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Spinocerebellar Ataxia Type 6

Synonym: SCA6

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Summary

Clinical characteristics

Spinocerebellar ataxia type 6 (SCA6) is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. The age of onset ranges from 19 to 73 years; mean age of onset is between 43 and 52 years. Initial symptoms are gait unsteadiness, stumbling, and imbalance (in ~90%) and dysarthria (in ~10%). Eventually all persons have gait ataxia, upper-limb incoordination, intention tremor, and dysarthria. Dysphagia and choking are common. Visual disturbances may result from diplopia, difficulty fixating on moving objects, horizontal gaze-evoked nystagmus, and vertical nystagmus. Hyperreflexia and extensor plantar responses occur in up to 40%-50%. Basal ganglia signs, including dystonia and blepharospasm, occur in up to 25%. Mentation is generally preserved.

Diagnosis/testing

The diagnosis of SCA6 rests on the use of molecular genetic testing to detect an abnormal CAG trinucleotide repeat expansion in *CACNA1A*. Affected individuals have 20 to 33 CAG repeats.

Management

Treatment of manifestations: Acetazolamide may eliminate episodes of ataxia; canes, walking sticks, and walkers to prevent falling; home modifications for safety and convenience; weighted eating utensils and dressing hooks; physical therapy and exercises enhancing balance and core strength; vitamin supplements particularly if caloric intake is reduced; feeding recommendations as per feeding therapist / occupational therapist; weight control, as obesity exacerbates ambulation and mobility problems; vestibular symptoms may be managed with medications including diphenhydramine, baclofen, and gabapentin. 4-aminopyridine may be helpful with vestibular symptoms and to suppress nystagmus; refractive or surgical management per ophthalmologist for diplopia; speech therapy and communication devices for dysarthria; clonazepam for REM sleep disorders; continuous positive airway pressure for sleep apnea.

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Surveillance: Annual or semiannual evaluation by a neurologist; driving ability should be assessed by professionals periodically. Annual consultations with a physiatrist and physical and/or occupational therapist; review need for walking aid(s) and home adaptations. Nutrition evaluation, video esophagram, and feeding assessments as needed. Ophthalmology and/or optometry evaluation as needed for prisms or surgery.

Agents/circumstances to avoid: Sedative hypnotics (ethanol or certain medications) that increase incoordination.

Genetic counseling

SCA6 is inherited in an autosomal dominant manner. Offspring of an affected individual have a 50% chance of inheriting an abnormal CAG trinucleotide repeat expansion in *CACNA1A*. Once a *CACNA1A* CAG repeat expansion has been identified in an affected family member, prenatal testing and preimplantation genetic testing for SCA6 are possible.

Diagnosis

Formal diagnostic criteria for spinocerebellar ataxia type 6 (SCA6) have not been established.

Suggestive Findings

SCA6 **should be suspected** in individuals with the following clinical and imaging findings:

- **Clinical findings** include adult-onset, slowly progressive cerebellar ataxia; dysarthria; and nystagmus.
- **Imaging findings.** Atrophy of the cerebellum, most pronounced in the cerebellar vermis, is present in symptomatic individuals with SCA6 [Butteriss et al 2005, Lukas et al 2011].

Establishing the Diagnosis

The diagnosis of SCA6 **is established** in a proband with a heterozygous CAG repeat expansion in *CACNA1A* by molecular genetic testing (see Table 1).

Allele sizes

- **Normal alleles.** ≤18 CAG repeats [Shizuka et al 1998]
- **Full-penetrance alleles.** 20-33 CAG repeats [Jodice et al 1997, Yabe et al 1998]. Asymptomatic individuals bearing an expansion of $(CAG)_{20}$ or greater are expected to develop symptoms at some time in their life. The most common pathogenic allele has 22 CAG repeats.
- **Alleles of questionable significance.** 19 CAG repeats. The clinical significance of alleles with 19 CAG repeats is unclear because alleles of this size have been documented in the following:
  - Meiotic expansion of a 19-CAG repeat allele into the known pathogenic range [Mariotti et al 2001, Shimazaki et al 2001]. In this instance, the allele is considered an "intermediate allele" or a "mutable normal allele" (i.e., it is not disease causing but predisposes to expansion into the abnormal range).
  - Elderly asymptomatic individuals [Ishikawa et al 1997, Mariotti et al 2001]
  - An individual with atypical features of SCA6 [Katayama et al 2000]
  - An ataxic individual homozygous for the 19-CAG repeat allele [Mariotti et al 2001]

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Targeted analysis for a heterozygous *CACNA1A* allele with more than 18 repeats should be performed first.
- **An ataxia multigene panel** that includes *CACNA1A* CAG-repeat analysis and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition at the most

reasonable cost 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.

