GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Spastic Paraplegia Type 4

[*Hereditary Spastic Paraplegia, Spastin Type; Spastic Paraplegia 4; SPG 4*]

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Initial Posting: April 17, 2003.
Last Revision: April 23, 2007.

Summary

Disease characteristics. Spastic paraplegia type 4 (SPG4) is characterized by insidiously progressive bilateral lower-limb spasticity. More than 50% of affected individuals have proximal or generalized weakness in the legs and impaired vibration sense. About one-third of indviduals have sphincter disturbances. Onset is mostly in young adulthood, although symptoms may start as early as one year of age and as late as 76 years of age. Intrafamilial variation is considerable.

Diagnosis/testing. The diagnosis of SPG4 in a proband is based on characteristic clinical symptoms and molecular genetic testing of the *SPG4* gene. Molecular genetic testing is available on a clinical basis and has a mutation detection rate of greater than 90%.

Management. No specific treatment exists for SPG4. Symptomatic treatment includes the use of antispastic drugs for leg spasticity, anticholinergic antispasmodic drugs for urinary urgency, and regular physiotherapy to stretch the spastic muscles. Children should be monitored for joint contractures.

Genetic counseling. SPG4 is inherited in an autosomal dominant manner. Most individuals diagnosed with SPG4 have an affected parent. The proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with SPG4 has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible; however, requests for prenatal testing of (typically) adult-onset diseases are not common.

Diagnosis

Clinical Diagnosis

The diagnosis of spastic paraplegia type 4 (SPG4) in a proband is based on the following:

- Characteristic clinical symptoms of insidiously progressive bilateral leg spasticity and weakness, often accompanied by urinary urgency and occasionally by lower-leg paresthesias
- Neurologic examination demonstrating corticospinal tract deficits affecting both legs (spastic weakness, hyperreflexia, and extensor plantar responses), often accompanied by mildly impaired vibration sensation in the distal legs
- Family history consistent with autosomal dominant inheritance
- Molecular genetic testing of the *SPG4* gene. Detection of disease-causing mutations in the *SPG4* gene confirms the diagnosis. A negative result does not absolutely exclude the diagnosis.

Note: (1) The best clinical predictors of the presence of a *SPG4* mutation are hyperreflexia in the lower limbs, more than two beats of ankle clonus, pes cavus, bladder symptoms, and increased tone in the legs [Nicholas et al 2004]. (2) The presence of other signs/symptoms (complicated HSP) does not exclude SPG4-associated HSP although it reduces its probability.

Brain and spinal cord MRI are useful in identifying anomalies of the cerebro-medullary junction and the cervical and dorsolumbar medulla that are part of disorders discussed in the differential diagnosis. Most MRI investigations are uninformative for SPG4, but mild vermis atrophy and/or a thin corpus callosum have been occasionally reported [Nielsen, Johnson et al 2004; Orlacchio, Kawarai et al 2004]. Cerebellar atrophy was also reported in two individuals without ataxia [Orlacchio, Kawarai et al 2004] and congenital arachnoid cysts were seen in one family [Orlacchio, Gaudiello et al 2004].

Electromyography (EMG) with **nerve conduction velocities (NCV)** is used to exclude peripheral nervous system involvement, which might raise the possibility of an alternative diagnosis.

Other

- Spinal evoked potentials may eventually reveal delayed prolongation of the central conduction time [Nielsen et al 2001].
- Whether paired transcranial magnetic stimulation may help confirm the diagnosis of SPG4 remains to be determined [Nielsen et al 2001].
- Reduced regional cerebral blood flow may be specific for SPG4-HSP [Scheuer et al 2005].

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.

Gene. *SPG4*, encoding the protein spastin, is the gene responsible for the SPG4 type of hereditary spastic paraplegia.

Clinical uses

- Diagnostic testing
- Predictive testing

- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** In theory, direct sequencing detects 100% of the point mutations or small deletions/insertions located in the exons or in the adjacent exon/intron boundaries.
- **Mutation scanning.** Several methods of detecting mutations without reading the entire coding sequence are available. The most frequently used to detect mutations in *SPG4* are SSCP (single-strand conformation polymorphism) and DHPLC (denaturing high-performance liquid chromatography). Although these methods are reliable, efficient, and cost effective, they do not detect point mutations with a sensitivity of 100%. DHPLC detects approximately 90%-95% of the point mutations, while SSCP detects only 70%-80% of all mutations.
- **Deletion/duplication analysis**

Note: (1) Uncommon mutations (e.g., gene rearrangements or large deletions/insertions, as well as mutations located outside the coding region) are not detectable with either sequence analysis or mutation scanning. Two large deletions have been reported so far [Sauter et al 2002, Iwanaga et al 2005]. (2) No mutation in the coding region was detected in two of 24 families linked to the *SPG4* locus [Fonknechten et al 2000], indicating that uncommon mutations indeed account for some of the *SPG4* mutations; the exact percentage remains unknown.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in SPG4

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*SPG4* missense, nonsense, small deletions/ insertions (frameshifts) and splice site mutations	~100%	Clinical Testing
Mutation scanning		70%-99% depending on the method used	
Deletion/duplication analysis	Large *SPG4* deletions	Unknown	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

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

Testing Strategy

Once non-genetic causes have been excluded, testing for SPG4 should be considered in simplex cases (i.e., individuals with no family history of spasticity), as mutations can be identified in about 10% of simplex cases [personal data].

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *SPG4*.

Clinical Description

Natural History

The cardinal clinical feature of SPG4 is insidiously progressive bilateral lower-limb spasticity. In addition to spasticity in the lower limbs associated with frequent brisk reflexes, ankle clonus,

and Babinski signs, individuals with SPG4 may also have increased reflexes in the upper limbs, but they are never tetraspastic. Along with pyramidal signs that include sphincter disturbances in one-third of affected individuals, more than 50% of individuals have proximal or generalized weakness in the lower limbs.

Onset is mostly in early adulthood, although symptoms may appear as early as age one year (when the child starts to walk) and as late as 76 years [personal observation].

Families in which some individuals are mildly affected while others are severely affected are reported [Matsuura et al 1997, Nance et al 1998, Nielsen et al 1998, Hentati et al 2000, Lindsey et al 2000, McMonagle et al 2000, Santorelli et al 2000, Higgins et al 2001, Mead et al 2001, Svenson et al 2001, Meijer et al 2002]. Disease severity generally worsens with the duration of the disease, although some individuals remain mildly affected all their lives. Wheelchair use and walking only with assistance occur in 17% and 20% of individuals, respectively. Disease progression is more rapid in individuals with late onset (>35 years) than in those with early onset. However, Orlacchio et al (2005) studied a large family with the 906delT mutation and found a significant correlation between disability and disease duration.

