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Spastic Paraplegia 8

Synonym: SPG8

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Summary

Clinical characteristics

Hereditary spastic paraplegia 8 (SPG8) is a slowly progressive pure spastic paraplegia of the lower limbs (i.e., pyramidal signs including hyperreflexia, spasticity, and occasionally clonus without other neurologic findings). Some affected individuals have urinary urgency that usually becomes apparent at the same time as the spasticity. Onset is between ages ten and 59 years. Affected individuals often become wheelchair dependent. While intra- and interfamilial phenotypic variability is high, SPG8 is typically more severe than other types of hereditary spastic paraplegia.

Diagnosis/testing

The diagnosis of SPG8 is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *WASHC5* identified by molecular genetic testing.

Management

Treatment of manifestations: A multidisciplinary approach to management of spasticity is recommended including neurology, physical therapy (PT), occupational therapy (OT), urology, speech and language pathology, feeding team, psychiatry/mental health, and social work.

Surveillance: Regular neurologic examinations to evaluate disease progression and response to treatment; urologist for assessment of bladder function and risk for urinary tract infection; PT/OT to assess mobility and activities of daily living; feeding team for nutrition and risk for aspiration; speech and language pathologist re dysarthria; and mental health clinician re depression.

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Genetic counseling

SPG8 is inherited in an autosomal dominant manner. More than 90% of individuals with SPG8 have an affected parent. Each child of an individual with SPG8 has a 50% chance of inheriting the *WASHC5* pathogenic variant. Once the *WASHC5* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Spastic paraplegia 8 (SPG8) **should be suspected/considered** in individuals with the following clinical and neuroimaging findings and family history [Reid et al 1999, Rocco et al 2000, Valdmanis et al 2007, de Bot et al 2013].

Clinical findings

- Onset in the 20s and 30s (range: age 20-60 years)
- Slowly progressive "pure" spastic paraplegia of the lower limbs (i.e., pyramidal signs including hyperreflexia, spasticity, and occasionally clonus without other neurologic findings)
- Mild distal decreased vibration sense
- Urinary urgency

Neuroimaging findings. Brain MRI is generally normal. In one moderately affected individual spine MRI showed significant atrophy of the thoracic spinal cord as determined by cross-sectional area measurements [Hedera et al 1999].

Other studies. Normal:

- Cerebrospinal fluid
- Electrophysiologic studies:
  - Nerve conduction velocity
  - Electromyography
- Biochemical testing
  - Vitamin B_{12}
  - Very long chain fatty acids
  - Lactate [Gasser et al 2010]

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

Establishing the Diagnosis

The diagnosis of spastic paraplegia 8 **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *WASHC5* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *WASHC5* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches include **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing and genome sequencing) depending on the phenotype [Chrestian et al 2016, Elert-Dobkowska et al 2019].

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 has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A hereditary spastic paraplegia multigene panel that includes *WASHC5* 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(s) are 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 8

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
WASHC5	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	One 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. 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. Gene-targeted deletion/duplication analysis detects deletions ranging from a single exon to the whole gene.
6. Ishiura et al [2014]

Clinical Characteristics

Clinical Description

Spastic paraplegia 8 (SPG8) is characterized by progressive lower-limb spasticity with hyperreflexia and extensor plantar reflexes. While intra- and interfamilial phenotypic variability is high, SPG8 is typically more severe than other types of hereditary spastic paraplegia.

Onset is between ages ten and 59 years (range: 18-26 years in 1 family [Rocco et al 2000] and 35-53 years in another [Valdmanis et al 2007, Bettencourt et al 2013]).

SPG8 is more often associated with wheelchair dependence than other types of autosomal dominant hereditary spastic paraplegia. In one family of 15 affected individuals, insidiously progressive spastic paraparesis began between ages 22 and 60 years (average: 37.2 years); ten of the 15 were wheelchair bound by age 40 years [Hedera et al 1999]. In another large family, six of 15 affected family members were wheelchair dependent [Reid et al 1999]. In the family reported by Rocco et al [2000], affected individuals usually became wheelchair bound in their 30s and 40s [Rocco et al 2000].