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 6

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CACNA1A	Targeted analysis for pathogenic variants [3]	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. PCR amplification can detect CAG trinucleotide repeat expansions up to ~100 repeats.

Clinical Characteristics

Clinical Description

To date, fewer than 10,000 individuals with spinocerebellar ataxia type 6 (SCA6) have been identified. The following description of the phenotypic features associated with this condition is based on these reported individuals.

Table 2. Features of Spinocerebellar Ataxia Type 6

Feature	% of Persons with Feature
Gait unsteadiness, upper-limb incoordination, intention tremor, & dysarthria	100%
Horizontal gaze-evoked nystagmus	70%-100%
Vertical nystagmus	65%-83%
Diplopia	50%
Hyperreflexia & extensor plantar responses	40%-50%
Dystonia & blepharospasm	<25%

SCA6 is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. The range in age of onset is from 19 to 73 years. The mean age of onset is between 43 and 52 years. Age of onset and clinical picture vary even within the same family; sibs with the same size full-penetrance allele may differ in age of onset by as much as 12 years, or exhibit, at least initially, an episodic course [Gomez et al 1997, Jodice et al 1997].

Initial symptoms are gait unsteadiness, stumbling, and imbalance in approximately 90% of individuals; the remainder present with dysarthria. Symptoms progress slowly, and eventually all persons have gait ataxia, upper-limb incoordination, intention tremor, and dysarthria. Dysphagia and choking are common.

Diplopia occurs in approximately 50% of individuals. Others experience visual disturbances related to difficulty fixating on moving objects, as well as horizontal gaze-evoked nystagmus (70%-100%) [Moscovich et al 2015] and vertical nystagmus (65%-83%), which is observed in fewer than 10% of those with other forms of SCA [Yabe et al 2003]. Other eye movement abnormalities, including periodic alternating nystagmus and rebound nystagmus, have also been described [Hashimoto et al 2003].

Hyperreflexia and extensor plantar responses occur in up to 40%-50% of individuals with SCA6.

Basal ganglia signs, such as dystonia and blepharospasm, are noted in up to 25% of individuals.

Mentation is generally preserved. Formal neuropsychological testing in one series revealed no significant cognitive deficits [Globas et al 2003].

Individuals with SCA6 do not have sensory complaints, restless legs, stiffness, migraine, primary visual disturbances, or muscle atrophy.

Life span is not shortened.

Other. REM sleep behavior disorders are rarely reported [Boesch et al 2006, Howell et al 2006].

Pregnancy. The severity of the disease increases during pregnancy. No effect on the viability of the fetus has been reported.

Neuropathology. Neuropathologic studies in individuals with SCA6 have demonstrated either selective Purkinje cell degeneration or a combined degeneration of Purkinje cells and granule cells [Gomez et al 1997, Sasaki et al 1998].

Genotype-Phenotype Correlations

Heterozygous individuals. Although the age of onset of symptoms of SCA6 correlates inversely with the length of the expanded CAG repeat, the same broad range of onset has been noted for individuals with 22 CAG repeats, the most common disease-associated allele [Gomez et al 1997, Schöls et al 1998]. In the few individuals with $(CAG)_{30}$ or $(CAG)_{33}$, onset has been later than in individuals with $(CAG)_{22}$ and $(CAG)_{23}$ [Matsuyama et al 1997, Yabe et al 1998]. A recent retrospective study showed even closer correlation of age of onset with the sum of the two allele sizes [Takahashi et al 2004].

Homozygous individuals. Several individuals who are homozygous for an abnormal expansion in *CACNA1A* have been reported [Geschwind et al 1997a, Ikeuchi et al 1997, Matsuyama et al 1997]. In three individuals, the onset was earlier and symptoms appeared to be slightly more severe than in individuals who were heterozygous [Geschwind et al 1997a, Ikeuchi et al 1997]; in one study age of onset correlated with the sum of two allele sizes [Takahashi et al 2004].

