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Spastic Paraplegia 3A

Synonyms: *ATL1*-HSP, SPG3A

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Summary

Clinical characteristics

Spastic paraplegia 3A (SPG3A; also known as *ATL1*-HSP) is characterized by progressive bilateral and mostly symmetric spasticity and weakness of the legs. Compared to other forms of autosomal dominant hereditary spastic paraplegia (HSP), in which diminished vibration sense (caused by degeneration of the corticospinal tracts and dorsal columns) and urinary bladder hyperactivity are present in all affected individuals, these findings occur in a minority of individuals with SPG3A. The average age of onset is four years. More than 80% of reported individuals manifest spastic gait before the end of the first decade of life. Most persons with early-onset *ATL1*-HSP have a "pure" ("uncomplicated") HSP; however, complicated HSP with axonal motor neuropathy and/or distal amyotrophy with lower motor neuron involvement (Silver syndrome phenotype) has been observed. The rate of progression in *ATL1*-HSP is slow, and wheelchair dependency or need for a walking aid (cane, walker, or wheelchair) is relatively rare.

Diagnosis/testing

The diagnosis of *ATL1*-HSP is established in a proband with suggestive findings and almost exclusively a heterozygous pathogenic variant in *ATL1* identified by molecular genetic testing. Note: The exceptions are two families with biallelic *ATL1* pathogenic variants.

Management

Treatment of manifestations: Treatment is symptomatic. Medical treatment of spasticity may begin with oral baclofen or tizanidine, followed by chemodenervation with botulinum A or B toxins if oral antispasticity medications are not tolerated. Intrathecal baclofen pump may be considered for those who improve on oral baclofen but have significant systemic adverse effects. Medical therapy should be combined with intensive physical therapy focused on stretching and strengthening exercises that may help delay or minimize muscle tendon contractures, scoliosis, and foot deformities. Distal weakness (typically affecting foot dorsiflexion) can be ameliorated by ankle-foot orthoses. Urinary urgency can be treated with anticholinergic antispasmodic drugs.

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Surveillance: No consensus exists regarding the frequency of clinical follow-up visits, but reevaluation once or twice yearly to identify and treat new complications is recommended.

Agents/circumstances to avoid: Dantrolene, as it can induce irreversible weakness, adversely affecting mobility.

Genetic counseling

ATL1-HSP is almost exclusively inherited in an autosomal dominant manner. More than 95% of individuals diagnosed with SPG3A have an affected parent; the proportion of individuals with *ATL1*-HSP caused by a *de novo* pathogenic variant is currently unknown. Each child of an individual with *ATL1*-HSP has a 50% chance of inheriting the pathogenic variant. Once the *ATL1* pathogenic variant has been identified in a family member with autosomal dominant *ATL1*-HSP, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Spastic paraplegia 3A (SPG3A; also known as *ATL1*-HSP) **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings

- Early age of onset, from infancy to ten years (average age: 4 years)
- Progressive bilateral and mostly symmetric lower-extremity weakness and spasticity resulting from axonal degeneration of the corticospinal tracts
- Diminished vibration sense caused by impairment of dorsal columns
- Urinary bladder hyperactivity

Family history consistent with autosomal dominant inheritance, including affected males and females in multiple generations and simplex cases (i.e., a single occurrence in a family). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ATL1*-HSP **is established** in a proband with suggestive findings and almost exclusively a heterozygous pathogenic variant in *ATL1* identified by molecular genetic testing (see Table 1). Note: The exceptions are two families with biallelic *ATL1* pathogenic variants.

Note: Identification of a heterozygous *ATL1* variant of uncertain significance does not establish or rule out a diagnosis of *ATL1*-HSP.

Molecular genetic testing approaches can include a combination of **gene-targeted 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. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *ATL1*-HSP has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A hereditary spastic paraplegia (HSP) multigene panel that includes *ATL1* 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 3A

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ATL1	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	One reported [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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. Dürr et al [2004], Ivanova et al [2007], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as 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. Meijer et al [2007]

Clinical Characteristics

Clinical Description

Spastic paraplegia 3A (SPG3A; also known as *ATL1*-HSP) is characterized by slowly progressive bilateral and mostly symmetric spasticity and weakness of the legs, and with a variable degree of diminished vibration sense (caused by degeneration of the corticospinal tracts and dorsal columns) and urinary bladder hyperactivity. The average age of onset is four years; more than 80% of affected individuals manifest spastic gait before age ten years. The rate of progression is slow; wheelchair dependency or need for an assistive walking device is relatively rare.

