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Spastic Paraplegia 11

Giovanni Stevanin, PhD[1]

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Summary

Clinical characteristics

Spastic paraplegia 11 (SPG11) is characterized by progressive spasticity and weakness of the lower limbs frequently associated with the following: mild intellectual disability with learning difficulties in childhood and/or progressive cognitive decline; peripheral neuropathy; pseudobulbar involvement; and increased reflexes in the upper limbs. Less frequent findings include: cerebellar signs (ataxia, nystagmus, saccadic pursuit); retinal degeneration; *pes cavus*; scoliosis; and parkinsonism with characteristic brain MRI features that include thinning of the corpus callosum. Onset occurs mainly during infancy or adolescence (range: age 1-31 years) and in rare cases as late as age 60 years. Most affected individuals become wheelchair bound one or two decades after disease onset.

Diagnosis/testing

The diagnosis of SPG11 is established in a proband with characteristic clinical and MRI findings and biallelic pathogenic variants in *SPG11* identified on molecular genetic testing.

Management

Treatment of manifestations: Care by a multidisciplinary team; physiotherapy to stretch spastic muscles; antispastic drugs such as baclofen; botulin toxin and intrathecal baclofen for severe and disabling spasticity when oral drugs are ineffective. Urodynamic evaluation when bladder dysfunction is evident; anticholinergic drugs for urinary urgency. Treatment of psychiatric manifestations by standard protocols.

Prevention of secondary complications: Treatment of sphincter disturbances to prevent urinary tract infection secondary to bladder dysfunction.

Surveillance: Evaluation every six months to adjust physiotherapy and medications.

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Genetic counseling

SPG11 is inherited in an autosomal recessive manner. If each parent is known to be heterozygous for an *SPG11* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for at-risk pregnancies are possible once the pathogenic variants in a family are known.

Diagnosis

Suggestive Findings

Spastic paraplegia 11 (SPG11) **should be suspected** in individuals with the following clinical and imaging findings.

Frequent clinical findings

- Progressive spasticity and weakness of the lower limbs
- Mild intellectual disability with learning difficulties in childhood and/or progressive cognitive decline with onset in the first to third decade
- Axonal, motor, or sensorimotor peripheral neuropathy (>80% of individuals) [Stevanin et al 2008, Orlacchio et al 2010, Daoud et al 2012, Özoğuz et al 2015, Manole et al 2016, Montecchiani et al 2016]
- Pseudobulbar involvement with dysarthria and/or dysphagia
- Increased reflexes in the upper limbs

Less frequent clinical findings

- Cerebellar signs (ataxia or ocular signs including nystagmus and/or saccadic pursuit)
- Retinal degeneration (Kjellin syndrome) * [Puech et al 2011]
- *Pes cavus*
- Scoliosis
- Extrapyramidal signs such as parkinsonism [Anheim et al 2009, Faber et al 2018a]

* Kjellin syndrome is characterized by retinal degeneration, autosomal recessive hereditary spastic paraplegia, and thin corpus callosum initially associated with spastic paraplegia 15 (SPG15) but more often occurring in individuals with SPG11. See Spastic Paraplegia 15.

Imaging findings on brain and spinal cord MRI

- Thinning of the corpus callosum (TCC) (>90% of individuals) [Stevanin et al 2008] particularly with long T_1 and T_2 values in the forceps minor of the corpus callosum, the so-called "ear of the lynx" sign which appears hyperintense on FLAIR and hypointense on T_1-weighted images [Pascual et al 2019]
- Cortical atrophy is frequently observed.
- White matter hyperintensities [França et al 2012]
  - Only frontal and occipital periventricular hyperintensities may be seen initially.
  - Periventricular, confluent leukoencephalopathy often increases in severity with disease duration [Hehr et al 2007, Stevanin et al 2008].
- Atrophy of both the brain stem and the cerebellum can be observed [Stevanin et al 2007].
- The basal ganglia may also be affected [Faber et al 2018b].

Note: 60% of individuals with TCC, cognitive impairment, and spastic paraparesis were found to have biallelic *SPG11* pathogenic variants [Stevanin et al 2008].

Establishing the Diagnosis

The diagnosis of spastic paraplegia 11 (SPG11) **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *SPG11* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SPG11* variants of uncertain significance (or identification of one known *SPG11* pathogenic variant and one *SPG11* variant of uncertain significance) does not establish or rule out the diagnosis.

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 SPG11 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, imaging, and electrophysiology findings suggest the diagnosis of SPG11, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SPG11* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications. Of note, 10%-20% of disease-associated variants are exon-sized or larger deletions and duplications [Günther et al 2016].
- **A spastic paraplegia multigene panel** that includes *SPG11* 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, 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 11

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SPG11	Sequence analysis [3]	~81% [4]
	Gene-targeted deletion/duplication analysis [5]	~19% [4]

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. Günther et al [2016]
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.

