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Spastic Paraplegia 4

Synonyms: *SPAST*-HSP, SPG4

Livia Parodi, PhD,[1] Siri Lynne Rydning, MD,[2] Chantal Tallaksen, MD, PhD,[3] and Alexandra Durr, MD, PhD[1]

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Summary

Clinical characteristics

Spastic paraplegia 4 (SPG4; also known as *SPAST*-HSP) is characterized by insidiously progressive bilateral lower-limb gait spasticity. More than 50% of affected individuals have some weakness in the legs and impaired vibration sense at the ankles. Sphincter disturbances are very common. Onset is insidious, mostly in young adulthood, although symptoms may start as early as age one year and as late as age 76 years. Intrafamilial variation is considerable.

Diagnosis/testing

The diagnosis of *SPAST*-HSP is established in a proband with characteristic clinical features and a heterozygous pathogenic variant in *SPAST* identified by molecular genetic testing.

Management

Treatment of manifestations: Antispastic drugs for leg spasticity; anticholinergic antispasmodic drugs for urinary urgency; regular physiotherapy to stretch spastic muscles and prevent contractures. Consideration of botulinum toxin and intrathecal baclofen when oral drugs are ineffective and spasticity is severe and disabling. Urodynamic evaluation in order to initiate treatment when sphincter disturbances become a problem.

Surveillance: Evaluation every 6-12 months to update medications and physical rehabilitation.

Author Affiliations: 1 Institut du Cerveau et de la Moelle Epinière Institut National de la Santé et de la Recherche Médicale Centre National de la Recherche Scientifique Assistance Publique – Hôpitaux de Paris Sorbonne Université – Pitié-Salpêtrière University Hospital Paris, France; Email: livia.parodi@icm-institute.org; Email: alexandra.durr@icm-institute.org. 2 Department of Neurology Oslo University Hospital; Institute of Clinical Medicine University of Oslo Oslo, Norway; Email: s.l.rydning@medisin.uio.no. 3 Department of Neurology Oslo University Hospital Oslo, Norway; Email: chantal.tallaksen@medisin.uio.no.

Genetic counseling

SPAST-HSP is inherited in an autosomal dominant manner with age-related, nearly complete penetrance and is characterized by significant intrafamilial clinical variability. Most individuals diagnosed with *SPAST*-HSP have an affected parent. The proportion of cases caused by a *de novo* pathogenic variant is low. Each child of an individual with *SPAST*-HSP has a 50% chance of inheriting the pathogenic variant. Prenatal testing and preimplantation genetic testing are possible if a pathogenic *SPAST* variant has been identified in an affected family member. Because of variable clinical expression, results of prenatal testing cannot be used to predict whether an individual will develop *SPAST*-HSP and, if so, what the age of onset, clinical course, and degree of disability will be.

Diagnosis

Suggestive Findings

Spastic paraplegia 4 (SPG4; also known as *SPAST*-HSP) **should be suspected** in individuals with the following:

- Characteristic clinical symptoms of insidiously progressive bilateral leg stiffness affecting gait with or without spasticity at rest and mild proximal weakness, often accompanied by urinary urgency
- Neurologic examination demonstrating corticospinal tract deficits affecting both legs (spastic weakness, hyperreflexia, and extensor plantar responses). Mildly impaired vibration sensation in the ankles is present in the majority of individuals.
- Family history consistent with autosomal dominant inheritance, or exclusion of other causes of spastic paraplegia in simplex cases (i.e., a single occurrence in a family)

Note: The presence of other signs/symptoms suggestive of complicated hereditary spastic paraplegia does not exclude *SPAST*-HSP, although it reduces its probability.

Brain and spinal cord MRI

- Often normal in individuals with *SPAST*-HSP
- Spinal cord atrophy can occur in *SPAST*-HSP, but is less pronounced than in other genetic causes of HSP.
- Mild vermis atrophy, a thin corpus callosum, subtle white matter changes, and/or cerebellar atrophy have been reported [Duning et al 2010, da Graça et al 2019].

