



Spastic Paraplegia 7

Synonym: Hereditary Spastic Paraplegia, Paraplegin Type

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Summary

Clinical characteristics

Spastic paraplegia 7 (SPG7) is characterized by insidiously progressive bilateral leg weakness and spasticity. Most affected individuals have decreased vibration sense and cerebellar signs. Onset is mostly in adulthood, although symptoms may start as early as age 11 years and as late as age 72 years. Additional features including ataxia (gait and limbs), spastic dysarthria, dysphagia, pale optic disks, ataxia, nystagmus, strabismus, ptosis, hearing loss, motor and sensory neuropathy, amyotrophy, scoliosis, *pes cavus*, and urinary sphincter disturbances may be observed.

Diagnosis/testing

The diagnosis of SPG7 is established in a proband with typical clinical findings and biallelic pathogenic variants in *SPG7* identified by molecular genetic testing.

Management

Treatment of manifestations: Drugs that may reduce spasticity and muscle tightness include baclofen, tizanidine, dantrolene, and diazepam. Physical therapy and assistive walking devices often reduce contractures, provide support, and promote stability. Occupational therapy and speech therapy help with activities of daily living.

Surveillance: Annual neurologic evaluation to identify potential complications of spasticity, such as contractures.

Genetic counseling

SPG7 is inherited in an autosomal recessive manner. Heterozygotes (carriers) are usually asymptomatic. Each sib of an affected individual 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. Carrier testing for at-risk relatives, prenatal testing for a

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pregnancy at increased risk and preimplantation genetic testing are possible if both pathogenic alleles have been identified in the family.

Diagnosis

Suggestive Findings

Spastic paraplegia 7 (SPG7) **should be suspected** in individuals with the following:

- Insidiously progressive bilateral leg weakness
- Spasticity
- Decreased vibratory sense
- Cerebellar signs
- Neurologic examination demonstrating EITHER of the following:
 - A pure phenotype of spastic paraplegia with hyperreflexia, extensor plantar responses, and mildly impaired vibration sensation in the distal legs
 - A complicated phenotype of spastic paraplegia including optic neuropathy, progressive external ophthalmoplegia/ptosis slowed speech, swallowing difficulties, palatal tremor, subtle cognitive impairment, urinary urgency, ataxia, nystagmus, strabismus, decreased hearing, scoliosis, *pes cavus*, motor and sensory neuropathy, and amyotrophy [Brugman et al 2008, Salinas et al 2008, Warnecke et al 2010, Pfeffer et al 2014]
- Neuroimaging findings of cerebellar atrophy (MRI) or white matter changes as detected by diffusion tensor imaging in the frontal lobes, the corticospinal tracts, and the brain stem
- Family history consistent with autosomal recessive inheritance

Establishing the Diagnosis

The diagnosis of SPG 7 **is established** in a proband with typical clinical findings and identification of biallelic pathogenic variants in *SPG7* by molecular genetic testing (see Table 1).

Note: A single *SPG7* pathogenic variant (p.Leu78*) was identified in a proband with a pure HSP phenotype suggesting that heterozygosity for an *SPG7* pathogenic variant may be sufficient to cause disease (i.e., autosomal dominant inheritance). However, this conclusion is challenged by the finding of unaffected p.Leu78* heterozygotes in other families as well as the possibility that the affected heterozygous individual had a second *SPG7* pathogenic variant which was not detected due to testing limitations [Sánchez-Ferrero et al 2013].

Because the phenotype of SPG7 is indistinguishable from many other forms of hereditary spastic paraplegia, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *SPG7*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- A **multigene panel** that includes *SPG7* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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](#).

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **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](#).