Most persons with early-onset *ATL1*-HSP have a "pure" or "uncomplicated" hereditary spastic paraplegia (HSP) phenotype. However, complex HSP phenotypes with axonal motor neuropathy and/or distal amyotrophy (like that observed in the Silver syndrome phenotype) have also been reported [Scarano et al 2005, Ivanova et al 2007, Salameh et al 2009]. In complicated forms with spastic quadriparesis, involvement of bulbar muscles can result in dysphagia and dysarthria [Yonekawa et al 2014].

Findings also seen in *ATL1*-HSP can include pes cavus deformities and scoliosis, possibly attributable to the early age of onset.

Other phenotypes observed in the spectrum of *ATL1*-HSP include the following:

- Adult-onset *ATL1*-HSP. Although it has been suggested that *ATL1*-HSP is a neurodevelopmental rather than a neurodegenerative disorder, identification of individuals with adult-onset *ATL1*-HSP argues strongly against this hypothesis [Sauter et al 2004, Zhu et al 2006]. Persons with adult-onset *ATL1*-HSP also tend to experience slower disease progression.
- Hereditary sensory neuropathy type ID (HSN1D), an axonal form of autosomal dominant hereditary motor and sensory neuropathy distinguished by prominent sensory loss that leads to painless injuries. A pathogenic *ATL1* missense variant was identified in a single family with HSN1D, in whom other known causative genes had been excluded [Guelly et al 2011, Leonardis et al 2012]. Two additional *ATL1* variants were identified in 115 unrelated individuals with the HSN1D phenotype [Guelly et al 2011].
- Clinical presentation with a pure autonomic failure followed by the development of spastic paraplegia was reported in one individual with a novel pathogenic *ATL1* splice site variant in exon 2 [Shin et al 2014]. Whether this represents an allelic condition or an atypical presentation of *ATL1*-HSP remains to be elucidated.
- Clinical presentation mimicking a severe neonatal-onset cerebral palsy with quadriparesis was reported in an individual with a *de novo ATL1* pathogenic variant [Yonekawa et al 2014]. The individual also experienced abnormal speech and swallowing with pseudobulbar palsy. Electrophysiologic studies showed axonal polyneuropathy.

Findings not universally seen in *ATL1*-HSP compared to other forms of autosomal dominant HSP include the following [Dürr et al 2004]:

- Hyperreflexia of the upper extremities
- Impairment of vibration sensation at the ankles
- Urinary bladder hyperactivity

Genotype-Phenotype Correlations

No specific genotype-phenotype correlations have been reported; however:

- Early-onset disease has been associated with missense variants around the GTPase binding domain.
- Late-onset disease has been associated with frameshift variants in the C terminus that result in premature truncation of the protein, as well as some missense variants in the GTPase binding domain [Tessa et al 2002, Sauter et al 2004].

Penetrance

Overall, penetrance of pathogenic variants is high (~80%-90%) [Dürr et al 2004]. In many familial cases, individuals with a heterozygous *ATL1* pathogenic variant had a normal neurologic examination even at an advanced age, arguing against significant age-dependent penetrance [Dürr et al 2004].

The lowest penetrance, 30%, was reported for the p.Arg415Trp heterozygous pathogenic variant detected in three affected individuals but also in nine unaffected family members [D'Amico et al 2004]. Reduced penetrance

of this variant was also observed in additional families in which mostly females were unaffected, suggesting (incorrectly) X-linked inheritance [Varga et al 2013].

Prevalence

Prevalence of autosomal dominant (AD) HSP has been estimated at 0.5-5:100,000 [McMonagle et al 2002, Ruano et al 2014].

SPG3A is the third most common cause of AD HSP in all age groups. Metanalysis of epidemiologic studies suggested that SPG3A accounts for about 5% of all AD HSP, with an estimated prevalence of 0.025-0.25:100,000 [Erfanian Omidvar et al 2021]. This estimated frequency of SPG3A is lower than previously reported, at 10%-15% of all AD HSP [Fink et al 1996].

SPG3A, the most common cause of early onset of AD HSP before age ten years, accounts for 40% of AD HSP in this age group [Dürr et al 2004].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ATL1*.

Differential Diagnosis

Hereditary spastic paraplegia (HSP) is a progressive condition with a gradual worsening of spasticity and weakness of the lower extremities. Overall, the age of onset, disease severity, and rate of progression differ among different types of autosomal dominant (AD) HSP; there is also considerable variability within the same genetic forms of HSP. For a general discussion of the differential diagnosis of spastic paraplegia/paraparesis syndrome, see Hereditary Spastic Paraplegia Overview.