Note: The MRI is useful in identifying anomalies of the brain, cerebro-medullary junction, and medulla that are characteristic of disorders discussed in Differential Diagnosis.

Electromyography (EMG) with **nerve conduction velocities (NCV)** is used to exclude peripheral nervous system involvement, which could raise the possibility of an alternative diagnosis as severe polyneuropathy is not a frequent symptom of *SPAST*-HSP. Karle et al performed neurophysiologic examinations of 128 individuals with HSP, including 35 individuals with *SPAST*-HSP, and showed that massively elongated central motor conduction time argued against *SPAST*-HSP; however, reduced amplitudes and prolonged latencies were reported, in particular in individuals with a *SPAST* pathogenic missense variant [Karle et al 2013].

Establishing the Diagnosis

The diagnosis of *SPAST*-HSP **is established** in a proband with Suggestive Findings by identification of a heterozygous pathogenic variant in *SPAST* by molecular genetic testing (see Table 1).

Note: (1) Failure to detect a pathogenic variant/deletion does not absolutely exclude the diagnosis. (2) Once non-genetic causes have been excluded, testing for *SPAST*-HSP should be considered in simplex cases (i.e.,

individuals with no family history of spasticity), as *SPAST* pathogenic variants can be identified in approximately 10%-20% of simplex cases [Erichsen et al 2009a, Shoukier et al 2009, Fei et al 2011].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *SPAST*-HSP is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with spastic paraplegia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *SPAST*-HSP, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SPAST* detects missense, nonsense, and splice site variants, as well as small intragenic deletions/insertions. The combination of *in silico* predictive algorithms and information retrieved from population databases is essential to establish the pathogenic role of variants of unknown significance [Richards et al 2015]. If no pathogenic variant is found on sequence analysis, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *SPAST* and other genes of interest (see Differential Diagnosis) 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 this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by spastic paraplegia, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

Table 1. Molecular Genetic Testing Used in Spastic Paraplegia 4

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SPAST	Sequence analysis [3]	75%-80% [4]
	Gene-targeted deletion/duplication analysis [5]	20%-25% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Benign variants can affect the phenotype (see Genotype-Phenotype Correlations and Molecular Genetics).
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Exon and multiexon deletions and duplications account for approximately 20%-25% of *SPAST* pathogenic variants [Beetz et al 2006, Depienne et al 2007b].

Clinical Characteristics

Clinical Description

The cardinal clinical feature of spastic paraplegia 4 (*SPAST*-HSP) is insidiously progressive bilateral lower-limb spasticity associated with brisk reflexes, ankle clonus, and bilateral extensor plantar responses. Sphincter disturbances are very frequent (77%), in particular urinary urgency and incontinence. Increased reflexes in the upper limbs may also occur (65%), but other symptoms and findings in the upper limbs are rare. A frequent additional feature is decreased, but not abolished, vibration sense at the ankles, occurring in 60% of individuals [Parodi et al 2018]. Around 50% of affected individuals have proximal weakness in the lower limbs [Kanavin & Fjermestad 2018, Parodi et al 2018, Schneider et al 2019].

Age at onset of symptoms ranges from infancy to the eighth decade. Age at onset is variable even among family members with the same pathogenic variant. A recent study including more than 500 individuals with *SPAST*-HSP confirmed that the age at onset is characterized by a bimodal distribution, with a major first peak before the first decade, and a second, lower one between the third and fifth decades. Penetrance is not complete; an estimated 6% of individuals remain asymptomatic throughout life. Penetrance is reported to be lower in females than in males [Parodi et al 2018].

Disease severity generally worsens with the duration of the disease, although some individuals remain mildly affected all their lives. Disease severity is variable even among family members with the same pathogenic variant. After long disease duration (20 years), approximately 50% of individuals need assistance for walking, and approximately 10% require a wheelchair. Disease progression is more rapid in individuals with late onset (age >35 years) than in those with early onset [Loureiro et al 2013, Chrestian et al 2016, Polymeris et al 2016, Parodi et al 2018].

Comparing men and women, Parodi et al [2018] observed that symptomatic females more often had increased upper-limb reflexes than males, representing a more severe and diffused disorder in women.