Penetrance

Penetrance is nearly 100%, although symptoms may not appear until the seventh decade.

Anticipation

Expansions of *CACNA1A* are not commonly observed in transmission from parent to child; thus, anticipation has not been observed in SCA6. The age of onset, severity, specific symptoms, and progression of the disease are variable and cannot be predicted by the family history or CAG repeat size.

Nomenclature

Hereditary forms of ataxia once known as Holmes type of cerebellar cortical degeneration, and later as autosomal dominant cerebellar ataxia type III (pure cerebellar ataxia), may have included SCA6.

Prevalence

The prevalence of SCA6 appears to vary by geographic area, presumably relating to founder effects. Estimated as the fraction of all kindreds with autosomal dominant spinocerebellar ataxia, rates for SCA6 are 1%-2% in Spain and France, 3% in China, 12% in the US, 13% in Germany, and 31% in Japan.

The overall prevalence of autosomal dominant ataxia is estimated at 1:100,000, and the prevalence of SCA6 at 0.02:100,000 to 0.31:100,000 [Geschwind et al 1997a, Ikeuchi et al 1997, Matsumura et al 1997, Matsuyama et al 1997, Riess et al 1997, Stevanin et al 1997, Schöls et al 1998, Pujana et al 1999, Jiang et al 2005]. In the most accurate assessment to date, Craig et al [2004] used a large collection of non-selected samples of genomic DNA; they estimated the prevalence of the pathogenic *CACNA1A* expansion in the United Kingdom at 5:100,000.

The frequency of *CACNA1A* expansions among individuals with ataxia and no known family history of ataxia was determined to be 5% in one study [Schöls et al 1998] and 43% in another [Geschwind et al 1997a]; however, premature death of parents may have hindered complete ascertainment (see Hereditary Ataxia Overview).

Genetically Related (Allelic) Disorders

Heterozygous *CACNA1A* pathogenic variants are also known to be associated with episodic ataxia type 2, progressive cerebellar ataxia, and familial hemiplegic migraine (see Table 3).

Table 3. Allelic Autosomal Dominant Disorders to Consider in the Differential Diagnosis of Spinocerebellar Ataxia Type 6

Disorder	Associated *CACNA1A* Pathogenic Variant(s)	Clinical Characteristics	Clinical Overlap w/SCA6
Episodic ataxia type 2 (EA2) (OMIM 108500)	Missense, nonsense, splice site, frameshift, & exon/ multiexon deletions	• Onset typically in childhood or early adolescence • Attacks of ataxia, vertigo, & nausea lasting hrs to days • Attacks can be assoc w/ dysarthria, diplopia, tinnitus, dystonia, hemiplegia, & headache. • Between attacks, individuals may initially be normal but eventually develop interictal findings incl nystagmus & ataxia. • After years of episodic ataxia, a condition of interictal ataxia indistinguishable from SCA6 may develop. [1]	• Individuals w/SCA6 may present w/EA. [2] • 1 family w/a *CACNA1A* missense variant had both SCA6 & EA2 phenotypes. [3] • 2 families w/a *CACNA1A* CAG repeat expansion had both SCA6 & EA2 phenotypes. [4]
Progressive cerebellar ataxia	Missense variants incl p.Gly293Arg in the P loop of the 1st domain, p.Ala454Thr in the I-II loop, & p.Arg1664Gln. [5]	• Severe progressive ataxia • Cerebellar atrophy	Very similar phenotype to that of SCA6 assoc w/CAG repeat expansions [6]

Table 3. continued from previous page.

Disorder	Associated *CACNA1A* Pathogenic Variant(s)	Clinical Characteristics	Clinical Overlap w/SCA6
Familial hemiplegic migraine (FHM) [7]	Missense, nonsense, & exon/ multiexon deletions	• Aura of hemiplegia assoc w/at least 1 other aura symptom (e.g., hemianopsia, hemisensory deficit, aphasia) followed by moderate-to-severe headache • Coma & seizures (can be triggered by minor head injury or angiography) • Trauma-triggered delayed cerebral edema [8]	• In a family w/EA2, affected members also had hemiplegia & 1 affected member had migraine during episodes of ataxia. [9] • In a family w/a *CACNA1A* missense variant, phenotypes of both SCA6 & FHM were observed. [10]