Other findings. The most frequent additional feature is decreased, but not abolished, vibration sense at the ankles occurring in 33%-59% of individuals [Durr et al 1996; Lindsey et al 2000; Mead et al 2001; Fonknechten et al 2000; Tallaksen et al 2003; Orlacchio, Kawarai et al 2004].

Pes cavus and mild spastic dysarthria may be observed.

Seizures, mental retardation and cerebellar ataxia are rare, but Nielsen, Johnson et al (2004) reported a family with complex HSP caused by a mutation in *SPG4*.

A single study mentioned the existence of mild sensory neuropathy in one individual probably for reasons independent of the *SPG4* mutation [Schulte et al 2003].

Subtle cognitive impairment has been observed [Byrne et al 1998, Heinzleff et al 1998, Webb & Hutchinson 1998, Reid et al 1999, Byrne et al 2000, McMonagle et al 2000, White et al 2000, Tallaksen et al 2003], but its relation to the disease remains controversial. Cognitive deficits appear late in the disease course and are not present in all affected members of a given family. When detected by neuropsychologic testing, the impairment is often subtle, limited to executive dysfunction, and without noticeable impact on daily living.

A few individuals with severe dementia have been reported, one of whom had neuronal loss, tau-immunoreactive neurofibrillary tangles in the hippocampus, and Lewy bodies in the substantia nigra on neuropathologic examination [White et al 2000]. Too few neuropathologic studies have been performed in SPG4 cases, however, for a general picture of the distribution of cortical and medullar lesions in the disease to emerge [Tallaksen et al 2003].

Genotype-Phenotype Correlations

No clear genotype-phenotype correlation could be shown in the largest study comparing missense and truncating mutations [Fonknechten et al 2000].

No significant difference in either age at onset or clinical severity exists among groups of individuals with missense or truncating mutations, although a meta-analysis demonstrated a tendency to earlier onset in individuals with missense mutations compared to those with other *SPG4* mutations [Yip et al 2003].

The age at onset and clinical severity are highly variable for a given mutation, even in the same family. Two family members with the same mutation can have in one case a pure and in the other a complex disease. For example, Orlacchio, Kawarai et al (2004) reported wide phenotypic variability with the N386S mutation. The intra- and interfamilial range of age at onset and disease duration was large. Some individuals had mental retardation and others showed MRI abnormalities such as thin corpus callosum or cerebellar atrophy [Orlacchio, Kawarai et al 2004].

Svenson and collaborators (2004) reported two rare nonsynonymous polymorphisms (C256T/S44L and C259A/P45Q). Homozygosity of L44 was found to be the cause of HSP inan individual with mild late-onset disease and no family history of spasticity. Individuals who have both a disease-causing mutation and one of the L44 or Q45 alleles seem to have very early onset, suggesting that these alleles could modify the HSP phenotype. Nevertheless, these alleles are rare, and early onset is not restricted to individuals who have both a mutation and a polymorphism. The extensive phenotypic variability in SPG4-associated HSP cannot therefore be explained exclusively by the S44L and P45Q polymorphisms.

A positive correlation between genotype and electrophysiologic phenotype has been reported [Bonsch et al 2003]. In a study using transcranial magnetic stimulation, individuals from two pedigrees with different mutations in *SPG4* showed different degrees of disturbance in the motor system with respect to motor evoked potential amplitude, central motor conduction time, and central motor threshold [Bonsch et al 2003]. These results must be confirmed, however, with more families.

Penetrance

Penetrance is age dependent and incomplete even in older individuals who have a *SPG4* mutation. It is estimated to be 85% by age 45 years [Fonknechten et al 2000]. Age dependence is explained partly by variability in age at onset and partly by difficulty in determining with precision the age of onset when it is insidious.

Penetrance is greater if pyramidal signs as well as spastic gait are considered: about 6% of individuals who have a *SPG4* mutation are completely asymptomatic on examination; approximately 20% have abnormal signs when examined, but no awareness of being affected.

Anticipation

Anticipation (earlier age at onset or increased severity in successive generations) was proposed by several groups in some families [Raskind et al 1997]. The exclusion of the involvement of a CAG repeat expansion in *SPG4* led to the hypothesis that the clinically observed anticipation in some families was in fact the result of ascertainment bias. The bias includes the variability in age at onset and the tendency to investigate pyramidal signs earlier in children compared to the investigation of spastic gait in the parents.

Prevalence

Skre (1974) estimated the prevalence of all dominant hereditary spastic paraplegia in Norway to be 12.4/100,000. McMonagle et al (2002) estimated the prevalence of pure dominant hereditary spastic paraplegia in Ireland to be 1.27/100,000. The estimate for most countries is around 2-6/100,000.

SPG4 is estimated to account for 15%-40% of the pure dominant forms of hereditary spastic paraplegia [Durr et al 1996, Meijer et al 2002]. Geographical prevalence may vary: Meijer et al (2002) found fewer families with SPG4 among North American families than expected from reports in European families [Durr et al 1996, Fonknechten et al 2000].

Whether certain populations are at greater risk for SPG4 than others is not known.

Differential Diagnosis

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

See Hereditary Spastic Paraplegia overview for a review of the differential diagnosis. In the case of a definite autosomal dominant hereditary spastic paraplegia, other types of autosomal dominant pure spastic paraplegia that need to be considered are SPG3, SPG6, SPG8, SPG10, SPG12, SPG13, and SPG19.

SPG4 is the most frequent form of autosomal dominant hereditary spastic paraplegia, accounting for an estimated 15%-40% of the pure dominant forms of hereditary spastic paraplegia [Durr et al 1996, Meijer et al 2002]. Because *SPG4* is the most common gene involved in AD-HSP, it is the first and most relevant gene to be tested.

No significant differences have been established between SPG4 and other types of pure dominant spastic paraplegia with the exception of SPG3A. SPG3A, encoding atlastin, is the second most frequent gene involved in AD-HSP. Durr et al (2004) have shown that SPG3A-related disease is a pure form of HSP associated with earlier onset than SPG4 HSP. In SPG3A, impairment of vibration sense at the ankles and increased reflexes in the upper limbs are less frequent. There are also fewer sphincter disturbances, more muscle wasting in the lower limbs and more scoliosis in SPG3 [Durr et al 1996, Durr et al 2004]. As a consequence, an individual with pure and very early-onset HSP should be tested for SPG3A before being considered for SPG4.

In simplex cases (spasticity in one individual in a family), all possible causes of spasticity in the legs have to be considered because some non-genetic causes of spasticity are more common than SPG4.

Management

Evaluations Following Initial Diagnosis

Whether **neuropsychologic testing** should be performed to assess the cognitive impairment frequently reported in individuals with SPG4 remains unclear. So far, no consensus exists on the type of tests that should be performed, the timing of the tests, and the purpose. Considering that cognitive impairment is often absent or is detectable only by neuropsychologic testing, one should be wary of increasing the burden of individuals with SPG4, and probably only advise further testing when required by the affected individual.