Leg spasms are frequent and may also develop before the onset of spasticity. Spasms are more frequent after physical activity, and tend to disappear when spasticity becomes more severe.

Bladder dysfunction remains one of the most frequent problems for affected individuals and may be more frequent in individuals with *SPAST*-HSP than in all individuals with HSP; Schneider et al [2019] reported

urologic involvement in 91.2% of individuals with *SPAST*-HSP compared to 74.5% of individuals with HSP. The most frequent symptoms are urinary incontinence, hesitancy, increased frequency of micturition, and urgency. Incomplete bladder emptying may also occur [Braschinsky et al 2010]. The anal sphincter may also be affected, resulting in uncontrollable flatulence or fecal incontinence, affecting respectively 31.4% and 8.7% of individuals with HSP in one study [Kanavin & Fjermestad 2018]. In a study of urodynamic findings in 29 individuals with HSP, Fourtassi et al [2012] described signs of central neurogenic bladder in 82.7%, with detrusor overactivity in 52% and detrusor sphincter dyssynergia in 65.5%.

Pes cavus and mild spastic dysarthria may be observed.

Subtle cognitive impairment has been documented [Erichsen et al 2009b]; but its relation to the disease remains undetermined. Cognitive deficits appear late in the disease course and are not present in all affected members of a given family. When detected by neuropsychological testing, the impairment is often subtle, limited to executive dysfunction, and without noticeable effect on daily living. No definite correlation with the type of pathogenic variant in *SPAST* has been established.

Extensive neuropsychological assessment of nine adults with *SPAST*-HSP (including one asymptomatic individual) identified cognitive impairment fulfilling multidomain non-amnesic mild cognitive impairment criteria, with executive impairment and impaired social cognition [Chamard et al 2016] as suggested by Tallaksen et al [2003], where a familial aggregation of cognitive impairment suggested the implication of modifiers. In the large *SPAST*-HSP study by Parodi et al [2018], intellectual disability was described in 4.2%.

Other findings compatible with a complex form of HSP are uncommon in *SPAST*-HSP but do not exclude the diagnosis. Also, whether these additional findings are related to *SPAST*-HSP or coincidental remains to be clarified.

Neuropathy has been reported in individuals with *SPAST*-HSP, but without compelling evidence of a shared underlying pathologic mechanism. Kumar et al [2012] found peripheral abnormalities in nerve conduction studies in two of 11 individuals with *SPAST*-HSP.

Non-motor symptoms are more frequent than previously acknowledged. Servelhere et al [2016] studied 30 individuals and found that fatigue, pain, and depression were frequent and often severe manifestations in individuals with *SPAST*-HSP.

Restless legs syndrome has been associated with *SPAST*-HSP [Sperfeld et al 2007], but this remains to be confirmed.

Hand tremor was reported in 10% of a large cohort of Dutch individuals with *SPAST*-HSP [de Bot et al 2010].

Seizures, intellectual disability, and cerebellar ataxia are rare. A few individuals with severe dementia have been reported [Murphy et al 2009]. However, too few neuropathologic studies have been performed in persons with *SPAST*-HSP for a general picture of the distribution of cortical and medullar lesions in the disease to emerge.

Neuroimaging. Newer MRI studies using advanced neuroimaging techniques have shown widespread involvement of gray and white matter in individuals with *SPAST*-HSP [Lindig et al 2015, Rezende et al 2015, Liao et al 2018, Rucco et al 2019]. In a study of 11 individuals, fractional anisotropy was reduced in the corticospinal tracts, cingulate gyri, and splenium of the corpus callosum [Rezende et al 2015]. Resting-state fMRI studies in 12 individuals with *SPAST*-HSP showed abnormal functional activity in several brain areas [Liao et al 2018]. Rucco et al [2019] performed magnetoencephalography of ten individuals with *SPAST*-HSP and described global network rearrangements. Using diffusion tensor imaging and tract-based special statistics, Lindig et al [2015] found that imaging findings in the 15 included individuals correlated with disease duration and severity.