Affected individuals also demonstrate weakness, a minor component that is probably secondary to reduced mobility.

Some affected individuals have urinary urgency that usually becomes apparent at the same time as the spasticity.

Decreased vibration sense is an additional finding on neurologic examination [Depienne et al 2007].

Other studies. Muscle biopsy is normal [Hedera et al 1999, Rocco et al 2000].

Genotype-Phenotype Correlations

The number of pathogenic variants reported to date is too small to draw any genotype-phenotype correlations.

Nomenclature

"Uncomplicated" (or pure) hereditary spastic paraplegia. Neurologic impairment is limited to progressive lower-extremity spastic weakness, hypertonic urinary bladder disturbance, and mild decrease of lower-extremity vibration sense and, occasionally, joint position sense. While manifestations may be disabling, life span is not shortened.

"Complicated/complex" (syndromic) hereditary spastic paraplegia. The impairment present in uncomplicated hereditary spastic paraplegia is accompanied by other system involvement or other neurologic findings (in the absence of other causes for these additional features, such as diabetes mellitus). Other findings may include ataxia, seizures, intellectual disability, dementia, muscle atrophy, extrapyramidal disturbance, and peripheral neuropathy.

Penetrance

The penetrance for SPG8 is estimated between 90% and 100% [Valdmanis et al 2007].

Prevalence

The prevalence of all hereditary spastic paraplegia is 1-18:100,000 [McMonagle et al 2002]. Pathogenic variants in *WASHC5* account for approximately 4%-5% of hereditary spastic paraplegia [Valdmanis et al 2007, Chrestian et al 2016].

Pathogenic variants in *WASHC5* have been identified in North American, British, and Brazilian populations. It is expected that *WASHC5* pathogenic variants would have a similar prevalence in other populations [Valdmanis et al 2007].

Genetically Related (Allelic) Disorders

Ritscher-Schinzel syndrome is associated with biallelic *WASHC5* pathogenic variants.

Differential Diagnosis

Hereditary spastic paraplegia 8 (SPG8) is indistinguishable clinically from other forms of autosomal dominant hereditary spastic paraplegia (see Hereditary Spastic Paraplegia Overview, Causes).

Other conditions that may be associated with spasticity include hereditary disorders (e.g., amyotrophic lateral sclerosis, adrenomyeloneuropathy, mitochondrial disorders) and acquired disorders (e.g., tropical spastic paraplegia caused by HTLV1 infection, vitamin B_{12} deficiency, multiple sclerosis, and cervical myelopathy) (see Hereditary Spastic Paraplegia Overview, Differential Diagnosis) [Gasser et al 2010].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spastic paraplegia 8 (SPG8), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with Spastic Paraplegia 8

System/Concern	Evaluation	Comment
Spasticity	Neurologic exam	Assess degree of spasticity & assoc signs.
Musculoskeletal	Orthopedics / physical medicine & rehabilitation / PT eval	To incl assessment of: • Muscle tone; joint range of motion; posture; mobility; strength, coordination & endurance; pain; bedsores • Need for adaptive devices • Footwear needs • PT needs
	OT	To assess: • Fine motor function (e.g., hands, feet, face, fingers, & toes) • Activities of daily living
Bladder function	Referral to urologist; consider urodynamic eval.	To address spastic bladder symptoms: urgency, frequency, difficulty voiding
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)
Mental health	Eval for symptoms of depression	
Genetic counseling	By genetics professionals [2]	To inform affected individuals & their families re nature, MOI, & implications of SPG8 to facilitate medical & personal decision making

Table 2. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Use of community or online resources; • Social work involvement for caregiver support; • Home nursing referral.	