Neuro-urologic examination is advised for individuals who complain of sphincter disturbances.

Treatment of Manifestations

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

Symptomatic treatment includes the use of:

- Antispastic drugs for leg spasticity
- Anticholinergic antispasmodic drugs for urinary urgency
- Physiotherapy every two to five weeks for stretching of the spastic muscles

Botulin toxin and intrathecal baclofen can be proposed when oral drugs are ineffective and spasticity is severe and disabling.

When sphincter disturbances become a problem for the affected individual, urodynamic evaluation should be performed in order to adapt treatment and monitor follow-up [Jensen et al 1998].

Prevention of Secondary Complications

Follow-up of the sphincter disturbances is important to prevent bladder dysfunction.

Early regular physiotherapy can prevent contractures to a certain extent.

Surveillance

Specialized outclinic evaluations are suggested every six months to update medications and physical rehabilitation.

Therapies Under Investigation

Search ClinicalTrials.gov 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, 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

SPG4 is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Individuals diagnosed with SPG4 usually have a symptomatic parent who has the *SPG4* mutation; however, a parent with the *SPG4* mutation may have no symptoms.
- A proband with SPG4 may have the disorder as the result of a *de novo* gene mutation; while no *de novo* mutations have been observed so far, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include neurologic examination for evidence of spasticity and molecular genetic testing if a *SPG4* mutation has been identified in a family member.

Note: Although most individuals diagnosed with SPG4 have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, late onset of the disease in the affected parent, or incomplete penetrance.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low. If a *SPG4* mutation cannot be detected in the DNA of either parent of the proband, the possibility of germline mosaicism in a parent should be considered. No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband. Each child of an individual with SPG4 has a 50% chance of inheriting the mutation.

Other family members. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have the *SPG4* mutation present in the affected family member, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for SPG4 is available using the same techniques described in Molecular Genetic Testing. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. In addition, no interventions exist that prevent or delay the onset of symptoms in an at-risk individual who is identified as having a *SPG4* mutation. When testing at-risk individuals for SPG4, an affected family member should be tested first to confirm that the disorder in the family is actually SPG4 and to identify the specific mutation.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of SPG4, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up evaluations.

Testing of at-risk individuals during childhood. Consensus holds that individuals younger than 18 years of age who are at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications [Bloch & Hayden 1990, Harper & Clarke 1990]. In addition, no preventive treatment is available.

Individuals younger than 18 years of age who are symptomatic usually benefit from having a specific diagnosis established. (See also the National Society of Genetic Counselors resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.)

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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 in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

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 about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele 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 of (typically) adult-onset diseases 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

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 Type 4

Gene Symbol	Chromosomal Locus	Protein Name
SPAST	2p22-p21	Spastin

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 Type 4

182601	SPASTIC PARAPLEGIA 4, AUTOSOMAL DOMINANT; SPG4
604277	SPG4 GENE; SPG4

Table C. Genomic Databases for Spastic Paraplegia Type 4

Gene Symbol	Entrez Gene	HGMD
SPAST	6683 (MIM No. 604277)	SPAST

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

Normal allelic variants: *SPG4* spans a physical distance of approximately 90 kb and is composed of 17 exons. The coding region contains very few rare polymorphisms.

- One synonymous polymorphism (1004G>A/Pro293Pro) located in exon 6 is found in about 1.5%-2% of the Caucasian population [personal data].
- A nonsynonymous polymorphism (1417G>A/Arg431Gln) was found only once in the spouse of an affected individual [Meijer et al 2002].
- Svenson and collaborators (2004) reported two rare nonsynonymous polymorphisms (256C>T/Asn44Leu and 259C>A/Pro45Gln) in a control population with frequencies of 0.6% and 0.2%, respectively. Leu44 was previously reported to cause HSP at the homozygous state in an isolated individual with mild late-onset HSP [Lindsey et al 2000]. The Leu44 and Gln45 alleles were shown to segregate independently of the disease in two families and independently of a heterozygous disease-causing mutation in another family. Asn44 could theoretically be phosphorylated by a proline-directed serine/threonine cyclin-dependent kinase (Cdk). Individuals who have both a disease-causing mutation and one of the Leu44 or Gln45 alleles seem to have very early-onset disease, suggesting that these alleles could modify the HSP phenotype [Svenson et al 2004].

Pathologic allelic variants: All types of DNA alterations are observed in almost every exon or splice site. Since recurrent mutations in *SPG4* are exceptional, mutation detection requires the analysis of the whole coding sequence.

More than 140 mutations have been identified in the *SPG4* gene to date (see Table 2).

- Ninety-four truncating mutations and two large deletions have been reported [Bürger et al 2000, Fonknechten et al 2000, Hentati et al 2000, Lindsey et al 2000, Santorelli et al 2000, De Bantel et al 2001, Higgins et al 2001, McMonagle et al 2001, Mead et al 2001, Namekawa et al 2001, Svenson et al 2001, Meijer et al 2002, Proukakis et al 2002, Qin et al 2003, Proukakis et al 2003, Bürk et al 2005, Iwanaga et al 2005, Orlacchio et al 2005, Patrono et al 2005], including two leaky splice site mutations [Svenson et al 2001].
- Forty-one missense mutations and three in-frame deletions have been reported [Fonknechten et al 2000; Lindsey et al 2000; McMonagle et al 2001; Svenson et al 2001; Ki et al 2002; Meijer et al 2002; Yabe et al 2002; Molon et al 2003; Chinnery et al 2004; Falco et al 2004; Orlacchio, Gaudiello et al 2004; Tang et al 2004; Patrono et al 2005]. The former are all located within the spastin AAA cassette except one (Glu112Lys) [Patrono et al 2005]. (See Table 2.)

Normal gene product: *SPG4* encodes a 616-amino acid protein that is a putative nuclear member of the AAA (ATPases associated with diverse cellular activities) protein family named spastin. *SPG4* is ubiquitously expressed in adult and fetal human tissues, showing slightly higher expression in the fetal brain. *SPG4* undergoes alternate splicing with variable inclusion of exon 4. No mutations have been reported in exon 4, however, suggesting that the isoform lacking exon 4 is the predominant functional form of spastin in the nervous system.

Paraplegin, encoded by *SPG7* an autosomal recessive form of HSP, is also a member of the AAA family (see Hereditary Spastic Paraplegia Overview). These proteins share very little homology outside the AAA motif, however, suggesting that spastin does not belong to the same AAA subclass as paraplegin and other related metalloproteinases. The AAA domain of spastin is located in the C-terminus of the protein between amino acids 342 and 599.

Immunohistochemical studies on post mortem humain brain revealed that spastin is widely expressed in the neurons of the central nervous system, including the cortex and striatum [Wharton et al 2003]. Distal degeneration of long tracts in the spinal cord is associated with a microglial reaction. Observations are consistent with an alteration of the cytoskeleton in the motor system as well as a tau-pathology outside the motor system.

