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Spastic Paraplegia 15

Synonyms: Hereditary Spastic Paraplegia Type 15, HSP-*ZFYVE26*, SPG15, *ZFYVE26*-Related Hereditary Spastic Paraplegia

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Summary

Clinical characteristics

Spastic paraplegia 15 (SPG15), typically an early-onset complex hereditary spastic paraplegia, is characterized by progressive spasticity that begins in the lower extremities and is associated with several manifestations resulting from central and peripheral nervous system dysfunction. While onset of spasticity is typically in mid- to late childhood or adolescence (i.e., between ages 5 and 18 years), other manifestations, such as developmental delay or learning disability, may be present earlier, often preceding motor involvement. Individuals with adult onset have also been reported.

Diagnosis/testing

The diagnosis of SPG15 is established in a proband with suggestive findings and biallelic pathogenic variants in *ZFYVE26* identified by molecular genetic testing. Findings suggestive of SP15 on brain MRI may include thinning of the corpus callosum and characteristic signal changes in the periventricular white matter, known as the "ears of the lynx" sign.

Management

Treatment of manifestations: At present, no treatment prevents, halts, or reverses neuronal degeneration in SPG15. Treatment is directed at reducing symptoms and preventing secondary complications. Multidisciplinary care involving a neurologist, clinical geneticist, developmental specialist, orthopedic surgeon/physiatrist, physical therapist, occupational therapist, speech and language pathologist, and feeding and nutrition team is recommended.

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Surveillance: Affected individuals should be evaluated periodically (i.e., every 6-12 months) by an interdisciplinary team to assess disease progression, maximize ambulation and communication skills, and reduce other manifestations.

Genetic counseling

SPG15 is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *ZFYVE26* pathogenic variant, each sib of an affected individual has at conception 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. Once the *ZFYVE26* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for spastic paraplegia 15 (SPG15) have been published.

Suggestive Findings

Spastic paraplegia 15 (SPG15) **should be suspected** in individuals with the following clinical and brain imaging findings and family history.

Clinical findings

- Spasticity and weakness with progression from a spastic diplegia to a spastic tetraplegia with associated pyramidal signs (Babinski sign, hyperreflexia, ankle clonus)
- Learning disability or intellectual disability, progressive cognitive impairment
- Dysarthria and cerebellar signs
- Peripheral neuropathy (axonal sensorimotor neuropathy)
- Distal amyotrophy / loss of muscle bulk
- Less common:
  - Extrapyramidal movement disorders including focal dystonia and parkinsonism
  - Retinopathy
  - Sensorineural hearing impairment
  - Epilepsy
  - Cataracts

Laboratory findings

- Nerve conduction studies show an axonal sensorimotor neuropathy in a subset of affected individuals.
- Electroretinography may show changes consistent with retinopathy in a subset of affected individuals.

Brain imaging

- Thinning of the corpus callosum (most commonly the anterior parts) (70%)
- Periventricular white matter signal changes (>50%). The periventricular white matter signal changes in SPG15 can have a characteristic appearance involving the forceps minor. This is known as the "ears of the lynx" sign, as hypointense signal on T_1-weighted and hyperintense signal on FLAIR images on axial views resemble the shape of the ears of a lynx with its characteristic apical hair tuft [Pascual et al 2019] (Figure 1).
- Cerebral and cerebellar atrophy (~25%)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