Based on information provided by Spastic Paraplegia Foundation
MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Kanavin & Fjermestad [2018]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

No cures or specific drug treatments exist for hereditary spastic paraplegia; management is supportive (see Table 3). A multidisciplinary approach to management of spasticity is reviewed by Young [1994].

Table 3. Treatment of Manifestations in Individuals with Spastic Paraplegia 8

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	Individualized PT program	• Stretching exercises to improve flexibility, ↓ spasticity & maintain or improve joint range of motion & prevent joint contractures • 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; activites of daily living
	Reduction of spasticity	Massage, ultrasound, whirlpool, anodal spinal direct current stimulation [1]
	Antispasmodic drugs	Baclofen, botulinum toxin, dantrolene, tizanidine (used 1 at a time) [2] esp early in disease course to decrease cramps, make leg muscles less tight, & facilitate walking
Bladder function	Spastic bladder symptoms: urgency, frequency, difficulty voiding	Treatment can incl anticholinergics such as oxybutynin (Ditropan XL®), solifenacin (Vesicare®), and mirabegron (Myrbetriq®).
Dysphagia	Gastroenterology / 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		• 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)

Table 3. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Activities of daily living	PT	• 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
Clinical depression	Psychiatry	Psychotherapy & SSRI
Social support	Social services & support groups	To help cope w/diagnosis

OT = occupational therapy; PT = physical therapy; SSRI = selective serotonin reuptake inhibitor
1. Demonstrated by Ardolino et al [2018] in a randomized controlled trial.
2. Oral baclofen can be tried first, and can also 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

Table 4. Recommended Surveillance for Individuals with Spastic Paraplegia 8

System/Concern	Evaluation	Frequency
Spasticity	Neurologic exam re disease progression & response to current treatment	1-2 per yr
Bladder function	Per treating urologist, incl monitoring for urinary tract infection	1-2 per yr
Dysphagia	Gastroenterology / nutrition / feeding team re nutrition & risk for aspiration	1-2 per yr
Dysarthria	Per neurologic & speech/language assessment	1-2 per yr
Bowel function	Per symptoms	1-2 per yr
Mobility	Neurologic exam, rehabilitation medicine, & PT assessment	1-2 per yr
Activities of daily living	OT & PT	As needed
Clinical depression	Per mental health clinician	1-2 per yr

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.

Pregnancy Management

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Bettencourt et al [2013] reported two individuals with partial response to L-dopa, a finding that requires further study as the mechanism of action is unknown.

Of the two studies currently recruiting patients with hereditary spastic paraplegia, one involves a therapy. The NCT04180098 study will assess the effectiveness of the physical therapy intervention C-Mill in improving gait adaptability.

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.

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 8 (SPG8) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- More than 90% of individuals diagnosed with SPG8 have an affected parent.
- A proband with SPG8 may have the disorder as the result of a *de novo* pathogenic variant; the proportion of individuals with a *de novo WASHC5* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo WASHC5* pathogenic variant include neurologic evaluation and molecular genetic testing of both parents.
- If the *WASHC5* 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 WASHC5* pathogenic variant.
- The family history of some individuals diagnosed with SPG8 may appear to be negative because of failure to recognize the disorder in family members with a milder phenotypic presentation, 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 molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the *WASHC5* pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

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 pathogenic variant identified in the proband, the risk to the sibs is 50%. Note: Age of onset, severity, type of symptoms, and rate of disease progression may vary between family members heterozygous for the same *WASHC5* pathogenic variant.
- If the proband has a known *WASHC5* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *WASHC5* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for SPG8 because of the possibility of age-related

penetrance in a parent heterozygous for the *WASHC5* variant or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with SPG8 has a 50% chance of inheriting the *WASHC5* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *WASHC5* 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 is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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.

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

- Predictive testing for at-risk relatives is possible once the SPG8-related pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

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

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

In a family with an established diagnosis of SPG8, it is appropriate to consider testing of symptomatic individuals regardless of age.