Subcellular localization of spastin remains controversial. Overexpressed spastin proteins are found in the cytoplasm or the perinuclear area [Errico et al 2002, McDermott et al 2003] while the endogenous protein is at least partly located in the nucleus of HeLa cells and mouse motor neurons [Charvin et al 2003]. Wharton and colleagues confirmed on post mortem human brain that spastin showed both cytoplasmic and nuclear expression in neurons [Wharton et al 2003]. Spastin could also have a role in synaptic localization as *Drosophila* spastin is enriched in axons and synaptic connexions of *Drosophila* neurons [Trotta et al 2004, Sherwood et al 2004].

Emerging evidence suggests that spastin plays a role in microtubule dynamics. Overexpression of spastin seems to promote microtubule disassembly in cellular models [Errico et al 2002]. Spastin could act as a microtubule-severing protein such as katanin, an AAA protein of the same subfamily that contributes to the regulation of microtubule length and dynamics during mitosis and meiosis. Furthermore, Ciccarelli and colleagues (2003) identified a region of approximately 80 amino acids in the N-terminus of spastin that they named MIT (for microtubule-interacting and trafficking molecules domain); the region is also shared by spartin, the protein mutated in the Amish type of hereditary spastic paraplegia (SPG 20). This region corresponds to a domain present in several proteins, all of which are implicated in endosomal trafficking models [Ciccarelli et al 2003]. These observations led to the proposition that spastin plays a role in intracellular organelle trafficking via its interaction with the microtubule cytoskeleton.

Abnormal gene product: Haploinsufficiency has been postulated on the basis of the observation of reduced spastin mRNA in individuals with premature protein termination [Bürger et al 2000]. The level of spastin mRNA has been tested and found to be reduced, probably as a consequence of RNA instability. Reduced levels of functional spastin are not well tolerated, since two leaky splice site mutations that create both wild type and aberrant splice variants are pathogenic.

The finding that *SPG4* mutations in the AAA domain lead to constitutive binding to microtubules suggests a dominant-negative effect [Errico et al 2002]. McDermott et al (2003) have shown that the abnormal interaction of mutant spastin with microtubules results in a change in the distribution of intracellular organelles such as mitochondria or peroxisomes. The impairment of microtubule-dependent organelle transport could thus be responsible for the degeneration of long corticospinal axons underlying the pathogenesis of hereditary spastic paraplegia [McDermott et al 2003]. However, the aforementioned results were obtained by overexpression of mutant and wild type spastin fusion proteins, mostly in cell lines, which may not be the appropriate model to mimic the defects in pyramidal tract neurons in affected individuals. Other approaches have thus been developed to reproduce haploinsufficiency: loss of function of *Drosophila* spastin, either by RNAi or knock-out, affected the morphology and function of the neuromuscular synapse by modulating microtubule dynamics in synaptic terminals [Trotta et al 2004, Sherwood et al 2004]. These results, however, have not yet been confirmed in a mammal model.

Resources

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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.

Association Strumpell Lorrain (ASL)
http://assoc.orange.fr/asl.spastic/

Spastic Paraplegia Foundation, Inc.
11 Douglas Green
Woburn MA 01801
Phone: 703-495-9261
Email: community@sp-foundation.org
sp-foundation.org

National Ataxia Foundation
2600 Fernbrook Lane Suite 119
Minneapolis MN 55447
Phone: 763-553-0020
Fax: 763-553-0167
Email: naf@ataxia.org
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

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.

The National Society of Genetic Counselors (1995) Resolution on prenatal and childhood testing for adult-onset disorders.

Literature Cited

Bloch M, Hayden MR. Opinion: predictive testing for Huntington disease in childhood: challenges and implications. Am J Hum Genet. 1990;46:1–4. [PubMed: 2136787]

Bonsch D, Schwindt A, Navratil P, Palm D, Neumann C, Klimpe S, Schickel J, Hazan J, Weiller C, Deufel T, Liepert J. Motor system abnormalities in hereditary spastic paraparesis type 4 (SPG4) depend on the type of mutation in the spastin gene. J Neurol Neurosurg Psychiatry. 2003;74:1109–12. [PubMed: 12876245]

Burger J, Fonknechten N, Hoeltzenbein M, Neumann L, Bratanoff E, Hazan J, Reis A. Hereditary spastic paraplegia caused by mutations in the SPG4 gene. Eur J Hum Genet. 2000;8:771–6. [PubMed: 11039577]

Burk K, Dalski A, Purmann S, Zuhlke C. Detection of a novel SPG4-nonsense-mutation in a large German pedigree with pure spastic paraplegia. J Neurol. 2005;252:371. [PubMed: 15739043]

Byrne PC, McMonagle P, Webb S, Fitzgerald B, Parfrey NA, Hutchinson M. Phenotype of AD-HSP due to mutations in the SPAST gene: comparison with AD-HSP without mutations. Neurology. 2000;55:1794–800. [PubMed: 11134375]

Byrne PC, Webb S, McSweeney F, Burke T, Hutchinson M, Parfrey NA. Linkage of AD HSP and cognitive impairment to chromosome 2p: haplotype and phenotype analysis indicates variable expression and low or delayed penetrance. Eur J Hum Genet. 1998;6:275–82. [PubMed: 9781032]

Charvin D, Cifuentes-Diaz C, Fonknechten N, Joshi V, Hazan J, Melki J, Betuing S. Mutations of SPG4 are responsible for a loss of function of spastin, an abundant neuronal protein localized in the nucleus. Hum Mol Genet. 2003;12:71–8. [PubMed: 12490534]

Chinnery PF, Keers SM, Holden MJ, Ramesh V, Dalton A. Infantile hereditary spastic paraparesis due to codominant mutations in the spastin gene. Neurology. 2004;63:710–2. [PubMed: 15326248]

Ciccarelli FD, Proukakis C, Patel H, Cross H, Azam S, Patton MA, Bork P, Crosby AH. The identification of a conserved domain in both spartin and spastin, mutated in hereditary spastic paraplegia. Genomics. 2003;81:437–41. [PubMed: 12676568]

De Bantel A, McWilliams S, Auysh D, Echol C, Sambuughin N, Sivakumar K. Novel mutation of the spastin gene in familial spastic paraplegia. Clin Genet. 2001;59:364–5. [PubMed: 11359470]

Durr A, Davoine CS, Paternotte C, von Fellenberg J, Cogilinicean S, Coutinho P, Lamy C, Bourgeois S, Prud'homme JF, Penet C, Mas JL, Burgunder JM, Hazan J, Weissenbach J, Brice A, Fontaine B. Phenotype of autosomal dominant spastic paraplegia linked to chromosome 2. Brain 119 (Pt. 1996;5): 1487–96. [PubMed: 8931574]