EA = episodic ataxia
1. Baloh et al [1997]
2. In one study, up to 33% of individuals with ≥21 CAG repeats in *CACNA1A* had episodic features prominent enough to warrant the diagnosis of EA2 [Geschwind et al 1997a]. In one family with a CAG repeat expansion, some members had episodic ataxia and others had progressive ataxia; in all affected members the abnormal allele had 23 CAG repeats [Jodice et al 1997].
3. Cricchi et al [2007]
4. Jodice et al [1997]
5. As these pathogenic variants do not act through nuclear translocation of an expanded polyglutamine tract in the C terminus, the disease presumably occurs through perturbed calcium channel function caused by the abnormal allele [Chen & Piedras-Renteria 2007, Kordasiewicz & Gomez 2007].
6. Yue et al [1997], Tonelli et al [2006], Cricchi et al [2007]
7. The two clinical forms of FMH are: (1) pure FHM (found in 80% of affected families), in which interictal examination is normal in all family members, and (2) FHM with permanent cerebellar symptoms (found in 20% of affected families), in which some family members show interictal nystagmus and/or ataxia.
8. Trauma-triggered delayed cerebral edema has been associated with the *CACNA1A* missense variant p.Ser218Leu [Kors et al 2001].
9. Jen [1999]
10. Alonso et al [2003]

Heterozygous pathogenic variants in *CACNA1A* are also known to be associated with early-infantile epileptic encephalopathy (see OMIM 617106).

Differential Diagnosis

Individuals with spinocerebellar ataxia type 6 (SCA6) may present with unexplained ataxia that is part of the larger differential diagnosis of hereditary and acquired ataxias (see Hereditary Ataxia Overview).

It is difficult and often impossible to distinguish spinocerebellar ataxia type 6 (SCA6) from the other hereditary ataxias (see Hereditary Ataxia Overview). The differential diagnosis should also include Parkinson disease and acquired causes of cerebellar ataxia.

SCA6-related *CACNA1A* pathogenic variants should be in the differential diagnosis of adult-onset sporadic progressive ataxia, multiple system atrophy (MSA).

Table 4. Proportion of Individuals with SCA6 Manifesting Phenotypic Features Compared with Individuals with SCA1, SCA3, and SCA2

Phenotypic Feature	SCA2	SCA1	SCA3	SCA6
Cerebellar dysfunction	100%	100%	100%	100%
Reduced saccadic velocity	71%-92%	50%	10%	0%-6%
Myoclonus	0%-40%	0%	4%	0%
Dystonia or chorea	0%-38%	20%	8%	0%-25%

Table 4. continued from previous page.

Phenotypic Feature	SCA2	SCA1	SCA3	SCA6
Pyramidal involvement	29%-31%	70%	70%	33%-44%
Peripheral neuropathy	44%-94%	100%	80%	16%-44%
Intellectual impairment	31%-37%	20%	5%	0%

Percentages modified from Geschwind et al [1997a], Geschwind et al [1997b], Schöls et al [1997a], and Schöls et al [1997b]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 6 (SCA6), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Spinocerebellar Ataxia Type 6

System/Concern	Evaluation	Comment
Neurologic	Neurologic examination	Incl annual use of rating scale to assess progression
	Brain MRI	To evaluate extent of atrophy of cerebellum or other structures
	Videofluoroscopic swallow study	To identify safest behaviors & consistency of food least likely to trigger aspiration
	Physical therapy evaluation	To assess risk of falling, determine whether assisted ambulation is necessary, & advise regarding exercise
Ophthalmologic	Consultation w/ophthalmologist	
Other	Consultation w/clinical geneticist &/or genetic counselor	
	Family support/resources	Patients & their families should be informed about natural history, treatment, mode of inheritance, genetic risks to other family members, & consumer-oriented resources.

Treatment of Manifestations

Management for individuals with SCA6 is supportive.

Table 6. Treatment of Manifestations in Individuals with Spinocerebellar Ataxia Type 6

Manifestation/ Concern	Treatment	Considerations/Other
Ataxia	Acetazolamide	May eliminate episodes of ataxia but does not delay or slow overall progression
	Physical medicine & rehabilitation / PT / OT	• Canes, walking sticks, & walkers help prevent falling. • Modification of home w/aids incl grab bars, raised toilet seats, & ramps to accommodate motorized chairs may be necessary. • Weighted eating utensils & dressing hooks help maintain sense of independence.
	• Regular physical activity • PT & exercises enhancing balance & core strength	However, neither exercise nor physical therapy stems progression of incoordination or muscle weakness.

