GENEReviews

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Spastic Paraplegia 7

[*Hereditary Spastic Paraplegia, Paraplegin Type*]

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Summary

Disease characteristics. 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 is mostly in adulthood, although symptoms may start as early as age 11 years and as late as age 72 years. Additional features such as hyperreflexia in the arms, sphincter disturbances, spastic dysarthria, dysphagia, pale optic disks, ataxia, nystagmus, strabismus, decreased hearing, scoliosis, *pes cavus*, motor and sensory neuropathy, and amyotrophy may be observed.

Diagnosis/testing. The diagnosis of SPG7 is suspected in individuals with characteristic neurologic findings and is confirmed by detection of disease-causing mutations in *SPG7*, the gene encoding the protein paraplegin. *SPG7* is the only gene known to be associated with SPG7. Sequence analysis and deletion analysis are clinically available.

Management. No specific treatment for SPG7 exists. 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 helps with activities of daily living. Surveillance includes 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. Prenatal diagnosis for pregnancies at increased risk is possible if both disease-causing alleles have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of spastic paraplegia 7 (SPG7) is suspected in the presence of the following:

- Insidiously progressive bilateral leg weakness

- Spasticity
- Decreased vibratory sense caused by degeneration of cortical spinal axons and dorsal columns
- Neurologic examination demonstrating:
  - A pure phenotype of spastic paraplegia with hyperreflexia, extensor plantar responses, and mildly impaired vibration sensation in the distal legs

    OR
  - In some individuals, a complicated phenotype of spastic paraplegia including pale optic disks, slowed speech, swallowing difficulties, urinary urgency, ataxia, nystagmus, strabismus, decreased hearing, scoliosis, *pes cavus*, motor and sensory neuropathy, and amyotrophy [Harding 1983, De Michele et al 1998, Fink 2003, Wilkinson et al 2004, Elleuch et al 2006]
- Family history consistent with autosomal recessive inheritance

The diagnosis is confirmed by detection of disease-causing mutations in the *SPG7* gene.

Testing

Neuroimaging

- In a few individuals, cerebral MRI may show cerebellar (or, less frequently, cortical) atrophy [De Michele et al 1998, Wilkinson et al 2004, Elleuch et al 2006].
- Spinal imaging studies are useful in the differential diagnosis to exclude other anomalies of the ponto-medullary 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].
- Paired transcranial magnetic stimulation (TMS) may show delayed prolongation of the central motor conduction time and motor threshold in some affected individuals. The intracortical inhibition seems normal in SPG7 [Nardone et al 2003].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *SPG7*, which encodes the protein paraplegin, is the only gene known to be associated with SPG7 [Casari et al 1998].

Clinical uses

- Diagnostic testing
- Predictive testing
- Carrier testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** All currently known missense, nonsense, and splice site mutations can be detected using sequence analysis.
- **Deletion/duplication analysis.** Deletion/duplication analysis for the 9.5-kb deletion that includes exons 12-17 as described by Casari et al 1998 is available on a clinical basis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Spastic Paraplegia 7

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*SPG7* sequence variants	100% [1]	Clinical Testing
Deletion/duplication analysis	9.5 kb deletion involving exons 12-17 of SPG7 [2]	Unknown	

1. The disease is defined by presence of an *SPG7* mutation; therefore, the mutation detection rate is by definition 100%.
2. See Table 4.

Table 3 shows PCR primers for molecular diagnosis.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *SPG7*.

Clinical Description

Natural History

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 is mostly in adulthood, 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].

Additional features such as hyperreflexia in the arms, sphincter disturbances, spastic dysarthria, dysphagia, pale optic disks, ataxia, nystagmus, strabismus, decreased hearing, scoliosis, *pes cavus*, motor and sensory neuropathy, and amyotrophy may be observed [Harding 1983, De Michele et al 1998, Fink 2003, Wilkinson et al 2004, Elleuch et al 2006].

Progression of disease may be rapid with severe disability after eight years' duration [Elleuch et al 2006, Schüle et al 2006].

Serum creatine kinase concentration may be slightly above the normal range in some cases.

Electromyography (EMG) with nerve conduction velocities (NCV) may reveal axonal sensory motor neuropathy.