Durr A, Camuzat A, Colin E, Tallaksen C, Hannequin D, Coutinho P, Fontaine B, Rossi A, Gil R, Rousselle C, Ruberg M, Stevanin G, Brice A. Atlastin1 mutations are frequent in young-onset autosomal dominant spastic paraplegia. Arch Neurol. 2004;61:1867–72. [PubMed: 15596607]

Errico A, Ballabio A, Rugarli EI. Spastin, the protein mutated in autosomal dominant hereditary spastic paraplegia, is involved in microtubule dynamics. Hum Mol Genet. 2002;11:153–63. [PubMed: 11809724]

Falco M, Scuderi C, Musumeci S, Sturnio M, Neri M, Bigoni S, Caniatti L, Fichera M. Two novel mutations in the spastin gene (SPG4) found by DHPLC mutation analysis. Neuromuscul Disord. 2004;14:750–3. [PubMed: 15482961]

Fonknechten N, Mavel D, Byrne P, Davoine CS, Cruaud C, Boentsch D, Samson D, Coutinho P, Hutchinson M, McMonagle P, Burgunder JM, Tartaglione A, Heinzlef O, Feki I, Deufel T, Parfrey N, Brice A, Fontaine B, Prud'homme JF, Weissenbach J, Durr A, Hazan J. Spectrum of SPG4 mutations in autosomal dominant spastic paraplegia. Hum Mol Genet. 2000;9:637–44. [PubMed: 10699187]

Harper PS, Clarke A. Should we test children for "adult" genetic diseases? Lancet. 1990;335:1205–6. [PubMed: 1971046]

Hazan J, Fonknechten N, Mavel D, Paternotte C, Samson D, Artiguenave F, Davoine CS, Cruaud C, Durr A, Wincker P, Brottier P, Cattolico L, Barbe V, Burgunder JM, Prud'homme JF, Brice A, Fontaine B, Heilig B, Weissenbach J. Spastin, a new AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. Nat Genet. 1999;23:296–303. [PubMed: 10610178]

Heinzlef O, Paternotte C, Mahieux F, Prud'homme JF, Dien J, Madigand M, Pouget J, Weissenbach J, Roullet E, Hazan J. Mapping of a complicated familial spastic paraplegia to locus SPG4 on chromosome 2p. J Med Genet. 1998;35:89–93. [PubMed: 9507385]

Hentati A, Deng HX, Zhai H, Chen W, Yang Y, Hung WY, Azim AC, Bohlega S, Warner C, Laing NG, Cambi F, Mitsumoto H, Roos RP, Boustany RM, Ben Hamida M, Hentati F, Siddique T. Novel mutations in spastin gene and absence of correlation with age at onset of symptoms. Neurology. 2000;55:1388–90. [PubMed: 11087788]

Higgins JJ, Loveless JM, Goswami S, Nee LE, Cozzo C, De Biase A, Rosen DR. An atypical intronic deletion widens the spectrum of mutations in hereditary spastic paraplegia. Neurology. 2001;56:1482–5. [PubMed: 11402104]

Iwanaga H, Tsujino A, Shirabe S, Eguchi H, Fukushima N, Niikawa N, Yoshiura K, Eguchi K. Large deletion involving the 5'-UTR in the spastin gene caused mild phenotype of autosomal dominant hereditary spastic paraplegia. Am J Med Genet A. 2005;133:13–7. [PubMed: 15637712]

Jensen LN, Gerstenberg T, Kallestrup EB, Koefoed P, Nordling J, Nielsen JE. Urodynamic evaluation of patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24. J Neurol Neurosurg Psychiatry. 1998;65:693–6. [PubMed: 9810939]

Ki CS, Lee WY, Han DH, Sung DH, Lee KB, Lee KA, Cho SS, Cho S, Hwang H, Sohn KM, Choi YJ, Kim JW. A novel missense mutation (I344K) in the SPG4 gene in a Korean family with autosomal-dominant hereditary spastic paraplegia. J Hum Genet. 2002;47:473–7. [PubMed: 12202986]

Lindsey JC, Lusher ME, McDermott CJ, White KD, Reid E, Rubinsztein DC, Bashir R, Hazan J, Shaw PJ, Bushby KM. Mutation analysis of the spastin gene (SPG4) in patients with hereditary spastic paraparesis. J Med Genet. 2000;37:759–65. [PubMed: 11015453]

Matsuura T, Sasaki H, Wakisaka A, Hamada T, Moriwaka F, Tashiro K. Autosomal dominant spastic paraplegia linked to chromosome 2p: clinical and genetic studies of a large Japanese pedigree. J Neurol Sci. 1997;151:65–70. [PubMed: 9335012]

McDermott CJ, Grierson AJ, Wood JD, Bingley M, Wharton SB, Bushby KM, Shaw PJ. Hereditary spastic paraparesis: disrupted intracellular transport associated with spastin mutation. Ann Neurol. 2003;54:748–59. [PubMed: 14681884]

McMonagle P, Byrne P, Burke T, Parfrey N, Hutchinson M. Clinical and pathologic findings in hereditary spastic paraparesis with spastin mutation. Neurology. 2001;56:139.

McMonagle P, Byrne PC, Fitzgerald B, Webb S, Parfrey NA, Hutchinson M. Phenotype of AD-HSP due to mutations in the SPAST gene: comparison with AD-HSP without mutations. Neurology. 2000;55:1794–800. [PubMed: 11134375]

McMonagle P, Webb S, Hutchinson M. The prevalence of "pure" autosomal dominant hereditary spastic paraparesis in the island of Ireland. J Neurol Neurosurg Psychiatry. 2002;72:43–6. [PubMed: 11784824]

Mead SH, Proukakis C, Wood N, Crosby AH, Plant GT, Warner TT. A large family with hereditary spastic paraparesis due to a frame shift mutation of the spastin (SPG4) gene: association with multiple sclerosis in two affected siblings and epilepsy in other affected family members. J Neurol Neurosurg Psychiatry. 2001;71:788–91. [PubMed: 11723204]

Meijer IA, Hand CK, Grewal KK, Stefanelli MG, Ives EJ, Rouleau GA. A locus for autosomal dominant hereditary spastic ataxia, SAX1, maps to chromosome 12p13. Am J Hum Genet. 2002;70:763–9. [PubMed: 11774073]

Molon A, Montagna P, Angelini C, Pegoraro E. Novel spastin mutations and their expression analysis in two Italian families. Eur J Hum Genet. 2003;11:710–3. [PubMed: 12939659]

Namekawa M, Takiyama Y, Sakoe K, Nagaki H, Shimazaki H, Yoshimura M, Ikeguchi K, Nakano I, Nishizawa M. A Japanese SPG4 family with a novel missense mutation of the SPG4 gene: intrafamilial variability in age at onset and clinical severity. Acta Neurol Scand. 2002;106:387–91. [PubMed: 12460147]