Genotype-Phenotype Correlations

Recently, after analyzing a cohort of more than 500 individuals with *SPAST*-HSP, Parodi et al [2018] showed that missense variants were associated with an earlier age of onset (by 10 years), when compared to truncating variants. This finding provides an explanation for the bimodal age of onset distribution typical of *SPAST*-HSP.

It is important to note that age at onset and clinical severity are highly variable for a given variant, even in the same family. The observed difference in age of onset between related individuals ranged from 27 years to 69 years [Parodi et al 2018]. Furthermore, two family members with the same variant can have in one case a pure spastic paraparesis and in the other a complex disease. For example, Orlacchio et al [2004] reported wide phenotypic variability with the p.Asn386Ser variant, with some individuals presenting with intellectual disability and others showing brain MRI abnormalities including thin corpus callosum or cerebellar atrophy.

The most plausible explanation for intra and interfamilial variability is the presence of genetic modifiers. Svenson et al [2004] reported two rare nonsynonymous *SPAST* variants, c.131C>T (p.Ser44Leu) and c.134C>A (p.Pro45Gln) acting as age-of-onset modifiers. In several analyzed families, the individuals who had a *SPAST* pathogenic variant on one allele and either a c.131C>T or c.134C>A variant on the other allele (*in trans*) had a very early onset, suggesting that these alleles could modify the HSP phenotype [Svenson et al 2004, McDermott et al 2006, personal communication]. The *SPAST* variant c.131C>T has a frequency of 0.4% in a control population, c.134C>A is even more rare in the gnomAD Database (see bioRxiv). In addition to the two *SPAST* variants, an *HSPD1* variant was proposed as a *SPAST*-HSP age-at-onset modifier [Svenstrup et al 2009], but its role remains under discussion.

Penetrance

Penetrance is age dependent and mostly complete in individuals with *SPAST*-HSP. It is estimated to be 85% by age 45 years [Fonknechten et al 2000] and complete at 70 years [Parodi et al 2018]. It should be emphasized that age dependence is explained partly by variability in age at onset and partly by the difficulty in determining the precise age of onset; thus, neurologic examination is important. Penetrance is greater if pyramidal signs as well as spastic gait are considered: approximately 6% of individuals who have a *SPAST* variant are completely asymptomatic on examination; approximately 20% have abnormal signs when examined, but no awareness of being affected.

Penetrance may be sex dependent. Parodi et al [2018] reported a higher penetrance in males (94%) than females (88%), and greater sex discordance in individuals with onset before the third decade (91% vs 70%).

Nomenclature

The gene in which mutation is responsible for spastic paraplegia at the SPG4 locus, *SPAST*, was previously known as *SPG4*.

SPAST-HSP may also be referred to as SPG4. Previously it was also known as hereditary spastic paraplegia, spastin type [Marras et al 2016].

Prevalence

The most recent epidemiologic study estimates a global prevalence of autosomal dominant-HSP (AD-HSP) of 1-5:100,000 [Ruano et al 2014].

Among AD-HSPs, *SPAST* is the most frequently associated gene in both familial and simplex cases [Lo Giudice et al 2014, Ruano et al 2014]. Reports from many European countries as well as the US, Canada, Japan, and China appear to indicate that *SPAST*-HSP accounts for 40% of inherited AD-HSPs and 20% of simplex HSPs [Erichsen et al 2009a, Takiyama et al 2010, Fei et al 2011, Lo Giudice et al 2014, Ruano et al 2014].

Geographic prevalence may vary; Meijer et al [2002] found fewer families with *SPAST*-HSP among North American families than expected from reports in European families.

Genetically Related (Allelic) Disorders

Some individuals with a *SPAST* pathogenic variant have lower motor neuron degeneration, leading to an ALS-like phenotype [Meyer et al 2005, Parodi et al 2017].

Differential Diagnosis

See Hereditary Spastic Paraplegia Overview for a review of the differential diagnosis.

SPAST-HSP is the most frequently occurring form of autosomal dominant hereditary spastic paraplegia, accounting for an estimated 40% of AD-HSP [Lo Giudice et al 2014]. Because *SPAST* is the most commonly involved gene in AD-HSP, it is the first and most relevant gene to be tested. The other main types of autosomal dominant pure spastic paraplegia to consider are SPG3A, SPG31, and SPG10.