ATL1 pathogenic variants have been confirmed as the most common cause of early-onset HSP, accounting for approximately 30%-50% of all AD HSP with onset before age ten years [Abel et al 2004, Dürr et al 2004].

Spastic paraplegia 3A (SPG3A; also known as *ATL1*-HSP) accounts for approximately 5% of all AD HSP [Erfanian Omidvar et al 2021], which is lower than previous estimates of 10%-15% [Fink et al 1996]. In an analysis of a large cohort of individuals in whom a *SPAST* (formerly known as *SPG4*) pathogenic variant was not identified, 40% had pathogenic variants in *ATL1* [Dürr et al 2004].

ATL1-HSP needs to be differentiated from other forms of AD HSP (see Table 2).

Table 2. Autosomal Dominant Hereditary Spastic Paraplegias of Interest in the Differential Diagnosis of Spastic Paraplegia 3A

Gene	Disorder	Clinical Features of Differential Diagnosis Disorder [1]
KIF5A	SPG10	• Axonal motor neuropathy common [2] • Probably 2nd most common cause of early-onset AD HSP
NIPA1	SPG6	• Occasionally manifests in infancy [3] • Probably most aggressive form of AD HSP • → wheelchair dependency in a relatively short period of time
REEP2	SPG72	• Early age of onset (age <4 yrs) • Mild postural tremor common [4]
SLC33A1	SPG42	• May have onset in 1st decade • Mild, minimally progressive clinical course • Pes cavus & distal amyotrophy common [5] • Reported in a single family

Table 2. continued from previous page.

Gene	Disorder	Clinical Features of Differential Diagnosis Disorder [1]
SPAST	SPG4	• Occasionally presents in infancy • Tends to have more progressive course [4] • Most common type of AD HSP
RTN2	SPG12	• Usual onset age <10 yrs [6] • Uncomplicated phenotype

AD HSP = autosomal dominant hereditary spastic paraplegia
1. See Hereditary Spastic Paraplegia Overview.
2. Reid et al [2002]
3. Bien-Willner et al [2006]
4. Esteves et al [2014]
5. Blair et al [2007]
6. Montenegro et al [2012]

Cerebral palsy. Additional considerations for *ATL1*-HSP include a diplegic or quadriplegic form of cerebral palsy, as the majority of such individuals tend to have very early onset of clinical manifestations and a slow progression, which may suggest a static clinical course [Rainier et al 2006, Yonekawa et al 2014, Andersen et al 2016]. The presence of a positive family history with an affected parent typically does not present any diagnostic dilemmas. However, incomplete penetrance or a *de novo ATL1* pathogenic variant (i.e., an apparently negative family history) may lead to the diagnosis of diplegia caused by periventricular leukomalacia or perinatal hypoxic-ischemic injury. Normal pre- and perinatal history and unremarkable neuroimaging should prompt consideration of HSP, including *ATL1*-HSP.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spastic paraplegia 3A (SPG3A; also known as *ATL1*-HSP), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Spastic Paraplegia 3A

System/Concern	Evaluation	Comment
Spasticity	Neurologic exam	Assess degree of spasticity. [1]
Motor & sensory neuropathy		NCV, EMG
Musculoskeletal	Physical medicine & rehabilitation / PT eval	To include assessment of: • Muscle tone; joint range of motion; posture; mobility; strength, coordination, & endurance; pain; bedsores • Need for adaptive devices • Footwear needs • Physical therapy needs
	Orthopedics	To assess for scoliosis, foot deformities
	OT	• To assess small motor function, e.g., hands, feet, face, fingers, & toes • To assess ADL
Bladder function	Referral to urologist; consider urodynamic eval.	To address spastic bladder symptoms: urgency, frequency, difficulty voiding

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Bowel function	Referral to gastroenterologist	To assess constipation & fecal incontinence [1]
Bulbar muscle weakness	Assessment by speech/language pathologist	• Speech disorder (dysarthria) • Swallowing disorder (dysphagia)
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *ATL1*-HSP to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for caregiver support.	

