

8. Allelic with hereditary sensory and autonomic neuropathy type 2C and AD intellectual disability type 9

9. Allelic with Charcot-Marie-Tooth neuropathy type 2U

10. Allelic with autosomal recessive intellectual disability type 42

11. Allelic with Boucher-Neuhauser syndrome, Gordon-Holmes syndrome, Oliver-McFarlane syndrome, and Laurence-Moon syndrome

Table 3. Hereditary Spastic Paraplegia: Genes and Distinguishing Clinical Features – X-Linked Inheritance

Gene [1]	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other	References	
						GeneReview or OMIM Entry	Citation
L1CAM	SPG1 [2]	Complicated	Infancy	• ID • Adducted thumbs • Corpus callosum hypoplasia • Aphasia • Obstructive hydrocephalus	Rare	L1 Syndrome	Jouet et al [1994], Schrander-Stumpel et al [1995], Yamasaki et al [1995], Finckh et al [2000]
PLP1 [3]	SPG2	Complicated	Early-childhood to juvenile onset (in manifesting female heterozygotes: onset in 4th-7th decade)	• Pure HSP phenotype present in early stages; later, other signs emerge • Nystagmus • Optic atrophy • Dysarthria • ID • Variable degree of leukodystrophy on MRI	• Rare • In heterozygous females: variable phenotype w/ relatively late onset & mild clinical manifestations	*PLP1*-Related Disorders	Saugier-Veber et al [1994], Cambi et al [1996], Hodes et al [1999], Sivakumar et al [1999]
SLC16A2	SPG22	Complicated	Early childhood	• Severe ID • Infantile hypotonia • Progressive spasticity • Ataxia • Dystonia • ↑ T3 & normal to mildly ↑ TSH • ↓ T4 hypomyelination on neuroimaging	• Rare • SPG22 is a proposed designation. [4] • Also referred to as Allan-Herndon-Dudley syndrome [5]	Allan-Herndon-Dudley Syndrome	Dumitrescu et al [2004], Boccone et al [2010]

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; HSP = hereditary spastic paraplegia; ID = intellectual disability

1. Genes are listed alphabetically.

2. SPG1 is more commonly referred to as MASA syndrome (*m*ental retardation [intellectual disability], *a*phasia [delayed speech], *s*pastic paraplegia, *a*dducted thumbs). Allelic disorders are X-linked hydrocephalus with stenosis of the aqueduct of Sylvius and X-linked complicated corpus callosum agenesis.

3. Allelic with Pelizaeus-Merzbacher disease

4. OMIM 300523

5. Because of the overlap between the clinical phenotype in individuals with *SLC16A2* abnormalities and in those with a previously described syndrome, Allan-Herndon-Dudley syndrome (AHDS), Schwartz et al [2005] analyzed *SLC16A2* in six families with AHDS. *SLC16A2* pathogenic variants were identified in all six; therefore, AHDS is now synonymous with MCT8-specific thyroid hormone cell-membrane transporter deficiency due to pathogenic variants in *SLC16A2* (see Allan-Herndon-Dudley Syndrome).

Table 4. Hereditary Spastic Paraplegia: Gene and Distinguishing Clinical Features – Maternal (Mitochondrial) Inheritance

Gene	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features
MT-ATP6	Not assigned	Complicated	Adult	Cardiomyopathy, diabetes mellitus, sensory polyneuropathy

Verny et al [2011]

3. Differential Diagnosis of Hereditary Spastic Paraplegia

The differential diagnosis includes the following:

- **Structural abnormalities** involving the brain or spinal cord (e.g., tethered cord syndrome and spinal cord compression)
- **Vascular abnormalities** including arteriovenous abnormalities or fibrocartilaginous embolism
- **Demyelinating disorders** including primary progressive multiple sclerosis or Devi's disease (neuromyelitis optica)
- **Paraneoplastic myelopathies** including those associated with anti-GAD65 antibodies
- **Other motor neuron disorders** such as slowly progressive amyotrophic lateral sclerosis (ALS) or primary lateral sclerosis (PLS)
- **Leukodystrophies** such as steadily progressive multiple sclerosis, B_{12} deficiency, Krabbe disease, metachromatic leukodystrophy, and adrenomyeloneuropathy
- **Spinocerebellar ataxias (SCAs)** including Machado-Joseph disease (SCA 3), Friedreich ataxia, spastic ataxia of Charlevoix-Saguenay, or other spastic ataxias. See Hereditary Ataxias.
- **Diplegic form of cerebral palsy (CP)** with corresponding MR imaging abnormalities. However, several individuals with presumed CP have had pathogenic variants in genes associated with HSP identified on molecular genetic testing associated with either an autosomal dominant or autosomal recessive inheritance [Rainier et al 2006, Hedera 2013].
- **Infection** including human immunodeficiency virus (HIV/AIDs), tropical spastic paraplegia (also known as human T-cell leukemia virus 1 [HTLV1] -associated myelopathy), and neurosyphilis
- **Metabolic disorders** (reviewed in Hedera [2016]) including homocysteine remethylation defects (due to methylene tetrahydrofolate reductase [MTHFR] deficiency), cobalamin C disease, urea cycle defects, biotinidase deficiency, phenylketonuria, glycine encephalopathy, cerebral folate deficiency, homocarnosinosis, cerebrotendinous xanthomatosis, adult polyglucosan body disease, and nucleoside phosphorylase deficiency
- **Nutritional disorders** (reviewed in Hedera [2016]) including copper deficiency, vitamin B_{12} and E deficiencies
- **Early-onset dementias** including frontotemporal dementia-ALS (see Amyotrophic Lateral Sclerosis Overview) and familial Alzheimer disease caused by pathogenic variants in *PSEN1* (encoding presenilin-1), *PSEN2* (encoding presenilin-2), or APP (encoding amyloid precursor protein) (See Alzheimer Disease.)
- **Dopa-responsive dystonia.** It is important to consider dopa-responsive dystonia in all individuals – particularly children – with progressive gait disturbance. See GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia, Tyrosine Hydroxylase Deficiency.