Table 1. Molecular Genetic Testing Used in Spastic Paraplegia 7

Gene ¹	Method	Proportion of Pathogenic Variants ² Detectable by Method
SPG7	Sequence analysis ³	>98% ⁴
	Gene-targeted deletion/duplication analysis ⁵	<2% 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. Arnoldi et al [2008], Brugman et al [2008], Klebe et al [2012], van Gassen et al [2012], Sánchez-Ferrero et al [2013], Pfeffer et al [2015]

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. Casari et al [1998], Arnoldi et al [2008], Klebe et al [2012], van Gassen et al [2012], Sánchez-Ferrero et al [2013]

Clinical Characteristics

Clinical Description

Spastic paraplegia 7 (SPG7) is characterized by insidiously progressive bilateral lower-limb weakness and spasticity. Most affected individuals have proximal or generalized weakness in the legs and impaired vibration sense.

Onset typically occurs in adulthood, around age 30-45 years, although symptoms may start as early as age 11 years and as late as age 72 years [De Michele et al 1998, McDermott et al 2001, Wilkinson et al 2004].

Presentation. The first sign is typically insidiously progressive bilateral leg weakness.

Additional features. Other signs and symptoms can be observed [Brugman et al 2008, Salinas et al 2008, Warnecke et al 2010, Almontashiri et al 2014, Pfeffer et al 2014] including the following:

- Cerebellar and motor signs
 - Ataxia (gait and limbs)
 - Spastic dysarthria
 - Dysphagia
- Ophthalmic findings
 - Pale optic disks

- Nystagmus
- Strabismus
- Ptosis
- Hearing loss of conductive/neurosensory /mixed type
- Peripheral neuromuscular findings
 - Motor and sensory neuropathy
 - Amyotrophy
- Orthopedic issues
 - Scoliosis
 - *Pes cavus*
- Urinary sphincter disturbances

Progression. Severe disability of gait due to leg spasticity may develop as soon as eight years after onset of symptoms, and some individuals are confined to a wheelchair [Elleuch et al 2006, Schüle et al 2006].

Findings on Neuroimaging and Other Investigations

Neuroimaging

- In a few individuals, conventional cerebral MRI may show cerebellar (or, less frequently, cortical) atrophy [Salinas et al 2008, Hourani et al 2009, Warnecke et al 2010].
- White matter changes as detected by diffusion tensor imaging in the frontal lobes, the corticospinal tracts, and the brain stem are specific to SPG7.
- Spinal imaging studies are useful in the differential diagnosis to exclude other anomalies of the pontomedullary junction and of the cervical and dorsolumbar medulla.

Other investigations

- Spinal evoked potentials may reveal delayed prolongation of the central conduction time [Nielsen et al 2001].
- Electromyography with nerve conduction velocities may reveal axonal sensory motor neuropathy.
- Paired transcranial magnetic stimulation may show delayed prolongation of the central motor conduction time and motor threshold in some affected individuals in lower limb muscles [Warnecke et al 2010]. Intracortical inhibition appears normal in SPG7 [Nardone & Tezzon 2003].
- Optical coherence tomography is useful for detecting subclinical optic neuropathy [Klebe et al 2012].
- A battery of neuropsychological tests may reveal mild impairment of visuoconstructive and executive functions in some individuals [Warnecke et al 2010].
- Serum creatine kinase activity may be slightly above the normal range in some cases.
- Muscle biopsy has revealed the following:
 - Changes of denervation with partial reinnervation
 - Atrophic, angulated fibers, predominantly type II
 - Ragged-red fibers, which are positive for the histoenzymatic reaction to succinate dehydrogenase and negative for cytochrome *c* oxidase (COX, the complex IV of the mitochondrial respiratory chain), indicating an oxidative phosphorylation defect [Casari et al 1998, McDermott et al 2001, Wilkinson et al 2004, Tzoulis et al 2008].

Genotype-Phenotype Correlations

No genotype-phenotype correlations can be proposed based on published studies.

Prevalence

The prevalence of SPG7 is estimated at between 1:100,000 and 9:100,000 for most countries (www.orpha.net).

Genetically Related (Allelic) Disorders

Primary lateral sclerosis (PLS). Compound heterozygous pathogenic variants in *SPG7* were reported as cosegregating with PLS in an autosomal recessive manner in five individuals from the same family [Yang et al 2016].