Based on information provided by Spastic Paraplegia Foundation
ADL = activities of daily living; EMG = electromyography; MOI = mode of inheritance; NCV = nerve conduction velocity; OT = occupational therapy; PT = physical therapy
1. Spastic Paraplegia Rating Scale (SPRS) [Schüle et al 2006]
2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Treatment for spasticity, distal weakness, and urinary bladder dysfunction (the primary manifestations of *ATL1*-HSP) is symptomatic. See Table 4.

Management by multidisciplinary specialists including a physiatrist, physical therapist, and speech therapist is recommended.

Table 4. Treatment of Manifestations in Individuals with Spastic Paraplegia 3A

Manifestation/Concern	Treatment	Considerations/Other
Spasticity / Distal weakness	Individualized PT program	• Stretching exercises to improve flexibility, ↓ spasticity, & maintain or improve joint range of motion & prevent joint contractures [1] • Aerobic exercise to improve cardiovascular fitness to maintain & improve muscle strength, coordination, & balance • Strengthening exercises to improve posture, walking, arm strength to improve use of mobility aids, ADL
	Reduction of spasticity	• Massage, ultrasound, electrical stimulation, whirlpool • Anodal spinal direct current stimulation [2]
	Antispasmodic drugs	Baclofen, botulinum toxin, dantrolene, tizanidine (used 1 at a time), [3] especially early in disease course to ↓ cramps, make leg muscles less tight, & facilitate walking
Musculoskeletal	Correction & stabilization of scoliosis	Orthopedic consult for management of scoliosis: bracing, possible spinal surgery
	Correction of pes cavus	Physical therapy for pes cavus, orthotics, botulinum toxin therapy, possible corrective surgery by orthopedic surgery
Bladder dysfunction	Spastic bladder symptoms: urgency, frequency, difficulty voiding, incontinence	Treatment can incl anticholinergics such as oxybutynin (Ditropan XL®), solifenacin (Vesicare®), and mirabegron (Myrbetriq®).

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Dysphagia	Gastroenterologist / nutrition / feeding team eval	• Determine exact cause of swallowing malfunction. • Modify food types & consistency, head positioning during swallowing, & exercises to improve swallowing.
Dysarthria	Speech/language pathologist	To help maintain vocal control, improve speech, breathing techniques, & communication in general
Bowel function	Symptoms: constipation & fecal incontinence	Stool softeners
Mobility & ADL	PT	• Feet: appropriate footwear; orthotics (shoe inserts, splints, braces) to address gait problems, improve balance, relieve &/or improve pressure sores • Gait training; use of assistive walking devices (e.g., canes, walker, walker w/wheels, walker w/seat, wheelchairs) • Transfers (e.g., from bed to wheelchair, wheelchair to car) • Training how to fall to minimize risk of injury
	OT	• To accomplish tasks such as mobility, washing, dressing, eating, cooking, grooming • To assist w/household modifications to meet special needs
Social support	Social services & support groups	To help cope w/diagnosis

ADL = activities of daily living; OT = occupational therapy/therapist; PT = physical therapy/therapist
1. The role of surgical hamstring and heel cord lengthening and release of the adductor longus remains unknown, but should be considered if contractures appear.
2. Demonstrated by Ardolino et al [2021] in a randomized controlled trial
3. Baclofen can be tried first, and can be used with an intrathecal pump in some cases. The entire therapeutic range of doses in all four drugs is used. The drugs are administered before sleep if nocturnal cramps are problematic, otherwise three to four times per day. It usually takes a few days for their effects to become evident. No significant toxicity limits their use.

Surveillance

There is no consensus regarding the frequency of clinical follow-up visits, but routine reevaluations are warranted (see Table 5).

Table 5. Recommended Surveillance for Individuals with Spastic Paraplegia 3A

System/Concern	Evaluation	Frequency
Spasticity	Neurologic exam re disease progression & response to current treatment	1-2x/yr
Bladder function	Per treating urologist, incl monitoring for urinary tract infection	
Dysphagia	Gastroenterologist / nutrition / feeding team re nutrition & risk for aspiration	
Dysarthria	Per neurologic assessment & speech/language assessment	
Scoliosis	General medical exam of musculoskeletal system	
Bowel function	Per symptoms	
Mobility & ADL	Rehabilitation medicine, PT, & OT	

ADL = activities of daily living; OT = occupational therapist; PT = physical therapist

Agents/Circumstances to Avoid

Dantrolene should be avoided in persons who are ambulatory as it may induce irreversible weakness, which can adversely affect overall mobility.