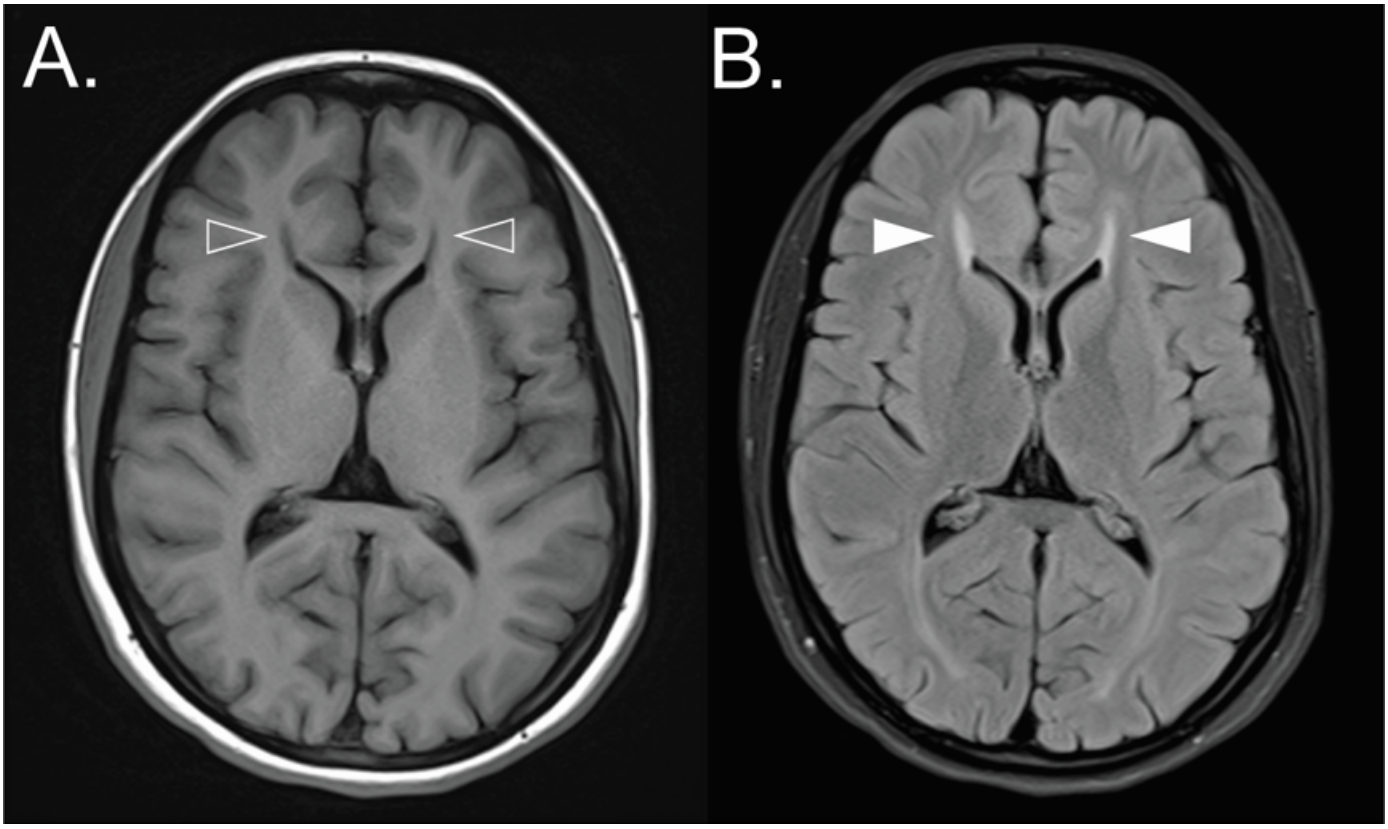

Figure 1. Ears of the lynx sign in SPG15

Axial T_1-weighted image (A) and axial T_2-FLAIR image (B) of a female age 20 years with SPG15 show hypointense signal on T_1 (open triangles) and hyperintense signal on T_2- FLAIR images (filled triangles) in the forceps minor. These signal changes resemble the shape of the ears of a lynx with their characteristic apical hair tuft and have been designated the "ears of the lynx" sign.

Establishing the Diagnosis

The diagnosis of SPG15 **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ZFYVE26* identified by 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 *ZFYVE26* variants of uncertain significance (or identification of one known *ZFYVE26* pathogenic variant and one *ZFYVE26* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (Option 1), whereas genomic testing does not (Option 2).