4. Evaluation Strategies to Identify the Genetic Cause of Hereditary Spastic Paraplegia in a Proband

Establishing a specific genetic cause of hereditary spastic paraplegia (HSP):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;

- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history and physical examination is directed at identifying neurologic features associated with HSP as well as any additional features that could indicate the presence of a complicated HSP (see Clinical Characteristics and Tables 1, 2, 3, and 4).

Family history includes a three-generation family history with attention to other relatives with possible HSP. Documentation of relevant findings in family members can be accomplished either through direct examination of those individuals or through review of their medical records including neuroimaging, neuropathology, neurologic examination, and results of molecular genetic testing. Autosomal dominant, autosomal recessive, and X-linked or maternal (mitochondrial) inheritance patterns have all been reported with HSP.

Exclusion of other disorders. See Differential Diagnosis.

Molecular genetic testing approaches can include a combination of gene-targeted testing (single-gene testing or multigene panel) and comprehensive genomic testing (exome sequencing, exome array). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **Concurrent or serial single-gene testing** can be considered if clinical findings and/or family history indicate that involvement of a particular gene or small subset of genes is most likely (see Tables 1, 2, 3, and 4).
- **A multigene panel** that includes some or all of the genes listed in Table 1 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. **Exome array** (when clinically available) may be considered if exome sequencing is not diagnostic.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

5. Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hereditary spastic paraplegia (HSP) can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner or by maternal (mitochondrial) inheritance, depending on the genetic subtype in a family.

Several types of HSP (e.g., those associated with pathogenic variants in *ATL1*, *SPG7*, *ALDH18A1*, and possibly *SPG11*) may be inherited either as autosomal recessive or autosomal dominant disorders (see Causes of Hereditary Spastic Paraplegia).

Risk to Family Members

Autosomal Dominant HSP

Parents of a proband

- Most individuals diagnosed as having an autosomal dominant HSP have an affected parent.
- Occasionally, a proband with HSP may have the disorder as the result of a *de novo* pathogenic variant. The frequency of *de novo* variants causing autosomal dominant HSP is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing of both parents for the pathogenic variant identified in the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Parental germline mosaicism has been reported in *SPAST*-related HSP (SPG4) [Aulitzky et al 2014]. The incidence of parental germline mosaicism is probably very low, but no conclusive epidemiologic data are available.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents: if one of the proband's parents has a pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The age of onset and degree of disability are highly variable among members of the same family, in different families with the same pathogenic variant, or between genetic types of HSP.
- If the HSP-related pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant HSP is at a 50% risk of inheriting the HSP-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Autosomal Recessive HSP

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one HSP-related pathogenic variant).
- Heterozygotes (carriers) are typically asymptomatic. The only known exception to this rule is *SPG7*, where an apparently dominant inheritance was suggested for otherwise autosomal recessive HSP [McDermott et al 2001].

Sibs of a proband

- At conception, each sib has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes are typically asymptomatic if the pattern of inheritance is consistent with autosomal recessive mode and affected individuals harbor biallelic pathogenic variants.

Offspring of a proband. The offspring of an individual with autosomal recessive HSP are obligate heterozygotes (carriers) for an HSP-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an HSP-related pathogenic variant.

X-Linked HSP

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the HSP-related pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one individual with X-linked HSP, the mother of an affected male is an obligate carrier of the HSP-related pathogenic variant. If a woman has more than one affected child and if the HSP-related pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism (maternal germline and somatic mosaicism in *L1CAM*-related HSP [SPG1] has been reported [Du et al 1998, Vits et al 1998]).
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* HSP-related pathogenic variant, in which case the mother is not a heterozygote.

Parents of a female proband

- A female proband may have inherited the HSP-related pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can determine if the pathogenic variant was inherited.

Sibs of a male proband

- The risk to sibs depends on the genetic status of the mother.
  - If the mother of the proband with X-linked HSP has an HSP-related pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the variant will be affected; females who inherit the variant will be heterozygotes and may have a range of clinical manifestations (see Table 3).
  - If the proband represents a simplex case (i.e., a single occurrence in a family) and if the HSP-related pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of maternal germline mosaicism.
- The age of onset, penetrance, and degree of disability are not predictable in members of the same family, in different families with the same pathogenic variant, or between genetic types of HSP.