Muscle biopsy may shed light on the pathogenic process and reveal the following:

- Changes of denervation with partial reinnervation

- Atrophic, angulated fibers, predominatly type II
- Ragged-red fibers, which are positive for the histoenzymatic reaction to succinate dehydrogenase (SDH) and negative for cytochrome c oxidase (COX, the complex IV of the mitochondrial respiratory chain), indicating an oxidative phosphorylation (OXPHOS) defect [Casari et al 1998, McDermott et al 2001, Wilkinson et al 2004].

Genotype-Phenotype Correlations

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

Prevalence

The prevalence of SPG7 is estimated to be around 2-6/100,000 for most countries.

Autosomal recessive inheritance appears relatively uncommon outside regions with a high rate of consanguineous marriages. Of note, a significant proportion of individuals with autosomal recessive SPG7 may present as simplex cases (i.e., a single occurrence in a family).

SPG7 is estimated to account for 5%-12% autosomal recessive HSP [Casari, personal observation; McDermott et al 2001; Elleuch et al 2006].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

No significant differences exist between spastic paraplegia 7 (SPG7) and other types of pure autosomal dominant and autosomal recessive spastic paraplegia [Fink 2002, 2003]. See Hereditary Spastic Paraplegia Overview for a review.

Other conditions that need to be considered in the differential diagnosis of SPG7:

- Structural abnormalities of the brain or spinal cord
- Adrenomyeloneuropathy and other leukodystrophies (e.g., Krabbe disease, arylsulfatase A deficiency [metachromatic leukodystrophy]) [Bajaj et al 2002]
- Vitamin B12 deficiency
- Multiple sclerosis
- Tropical spastic paraplegia (caused by HTLV1 infection)
- Dopa-responsive dystonia
- Amyotrophic lateral sclerosis (ALS)
- Primary lateral sclerosis (PLS)
- Arginase deficiency [Prasad et al 1997]

Management

Evaluations Following Initial Diagnosis

Evaluation by a multidisciplinary team that includes a general practitioner, neurologist, medical geneticist, physical therapist, social worker, and psychologist should be considered in individuals with spastic paraplegia 7 (SPG7).

Treatment of Manifestations

No specific drug treatments or cures exist for SPG7.

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 [Young 1994].

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

Occupational therapy is often helpful in managing activities of daily living.

Surveillance

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

Therapies Under Investigation

In an SPG7 mouse model using intramuscular viral delivery of the gene to correct some of the defects, Pirozzi et al (2006) observed an improvement of neuropathologic changes and mitochondrial morphology, described by Ferreirinha et al (2004), in the peripheral nerves of parapegin-deficient mice. This approach may offer hope for future treatment strategies.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic. A single family in which an *SPG7* mutation cosegregates with an HSP phenotype of apparent dominant inheritance has been identified [McDermott et al 2001].

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with SPG7 are obligate heterozygotes (carriers) for a disease-causing mutation in the *SPG7* gene.

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

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the *SPG7* mutations have been identified 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 testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for typically adult-onset conditions such as SPG7 are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Spastic Paraplegia 7

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
SPG7	*SPG7*	16q24.3	Paraplegin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Spastic Paraplegia 7

602783	PARAPLEGIN; SPG7
607259	SPASTIC PARAPLEGIA 7, AUTOSOMAL RECESSIVE; SPG7

Table C. Genomic Databases for Spastic Paraplegia 7

Gene Symbol	Entrez Gene	HGMD
SPG7	6687 (MIM No. 602783)	SPG7

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: *SPG7* spans a physical distance of approximately 52 kb and is composed of 17 exons (Table 2).

Table 2. Frequency of *SPG7* Polymorphisms in Patient and Control Chromosomes

Location	Nucleotide Change	Protein Consequence	Frequency in Individuals with HSP (%)	Frequency in Controls (%)
Exon 1	4 G>A	Ala2Thr	1.5	1.7
Exon 1	9 G>T	Val3Val	0.7	1.2
Exon 1	120 G>A	Gly40Gly	0.7-5.7	1-3.5
Exon 2	199 C>T	Leu67Leu	1.5	0.7
Intron 4	IVS4 + 12 C>T	—	73	56
Intron 4	618 + 12 T>C	—	2.9	ND
Intron 7	IVS7 + 5 G>A	—	2.8	3
Intron 7	862-34 G>T	—	33.1	70.5
Exon 7	881 G>A	Arg294His	0.7	0.4
Intron 7	987 +5 A>G	—	59.7	52
Intron 7	987 +57 G>T	—	0.7	1.4
Intron 7	IVS/ + 17G>C	—	2.8	2
Intron 7	IVS7 + 38G>A	—	4.2	5
Exon 8	1032 C>T	Gly344Gly	3.6	2.2
Intron 10	IVS10 + 19G>A	—	2.8	5
Intron 11	1450 + 29 G>A	—	30.2	44