With the exceptions of SPG3A, SPG31, and SPG10, no significant differences have been established between SPG4 and other types of pure dominant spastic paraplegia.

Table 2. Other Types of Autosomal Dominant Pure Spastic Paraplegia (AD-HSP) to Consider in the Differential Diagnosis of *SPAST*-HSP

Gene(s)	Disorder	Clinical Features Distinguishing the Disorder from *SPAST*-HSP
ATL1	SPG3A	• Earlier onset (often age <10 yrs) • More muscle wasting in lower limbs & scoliosis • Fewer sphincter disturbances • Less frequent impairment of vibration sense at the ankles & ↑ reflexes in upper limbs • 2nd most common type of AD-HSP
KIF5A	SPG10 (OMIM 604187)	More frequent peripheral neuropathy, amyotrophy, or parkinsonism
REEP1	SPG31 (OMIM 610250)	• More frequent peripheral neuropathy or amyotrophy • 3rd most common type of AD-HSP

In simplex cases (i.e., spasticity in one individual in a family), all possible causes of spasticity in the legs must be considered because several non-genetic causes of spasticity are more common than *SPAST*-HSP.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spastic paraplegia 4 (*SPAST*-HSP), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neuro-urologic examination is advised for individuals who have sphincter disturbances.
- Whether neuropsychological testing should be performed to assess the cognitive impairment frequently reported in individuals with *SPAST*-HSP remains unclear. So far, no consensus exists on the type of tests that should be performed, or on the timing or purpose of the tests. Considering that cognitive impairment is often absent or is detectable only by neuropsychological testing, one should be wary of increasing the burden of individuals with *SPAST*-HSP, and probably only recommend further testing when required by the affected individual.

- Electrophysiologic investigations may be advisable in case of pain and/or edema in the lower limbs to evaluate for associated neuropathy. Neuropathy, while not a feature of *SPAST*-HSP per se, may occur in individuals with *SPAST*-HSP for other reasons and should be investigated and adequately treated. Because of the underlying HSP, the neuropathy may remain undiagnosed if routine investigations are not conducted.
- Spinal MRI examination to exclude any additional degenerative disorder can be considered if unusual symptoms or pain are present.
- Consultation with a clinical geneticist and/or genetic counselor is appropriate.

Treatment of Manifestations

Treatment is symptomatic as there is still no curative or disease-modifying treatment for *SPAST*-HSP. Care by a multidisciplinary team that includes a general practitioner, neurologist, clinical geneticist, physiotherapist, physical therapist, social worker, and psychologist should be considered.

Symptomatic treatment includes use of the following:

- Antispastic drugs for leg spasticity
- Anticholinergic antispasmodic drugs for urinary urgency
- Regular physiotherapy for stretching of spastic muscles. Stretching should be done manually at all levels (hips, knees, ankles) and preceded by heat conditioning. Early regular physiotherapy can prevent contractures to a certain extent. Intensive and early physiotherapy delays the development of symptoms related to spasticity and prolongs the ability to walk [Author, personal observation]. To date, the effectiveness of physical therapy in individuals with HSP is only documented in a small number of case reports and uncontrolled studies.

Botulinum toxin and intrathecal baclofen can be proposed when oral drugs are ineffective and spasticity is severe and disabling. In children, orthopedic treatment and botulinum toxin injections may also contribute to better ambulatory function. A recent study of a mixed cohort of 33 individuals with HSP suggested that botulinum toxin-A injections provide some benefits, not only for spasticity, but also for fatigue [Servelhere et al 2018]. However, studies are scarce and more systematic studies are needed to confirm these observations.

Urodynamic evaluation should be performed early in all affected individuals complaining of urgency or other problems, such as voiding difficulties, urine retention, and/or frequent urinary infections. Such symptoms should be monitored and treated according to individual needs and disease evolution. Follow up of the sphincter disturbances is important to prevent bladder dysfunction. Treatment options include anticholinergic drugs and intravesical botulinum-toxin injections [Joussain et al 2019].