Prenatal Testing and Preimplantation Genetic Testing

Once the *WASHC5* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for SPG8 are possible. Note: Age of onset, severity of disease, type of symptoms, and rate of disease progression are variable and cannot be accurately predicted by molecular genetic testing.

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
  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
- **Tom Wahlig Foundation**
  Tom Wahlig Stiftung
  Germany
  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

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 8: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
WASHC5	8q24.13	WASH complex subunit 5	KIAA0196 database	WASHC5	WASHC5

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 8 (View All in OMIM)

603563	SPASTIC PARAPLEGIA 8, AUTOSOMAL DOMINANT; SPG8
610657	WASH COMPLEX, SUBUNIT 5; WASHC5

Molecular Pathogenesis

WASHC5 encodes strumpellin, a Wiskott-Aldrich syndrome (see *WAS*-Related Disorders) protein and Scar homolog (WASH) complex that also includes KIAA1033 (SWIP), FAM21, CCDC53, WASH1 [Derivery & Gautreau 2010, Pan et al 2010]. The protein contains one spectrin repeat and one highly conserved domain of unknown significance [Valdmanis et al 2007]. The spectrin domain is involved in interaction with the cytoskeletal matrix of the cell and can facilitate binding to other spectrin-repeat-containing proteins. The WASH complex is involved in retromer-dependent endosomal protein sorting. Strumpellin physically binds the valosin-containing protein (VCP) [Clemen et al 2010].

WASHC5 is expressed in all tissues; the mRNA is present in many regions of the brain [Valdmanis et al 2007].

Mechanism of disease causation. Unknown; however, a haploinsufficiency mechanism has been proposed based on the following:

- Cells lacking strumpellin have abnormally enlarged lysosomes. Furthermore, defective endosomal tubule fission was found to cause these lysosomal abnormalities, a mechanism shared with spastin disease models (see Spastic Paraplegia 4) [Allison et al 2017, Song et al 2018].
- The p.Asn471Asp pathogenic variant, within the spectrin-binding domain, does not impair the interaction of strumpellin and VCP, but could impair interactions with other proteins [Clemen et al 2010].
- Delivery of *WASHC5* mRNA, encoding the p.Leu619Phe and p.Val626Phe protein variants, did not yield an overt phenotype in zebrafish, failing to show a toxic gain-of-function mechanism [Valdmanis et al 2007].
- A pathogenic heterozygous deletion of exon 11-15 includes the spectrin repeat domain and the conserved domain [Ishiura et al 2014].
- Ma et al [2018] also reported a frameshift variant affecting the same domains (c.1128delG; p.Met377CysfsTer24), further supporting their important role in SPG8.
- Finally, the pathogenic variants p.Val626Phe, p.Leu619Phe, and p.Asn471Asp were still able to co-immunoprecipitate with the WASH complex without changing its localization [Freeman et al 2013].

A murine *WASHC5* knockout was embryonic lethal when homozygous and did not show a clinical or biochemical phenotype when heterozygous [Jahic et al 2015].

Table 5. Notable *WASHC5* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_014846.3 NP_055661.3	c.1876G>T (1956G>T)	p.Val626Phe	Identified in 4 families from North America & Britain, suggesting a recurrent variant [Valdmanis et al 2007]
	c.2087G>C	p.Gly696Ala	Identified in a large Dutch family [de Bot et al 2013]
	c.1128delG	p.Met377CysfsTer24 (p.L376fs)	Variant w/youngest age of onset (5 yrs) [Ma et al 2018]
	g.126138189_126142822del (4634 bp); del exons 11-15		Large deletion, indicating haploinsufficiency as a potential mechanism [Ishiura et al 2014]

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

Chapter Notes

Revision History

- 21 May 2020 (bp) Comprehensive update posted live
- 25 July 2013 (me) Comprehensive update posted live
- 13 August 2008 (me) Review posted live
- 16 June 2008 (pnv) Original submission

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