Option 1

A hereditary spastic paraplegia, cerebral palsy, ataxia or leukodystrophy multigene panel that includes *ZFYVE26* 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 15

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ZFYVE26	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [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. Boukhris et al [2008], Hanein et al [2008], Denora et al [2009], Goizet et al [2009], Schüle et al [2009], Schicks et al [2011], Yoon et al [2013], Mallaret et al [2014], Pensato et al [2014], Renvoisé et al [2014], Kara et al [2016], Vinci et al [2018], Özdemir et al [2019], Pascual et al [2019], Araujo 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. Gene-targeted deletion/duplication analysis has not identified any deletions or duplications.

Clinical Characteristics

Clinical Description

Spastic paraplegia 15 (SPG15), a form of early-onset complex hereditary spastic paraplegia, is characterized by progressive spasticity that begins in the lower extremities and is associated with several manifestations resulting from central and peripheral nervous system dysfunction (Table 2). Dysfunction of other organ systems has not been established. Onset is typically in mid- to late childhood or adolescence (i.e., between ages 5 and 18 years), though subtle manifestations, such as developmental delay or learning disability, may be present earlier and often precede motor involvement. Individuals with adult onset have been reported. Though natural history data are currently not available, SPG15 is thought to be a progressive disorder. The oldest reported individuals with SPG15 are adults.

The following clinical description of SPG15 is based on a review of more than 70 individuals with biallelic pathogenic variants in *ZFYVE26* [Boukhris et al 2008; Hanein et al 2008; Denora et al 2009; Goizet et al 2009; Schüle et al 2009; Schicks et al 2011; Yoon et al 2013; Mallaret et al 2014; Pensato et al 2014; Renvoisé et al 2014;

Kara et al 2016; Vinci et al 2018; Özdemir et al 2019; Pascual et al 2019; Araujo et al 2020; Authors, clinical experience].

Of note, some clinical features may present or progress in an age-dependent manner.

Table 2. Spastic Paraplegia 15: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Spasticity	>95%	Lower extremities are involved first & more severely than upper extremities.
Pyramidal signs	>95%	Babinski sign, hyperreflexia, ankle clonus
Cognitive impairment	>85%	Intellect ranges from normal, learning disability, intellectual disability (often mild to moderate) to progressive cognitive decline.
Cerebellar dysfunction	~55%	Ataxia, dysarthria, nystagmus
Dysarthria	~55%	Bulbar/cerebellar
White matter signal changes	>50%	Most commonly involving periventricular white matter, incl the ears of the lynx sign
Peripheral neuropathy & distal amyotrophy	~40%	Axonal motor & sensory neuropathy on nerve conduction studies; loss of distal muscle bulk, esp in lower extremities
Extrapyramidal movement disorder	~25%	Dystonia (often focal), parkinsonism (variable response to L-dopa)
Pes cavus	~20%	
Neurogenic bladder dysfunction	~20%	Urinary urgency, incontinence
Pigmentary retinopathy	~15%	Variable & possibly underdiagnosed (may go unnoticed clinically); part of Kjellin syndrome

Spasticity. Many individuals have a history of delayed motor milestones. First reported manifestations are often poor balance, clumsiness, and gait impairment, typically in mid- to late childhood. Over time these findings evolve into progressive lower extremity weakness and spasticity with associated pyramidal signs (extensor plantar reflex, hyperreflexia, ankle clonus).

Many individuals, over the course of years, become nonambulatory and ultimately require mobility aids or a wheelchair.

Spasticity progresses to involve the upper extremities in some cases, resulting in a spastic tetraplegia, but continues to be more severe in the legs.

Associated complications may include dysphagia, contractures secondary to progressive spasticity, scoliosis, foot deformities, and dysregulation of bladder and bowel function.