Intron 11	1552 + 65 A>C	—	30.2	41.8
Exon 11	1457 G>A	Arg486Gly	0.7	0.7
Exon 11	1507 A>G	Thr503Ala	2.8-27.3	6-35.6
Exon 11	1529 C>T	Ala510Val	1.4-9.6	4-0
Intron 12	1553 47 G>T	—	0.7	11.5
Intron 12	IVS12 + 13C>T	—	1.4-11.5	4-12
Intron 13	1664 -15 C>A	—	0.7	1
Intron 13	1779 + 47 G>C	—	27.3	36
Intron 13	IVS13 + 45G>C	—	20	31
Exon 14	1816 C>T	Gly605Gly	0	1
Intron 15	1937 -22 C>T	—	0.7	0.6
Exon 15	2037 G>A	Ala679Ala	0.7	0.6
Exon 15	2063 G>A	Arg688Gln	7.1-27.3	24-33.1
Exon 17	2283 G>A	Gln761Gln	2.8	2
Exon 17	2292 C>T	Ile764Ile	2.8-0.7	5.7 -22
Exon 17/ 3' UTR	2421 C>T 3'UTR	—	0.7	1.8

Patient chromosomes: n=70; control chromosomes: n=100 [Wilkinson et al 2004]
Patient chromosomes: n=136; control chromosomes: n=275 [Elleuch et al 2006]

Pathologic allelic variants: All types of DNA alterations are observed in almost every exon or splice site. Missense mutations are the most frequent subgroup. Missense mutations and truncating mutations have been reported within the paraplegin functional domain. See Table 3 for primers used in molecular genetic testing [Casari, unpublished data; McDermott et al 2001].

To date, sixteen mutations have been confirmed in SPG7 (Table 4).

Table 4. Mutations in *SPG7*

Location	Nucleotide Change	Effect on Protein	Reference
Exon 1	1A>T	No translation initiation	Elleuch et al 2006
Exon 1	28G>A	Ala10Ser	Wilkinson et al 2004
Exon 2	244-246delACA	Gln82del	Elleuch et al 2006
Exon 6	784del2	Frameshift, truncated protein	Casari et al 1998
Exon 6	850-851 delTTinsC	Phe284ProfsX44	Elleuch et al 2006
Exon 8	1057-1085del29	Frameshift 353-384X385	Wilkinson et al 2004
Exon 11	1450-1458del9	Glu,Arg,Arg484-486del	McDermott et al 2001
Exon 11	1519 C>T	Glu507X	Elleuch et al 2006
Exon 13	1715C>T	Ala572Val	Wilkinson et al 2004
Exon 12-17	del 9,5 kb	Large deletion of the peptidase M41 family domain	Casari et al 1998
Exon 13	1729G>A	Gly577Ser	Wilkinson et al 2004
Exon 13	1742-1744del3	Val581del	Elleuch et al 2006
Exon 14	1904C>T	Ser635Leu	Elleuch et al 2006
Exon 15	1948G>C	Asp650His	Elleuch et al 2006
Exon 15	2026T>C	Phe676Leu	Wilkinson et al 2004
Exon 17	2228 Ins A	Frameshift, stop codon	Casari et al 1998

Normal gene product: Paraplegin, comprising 795 amino acids, is in the AAA (ATPases associated with diverse cellular activities) family — as is spastin, encoded by *SPAST*, mutations in which cause SPG4, an autosomal dominant form of HSP [Hazan et al 1999] (see also Hereditary Spastic Paraplegia Overview). Paraplegin and spastin belong to different subclasses of the AAA family, since mitochondrial function of spastin has been excluded but demonstrated as a function of paraplegin.

Paraplegin is ubiquitously expressed in adult and fetal human tissues.

Paraplegin shares its closest amino acid sequence homology with the yeast mitochondrial metalloprotease Afg3, Rca1, and Yme1 [Casari et al 1998, Settasatian et al 1999]. Yeast mitochondrial ATPases demonstrate both proteolytic and chaperone-like activities at the inner mitochondrial membrane, where they are involved in the assembly and degradation of proteins in the respiratory chain complex [Pearce 1999]. Two additional human genes encoding protein highly homologous to paraplegin, *AFG3L2* and *YME1L1*, have been discovered [Banfi et al 1999, Coppola et al 2000]. 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 localized in the central part of the protein between aa 344 and 534.