Evaluation of Relatives at Risk

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

Pregnancy Management

The use of regional anesthesia, such as spinal or epidural anesthesia, during delivery in women with *ATL1*-HSP and spinal cord involvement has traditionally been avoided due to the theoretic risk of exacerbating the degree of weakness and spasticity. However, several instances of successful regional anesthesia in individuals with hereditary spastic paraplegia have been reported [Thomas et al 2006, Ponsonnard et al 2017].

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. Note: There may not be clinical trials for this disorder.

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 3A (SPG3A; also known as *ATL1*-HSP) is almost exclusively inherited in an autosomal dominant manner.

Autosomal recessive inheritance of *ATL1*-HSP has been reported in two families [Khan et al 2014, Willkomm et al 2016]. For information about genetic counseling issues related to autosomal recessive inheritance, see Hereditary Spastic Paraplegia Overview.

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- Most individuals (>95%) diagnosed with *ATL1*-HSP have an affected parent.
- A proband with *ATL1*-HSP may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals diagnosed with *ATL1*-HSP as the result of a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant (i.e., a proband who appears to represent a simplex case).

- 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.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.

- The family history of some individuals diagnosed with *ATL1*-HSP may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate 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 genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *ATL1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%. A sib who inherits a familial *ATL1* pathogenic variant is likely to develop clinical manifestations of the disorder. (Overall penetrance of *ATL1* pathogenic variants is high; only three families with incomplete penetrance have been reported in the literature [D'Amico et al 2004, Varga et al 2013].) Intrafamilial variability in SPG3A is less common than in other types of hereditary spastic paraplegia.
- If the *ATL1* pathogenic variant identified in the proband 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 have not been tested for the *ATL1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low (<5%). However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *ATL1*-HSP because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant *ATL1*-HSP has a 50% chance of inheriting the *ATL1* 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 an *ATL1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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 the *ATL1* pathogenic variant has been identified in a family member with autosomal dominant *ATL1*-HSP, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is 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.

- **HSP Research Foundation**
  Australia
  Email: inquiries@hspersunite.org.au
  hspersunite.org.au
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Hereditary Spastic Paraplegia
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  Email: information@sp-foundation.org
  sp-foundation.org

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 3A: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATL1	14q22.1	Atlastin-1	ATL1 homepage - Leiden Muscular Dystrophy pages	ATL1	ATL1

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 3A (View All in OMIM)

182600	SPASTIC PARAPLEGIA 3, AUTOSOMAL DOMINANT; SPG3A
606439	ATLASTIN GTPase 1; ATL1
613708	NEUROPATHY, HEREDITARY SENSORY, TYPE ID; HSN1D

Molecular Pathogenesis

ATL1 encodes atlastin-1, which belongs to the subclass of GTPases called dynamins. Dynamins play a role in vesicle transport, especially in the process of recycling of the vesicles. Atlastin-1 has two transmembrane domains and a GTP binding domain with catalytic activity [Zhu et al 2003]. Atlastin-1 is predominantly expressed in the pyramidal neurons giving the origin to the pyramidal tracts which undergo axonal degeneration in individuals with *ATL1*-HSP. It localizes predominantly to the endoplasmic reticulum (ER) and Golgi complex but is also found in other subcellular compartments, including the axonal growth cones [Zhu et al 2003, Zhu et al 2006, Hu et al 2009, Park et al 2010].

Atlastin-1 interacts with spastin, encoded by *SPAST*, in which heterozygous pathogenic variants cause spastic paraplegia 4 (also known as *SPAST*-HSP), the most common cause of autosomal dominant hereditary spastic paraplegia [Sanderson et al 2006].

Mechanism of disease causation. A gain-of-function or dominant-negative mechanism has been proposed based on the following observations:

- Most disease-causing missense variants cluster around the GTPase domain, resulting in reduction of catalytic activity.
- Atlastin-1 forms tetrameric complexes; therefore, heterocomplexes of normal and abnormal atlastin-1 may interfere with tetramer activity [Zhu et al 2003].
- Expression of pathogenic variants of atlastin-1 results in abnormal connectivity of ER complex. These ER-shaping defects may represent a novel neuropathogenic mechanism [Hu et al 2009].
- Atlastin-1 is expressed in neuronal growth cones. Knockdown of atlastin-1 expression was found to impair axonal elongation [Zhu et al 2006].

Table 6. Notable *ATL1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_015915.4 NP_056999.2	c.470T>G	p.Leu157Trp	Rainier et al [2006]
	c.715C>T (884C>T)	p.Arg239Cys	Recurrent variant, possibly caused by methylated CpG dinucleotide hot spot [Zhao et al 2001]
	c.1243C>T	p.Arg415Trp	This variant shows incomplete penetrance [D'Amico et al 2004].