Amyotrophic lateral sclerosis (ALS). Four individuals with nonfamilial ALS were found to heterozygous pathogenic variants in *SPG7* [Krüger et al 2016].

Spinocerebellar ataxia (SCA). It is often difficult to clinically discriminate between hereditary spastic paraplegia (HSP) and SCA as the disorders can share multiple features. Several *SPG7* pathogenic variants have been reported to be associated with an ataxia phenotype [Pfeffer et al 2015, Choquet et al 2016, Synofzik & Schule 2017].

Differential Diagnosis

No significant differences exist between spastic paraplegia 7 (SPG7) and other types of pure autosomal dominant and autosomal recessive spastic paraplegia [Fink 2002, Fink 2003, Salinas et al 2008] (see [Hereditary Spastic Paraplegia Overview](#) for a review). However, Brugman et al [2008] reported that *SPG7* pathogenic variants are less likely to be found in adult-onset cases in which upper motor neuron symptoms (UMN) are present in the arms and in adult-onset cases with UMN symptoms involving the bulbar region.

Other conditions that need to be considered in the differential diagnosis of SPG7 are summarized in Table 2.

Table 2. Other Disorders to Consider in the Differential Diagnosis of SPG7

DiffDx Disorder	Gene(s)	MOI	Clinical Features of the DiffDx Disorder	
			Overlapping w/SPG7	Distinguishing from SPG7
Adrenomyeloneuropathy and other leukodystrophies (e.g., Krabbe disease, arylsulfatase A deficiency [metachromatic leukodystrophy])	<i>ABCD1</i> <i>GALC</i> <i>ARSA</i>	XL AR	Paraplegia neuropathy	<ul style="list-style-type: none"> Dementia On MRI: leukodystrophy, adrenal dysfunction, long-chain fatty acid accumulation
Spinocerebellar ataxia type 28	<i>AFG3L2</i>	AD	Paraplegia; ataxia	Rare dystonia or parkinsonism
Dopa-responsive dystonia	<i>GCH1</i>	AD	Brisk reflexes; spasticity; extensor plantar responses	<ul style="list-style-type: none"> Young-onset dystonia parkinsonism responsive to levodopa Diurnal variation
Amyotrophic lateral sclerosis	See footnote 1.	AD AR XL	Spasticity	Muscle atrophy, weakness & fasciculations
Primary lateral sclerosis ²	Unknown	NA	Spasticity	Survival 15-20 years
Arginase deficiency	<i>ARG1</i>	AR	Spasticity	<ul style="list-style-type: none"> Epileptic seizures Severe mental retardation ↑ plasma arginine Hyperammonemia
Structural abnormalities of the brain or spinal cord	NA	NA	Gait difficulties	On MRI: spine abnormalities

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of the DiffDx Disorder	
			Overlapping w/SPG7	Distinguishing from SPG7
Vitamin B ₁₂ deficiency	NA	NA	Unsteady gait	<ul style="list-style-type: none"> • Subacute combined degeneration • Improvement after vitamin B₁₂ supplementation
Primary progressive multiple sclerosis	NA	NA	Spasticity	<ul style="list-style-type: none"> • MRI white matter changes • Oligoclonal IgG bands • ↑ IgG index
Progressive external ophthalmoplegia	Various	AR AD	Eyelid ptosis	<ul style="list-style-type: none"> • External ophthalmoplegia • Proximal myopathy • No pyramidal signs
Tropical spastic paraplegia (caused by HTLV1 infection)	NA	NA	Paraplegia	HTLV-1 serology
Optic neuropathy	<i>KLC2</i> ³ <i>MFN2</i> ⁴	AR AD	Pale optic disks	No pyramidal signs

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; NA = not applicable; XL = X-linked

1. See [Phenotypic Series: Amyotrophic lateral sclerosis](#) for a list of genes associated with this phenotype in OMIM.

2. Brugman et al [2008]

3. Melo et al [2015]

4. Züchner et al [2006]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spastic paraplegia 7 (SPG7), the following evaluations are recommended if they have not already been completed:

- Ophthalmologic evaluation
- Hearing testing
- Urologic evaluation in case of bladder dysfunction
- Consultation with a clinical geneticist and/or genetic counselor

Evaluation by a multidisciplinary team that includes a general practitioner, neurologist, physical therapist, social worker, and psychologist should be considered.