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Nutrition	Vitamin supplements	Particularly if caloric intake is reduced
	Feeding recommendations per feeding therapist / OT	
	Weight control	Obesity can exacerbate difficulties w/ambulation & mobility.
Vertigo/ Osscilopsia	Diphenhydramine, baclofen, gabapentin	• May reduce vertigo &/or osscilopsia • Some literature supports 4-aminopyridine for vestibular symptoms. [1]
Diplopia	Refractive or surgical management per ophthalmologist	Some literature supports 4-aminopyridine for suppression of nystagmus. [1]
Dysarthria	Speech therapy	Communication devices such as writing pads & computer-based devices as needed
REM sleep behavior disorders	Clonazepam	Unless sedative effects increase imbalance in the morning
Sleep apnea	Continuous positive airway pressure	

OT = occupational therapist/therapy; PT = physical therapist/therapy
1. Jayabal et al [2016]

Surveillance

Table 7. Recommended Surveillance for Individuals with Spinocerebellar Ataxia Type 6

System/Concern	Evaluation	Frequency
Ataxia	Neurologic evaluation	Every 6-12 mos
	Physiatrist & physical &/or occupational therapist consultations	Every 12 mos to review need for walking aid(s) & home adaptations
Nutrition	• Nutrition evaluation • Video esophagram • Feeding assessment when dysphagia becomes troublesome	As needed (e.g., w/any change in nutrition/feeding status)
Diplopia	Evaluation w/ophthalmologist &/or optometrist for prisms or surgery	As needed (e.g., when other interventions fail)
	Assessment of driving ability by professional	Periodically

Agents/Circumstances to Avoid

Agents with sedative/hypnotic properties such as ethanol or certain medications may produce marked increases in incoordination.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Although the disease rarely manifests during years of fertility, measures to support imbalance should be enhanced in symptomatic pregnant women.

Therapies Under Investigation

Gazulla & Tintore [2007] suggested gabapentin and pregabalin as potential therapeutic agents.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Tremor-controlling drugs are not usually effective in reducing cerebellar tremors.

The growing interest in cannabidiol (CBD) requires further empiric experience or clinical trials.

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

Spinocerebellar ataxia type 6 (SCA6) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Because penetrance of SCA6 is 100%, most individuals diagnosed with SCA6 have an affected parent.
- A proband with SCA6 may have the disorder as the result of an expansion of an intermediate or mutable normal allele inherited from an unaffected parent [Mariotti et al 2001, Shimazaki et al 2001].
- Recommendations for the evaluation of parents of an individual with SCA6 and no known family history of SCA6 include clinical evaluation and molecular genetic testing.
- Although most individuals diagnosed with SCA6 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, 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.

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the parents:

- If one parent has a full-penetrance *CACNA1A* allele, the risk to each sib of inheriting the pathogenic *CACNA1A* allele is 50%. Although the penetrance of SCA6 is nearly 100%, age of onset and clinical picture vary within families; sibs with the same size full-penetrance allele may differ in age of onset by as much as 12 years, or exhibit, at least initially, an episodic course (see Clinical Description).
- If one parent has an intermediate or mutable normal *CACNA1A* allele (i.e., a 19-CAG repeat allele), the risk to each sib of inheriting the unstable allele is 50%. Further intergenerational expansion has been observed, but is extremely rare.
- If an expanded *CACNA1A* allele cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the theoretic possibility of parental germline mosaicism.

- If the parents have not been tested for an expanded *CACNA1A* allele but are clinically unaffected, sibs are still presumed to be at increased risk for SCA6 because of the possibility of late onset of SCA6 in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual with SCA6 has a 50% chance of inheriting the expanded *CACNA1A* allele.
- Although repeat-size changes can occur in SCA6 alleles in subsequent generations, they are much rarer than those in other repeat expansion disorders.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has an SCA6-causing *CACNA1A* allele, his or her family members may be at risk.

Related Genetic Counseling Issues

At-risk individuals. The age of onset, severity, specific symptoms, and progression of SCA6 are variable and cannot be predicted by the family history or results of molecular genetic testing.