Variants listed in the table have been provided by the author. *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.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

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Revision History

- 18 June 2020 (bp) Comprehensive update posted live
- 11 December 2014 (me) Comprehensive update posted live
- 9 February 2012 (cd) Revision: single-exon deletion in *ATL1* found to cause SPG3A [Sulek et al 2013]; HSN ID identified as allelic disorder
- 21 September 2010 (me) Review posted live
- 26 April 2010 (ph) Original submission

References

Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 7-12-22.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 7-12-22.

Literature Cited

Abel A, Fonknechten N, Hofer A, Dürr A, Cruaud C, Voit T, Weissenbach J, Brice A, Klimpe S, Auburger G, Hazan J. Early onset autosomal dominant spastic paraplegia caused by novel mutations in SPG3A. Neurogenetics. 2004;5:239–43. PubMed PMID: 15517445.

Andersen EW, Leventer RJ, Reddihough DS, Davis MR, Ryan MM. Cerebral palsy is not a diagnosis: a case report of a novel atlastin-1 mutation. J Paediatr Child Health. 2016;52:669–71. PubMed PMID: 27333849.

Ardolino G, Bocci T, Nigro M, Vergari M, Di Fonzo A, Bonato S, Cogiamanian F, Cortese F, Cova I, Barbieri S, Priori A. Spinal direct current stimulation (tsDCS) in hereditary spastic paraplegias (HSP): a sham-controlled crossover study. J Spinal Cord Med. 2021;44:46–53. PubMed PMID: 30508408.

Bien-Willner R, Sambuughin N, Holley H, Bodensteiner J, Sivakumar K. Childhood-onset spastic paraplegia with NIPA1 gene mutation. J Child Neurol. 2006;21:974–7. PubMed PMID: 17092466.

Blair MA, Riddle ME, Wells JF, Breviu BA, Hedera P. Infantile onset of hereditary spastic paraplegia poorly predicts the genotype. Pediatr Neurol. 2007;36:382–6. PubMed PMID: 17560499.

D'Amico A, Tessa A, Sabino A, Bertini E, Santorelli FM, Servidei S. Incomplete penetrance in an SPG3A-linked family with a new mutation in the atlastin gene. Neurology. 2004;62:2138–9. PubMed PMID: 15184642.

Dürr A, Camuzat A, Colin E, Tallaksen C, Hannequin D, Coutinho P, Fontaine B, Rossi A, Gil R, Rousselle C, Ruberg M, Stevanin G, Brice A. Atlastin1 mutations are frequent in young-onset autosomal dominant spastic paraplegia. Arch Neurol. 2004;61:1867–72. PubMed PMID: 15596607.

Erfanian Omidvar M, Torkamandi S, Rezaei S, Alipoor B, Omrani MD, Darvish H, Ghaedi H. Genotype-phenotype associations in hereditary spastic paraplegia: a systematic review and meta-analysis on 13,570 patients. J Neurol. 2021;268:2065–82. PubMed PMID: 31745725.

Esteves T, Durr A, Mundwiller E, Loureiro JL, Boutry M, Gonzalez MA, Gauthier J, El-Hachimi KH, Depienne C, Muriel MP, Acosta Lebrigio RF, Gaussen M, Noreau A, Speziani F, Dionne-Laporte A, Deleuze J-F, Dion P, Coutinho P, Rouleau GA, Zuchner S, Brice A, Stevanin G, Darios F. Loss of association of REEP2 with membranes leads to hereditary spastic paraplegia. Am J Hum Genet. 2014;94:268–77. PubMed PMID: 24388663.

Fink JK, Heiman-Patterson T, Bird T, Cambi F, Dubé MP, Figlewicz DA, Haines JL, Hentati A, Pericak-Vance MA, Raskind W, Rouleau GA, Siddique T. Hereditary spastic paraplegia: advances in genetic research. Neurology. 1996;46:1507–14. PubMed PMID: 8649538.

Guelly C, Zhu PP, Leonardis L, Papić L, Zidar J, Schabhüttl M, Strohmaier H, Weis J, Strom TM, Baets J, Willems J, De Jonghe P, Reilly MM, Fröhlich E, Hatz M, Trajanoski S, Pieber TR, Janecke AR, Blackstone C, Auer-Grumbach M. Targeted high-throughput sequencing identifies mutations in atlastin-1 as a cause of hereditary sensory neuropathy type I. Am J Hum Genet. 2011;88:99–105. PubMed PMID: 21194679.