Clinical Characteristics

Clinical Description

Onset of spastic paraplegia 11 (SPG11) occurs mainly during infancy or adolescence (age 1-31 years) and is characterized by gait disorders or less frequently by intellectual disability [Stevanin et al 2007, Stevanin et al 2008, Kara et al 2016]. Later onset (age 50-60 years) was reported in a few individuals [Rubegni et al 2015, Kawarai et al 2015].

Approximately ten years after onset, most affected individuals have the complete clinical picture of SPG11, including progressive lower-limb spasticity, atrophy of the corpus callosum with intellectual disability, and/or progressive cognitive decline. Thinning of the corpus callosum appears to correlate with disease severity [Kara et al 2016]. Most affected individuals become wheelchair bound one or two decades after disease onset [Stevanin et al 2008, Puech et al 2011].

Cognitive decline with low Mini Mental State Evaluation (MMSE) scores, found in the majority of affected individuals, worsens with time and includes severe short-term memory impairment, emotional lability, childish behavior, reduced verbal fluency, and attention deficit indicative of executive dysfunction [Hehr et al 2007, Stevanin et al 2008]. Psychiatric problems with behavioral disturbances are observed. Most individuals with SPG11 display little concern over the progression of their motor disease [Stevanin et al 2008]. All these findings correlate with the frontal atrophy detected on follow-up brain MRI.

Intellectual disability, found in most individuals with early onset, is characterized by learning difficulties in childhood and low IQ.

Eye findings can include the following:

- Macular excavation or degeneration as reported in the Kjellin syndrome [Orlén et al 2009, Puech et al 2011]
- Strabismus
- Cerebellar ocular signs such as abnormal saccadic pursuit and nystagmus in individuals with the longest disease duration

- Visual evoked potentials with increased latencies and decreased amplitudes [Stevanin et al 2008]

Additional features are severe weakness, dysarthria, distal or generalized muscle wasting, and less frequently, *pes cavus*, scoliosis, parkinsonism, epilepsy, and orthostatic hypotension [Kara et al 2016]. Individuals with the longest disease duration may have swallowing difficulties [Stevanin et al 2008].

Electromyography (EMG) and nerve conduction velocities (NCVs) frequently show signs of axonal sensorimotor neuropathy particularly when disease duration exceeds ten years [Stevanin et al 2008].

Sural nerve biopsies have shown loss of unmyelinated nerve fibers and accumulation of pleomorphic membranous material in unmyelinated axons [Hehr et al 2007].

Genotype-Phenotype Correlations

Missense and splice site variants are more often associated with later onset [Kawarai et al 2015, Rubegni et al 2015] and mild disease severity [Kara et al 2016].

Nomenclature

SPG11 is one of several autosomal recessive disorders in which hereditary spastic paraplegia is associated with thin corpus callosum (HSP-TCC).

Based on the EMG and NCV patterns and on anterior horn cell abnormalities seen in some affected individuals, several authors have characterized SPG11 as upper and lower motor neuron disease [Stevanin et al 2008], juvenile amyotrophic lateral sclerosis with long disease duration [Orlacchio et al 2010, Daoud et al 2012, Özoğuz et al 2015, Manole et al 2016], or Charcot-Marie-Tooth neuropathy [Montecchiani et al 2016].

Prevalence

The estimated prevalence for HSP of all types ranges from 1:100,000 to 10:100,000 depending on the country. Since SPG11 was found to account for 19%-31% of autosomal recessive HSP [Stevanin et al 2008, Kara et al, 2016], a prevalence of 1.25:100,000 for SPG11 can be estimated.

As expected in autosomal recessive disorders, most families with SPG11 originate from countries in which consanguinity is common, particularly the Mediterranean basin or the Middle East [Hehr et al 2007, Stevanin et al 2008, Boukhris et al 2009, Denora et al 2009, Özoğuz et al 2015, Kara et al 2016]. However, SPG11 has been reported in families worldwide [Hehr et al 2007, Stevanin et al 2007, Southgate et al 2010, Rajakulendran et al 2011, Özoğuz et al 2015, Kara et al 2016].

Genetically Related (Allelic) Disorders

SPG11 pathogenic variants are associated with a spectrum of clinical manifestations resulting from first and/or second motor neuron degeneration. This includes pure or complex HSP [Stevanin et al 2008], amyotrophic lateral sclerosis [Orlacchio et al 2010, Daoud et al 2012, Özoğuz et al 2015, Manole et al 2016] and Charcot-Marie-Tooth neuropathy [Montecchiani et al 2016], regardless of the nature of the pathogenic variants. Individuals with multiple sclerosis have also been found to have *SPG11* pathogenic variants [Romagnolo et al 2014, Mukai et al 2018].