Namekawa M, Takiyama Y, Sakoe K, Shimazaki H, Amaike M, Niijima K, Nakano I, Nishizawa M. A large Japanese SPG4 family with a novel insertion mutation of the SPG4 gene: a clinical and genetic study. J Neurol Sci. 2001;185:63–8. [PubMed: 11266693]

Nance MA, Raabe WA, Midani H, Kolodny EH, David WS, Megna L, Pericak-Vance MA, Haines JL. Clinical heterogeneity of familial spastic paraplegia linked to chromosome 2p21. Hum Hered. 1998;48:169–78. [PubMed: 9618065]

Nicholas AP, O'Hearn E, Holmes SE, Chen DT, Margolis RL. Clinical signs and symptoms in a large hereditary spastic paraparesis pedigree with a novel spastin mutation. Mov Disord. 2004;19:641–8. [PubMed: 15197701]

Nielsen JE, Johnsen B, Koefoed P, Scheuer KH, Gronbech-Jensen M, Law I, Krabbe K, Norremolle A, Eiberg H, Sondergard H, Dam M, Rehfeld JF, Krarup C, Paulson OB, Hasholt L, Sorensen SA. Hereditary spastic paraplegia with cerebellar ataxia: a complex phenotype associated with a new SPG4 gene mutation. Eur J Neurol. 2004;11:817–24. [PubMed: 15667412]

Nielsen JE, Koefoed P, Kjaergaard S, Jensen LN, Norremolle A, Hasholt L. Prenatal diagnosis of autosomal dominant hereditary spastic paraplegia (SPG4) using direct mutation detection. Prenat Diagn. 2004;24:363–6. [PubMed: 15164410]

Nielsen JE, Krabbe K, Jennum P, Koefoed P, Jensen LN, Fenger K, Eiberg H, Hasholt L, Werdelin L, Sorensen SA. Autosomal dominant pure spastic paraplegia: a clinical, paraclinical, and genetic study. J Neurol Neurosurg Psychiatry. 1998;64:61–6. [PubMed: 9436729]

Nielsen JE, Jennum P, Fenger K, Sorensen SA, Fuglsang-Frederiksen A. Increased intracortical facilitation in patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p. Eur J Neurol. 2001;8:335–9. [PubMed: 11422430]

Orlacchio A, Gaudiello F, Totaro A, Floris R, St George-Hyslop PH, Bernardi G, Kawarai T. A new SPG4 mutation in a variant form of spastic paraplegia with congenital arachnoid cysts. Neurology. 2004;62:1875–8. [PubMed: 15159500]

Orlacchio A, Kawarai T, Gaudiello F, Totaro A, Schillaci O, Stefani A, Floris R, St George-Hyslop PH, Sorbi S, Bernardi G. Clinical and genetic study of a large SPG4 Italian family. Mov Disord. 2005;20:1055–9. [PubMed: 15858810]

Orlacchio A, Kawarai T, Totaro A, Errico A, St George-Hyslop PH, Rugarli EI, Bernardi G. Hereditary spastic paraplegia: clinical genetic study of 15 families. Arch Neurol. 2004;61:849–55. [PubMed: 15210521]

Patrono C, Casali C, Tessa A, Cricchi F, Fortini D, Carrozzo R, Siciliano G, Bertini E, Santorelli FM. Missense and splice site mutations in SPG4 suggest loss-of-function in dominant spastic paraplegia. J Neurol. 2002;249:200–5. [PubMed: 11985387]

Patrono C, Scarano V, Cricchi F, Melone MA, Chiriaco M, Napolitano A, Malandrini A, De Michele G, Petrozzi L, Giraldi C, Santoro L, Servidei S, Casali C, Filla A, Santorelli FM. Autosomal dominant hereditary spastic paraplegia: DHPLC-based mutation analysis of SPG4 reveals eleven novel mutations. Hum Mutat. 2005;25:506. [PubMed: 15841487]

Proukakis C, Auer-Grumbach M, Wagner K, Wilkinson PA, Reid E, Patton MA, Warner TT, Crosby AH. Screening of patients with hereditary spastic paraplegia reveals seven novel mutations in the SPG4 (Spastin) gene. Hum Mutat. 2003;21:170. [PubMed: 12552568]

Proukakis C, Hart P, Cornish A, Warner T, Crosby A. Three novel spastin (SPG4) mutations in families with autosomal dominant hereditary spastic paraplegia. J Neurol Sci. 2002;201:65. [PubMed: 12163196]

Qin W, Zhang T, Han J, Tang L, Li X, Feng G, Liu W, He L. A novel insertion mutation in spastin gene is the cause of spastic paraplegia in a Chinese family. J Neurol Sci. 2003;210:35–9. [PubMed: 12736085]

Raskind WH, Pericak-Vance MA, Lennon F, Wolff J, Lipe HP, Bird TD. Familial spastic paraparesis: evaluation of locus heterogeneity, anticipation, and haplotype mapping of the SPG4 locus on the short arm of chromosome 2. Am J Med Genet. 1997;74:26–36. [PubMed: 9034002]

Reid E, Grayson C, Rubinsztein DC, Rogers MT, Rubinsztein JS. Subclinical cognitive impairment in autosomal dominant "pure" hereditary spastic paraplegia. J Med Genet. 1999;36:797–8. [PubMed: 10528866]

Santorelli FM, Patrono C, Fortini D, Tessa A, Comanducci G, Bertini E, Pierallini A, Amabile GA, Casali C. Intrafamilial variability in hereditary spastic paraplegia associated with an SPG4 gene mutation. Neurology. 2000;55:702–5. [PubMed: 10980739]

Sauter S, Miterski B, Klimpe S, Bonsch D, Schols L, Visbeck A, Papke T, Hopf HC, Engel W, Deufel T, Epplen JT, Neesen J. Mutation analysis of the spastin gene (SPG4) in patients in Germany with autosomal dominant hereditary spastic paraplegia. Hum Mutat. 2002;20:127–32. [PubMed: 12124993]

Scheuer KH, Nielsen JE, Krabbe K, Simonsen C, Koefoed P, Sorensen SA, Gade A, Paulson OB, Law I. Reduced regional cerebral blood flow in SPG4-linked hereditary spastic paraplegia. J Neurol Sci. 2005;235:23–32. [PubMed: 15939438]

Schulte T, Miterski B, Bornke C, Przuntek H, Epplen JT, Schols L. Neurophysiological findings in SPG4 patients differ from other types of spastic paraplegia. Neurology. 2003;60:1529–32. [PubMed: 12743246]

Sherwood NT, Sun Q, Xue M, Zhang B, Zinn K. Drosophila spastin regulates synaptic microtubule networks and is required for normal motor function. PLoS Biol. 2004;2:e429. [PubMed: 15562320]

Skre H. Hereditary spastic paraplegia in Western Norway. Clin Genet. 1974;6:165–83. [PubMed: 4426134]