Cognitive impairment. Many individuals experience delayed speech development and/or a learning disability. The degree of cognitive impairment associated is variable and ranges from learning disabilities to mild or moderate intellectual disability. Normal cognition has also been reported. A subset of individuals shows cognitive decline with disease progression.

Cerebellar dysfunction ranges from dysarthria, dysmetria, dysdiadochokinesia, intention tremor, and nystagmus to cerebellar ataxia.

Dysarthria of bulbar and/or cerebellar origin often develops along with the spastic paraplegia.

White matter signal changes (see Suggestive Findings). The most common neuroimaging findings:

- Thinning of the corpus callosum
- Signal abnormalities of the periventricular white matter
- Cerebral and/or cerebellar atrophy

Peripheral neuropathy. With disease progression there is often a loss of muscle bulk, particularly in the distal lower extremities. Nerve conduction studies may show an axonal sensorimotor neuropathy in a subset of affected individuals.

Extrapyramidal movement disorder. A subset of individuals may present with extrapyramidal movement disorders, which may include focal dystonia, often of the limbs, or parkinsonism with bradykinesia, rigidity, tremor, and postural instability.

Pigmentary retinopathy, classically described as part of Kjellin syndrome, may be present in a subset of individuals and is likely underdiagnosed as overt deficits may not be present early in the disease course. Clinical manifestations of the retinopathy, such as defective dark adaptation, color vision loss, changes in visual fields, and central vision loss, are difficult to establish since most affected individuals have intellectual disability and often are nonverbal. Early-onset cataracts have also been reported.

Other

- Seizures are uncommon.
- Sensorineural hearing impairment is found in a subset of individuals.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *ZFYVE26* have been identified.

Nomenclature

Hereditary spastic paraplegia (HSP) is classified clinically as "uncomplicated" (nonsyndromic) or "complicated" (syndromic).

- Uncomplicated (or "pure") HSP is characterized by progressive lower-extremity spasticity and weakness, bladder dysfunction, and diminution of lower-extremity vibration sensation [Harding 1983]. Though symptoms may be disabling, life expectancy is typically normal.
- Complicated HSP, such as SPG15, is characterized by the impairments present in uncomplicated HSP plus other neurologic findings (intellectual disability, extrapyramidal movement disorders, cerebellar dysfunction, peripheral neuropathy, muscle atrophy, seizures, and others).
- Kjellin syndrome refers to a syndrome consisting of retinal degeneration and spastic paraplegia accompanied by cognitive impairment. The clinical description preceded the discovery of the genes now known to be associated with SPG11 and SPG15. Both SPG11 and SPG15 can present with Kjellin syndrome.

Prevalence

SPG15 is rare. To date about 75 individuals have been reported.

Families with SPG15 have been reported from North America, Europe, the Middle East, Indian subcontinent, East Asia, and South America. Many affected individuals have a history of consanguinity; however, this could be the result of ascertainment bias, as initial reports have mainly focused on families from countries with high rates of consanguinity. More recently, SPG15 has been reported in populations with low rates of consanguinity, often associated with compound heterozygous variants.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ZFYVE26*.

Differential Diagnosis

SPG15 is one of the more common forms of complex hereditary spastic paraplegia with onset typically during childhood or adolescence. The initial clinical presentation of SPG15 is often nonspecific.

A clinical differential diagnosis, after exclusion of acquired causes of spasticity, is best built on the combination of spasticity and neuroimaging findings. The most common neuroimaging findings:

- Thinning of the corpus callosum
- Signal abnormalities of the periventricular white matter
- Cerebral and/or cerebellar atrophy

While these findings are not specific, they can help guide a differential diagnosis. A thin corpus callosum is found in a number of hereditary spastic paraplegias. In SPG15, thinning of the corpus callosum tends to be identified in the anterior parts, in contrast to the AP-4-associated hereditary spastic paraplegias (SPG47, SPG50, SPG51, and SPG52) and others in which thinning of the corpus collosum is typically identified in the posterior parts [Ebrahimi-Fakhari et al 2020].