Differential Diagnosis

See Hereditary Spastic Paraplegia Overview. The relative frequency of spastic paraplegia 11 (SPG11) varies according to phenotype and geographic origin. In Portugal, it accounts for 13% of all forms of spastic paraplegia regardless of the inheritance mode [Morais et al 2017]. SPG11 accounts for 5%-20% of autosomal recessive

spastic paraplegias [Stevanin et al 2008] and up to 30%-50% of autosomal recessive complex spastic paraplegia [Kara et al 2016, Morais et al 2017]. This frequency increases up to 59%-70% [Stevanin et al 2008, Boukhris et al 2009, Denora et al 2009] when mental impairment and thinning of the corpus callosum are associated. *SPG11* pathogenic variants can be found in a small proportion of individuals with a pure spastic paraplegia (<10%) but disease duration usually fewer than five years [Denora et al 2009].

There are other forms of spastic paraplegia associated with thinning of the corpus callosum and mental impairment and it is often difficult to distinguish them from SPG11 on clinical grounds (Table 2).

Table 2. Other Hereditary Spastic Paraplegias Associated with Thin Corpus Callosum (HSP-TCC) and Mental Impairment of Interest in the Differential Diagnosis of Spastic Paraplegia 11 (SPG11)

Gene(s)	Differential Disorder [1]	MOI	Clinical Features of Differential Disorder	
			Overlapping w/SPG11	Distinguishing from SPG11
AP4B1	SPG47	AR	Seizures; white matter abnormalities	Severe ID; facial dysmorphism; microcephaly; stereotypic laughter w/tongue protrusion
AP4M1	SPG50			
AP4E1	SPG51			
AP4S1	SPG52			
DDHD2	SPG54	AR	Leukodystrophy	Severe DD
ERLIN2	SPG18	AR	Also assoc w/epilepsy; DD	Agenesis of corpus callosum
SPG21	SPG21 (mast syndrome)	AR	Late-onset ataxia; adult-onset dementia & parkinsonism; polyneuropathy	Japanese & Amish origin; akinetic mutism seen in advanced disease; psychiatric disease
GBA2	SPG46	AR	TCC; cerebellar &cerebral atrophy; DD; cerebellar signs; polyneuropathy	Congenital cataract; male infertility (hypogonadism)
TECPR2	SPG49	AR	TCC reported occasionally	Central apnea; severe DD; microcephaly; dysmorphic features; gastroesophageal reflux
ZFYVE26	SPG15	AR	DD; optic atrophy; ataxia; central retinal degeneration; polyneuropathy	No clinical features discriminate between SPG11 & SPG15.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; HSP = hereditary spastic paraplegia; ID = intellectual disability; MOI = mode of inheritance; TCC = thin corpus callosum
1. See Hereditary Spastic Paraplegia Overview

Lower motor neuron degeneration may mimic amyotrophic lateral sclerosis (ALS) when wasting is marked [Stevanin et al 2008, Orlacchio et al 2010, Daoud et al 2012]. The continuum between spastic paraplegia and ALS has been evidenced by the finding of lesions common to ALS in the brain of individuals with SPG11 [Denora et al 2016].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spastic paraplegia 11 (SPG11), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neuropsychological testing to assess the cognitive impairment and decline
- Neuro-urologic examination for those with sphincter disturbance
- Electrophysiologic investigations (e.g., ENMG, VEP, SEP)
- Ocular investigations (e.g., funduscopic examination, OCT)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No specific drug treatment or cure exists for SPG11.

Care by a multidisciplinary team that may include a general practitioner, neurologist, clinical geneticist, physiotherapist, physical therapist, social worker, and psychologist should be considered.

Symptomatic treatment to reduce pyramidal hyperactivity in the lower limbs includes the following:

- Physiotherapy for stretching of the spastic muscles to prevent contractures. Adapted dance or movements are also helpful to maintain strength (see www.clickanddance.com).
- Antispastic drugs such as baclofen and tizanidine
- Botulin toxin and intrathecal baclofen, which can be considered when oral drugs are ineffective and spasticity is severe and disabling

When sphincter disturbances become a problem, urodynamic evaluation should be performed in order to adapt treatment and monitor follow up. Anticholinergic drugs are indicated for urinary urgency.

Psychiatric manifestations should be treated in accordance with standard practice.

Prevention of Secondary Complications

Follow up of sphincter disturbances is important to prevent bladder dysfunction and infection.