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

- Predictive testing for at-risk relatives is possible once molecular genetic testing has identified a *CACNA1A* CAG repeat expansion in an affected family member.
- This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.
- 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 SCA6, it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once a *CACNA1A* CAG repeat expansion has been identified in an affected family member, prenatal testing and preimplantation genetic testing for SCA6 are possible. However, in general, age of onset, severity of disease, specific 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, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **NCBI Genes and Disease**
  Spinocerebellar ataxia
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 601 037 982
  Email: info@fedaes.org
  fedaes.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300

CoRDS Registry

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. Spinocerebellar Ataxia Type 6: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CACNA1A	19p13.13	Voltage-dependent P/Q-type calcium channel subunit alpha-1A	Calcium channel, voltage-dependent, P/Q type, alpha 1A subunit (CACNA1A) @ LOVD	CACNA1A	CACNA1A

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 Spinocerebellar Ataxia Type 6 (View All in OMIM)

183086	SPINOCEREBELLAR ATAXIA 6; SCA6
601011	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, P/Q TYPE, ALPHA-1A SUBUNIT; CACNA1A

Molecular Pathogenesis

CACNA1A encodes two distinct protein isoforms, an α1A subunit that serves as the pore-forming subunit of a voltage-dependent P/Q-type calcium channel (reviewed in Greenberg [1997]), and a transcription factor, α1ACT, which translocates to the nucleus and acts to enhance expression of several neuronally expressed genes [Du et al 2013]. Both α1A (some splice forms) and α1ACT bear the polymorphic CAG repeat that is expanded in spinocerebellar ataxia type 6 (SCA6).

P/Q-type calcium channels are high-voltage-activated calcium channels found primarily on neurons and expressed at high levels in granule cells and Purkinje cells of the cerebellar cortex. Their principal role is believed to be in synaptic transmission. α1A subunits are membrane glycoproteins approximately 2,400 amino acids in length that are the major pore-forming subunit of the P/Q-type voltage-gated calcium channel.

The discovery of the polymorphic CAG repeat in the 3' end *CACNA1A* was associated with the identification of a novel long splice form of the α1A mRNA [Zhuchenko et al 1997]. In the long splice form, inclusion of additional nucleotides at the end of exon 46 eliminates a stop codon and places an additional 237 nucleotides of 3' sequence, including the polymorphic CAG repeat, in translational frame. The CAG repeat encodes a tract of glutamine residues, in which wild type alleles range from four to 18 glutamine residues in length.

The α1ACT protein is encoded as a separate protein within the 3' portion of the long splice form of α1A subunit mRNA. The α1ACT polypeptide is translated from the α1A mRNA as a separate protein under the control of a cellular internal ribosomal entry site. α1ACT is a transcriptional protein that is translocated to nuclei and binds and enhances expression via a conserved AT-rich motif on several genes expressed in Purkinje cells. α1ACT expressed without α1A subunits accelerates neurite outgrowth in cultured neuronal cells and normalizes Purkinje cell dendrites and innervation when expressed in α1A knockout mice. α1ACT polypeptide bears the polymorphic polyglutamine tract [Du et al 2013, Du et al 2019].

The expanded CAG repeat in *CACNA1A* codes for an expanded polyglutamine tract present in the carboxy terminus of a long splice form of both the α1A subunit and the α1ACT protein [Zhuchenko et al 1997].

Mechanism of disease causation. While there is no consistent effect of the expanded polyglutamine tract on P/Q channel function, the polyqlutamine expansion alters gene binding, impairs transcription factor function, and is toxic to cells expressing the α1ACT – effects consistent with a loss of function.

***CACNA1A*-specific laboratory technical considerations.** Specific nomenclature designations for DNA and protein variants of *SCA6*, and other repeat expansion disorders, can be found here.

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Published Guidelines / Consensus Statements

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Chapter Notes

Revision History

- 21 November 2019 (sw) Comprehensive update posted live
- 18 July 2013 (me) Comprehensive update posted live
- 16 June 2008 (cd) Revision: mutation scanning/sequence analysis no longer available clinically
- 21 September 2007 (me) Comprehensive update posted live
- 8 January 2007 (cd) Revision: errata, Genotype-Phenotype Correlations, Heterozygous individuals
- 12 May 2005 (me) Comprehensive update posted live
- 11 April 2003 (me) Comprehensive update posted live
- 25 July 2000 (me) Comprehensive update posted live
- 23 October 1998 (pb) Review posted live
- 7 April 1998 (cg) Original submission

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