Similar to SPG11, the periventricular white matter signal changes in SPG15 can have a characteristic appearance involving the forceps minor. This is known as the "ears of the lynx sign," consisting of hypointense signal on T_1-weighted images and hyperintense signal on FLAIR images which, on axial views, resembles the shape of the ears of a lynx with its characteristic apical hair tuft [Pascual et al 2019]. (Note: It is also very difficult to distinguish SPG15 from SPG11 on clinical grounds alone and both disorders share a common molecular mechanism [Hirst et al 2013].)

In addition to SPG11, overlapping clinical features exist with other forms of complex hereditary spastic paraplegia associated with thinning of the corpus callosum (see Table 3).

Table 3. Autosomal Recessive Hereditary Spastic Paraplegias Associated with Thin Corpus Callosum (HSP-TCC) in the Differential Diagnosis of Spastic Paraplegia 15

Gene(s)	Disorder	Clinical Features That Differ From SPG15
AP4B1 *AP4E1* *AP4M1* *AP4S1*	SPG47, SPG50, SPG51, & SPG52 (AP-4-assoc hereditary SPG)	Early-onset moderate-to-severe DD/ID, postnatal microcephaly, epilepsy, ventriculomegaly often in the shape of colpocephaly. Peripheral neuropathy is uncommon. [1]
AP5Z1	SPG48 [2]	Onset of symptoms is often later, typically in adulthood [3]
DDHD2	SPG54 [2]	Optic nerve atrophy in a subset of affected persons
ERLIN2	SPG18 [2]	Typically, onset of spasticity is in early childhood [4]
FA2H	SPG35 (Fatty acid hydroxylase-associated neurodegeneration)	Optic nerve atrophy & oculomotor abnormalities are seen in a subset of affected persons. Atrophy of the pons is seen on brain MR imaging in the majority of affected persons. [5]
GBA2	SPG46 [2]	Ataxia is prominent. Hypogonadism in males.
SPG11	SPG11	No clinical features differentiate SPG11 & SPG15 w/certainty. Cerebellar signs, retinopathy, & hearing loss are less common in SPG11. [6]

Table 3. continued from previous page.

Gene(s)	Disorder	Clinical Features That Differ From SPG15
SPG21	SPG21 [2] (Mast syndrome)	Onset of manifestations is often later, typically in early adulthood. Psychosis is seen in a subset of affected persons.
TECPR2	SPG49	Central apneas & autonomic dysfunction are prominent.

DD/ID = developmental delay / intellectual disability; SPG = spastic paraplegia
1. Ebrahimi-Fakhari et al [2020]
2. See Hereditary Spastic Paraplegia Overview.
3. Hirst et al [2016]
4. Srivastava et al [2020]
5. Rattay et al [2019]
6. Goizet et al [2009]

See also Hereditary Spastic Paraplegia Overview.

Management

No clinical practice guidelines for spastic paraplegia 15 (SPG15) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spastic paraplegia 15 (SPG15), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Spastic Paraplegia 15