Hu J, Shibata Y, Zhu PP, Voss C, Rismanchi N, Prinz WA, Rapoport TA, Blackstone C. A class of dynamin-like GTPases involved in the generation of the tubular ER network. Cell. 2009;138:549–61. PubMed PMID: 19665976.

Ivanova N, Claeys KG, Deconinck T, Litvinenko I, Jordanova A, Auer-Grumbach M, Haberlova J, Löfgren A, Smeyers G, Nelis E, Mercelis R, Plecko B, Priller J, Zámecník J, Ceulemans B, Erichsen AK, Björck E, Nicholson G, Sereda MW, Seeman P, Kremensky I, Mitev V, De Jonghe P. Hereditary spastic paraplegia 3A associated with axonal neuropathy. Arch Neurol. 2007;64:706–13. PubMed PMID: 17502470.

Khan TN, Klar J, Tariq M, Anjum Baig S, Malik NA, Yousaf R, Baig SM, Dahl N. Evidence for autosomal recessive inheritance in SPG3A caused by homozygosity for a novel ATL1 missense mutation. Eur J Hum Genet. 2014;22:1180–4. PubMed PMID: 24473461.

Leonardis L, Auer-Grumbach M, Papić L, Zidar J. The N355K atlastin 1 mutation is associated with hereditary sensory neuropathy and pyramidal tract features. Eur J Neurol. 2012;19:992–8. PubMed PMID: 22340599.

McMonagle P, Webb S, Hutchinson M. The prevalence of "pure" autosomal dominant hereditary spastic paraparesis in the island of Ireland. J Neurol Neurosurg Psychiatry. 2002;72:43–6. PubMed PMID: 11784824.

Meijer IA, Dion P, Laurent S, Dupré N, Brais B, Levert A, Puymirat J, Rioux MF, Sylvain M, Zhu PP, Soderblom C, Stadler J, Blackstone C, Rouleau GA. Characterization of a novel SPG3A deletion in a French-Canadian family. Ann Neurol. 2007;61:599–603. PubMed PMID: 17427918.

Montenegro G, Rebelo AP, Connell J, Allison R, Babalini C, D'Aloia M, Montieri P, Schule R, Ishiura H, Price J, Strickland A, Gonzalez MA, Baumbach-Reardon L, Deconinck T, Huang J, Bernardi G, Vance JM, Rogers MT, Tsuji S, De Jonghe P, Pericak-Vance MA, Schöls L, Orlacchio A, Reid E, Züchner S. Mutations in the ER-shaping protein reticulon 2 cause the axon-degenerative disorder hereditary spastic paraplegia type 12. J Clin Invest. 2012;122:538–44. PubMed PMID: 22232211.

Park SH, Zhu PP, Parker RL, Blackstone C. Hereditary spastic paraplegia proteins REEP1, spastin, and atlastin-1 coordinate microtubule interactions with the tubular ER network. J Clin Invest. 2010;120:1097–110. PubMed PMID: 20200447.

Ponsonnard S, Damon A, Gueye EM. Anaesthesia and orphan disease: management of a case of Strumpell-Lorrain disease and review of the literature. Eur J Anaesthesiol. 2017;34:562–3. PubMed PMID: 28682816.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Rainier S, Sher C, Reish O, Thomas D, Fink JK. De novo occurrence of novel SPG3A/atlastin mutation presenting as cerebral palsy. Arch Neurol. 2006;63:445–7. PubMed PMID: 16533974.

Reid E, Kloos M, Ashley-Koch A, Hughes L, Bevan S, Svenson IK, Graham FL, Gaskell PC, Dearlove A, Pericak-Vance MA, Rubinsztein DC, Marchuk DA. A kinesin heavy chain (KIF5A) mutation in hereditary spastic paraplegia (SPG10). Am J Hum Genet. 2002;71:1189–94. PubMed PMID: 12355402.

Ruano L, Melo C, Silva MC, Coutinho P. The lobal epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. Neuroepidemiology. 2014;42:174–83. PubMed PMID: 24603320.

Salameh JS, Shenoy AM, David WS. Novel SPG3A and SPG4 mutations in two patients with Silver syndrome. J Clin Neuromuscul Dis. 2009;11:57–59. PubMed PMID: 19730024.