Neuropsychological testing may be suggested.

Treatment of Manifestations

No specific drug treatments or cures for SPG7 exist.

Drugs to reduce spasticity and muscle tightness include baclofen, tizanidine, dantrolene, and diazepam – preferably administered one at a time.

Management of spasticity by intrathecal baclofen or intramuscular botulinum toxin injections may be an option in selected individuals [Kawano et al 2018].

A combination of physical therapy and assistive walking devices are often used to reduce contractures, provide support, and promote stability.

Occupational therapy and speech therapy are often helpful in managing activities of daily living.

Prevention of Secondary Complications

Because individuals with advanced disease are bedridden they are at major risk of aspiration pneumonia, urinary tract infections and pulmonary embolism; careful monitoring is recommended to help avoid these complications.

Surveillance

Annual neurologic evaluation can help identify potential complications of spasticity that develop over time (e.g., contractures).

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](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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 7 (SPG7) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *SPG7* pathogenic variant).
- Findings of a subtle reduction of white matter integrity in the corpus callosum on diffusion tensor imaging have been reported in individuals heterozygous for an *SPG7* pathogenic variant [Warnecke et al 2010] and a single possibly manifesting heterozygote has been reported [Sánchez-Ferrero et al 2013]. However, heterozygotes are typically not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual 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 (carriers) are asymptomatic and typically are not at risk of developing the disorder (see **Parents of a proband**).

Offspring of a proband. The offspring of an individual with SPG7 are obligate heterozygotes (carriers) for a pathogenic variant in *SPG7*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SPG7* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *SPG7* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SPG7* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *SPG7* are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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](#).

- **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.**

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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 7: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>SPG7</i>	16q24.3	Paraplegin	alsod/SPG7 genetic mutations SPG7 database	SPG7	SPG7

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 7 ([View All in OMIM](#))

602783	SPG7 MATRIX AAA PEPTIDASE SUBUNIT, PARAPLEGIN; SPG7
607259	SPASTIC PARAPLEGIA 7, AUTOSOMAL RECESSIVE; SPG7

Gene structure. *SPG7* spans a physical distance of approximately 52 kb and comprises 17 exons. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Pathogenic missense, nonsense, frameshift, and splice site variants have been observed throughout *SPG7*. Missense variants occur most frequently. Missense and truncating variants, such as c.1454_1462del9 (reported as c.1450_1458del9 [McDermott et al 2001]), deletion of 9.5 kb [Casari et al 1998] and 2228insA [Casari et al 1998] have been reported to delete main protein functional domains.

Twenty-seven pathogenic variants have been reported in *SPG7* [Casari et al 1998, Arnoldi et al 2008, Brugman et al 2008, Klebe et al 2012, van Gassen et al 2012, Sánchez-Ferrero et al 2013, Pfeffer et al 2015]. The *SPG7* c.1529C>T (p.Ala510Val) variant is the most frequent variant found across populations [Sánchez-Ferrero et al 2013, Pfeffer et al 2015, Choquet et al 2016]. Although this variant and most others identified have been associated with an ataxic phenotype, recent efforts have focused on associating *SPG7* variants with additional clinical features. Recent studies suggest that cerebellar ataxia is a frequent feature among individuals with *SPG7*-related disease [Pfeffer et al 2015, Synofzik & Schule 2017]. The ataxic syndrome could even be a predominant feature over spasticity, as observed in a Japanese family segregating p.Arg398Ter [Yahikozawa et al 2015].