Sibs of a female proband

- The risk to sibs depends on the genetic status of the parents.

- If the mother of the proband has an HSP-related pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the variant will be affected; females who inherit the variant will be heterozygotes and may have a range of clinical manifestations (see Table 3).
- If the father of the proband has an HSP-related pathogenic variant, he will transmit it to all of his daughters and none of his sons.

- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the HSP-related pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism.
- The age of onset, penetrance, and degree of disability are not predictable in members of the same family, in different families with the same pathogenic variant, or between genetic types of HSP.

Offspring of a male proband. Affected males transmit the HSP-related pathogenic variant to:

- All of their daughters, who will be heterozygotes and may have a range of clinical manifestations (see Table 3);
- None of their sons.

Offspring of a female proband. Women with an HSP-related pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:

- Males who inherit the pathogenic variant will be affected.
- Females who inherit the variant will be heterozygotes and may have a range of clinical manifestations (see Table 3). This is best documented for *SPG2*, where female heterozygotes may show a mild paraparesis with late onset of the disease [Sivakumar et al 1999].

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the HSP-related pathogenic variant, the parent's family members may be at risk.

Heterozygote (carrier) detection. Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note:

(1) Females who are heterozygous for X-linked HSP may have a range of clinical manifestations (see Table 3).

(2) Identification of female heterozygotes requires either (a) prior identification of the HSP-related pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Maternal (Mitochondrial) Inheritance

Parents of a proband

- The father of a proband is not at risk of having the *MT-ATP6* pathogenic variant.
- The mother of a proband (usually) has the *MT-ATP6* pathogenic variant and may or may not have symptoms.
- Alternatively, the proband may have a *de novo* (somatic) mitochondrial pathogenic variant.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the mother.
- If the mother has the *MT-ATP6* pathogenic variant, all sibs of a proband will inherit the *MT-ATP6* pathogenic variant and may or may not have symptoms.

Offspring of a proband

- All offspring of females with a mtDNA pathogenic variant will inherit the pathogenic variant.
- Offspring of males with a mtDNA pathogenic variant are not at risk of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's mother. If the mother has an *MT-ATP6* pathogenic variant, her sibs and mother are also at risk.

Related Genetic Counseling Issues

Caution must be exercised when counseling an individual who has all the signs and symptoms of HSP but no similarly affected relatives. Such individuals may be diagnosed as having primary lateral sclerosis (PLS). While such individuals with no known family history of HSP may have autosomal recessive HSP (and thus low risk of transmitting the disorder to offspring), it is also possible that they have X-linked HSP, autosomal dominant HSP with reduced penetrance, a *de novo* pathogenic variant, a mtDNA pathogenic variant, mistaken paternity, or an environmentally acquired disorder.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including general discussion of potential risks to offspring and reproductive options) to young adults who are affected, carriers, or at risk of being affected or a carrier; however, it is not possible to make specific predictions about the potential severity of disease in offspring.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for hereditary spastic paraplegia are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **EURO HSP**

  Plateforme Maladies Rares

  99 Rue Didot

  Paris 75014

  France

  Phone: 33 1 56 53 52 61

  Email: president@eurohsp.eu

  www.eurohsp.eu

- **HSP Research Foundation**
  Australia
  Email: inquiries@hspersunite.org.au
  www.hspersunite.org.au
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  sp-foundation.org
- **Tom Wahlig-Foundation**
  Tom Wahlig Stiftung
  Germany
  www.hsp-info.de/en/foundation.htm
- **A.I. Vi.P.S.**
  Associazione Italiana Vivere la Paraparesi Spastica
  Via Tevere, 7
  20020 Lainate (MI)
  Italy
  Phone: 39 392 9825622
  Email: info@aivips.it
  www.aivips.it

Chapter Notes

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- 11 February 2021 (aa/ha/ph) Revision: added AD SPG30 and associated references; updated SPG1/MASA syndrome terminology information
- 27 September 2018 (ha) Comprehensive update posted live
- 6 February 2014 (me) Comprehensive update posted live
- 3 February 2009 (cd) Revision: sequence analysis for SPG5A available clinically
- 21 May 2008 (cd) Revision: pathogenic variants in *ZFYVE26* identified as causative of SPG15
- 4 March 2008 (cd) Revision: sequence analysis of entire coding region available for SPG8 and SPG33
- 4 October 2007 (cd) Revision: sequence analysis for SPG10 available on a clinical basis
- 11 July 2007 (me) Comprehensive update posted live
- 21 October 2004 (cd) Revision: arginase deficiency added
- 26 February 2004 (cd) Revision: testing for SPG6 clinically available

- 15 October 2003 (cd) Revision: test availability
- 22 September 2003 (me) Comprehensive update posted live
- 15 August 2000 (me) Overview posted live
- 21 March 2000 (jf) Original submission

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