Sanderson CM, Connell JW, Edwards TL, Bright NA, Duley S, Thompson A, Luzio JP, Reid E. Spastin and atlastin, two proteins mutated in autosomal-dominant hereditary spastic paraplegia, are binding partners. Hum Mol Genet. 2006;15:307–18. PubMed PMID: 16339213.

Sauter SM, Engel W, Neumann LM, Kunze J, Neesen J. Novel mutations in the Atlastin gene (SPG3A) in families with autosomal dominant hereditary spastic paraplegia and evidence for late onset forms of HSP linked to the SPG3A locus. Hum Mutat. 2004;23:98. PubMed PMID: 14695538.

Scarano V, Mancini P, Criscuolo C, De Michele G, Rinaldi C, Tucci T, Tessa A, Santorelli FM, Perretti A, Santoro L, Filla A. The R495W mutation in SPG3A causes spastic paraplegia associated with axonal neuropathy. J Neurol. 2005;252:901–3. PubMed PMID: 15742100.

Schüle R, Holland-Letz T, Klimpe S, Kassubek J, Klopstock T, Mall V, Otto S, Winner B, Schöls L. The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. Neurology. 2006;67:430–4. PubMed PMID: 16894103.

Shin JW, Jung KH, Lee ST, Moon J, Seong MW, Park SS, Lee SK, Chu K. Novel mutation in the ATL1 with autosomal dominant hereditary spastic paraplegia presented as dysautonomia. Auton Neurosci. 2014;185:141–3. PubMed PMID: 24969372.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Sulek A, Elert E, Rajkiewicz M, Zdzienicka E, Stepniak I, Krysa W, Zaremba J. Screening for the hereditary spastic paraplaegias SPG4 and SPG3A with the multiplex ligation-dependent probe amplification technique in a large population of affected individuals. Neurol Sci. 2013;34:239–42. PubMed PMID: 22203332.

Tessa A, Casali C, Damiano M, Bruno C, Fortini D, Patrono C, Cricchi F, Valoppi M, Nappi G, Amabile GA, Bertini E, Santorelli FM. SPG3A: An additional family carrying a new atlastin mutation. Neurology. 2002;59:2002–5. PubMed PMID: 12499504.

Thomas I, Thomas M, Scrutton M. Spinal anaesthesia in a patient with hereditary spastic paraplegia: case report and literature review. Int J Obstet Anesth. 2006;15:254–6. PubMed PMID: 16798455.

Varga RE, Schule R, Fadel H, Valenzuela I, Speziani F, Gonzalez M, Rudenskaia G, Nurnberg G, Thiele H, Altmuller J, Alvarez V, Gamez J, Garbern JY, Nurnberg P, Zuchner S, Beetz C. Do not trust the pedigree: reduced and sex-dependent penetrance at a novel mutation hotspot in ATL1 blurs autosomal dominant inheritance of spastic paraplegia. Hum Mutat. 2013;34:860–3. PubMed PMID: 23483706.

Willkomm L, Heredia R, Hoffmann K, Wang H, Voit T, Hoffman EP, Cirak S. Homozygous mutation in Atlastin GTPase 1 causes recessive hereditary spastic paraplegia. J Hum Genet. 2016;61:571–3. PubMed PMID: 26888483.

Yonekawa T, Oya Y, Higuchi Y, Hashiguchi A, Takashima H, Sugai K, Sasaki M. Extremely severe complicated spastic paraplegia 3A with neonatal onset. Pediatr Neurol. 2014;51:726–9. PubMed PMID: 25193411.

Zhao X, Alvarado D, Rainier S, Lemons R, Hedera P, Weber CH, Tukel T, Apak M, Heiman-Patterson T, Ming L, Bui M, Fink JK. Mutations in a novel GTPase cause autosomal dominant hereditary spastic paraplegia. Nat Genet. 2001;29:326–31. PubMed PMID: 11685207.

Zhu PP, Patterson A, Lavoie B, Stadler J, Shoeb M, Patel R, Blackstone C. Cellular localization, oligomerization, and membrane association of the hereditary spastic paraplegia 3A (SPG3A) protein atlastin. J Biol Chem. 2003;278:49063–71. PubMed PMID: 14506257.

Zhu PP, Soderblom C, Tao-Cheng JH, Stadler J, Blackstone C. SPG3A protein atlastin-1 is enriched in growth cones and promotes axon elongation during neuronal development. Hum Mol Genet. 2006;15:1343–53. PubMed PMID: 16537571.

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