System/Concern	Evaluation	Comment
Spasticity	Neurologic eval	• Clinical assessment may incl the Spastic Paraplegia Rating Scale [2] or Modified Ashworth Scale [3] to quantify motor manifestations & track progression. • Brain MRI (if not performed at diagnosis) • Consider EEG if seizures are a concern.
Cerebellar dysfunction		
Extrapyramidal movement disorders [1]		
Peripheral neuropathy		
Seizures		
Musculoskeletal	Orthopedics / physiatry / PT & OT eval	To incl PT/OT eval & assessment for mobility, activities of daily living, contractures, scoliosis, & foot deformities (incl *pes cavus*)
DD/ID, cognitive impairment	Developmental assessment	Depending on age: • To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education • Formal assessment of intellectual abilities
Dysarthria	Eval by speech & language specialist	Consider eval for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for those w/ expressive language difficulties.
Dysphagia		Swallow study if dysphagia &/or aspiration is a concern
Neurogenic bladder dysfunction	Urology eval	Consider urodynamic studies.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Bowel dysfunction	General care	Assess & treat constipation.
Ophthalmologic involvement	Ophthalmologic eval	Best corrected visual acuity; fundus exam &/or electroretinography for pigmentary retinopathy
Sensorineural hearing loss	Audiology eval	Audiometry or other formal hearing testing if hearing impairment is a concern
Genetic counseling	By genetics professionals [4]	To inform patients & their families re nature, MOI, & implications of SPG15 in order 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 parental support; • Need for home nursing referral.	

DD/ID = developmental delay / intellectual disability; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Dystonia and/or parkinsonism
2. Schüle et al [2006]
3. Bohannon & Smith [1987]
4. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

At present, no treatment prevents, halts, or reverses neuronal degeneration in SPG15. Treatment is directed at reducing symptoms and preventing secondary complications. Multidisciplinary care involving a neurologist, clinical geneticist, developmental specialist, orthopedic surgeon/physiatrist, physical therapist, occupational therapist, speech and language pathologist, and feeding team is recommended.

Table 5. Treatment of Manifestations in Individuals with Spastic Paraplegia 15

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity/ Weakness	• PT • Antispasticity medications (oral or intrathecal baclofen & others) • Botulinum toxin injections • Surgical treatment	• Progression of contractures, scoliosis, foot deformities, & loss of ambulation may be delayed w/PT & antispasticity treatment. • Consider need for positioning & mobility devices. • Monitor skin integrity.
Contractures, scoliosis, foot deformities (*pes cavus*)	• PT • Referral to orthopedic surgery	Assess need for orthoses/braces & mobility devices.
Cerebellar dysfunction	Assess fall risk & home safety.	Consider need for positioning & mobility devices.
Parkinsonism	Trial of L-dopa	• Variable response; evidence is limited. [1] • Assess treatment response w/Unified Parkinson's Disease Rating Scale.

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Dystonia	• Botulinum toxin injections for focal dystonia • Anti-dystonia medications	
DD/ID, cognitive impairment	• PT, OT • Consultation w/social worker	In adults, anticipate & assist w/issues of guardianship that may accompany progressive decline.
Dysarthria / Speech delay	Speech therapy by speech & language therapist	Assess utility of augmentative communication devices.
Dysphagia/ Aspiration	• Therapy by speech & language therapist • Anticholinergic agents for sialorrhea • G-tube feeds	Management by interdisciplinary aerodigestive team
Nutrition	Nutritional supplementation	Referral to nutritionist
Ophthalmologic involvement	Referral to ophthalmologist	
Neurogenic bladder	• Anticholinergic drugs for urinary urgency • Referral to urologist	
Bowel dysfunction, chronic constipation, GER	• Stool softeners, prokinetics, osmotic agents, or laxatives as needed • Proton pump inhibitors, histamine receptor antagonists, or antacids as needed • Consideration of fundoplication in refractory cases	Referral to gastroenterologist
Osteopenia	Vitamin D & calcium supplementation	
Routine health care	Standard immunizations per local guidelines	
Family & Community	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.	• Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. • Ongoing assessment of need for palliative care involvement &/or home nursing. • Referral to palliative care when deemed appropriate by family & health care providers

DD/ID = developmental delay / intellectual disability; GER = gastroesophageal reflux; OT = occupational therapy; PT = physical therapy

1. Schicks et al [2011], Araujo et al [2020]

Surveillance

Affected individuals should be evaluated periodically (i.e., every 6-12 months) by an interdisciplinary team that may include a neurologist, clinical geneticist, developmental specialist, orthopedic surgeon/physiatrist, physical therapist, occupational therapist, and speech and language pathologist, and feeding team to assess disease progression, maximize ambulation and communication skills, and reduce other manifestations.