Abnormal gene product: Atorino et al (2003) demonstrated that paraplegin co-assembles with a homologous protein, AFG3L2, in the mitochondrial inner membrane. The two proteins form a high molecular-weight complex that appears to be aberrant in HSP fibroblasts. The loss of this complex causes reduced complex I activity in mitochondria, which can be reversed by increased expression of wild type paraplegin. Furthermore, complementation studies in yeast demonstrate functional conservation of the human paraplegin/AFG3L2 complex with the yeast *m*-AAA protease and also assign proteolytic activity to this structure.

Biochemical analysis from two *SPG7* mutation-positive individuals 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 [Wilkinson et al 2004]. Nolden et al (2005) showed impaired mitochondrial protein synthesis in paraplegin-deficient mice. Degeneration of the corticospinal axons in individuals with SPG7 could be caused by mitochondrial impairment of regulation of the respiratory chain.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Institute of Neurological Disorders and Stroke
Hereditary Spastic Paraplegia

Spastic Paraplegia Foundation, Inc.
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National Ataxia Foundation
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www.ataxia.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 25 February 2008 (cd) Revision: deletion/duplication analysis available clinically

- 24 August 2006 (me) Review posted to live Web site
- 7 March 2005 (gc) Original submission

Table 3. Primers used in Molecular Genetic Testing for SPG7

SPG7 Exon	Forward Primer 5'↓3'	Reverse Primer 5'↓3'	Conditions			Size of PCR Products
			Temperature (°C)	$MgCl_2$	DMSO	
Exon 1	ATCACGCAGGCGCGGCTTTCAG	CTGGGCCTTAACAGAGCAGA	58	2	10%	271
Exon 2	GTTGGTGTGACCTCCAGTATTG	CTGAGAGGCGGTAAGTGTGC	52	2	—	197
Exon 3	TGTTGTCCTGTATGCCTCCC	CATCCAGAGGCAGCTACTGA	57	1.5	—	202
Exon 4a	CCGTGTCTGTTGCTCATGTG	CCAGGGTGCAGGTAGACTTC	56	2	—	273
Exon 4b	CGACTTTGTCCACGAGATG	GCTGCCAGCCTGTGCCCA	54	2	10%	165
Exon 5	GTAGGGTTGCTCGTCTGTC	AGCCAAGTTAGGTTTAGTTCA	54	2	—	244
Exon 6	TGTGCCTGCCTCTCTTTCTT	ACCAGAAAGAGTTCAGAGAGC	54	2	—	169
Exon 7	CCAGCTCCTTGCACTTTGTT	CCTCTGCTCACACCTCCCT	56	1.5	—	205
Exon 8	AGTGTTGCATTGTCTGCTGC	ATGTGTGAAAGGAGCCAGGT	56	2	—	252
Exon 9	CTGCCCATTTCCTGATTCTC	ACCTCCTCTGATGGTGCAAT	56	1.5	—	257
Exon 10	GCAGGGGAAATCTGTTGTGTC	CACCAAGAAGTGTCTTAGAG	54	2	—	281
Exon 11	CGACTGTCTTTCCTCCCCTGGT	GCCTCGATGCTGTTTGCG	54	2	—	211
Exon 12	CACACCGTGGCTGTTTGTG	CTGGGTATTTCTGGGGTTCA	56	1.5	—	202
Exon 13	CCACCGCGCCCAACTCATAC	GGACTCCCCACCCACCTTTG	61	1.5	—	215
Exon 14	CATCCTGCCTACTGACCTGG	AAGGAGTCATGCAGGGAAAA	61	1.5	—	250
Exon 15	TCTGCGCCTGCAGTGCTGA	CCTTGTGTGGTAGACCCA	56	1.5	—	286
Exon 16	CTTTGGTGCTGGAGCCAGG	GACCGTGGGTGCTGTGTGG	61	1.5	10%	200
Exon 17 (last)	ACATGCATATGCCTGTTCTTT	CTCAGCTGAAAAGCAACTCAG	57	1.5	—	312

G Casari, unpublished data. Primers are described in McDermott et al 2001.