Table 3. *SPG7* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias) ¹	Predicted Protein Change	Reference Sequences
del9.5 kb	--	NM_003119.3 NP_003110.1
c.1053dupC	--	
c.1192C>T	p.Arg398Ter	
c.1454_1462del9	p.Arg485_Glu487del	
c.1529C>T	p.Ala510Val	
c.2102A>C	p.His701Pro	
c.2216insA (2228insA ²)	--	

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.

1. Variant designation that does not conform to current naming conventions

2. Casari et al [1998]

Normal gene product. Paraplegin is a mitochondrial inner membrane protein that exerts protein quality control in a high molecular complex with AFG3L2. Both paraplegin and AFG3L2 belong to the AAA protein family (ATPases associated with diverse cellular activities) (see also [Hereditary Spastic Paraplegia Overview](#)).

Paraplegin and AFG3L2 coassemble in the mitochondrial inner membrane, forming a high molecular-weight complex [Atorino et al 2003]. Paraplegin is ubiquitously expressed in adult and fetal human tissues. The presence of two hydrophobic regions, which have the characteristics of transmembrane domains, allows identification of both paraplegin and AFG3L2 as integral membrane proteins. The AAA domain is in the central part of paraplegin between amino acid residues 344 and 534, while a coil-coil domain in the carboxy-terminal part of the molecule promotes assembly in the hexameric complex. In order to achieve maturation, paraplegin undergoes several cleavages upon its import in the mitochondria inner membrane by the mitochondrial processing peptidase and by the m-AAA protease complex itself [Koppen et al 2009]. Thus, the final processing of paraplegin in a mature form depends on its coassembly with AFG3L2 and, as recently demonstrated, the unphosphorylation of AFG3L2 in position p.Tyr179 [Almontashiri et al 2014].

In a recent paper paraplegin was identified as a molecular component/regulator of the mitochondrial permeability transition pore [Shanmughapriya et al 2015]; however another study demonstrated conflicting results [König et al 2016].

Abnormal gene product. Inactivation of the paraplegin-AFG3L2 complex causes reduced complex I activity in mitochondria. Loss of AFG3L2 function is associated with autosomal recessive spastic ataxia 5 and spinocerebellar ataxia 28 (see Differential Diagnosis).

Biochemical analysis from two individuals with confirmed *SPG7* pathogenic variants revealed a reduction in citrate synthase-corrected complex I and complex II/III activities in muscle and complex I activity in mitochondrial-enriched fractions from cultured myoblasts. Mitochondrial DNA damage has been observed in muscle biopsies of affected individuals with *SPG7* variants c.2102A>C and c.1053dupC [Tzoulis et al 2008, Wedding et al 2014]. Further studies should clarify how paraplegin can alter mitochondrial DNA; however, this could be an indirect effect of the dysfunction of the mAAA-protease complex, as paraplegin does not interact directly with the DNA.

In mouse, *AFG3L2* homozygous pathogenic variants appear more severe than paraplegin variants; null or missense *Afg3l2* mouse models developed marked impairment of axonal development leading to neonatal death

[Maltecca et al 2008]. The mice developed a severe early-onset tetraparesis and were found to have reduced myelinated fibers in the spinal cord and impaired respiratory chain complex I and III activity. The increased severity of the phenotype is explained by the higher neuronal expression of AFG3L2, but also the ability of AFG3L2 to form homocomplexes, while paraplegin requires coassembly with AFG3L2 to form functional complexes. Heterozygous pathogenic variants of *AFG3L2* have been associated with a dominant form of spinocerebellar ataxia (*SCA28*) [Di Bella et al 2010].

Gene expression regulation. *SPG7* is one of the targets of miR-224, which is located in an intron of the GABA A receptor ϵ subunit (*GABRE*) and produced in several models of cancer proliferation [Fu et al 2016].

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Chapter Notes

Revision History

- 25 October 2018 (ha) Comprehensive update posted live
- 23 December 2010 (me) Comprehensive update posted live
- 25 February 2008 (cd) Revision: deletion/duplication analysis available clinically
- 24 August 2006 (me) Review posted live
- 7 March 2005 (gc) Original submission

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