Table 6. Recommended Surveillance for Individuals with Spastic Paraplegia 15

System/ Concern	Evaluation	Frequency
Neurologic	Monitor & treat spasticity & extrapyramidal movement disorders.	At least annually, more frequently if needed
Musculoskeletal	• PT/OT eval • Monitor for musculoskeletal complications of spasticity. • Hip/spine x-rays as needed	
Eyes	Ophthalmologic eval for visual acuity & need for support services for the visually impaired	As needed
Gastrointestinal/ Nutrition	• Eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/dysphagia or aspiration risk.	
Pulmonary	Monitor for aspiration & pulmonary complications.	
Genitourinary	• Monitor bladder function. • Monitor for urinary tract infections. • Urodynamic testing	
Mental health	Monitor for depression or mood disorder.	
Family support & resources	Monitor family/caregiver needs & resources (social work involvement, home nursing referral)	

OT = occupational therapy; PT = physical therapy

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 15 (SPG15) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ZFYVE26* pathogenic variant based on family history).

- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *ZFYVE26* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *ZFYVE26* pathogenic variant, each sib of an affected individual has at conception 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 are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with SPG15 are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *ZFYVE26* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ZFYVE26* pathogenic variants in the family.

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, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ZFYVE26* pathogenic variants have been identified in an affected family member, prenatal 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.

- **The Maddi Foundation**

  Cambridge House

27 Cambridge Park
London E11 2PU
United Kingdom
www.themaddifoundation.com

- **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
- **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

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 15: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ZFYVE26	14q24.1	Zinc finger FYVE domain-containing protein 26	ZFYVE26 database	ZFYVE26	ZFYVE26

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 15 (View All in OMIM)

270700	SPASTIC PARAPLEGIA 15, AUTOSOMAL RECESSIVE; SPG15
612012	ZINC FINGER FYVE DOMAIN-CONTAINING PROTEIN 26; ZFYVE26

Molecular Pathogenesis

The ZFYVE26 protein, also known as spastizin, associates with the SPG11 protein and the adaptor protein complex 5 (AP-5) [Hirst et al 2013]. Loss-of-function variants in *SPG11* and *AP5Z1* cause SPG11 and SPG48, respectively.

ZFYVE26 is required for generating mature autophagosomes, a process that is impaired when the protein is defective or absent [Khundadze et al 2013, Vantaggiato et al 2013]. ZFYVE26 interacts with BECN1 and with its interacting proteins PIK3C3, UVRAG, and RUBCN, major regulators of autophagy and endocytosis. Because these interactions are lost in the presence of biallelic *ZFYVE26* loss-of-function variants, cells derived from individuals with SPG15 display accumulation of immature autophagosomes and impaired autophagosome-to-lysosome fusion [Vantaggiato et al 2013].

Zfyve26 knockout mice show an accumulation of large intraneuronal deposits of membrane-surrounded material (containing lysosomal markers), followed by axonal degeneration with progressive loss of both cortical motoneurons and cerebellar Purkinje cells [Khundadze et al 2013]. Collectively, these findings point to a dysfunction of the endosomal, autophagosomal, and lysosomal compartments in SPG15 [Khundadze et al 2013, Vantaggiato et al 2013, Renvoisé et al 2014]. Several converging lines of supportive evidence from work on SPG11 and AP-5 show that the SPG11/ZFYVE26 /AP-5 complex is involved in the reformation of lysosomes from autolysosomes and endolysosomes [Chang et al 2014, Khundadze et al 2019].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

For inquiries about research on SPG15, the authors suggest the foundations/organizations in Resources as well as the Hereditary Spastic Paraplegia (HSP) programs at Boston Children's Hospital and Massachusetts General Hospital.

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