Surveillance

Specialized outpatient evaluations are suggested every six to 12 months to update medications and physical rehabilitation.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

A double-blind crossover trial with gabapentin did not show improvement of spasticity in persons with *SPAST*-HSP [Scheuer et al 2007].

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

Spastic paraplegia 4 (*SPAST*-HSP) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Individuals diagnosed with *SPAST*-HSP usually have a symptomatic parent who has the *SPAST* pathogenic variant; however, a parent with the *SPAST* pathogenic variant may have no symptoms.
- An individual with *SPAST*-HSP may, more rarely, have the disorder as the result of a *de novo* pathogenic variant [Parodi et al 2018].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include neurologic examination for evidence of spasticity and molecular genetic testing if a *SPAST* pathogenic variant has been identified in a family member.
- 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. Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.
- The family history of some individuals diagnosed with *SPAST*-HSP may appear to be negative because of failure to recognize the disorder in family members, reduced (age-related) penetrance, or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected or has the pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Note: Significant intrafamilial variability in age of onset and clinical severity is observed in *SPAST*-HSP.
- If the proband has a known *SPAST* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents of a proband are clinically unaffected but have not undergone molecular genetic testing, sibs of the proband are still presumed to be at increased risk for *SPAST*-HSP because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *SPAST*-HSP has a 50% chance of inheriting the 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 or has the *SPAST* variant present in the affected family member, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once a *SPAST* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of at-risk individuals age <18 years)

- For asymptomatic minors at risk for typically adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.
- In a family with an established diagnosis of *SPAST*-HSP, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once a *SPAST* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Because of variable clinical expression, the results of prenatal testing cannot be used to predict whether an individual will develop *SPAST*-HSP and, if so, what the age of onset, clinical course, or degree of disability will be.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  eurohsp.eu
- **HSP Research Foundation**
  Australia
  Email: inquiries@hspersunite.org.au
  hspersunite.org.au
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  Email: information@sp-foundation.org
  sp-foundation.org
- **Tom Wahlig Foundation**
  Tom Wahlig Stiftung
  Germany
  hsp-info.de/en/foundation.htm
- **A.I. Vi.P.S.**
  Associazione Italiana Vivere la Paraparesi Spastica
  Italy
  Phone: 39 392 9825622
  Email: info@aivips.it
  aivips.it
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Hereditary Spastic Paraplegia
- **Norsk forening for Arvelig-Spastisk Paraparese / Ataksi (NASPA)**
  The Norwegian association for individuals with hereditary spastic paraplegia and ataxia
  PO Box 9217
  Oslo 0134
  Norway
  Phone: 47 24 10 24 00
  Fax: 47 24 10 24 99
  Email: naspa@nhf.no
  www.naspa.no

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Spastic Paraplegia 4: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SPAST	2p22.3	Spastin	SPAST database	SPAST	SPAST

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Spastic Paraplegia 4 (View All in OMIM)

182601	SPASTIC PARAPLEGIA 4, AUTOSOMAL DOMINANT; SPG4
604277	SPASTIN; SPAST

Molecular Pathogenesis

Introduction. *SPAST* encodes a 616-amino acid protein named spastin, a putative nuclear member of the AAA (ATPases associated with diverse cellular activities). Claudiani et al [2005] have shown that two spastin isoforms – M1 and M87, of 68 kd and 60 kd, respectively – were synthesized from the *SPAST* mRNA through usage of two different translational start sites. Spastin-M87 was detected in both spinal cord and cerebral cortex, whereas appreciable levels of spastin-M1 were observed only in spinal cord [Solowska et al 2010].

Spastin is widely expressed in the neurons of the central nervous system, including the cortex and striatum. Distal degeneration of long tracts in the spinal cord is associated with a microglial reaction [Wharton et al 2003]. In addition, the presence of a large number of thin axons in the pyramidal tracts may suggest the existence of a regeneration process [Parodi et al 2018]. Tau-pathology outside the motor system may also be observed [Wharton et al 2003] but is not common to all the analyzed cases [Parodi et al 2018].