Early regular physiotherapy helps to prevent contractures.

Surveillance

Specialized outpatient clinic evaluations are suggested every six months to adjust medication and physical rehabilitation that will depend on disease severity.

Annual brain MRI can be used to follow the atrophy of the corpus callosum, cerebellum, and brain stem, and to monitor increases in the size and intensity of white matter hyperintensities.

Annual electrophysiologic investigations (e.g., ENMG, VEP, SEP) are recommended to follow the extent of the disease.

Visual acuity should be assessed annually.

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. 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 11 (SPG11) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- In almost all cases, the parents of an affected child are heterozygotes (i.e., carriers of one *SPG11* pathogenic variant).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for a *SPG11* pathogenic variant and allow for reliable recurrence risk assessment. *De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].

  In one rare case, a proband inherited one *SPG11* pathogenic variant from a heterozygous parent and the second pathogenic variant occurred *de novo* in the proband (i.e., only one parent was a carrier) [Denora et al 2010].
- Heterozygotes (carriers) are typically asymptomatic but abnormal ocular fundus may occasionally be observed [Puech et al 2011].

Sibs of a proband

- If each parent is known to be heterozygous for an *SPG11* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Intrafamilial clinical variability is observed in SPG11; age at onset and associated clinical manifestations may vary among affected sibs.
- Heterozygotes (carriers) are typically asymptomatic but abnormal ocular fundus may occasionally be observed [Puech et al 2011].

Offspring of a proband. The offspring of an individual with SPG11 are obligate heterozygotes (carriers) of a pathogenic variant in *SPG11*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant in *SPG11*.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SPG11* 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variants have been identified in an affected family member, 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 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**
  Plateforme Maladies Rares
  99 Rue Didot
  Paris 75014
  France
  Phone: 33 1 56 53 52 61
  Email: president@eurohsp.eu
  www.eurohsp.eu
- **HSP Research Foundation**
  Australia
  Email: inquiries@hspersunite.org.au
  www.hspersunite.org.au
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  sp-foundation.org
- **Tom Wahlig-Foundation**
  Tom Wahlig Stiftung
  Germany
  www.hsp-info.de/en/foundation.htm
- **A.I. Vi.P.S.**
  Associazione Italiana Vivere la Paraparesi Spastica
  Via Tevere, 7
  20020 Lainate (MI)

Italy

Phone: 39 392 9825622

Email: info@aivips.it

www.aivips.it

- **EURORDIS-Rare Diseases Europe**

  Email: eurordis@eurordis.org

  Find a patient organization

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 11: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SPG11	*SPG11*	15q21.1	Spatacsin	SPG11 database	SPG11	SPG11

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 11 (View All in OMIM)

604360	SPASTIC PARAPLEGIA 11, AUTOSOMAL RECESSIVE; SPG11
610844	SPG11 VESICLE TRAFFICKING ASSOCIATED, SPATACSIN; SPG11

Molecular Pathogenesis

Introduction. *SPG11* encodes spatacsin, a protein strongly conserved through evolution. Neither *SPG11* nor spatacsin shows any significant sequence similarity to known cDNA or protein sequences. The spatacsin protein interacts with the SPG15 and SPG48 protein products [Słabicki et al 2010] and is an accessory protein of the adaptor protein 5 complex [Hirst et al 2011]. It is required for proper lysosomal tubulation and recycling [Chang et al 2014].

Mechanism of disease causation. Most pathogenic variants identified to date in *SPG11* predict truncation of the protein, demonstrating that pathogenicity results from loss of spatacsin function. The few disease-associated missense variants are likely to result in partial loss of spatacsin function since the phenotype is often milder.

The loss of spatacsin function is associated with reduced clearance of lipids from lysosomes with accumulation of gangliosides and cholesterol [Boutry et al 2018, Boutry et al 2019]. Consequently, cholesterol levels on membranes and calcium homeostasis are altered [Boutry et al 2019]. Spatacsin is also required for neurite formation [Martin et al 2012] and the GSK3b signaling pathway [Pozner et al 2018]. These data provide potential targets for preclinical studies.

Chapter Notes

Author Notes

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The author suggests the following organization for patient registries and information on ataxia and spastic paraparesis:

SPATAX Network
Institut du Cerveau et de la Moelle Epinière
Pitié-Salpêtrière Hospital
47 Bd de l'Hôpital
75013 Paris, France
Email: spatax@icm-institute.org
Web: www.spatax.wordpress.com

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- 19 December 2019 (sw) Comprehensive update posted live
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- 27 March 2008 (me) Review posted live
- 26 November 2007 (gs) Original submission

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