Svenson IK, Ashley-Koch AE, Gaskell PC, Riney TJ, Cumming WJ, Kingston HM, Hogan EL, Boustany RM, Vance JM, Nance MA, Pericak-Vance MA, Marchuk DA. Identification and expression analysis of spastin gene mutations in hereditary spastic paraplegia. Am J Hum Genet. 2001;68:1077–85. [PubMed: 11309678]

Svenson IK, Kloos MT, Gaskell PC, Nance MA, Garbern JY, Hisanaga S, Pericak-Vance MA, Ashley-Koch AE, Marchuk DA. Intragenic modifiers of hereditary spastic paraplegia due to spastin gene mutations. Neurogenetics. 2004;5:157–64. [PubMed: 15248095]

Tallaksen CM, Guichart-Gomez E, Verpillat P, Hahn-Barma V, Ruberg M, Fontaine B, Brice A, Dubois B, Durr A. Subtle cognitive impairment but no dementia in patients with spastin mutations. Arch Neurol. 2003;60:1113–8. [PubMed: 12925368]

Tang B, Zhao G, Xia K, Pan Q, Luo W, Shen L, Long Z, Dai H, Zi X, Jiang H. Three novel mutations of the spastin gene in Chinese patients with hereditary spastic paraplegia. Arch Neurol. 2004;61:49–55. [PubMed: 14732620]

Trotta N, Orso G, Rossetto MG, Daga A, Broadie K. The hereditary spastic paraplegia gene, spastin, regulates microtubule stability to modulate synaptic structure and function. Curr Biol. 2004;14:1135–47. [PubMed: 15242610]

Webb S, Hutchinson M. Cognitive impairment in families with pure autosomal dominant hereditary spastic paraparesis. Brain 121 (Pt. 1998;5):923–9. [PubMed: 9619194]

Wharton SB, McDermott CJ, Grierson AJ, Wood JD, Gelsthorpe C, Ince PG, Shaw PJ. The cellular and molecular pathology of the motor system in hereditary spastic paraparesis due to mutation of the spastin gene. J Neuropathol Exp Neurol. 2003;62:1166–77. [PubMed: 14656074]

White KD, Ince PG, Lusher M, Lindsey J, Cookson M, Bashir R, Shaw PJ, Bushby KM. Clinical and pathologic findings in hereditary spastic paraparesis with spastin mutation. Neurology. 2000;55:89–94. [PubMed: 10891911]

Yabe I, Sasaki H, Tashiro K, Matsuura T, Takegami T, Satoh T. Spastin gene mutation in Japanese with hereditary spastic paraplegia. J Med Genet. 2002;39:e46. [PubMed: 12161613]

Yip AG, Durr A, Marchuk DA, Ashley-Koch A, Hentati A, Rubinsztein DC, Reid E. Meta-analysis of age at onset in spastin-associated hereditary spastic paraplegia provides no evidence for a correlation with mutational class. J Med Genet. 2003;40:e106. [PubMed: 12960222]

Chapter Notes

Revision History

- 23 April 2007 (cd) Revision: deletion/duplication analysis clinically available
- 10 August 2005 (me) Comprehensive update posted to live Web site
- 17 April 2003 (me) Review posted to live Web site
- 25 September 2002 (ct) Original submission

Table 2. Mutations in the *SPG4* Gene

Exon	Mutation	Protein Consequence (Missense)	Type	Reference
1	c.1-114_540+1800 del2307		Large deletion	Iwanaga et al 2005
	c.65_83 dup 19		Frameshift	Proukakis et al 2003
	c.114 insC		Frameshift	Sauter et al 2002
	c.286delG		Frameshift	Lindsey et al 2000
	c.334G>T	p.E112X	Nonsense	Hentati et al 2000
	c.334G>A	p.E112K	Missense	Patrono et al 2005
	c.340G>T	p.E114X	Nonsense	Svenson et al 2001
	c.373G>T	p.E125X	Nonsense	Patrono et al 2005
	c.421C>T	p.Q141X	Nonsense	Patrono et al 2005
2	c.439G>T	p.E147X	Nonsense	Patrono et al 2005
	c.453_454 insA		Frameshift	Fonknechten et al 2000
3	c.562delG		Frameshift	Meijer et al 2002
	c.577C>T	p.Q193X	Nonsense	Fonknechten et al 2000
5	c.683-2A>G		Splicing mutation	Fonknechten et al 2000
	c.703_704 insA		Frameshift	Proukakis et al 2002
	c.707_708 delAA insG		Frameshift	Nielsen, Koefoed et al 2004
	c.706_710del5		Frameshift	Proukakis et al 2002
	c.710 insA		Frameshift	Hentati et al 2000
	c.716T>G	p.L239X	Nonsense	Bürk et al 2005
	c.727del11		Frameshift	Fonknechten et al 2000
	c.734C>G	p.S245X	Nonsense	Lindsey et al 2000
	c.746C>G	p.S249X	Nonsense	Sauter et al 2002
	c.748A>T	p.K229X	Nonsense	Fonknechten et al 2000
	c.757_758 insA		Frameshift	Fonknechten et al 2000
	c.781delT		Frameshift	Fonknechten et al 2000
	c.782C>A	p.S261X	Nonsense	Fonknechten et al 2000
	c.807C>G	p.Y269X	Nonsense	Fonknechten et al 2000
	c.839_840delAG		Frameshift	Sauter et al 2002
	c.870G>T	p.K290N	Splicing mutation	Svenson et al 2001
6	c.88 8delT		Frameshift	Sauter et al 2002
	c.906delT		Frameshift	Orlacchio et al 2005
	c.911delG		Frameshift	Sauter et al 2002
	c.945delG		Frameshift	Sauter et al 2002
	c.1004+2T>G		Splicing mutation	Fonknechten et al 2000
7	c.1005-1G>T		Splicing mutation	Proukakis et al 2003
	c.1031T>A	p.I344K	Missense	Ki et al 2002