Within the cells, spastin acts as a microtubule-severing protein and is responsible for different aspects of microtubule dynamics, such as their length, number, and mobility [Errico et al 2002]. Four proteic domains allow spastin to accomplish its enzymatic function, as well as to interact with other proteins.

- Spastin N-terminal domain is involved in both lipid metabolism [Papadopoulos et al 2015] and endoplasmic reticulum morphogenesis, after interacting with ATL1/SPG3A and REEP1/SPG31 [Park et al 2010].
- The microtubule-interacting and trafficking domain (MIT) allows spastin to interact with CHIMP1 and IST1, two proteins belonging to the endosomal-sorting complex required for transport (ESCRT-III), being therefore involved in both cytokinesis and endosomal-tubule recycling [Reid et al 2005, Connell et al 2009, Allison et al 2013].
- The microtubule-binding domain (MTBD) and the AAA ATPase cassette are responsible for the microtubule binding and ATP hydrolysis [White et al 2007].

Mechanism of disease causation. Spastin loss of function, and consequent haploinsufficiency, has been proposed as the mechanism of disease causation: the majority of *SPAST* pathogenic variants affect the AAA cassette domain and almost 20% of affected individuals were found to have large deletions [Depienne et al 2007a, Parodi et al 2018]. In addition, reduced spastin mRNA was observed in individuals with premature protein termination [Bürger et al 2000].

An alternative to the loss-of-function model, the finding that *SPAST* pathogenic variants in the AAA domain led to constitutive binding to microtubules, could suggest a dominant-negative effect [Errico et al 2002]. The abnormal spastin-microtubule interaction was observed leading to organelle transport impairments, possibly underlying degeneration of the corticospinal axons [McDermott et al 2003].

An additional alternative hypothesis was recently proposed by Solowska et al [2010] and Solowska et al [2014]. After observing that some of the *SPAST* pathogenic variants located outside the AAA cassette may act through another pathogenic mechanism, they generated a mouse model overexpressing human spastin and carrying a *SPAST* pathogenic variant. Adult homozygous mice presented with spastic-like tremors and gait impairments as well as decreased microtubule stability, leading the researchers to conclude in favor of a gain (rather than loss) -of-function mechanism [Qiang et al 2019].

In conclusion, the debate concerning *SPAST*-HSP pathogenic mechanism remains open. It must be emphasized that the *SPAST* mutation spectrum, which mostly includes pathogenic variants introducing premature termination codons and therefore leading to degradation of the mRNA by nonsense-mediated decay, argues in favor of haploinsufficiency (i.e., disease occurs once the level of functional spastin falls below a critical level), rather than a dominant-negative effect [Patrono et al 2002, Schickel et al 2007]. The recent observation that missense pathogenic variants are associated with earlier onset [Parodi et al 2018] may suggest, in specific cases, the existence of pathogenic mechanisms other than haploinsufficiency.

***SPAST*-specific laboratory considerations.** *SPAST* undergoes alternate splicing with variable inclusion of exon 4. No pathogenic variants have been reported in exon 4, however, suggesting that the isoform lacking exon 4 is the predominant functional form of spastin in the adult nervous system. This transcript variant is NM_199436.1 (see Table A, **Gene**).

Both exon/multiexon deletions and duplications may be pathogenic *SPAST* variants.

Table 3. Notable *SPAST* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_014946.3 NP_055761.2	c.131C>T	p.Ser44Leu	Earlier disorder onset, more severe phenotype [Svenson et al 2004, McDermott et al 2006]
	c.134C>A	p.Pro45Gln	Earlier disorder onset, more severe phenotype [Svenson et al 2004, McDermott et al 2006]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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Published Guidelines / Consensus Statements

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Chapter Notes

Author History

Christel Depienne, PhD; Hôpital Pitié Salpêtrière (2003-2019)
Alexandra Durr, MD, PhD (2003-present)
Livia Parodi, PhD (2019-present)
Siri Lynne Rydning, MD (2019-present)
Chantal Tallaksen, MD, PhD (2003-present)

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