	c.1039C>A	p.Q347K	Missense	Yabe et al 2002
	c.1082C>T	p.P361L	Missense	Chinnery et al 2004
	c.1085C>G	p.S362C	Missense	Hazan et al 1999
	c.1098+1G>T		Splicing mutation	Fonknechten et al 2000
8	c.1108G>A	p.G370R	Missense	Fonknechten et al 2000
	c.1114A>T	p.R372X	Nonsense	Sauter et al 2002
	c.1115delG		Frameshift	Sauter et al 2002
	c.1133T>A	p.L378Q	Missense	Tang et al 2004
	c.1134_1135 delGT		Frameshift	Proukakis et al 2003
	c.1142T>G	p.F381C	Missense	Fonknechten et al 2000
	c.1147_1148 insA		Frameshift	Namekawa et al 2001
	c.1032A>G	p.N386S	Missense	Orlacchio, Kawarai et al 2004
	c.1158T>G	p.N386K	Missense	Fonknechten et al 2000
	c.1163A>G	p.K388R	Missense	Fonknechten et al 2000
	c.1168A>G	p.M390V	Missense	Tang et al 2004
	c.1173+1G>A		Splicing mutation	Fonknechten et al 2000
9	c.1174delG		Frameshift	Fonknechten et al 2000
	c.1195C>T	p.S399L	Missense	Meijer et al 2002
	c.1209_1211delCTT	p.F404del	In-frame deletion	Proukakis et al 2002
	c.1215_1219del5		Frameshift	Fonknechten et al 2000
	c.1228A>C	p.S407R	Missense	Sauter et al 2002
	c.1242A>G	p.K414K	Splicing mutation	Svenson et al 2001
	c.1245+1G>A		Splicing mutation	Svenson et al 2001
	c.1245+1G>T		Splicing mutation	Bürger et al 2000
	c.1245+4A>G		Splicing mutation	Svenson et al 2001
	c.1245+6T>G		Splicing mutation	Svenson et al 2001
10	c.1262_1263delAA		Frameshift	Sauter et al 2002
	c.1270A>G	p.R424G	Missense	White et al 2000
	c.1270_1271 dup AG		Frameshift	Patrono et al 2005
	c.1276C>G	p.L426V	Missense	Fonknechten et al 2000
	c.1281delT		Frameshift	Lindsey et al 2000
	c.1291C>T	p.R431X	Nonsense	Fonknechten et al 2000
	c.1292_1294delGAG	p.R431_E 432>Q	In-frame deletion	Sauter et al 2002
	c.1300G>T	p.Q434X	Nonsense	Meijer et al 2002
	c.1307C>T	p.S436F	Missense	Hentati et al 2000
	c.1317delT		Frameshift	Molon et al 2003
	c.1321G>A	p.D441N	Missense	Sauter et al 2002
11	c.1322A>G	p.D441G	Missense	Bürger et al 2000

	c.1343G>A	p.C448Y	Missense	Hazan et al 1999
	c.1355_1357delAAG	p.E452del	In-frame deletion	Patrono et al 2005
	c.1360_1361 insGG		Frameshift	Qin et al 2003
	c.1361 insA		Frameshift	Svenson et al 2001
	c.1375A>G	p.R459G	Missense	Falco et al 2004
	c.1376G>C	p.Ar459T	Missense	Patrono et al 2005
	c.1378C>T	p.R460C	Missense	Falco et al 2004
	c.1379G>T	p.R460L	Missense	Fonknechten et al 2000
	c.1395delT		Frameshift	Hazan et al 1999
	c.1413+1G>A		Splicing mutation	Patrono et al 2005
	c.1413+2 insT		Splicing mutation	Svenson et al 2001
	c.1413+2del4		Splicing mutation	Patrono et al 2002
	c.1413+3A>C		Splicing mutation	Lindsey et al 2000
	c.1413+3_1413+6 delAAGT		Splicing mutation	Fonknechten et al 2000
	c.1413+5G>A		Splicing mutation	Fonknechten et al 2000
12	c.1414-2A>G		Splicing mutation	Meijer et al 2002
	c.1414-2A>G		Splicing mutation	Svenson et al 2001
	c.1435_1436delAG		Frameshift	Sauter et al 2002
	c.1437_1438delAG		Frameshift	Sauter et al 2002
	c.1449delGG		Frameshift	Fonknechten et al 2000
	c.1454C>T	p.A485V	Missense	Namekawa et al 2002
	c.1466C>T	p.P489L	Missense	Meijer et al 2002
	c.1468C>T	p.Q490X	Nonsense	Nielsen, Johnson et al 2004
	c.1492_1493+2del4		Splicing mutation	Bürger et al 2000
	c.1493+2T>A		Splicing mutation	Lindsey et al 2000
	c.1493+2_1493+5 insATGG		Splicing mutation	Patrono et al 2005
	c.1493+3610_1738 +391del		Large deletion	Sauter et al 2002
13	c.1494-2delA		Splicing mutation	Patrono et al 2002
	c.1496C>T	p.R499C	Missense	Hazan et al 1999
	c.1508G>T	p.R503L	Missense	Proukakis et al 2003
	c.1509del22		Frameshift	Fonknechten et al 2000
	c.1536G>C	p.E512D	Missense	Patrono et al 2002
	c.1536+1G>T		Splicing mutation	Fonknechten et al 2000
	c.1536+2T>C		Splicing mutation	Lindsey et al 2000
14	c.1537-2A>T		Splicing mutation	Fonknechten et al 2000
	c.1543delCTA		Frameshift	Tang et al 2004
	c.1559_1560 insTT		Frameshift	Fonknechten et al 2000

	c.1560del4		Frameshift	Fonknechten et al 2000
	c. 1577_1580delGAAG		Frameshift	Proukakis et al 2003
	c.1601 del8 ins30		Frameshift	Sauter et al 2002
	c.1601T>C	p.L534P	Missense	Molon et al 2003
15	c.1617-1G>T		Splicing mutation	Yabe et al 2002
	c.1651_1652GC>TA	p.A551Y	Missense	Sauter et al 2002
	c.1663G>A	p.D555N	Missense	Fonknechten et al 2000
	c.1667C>T	p.A556V	Missense	Fonknechten et al 2000
	c.1672_1673delCT		Frameshift	Sauter et al 2002
	c.1676G>A	p.G559D	Missense	Hentati et al 2000
	c.1684C>G	p.R562G	Missense	Svenson et al 2001
	c.1684C>T	p.R562X	Nonsense	Meijer et al 2002
	c.1685G>A	p.R562Q	Missense	Meijer et al 2002
	c.1687+1G>A		Splicing mutation	Fonknechten et al 2000
	c.1687+2T>G		Splicing mutation	Lindsey et al 2000
16	c.1688-2A>G		Splicing mutation	Hazan et al 1999
	c.1716C>T	p.T641I	Missense	Orlacchio, Gaudiello et al 2004
	c.1720delG		Frameshift	Proukakis et al 2003
	c.1728+1G>A		Splicing mutation	Fonknechten et al 2000
	c.1728+1G>T		Splicing mutation	Bürger et al 2000
	c.1728+2T>A		Splicing mutation	Proukakis et al 2003
	c.1728+2T>C		Splicing mutation	Lindsey et al 2000
17	c.1729-1G>C		Splicing mutation	Meijer et al 2002
	c.1739T>A	p.I580D	Missense	Sauter et al 2002
	c.1741C>T	p.R581X	Nonsense	Patrono et al 2005
	c.1750G>C	p.D584H	Missense	Lindsey et al 2000
	c.1821G>A	p.W607X	Nonsense	Patrono et al 2005
	c.1841C>T	p.T614I	Missense	Orlacchio, Gaudiello et al 2004
	c.1844C>T	p.T615I	Missense	Sauter et al 2002