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

Spinocerebellar Ataxia Type 6

[*SCA 6*]

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Initial Posting: October 23, 1998.
Last Revision: June 16, 2008.

Summary

Disease characteristics. Spinocerebellar ataxia type 6 (SCA6) is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. Mean age of onset is 43 to 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. *CACNA1A* is the only gene known to be associated with SCA6. 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. Molecular genetic testing reveals an expansion in more than 99% of affected individuals.

Management. *Treatment of manifestations:* acetazolamide to eliminate episodes of ataxia; vestibular suppressants to reduce vertigo; clonopin for REM sleep disorders; home modifications for safety and convenience; canes and walkers to prevent falling; speech therapy and communication devices for dysarthria; weighted eating utensils and dressing hooks; feeding assessment when dysphagia becomes troublesome; CPAP for sleep apnea. *Surveillance:* annual or semiannual evaluation by a neurologist. *Agents/circumstances to avoid:*sedative-hypnotics (ethanol or certain medications) that increase incoordination. *Other:* Tremor-controlling drugs are not usually effective in reducing cerebellar tremors.

Genetic counseling. SCA6 is inherited in an autosomal dominant manner. Offspring of affected individuals have a 50% chance of inheriting the *CACNA1A* mutation. Prenatal testing is possible for pregnancies at increased risk if the diagnosis has been confirmed in a family member; however, requests for prenatal diagnosis of (typically) adult-onset diseases are not common.

Diagnosis

Clinical Diagnosis

Spinocerebellar ataxia type 6 (SCA6) is suspected in individuals with adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. Because the phenotypic manifestations of SCA6 are not specific, the diagnosis of SCA6 rests on molecular genetic testing.

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. *CACNA1A* is the only gene known to be associated with SCA6.

Allele sizes. A polymorphic CAG repeat in exon 47 of the *CACNA1A* gene is unstable and is expanded in individuals with SCA6. The following are allele sizes for *CACNA1A*:

- **Normal alleles:** 18 or fewer CAG repeats [Shizuka et al 1998]
- **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 pathologic 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]
- **Full penetrance alleles:** 20 to 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 average disease-causing allele has 22 CAG repeats.

Clinical testing

- **Targeted mutation analysis.** Trinucleotide repeat analysis to determine the size of the CAG trinucleotide repeat in *CACNA1A* detects an expansion in more than 99% of affected individuals and is nearly 100% specific.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in SCA6

Test Method	Mutation Detected	Mutation Detection Frequency [1]	Test Availability
Targeted mutation analysis	*CACNA1A* CAG repeat expansion	99%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method

Testing Strategy

To confirm the diagnosis in a proband, molecular genetic testing of the *CACNA1A* must be performed to detect the CACNA1A CAG-repeat expansion.

Predictive testing for at-risk asymptomatic adult family members requires prior confirmation of the diagnosis in the family.

Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior confirmation of the diagnosis in the family.

Genetically Related (Allelic) Disorders

Several other disorders are caused by mutations in the *CACNA1A*.

Dominantly inherited ataxias may be caused by *CACNA1A* missense mutation, including p.Gly293Arg or p.Arg1664Gln. These disorders are similar to SCA6, but may have a more severe clinical presentation [Yue et al 1997, Tonelli et al 2006].

Episodic ataxia type 2 (EA2) is caused by *CACNA1A* mutations that predict protein truncation, abnormal splicing, or missense mutations. It typically starts in childhood or early adolescence and is characterized by attacks of ataxia, vertigo, and nausea that last hours to days. Attacks can be associated with dysarthria, diplopia, tinnitus, dystonia, hemiplegia, and headache. Between attacks, individuals may initially be normal but eventually develop interictal findings that can include nystagmus and ataxia. After years of episodic ataxia, a condition of interictal ataxia indistinguishable from SCA6 may develop [Baloh et al 1997]. Inheritance is autosomal dominant.

Familial hemiplegic migraine (FHM) is an autosomal dominant condition with an estimated penetrance of 80%-90% [Montagna 2000]. The two clinical forms are the following:

- Pure FHM (found in 80% of affected families), in which interictal examination is normal in all family members
- FHM with permanent cerebellar symptoms (found in 20% of affected families), in which some family members show interictal nystagmus and/or ataxia

Approximately 50% of families with FHM, including all those with permanent cerebellar symptoms, have missense mutations in *CACNA1A* [Battistini et al 1999, Ducros et al 1999, Friend et al 1999, Gardner et al 1999]. FHM is characterized by an aura of hemiplegia that is always associated with at least one other aura symptom such as hemianopsia, hemisensory deficit, or aphasia. The aura is followed by a moderate to severe headache. The phenotype includes coma and seizures [Ducros et al 2001], which can be triggered by minor head injury or angiography. Delayed cerebral edema is seen primarily in children and adolescents who sustain minor head trauma, have a lucid period, and subsequently develop uncontrollable cerebral swelling [McCrory & Berkovic 1998]. Trauma-triggered delayed cerebral edema has been associated with the *CACNA1A* missense mutation p.Ser218Leu [Kors et al 2001].

Despite their well-described phenotypes, SCA6, EA2, and FHM demonstrate clinical overlap:

- Individuals with SCA6 can present with episodic ataxia. In one study, up to 33% of individualss with 21 or more CAG repeats in *CACNA1A* had episodic features prominent enough to warrant the diagnosis of EA2 [Geschwind et al 1997].
- 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].
- In a family with EA2, affected members also had hemiplegia, and one affected member had migraine during episodes of ataxia [Jen 1999].
- In one family with a *CACNA1A* missense mutation, phenotypes of both SCA6 and FHM were observed [Alonso et al 2003].
- Some families with a *CACNA1A* mutation had both SCA6 and EA2 phenotypes [Jodice et al 1997, Cricchi et al 2007].

Clinical Description

Natural History

Spinocerebellar ataxia type 6 (SCA6) is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. The range in age of onset is from 19 to 71 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 aapproximately 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%) 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.

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, Schols 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 the *CACNA1A* gene have been reported [Matsuyama et al 1997, Ikeuchi et al 1997, Geschwind et al 1997, Takiyama et al 1998]. In three, the onset was earlier and symptoms

appeared more severe than in individuals who were heterozygous [Ikeuchi et al 1997, Geschwind et al 1997]; in one study age of onset correlated with the sum of two disease alleles [Takahashi et al 2004].

Note: The increase in severity of symptoms with homozygosity of the *CACNA1A* expansion is not as great as that observed in individuals with SCA3 (Machado-Joseph disease), another autosomal dominant cerebellar ataxia caused by a CAG repeat expansion [Lang et al 1994, Lerer et al 1996, Sobue et al 1996].

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 geographical 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. The prevalence of SCA6 is calculated to be 0.02/100,000 to 0.31/100,000 [Geschwind et al 1997, Ikeuchi et al 1997, Matsumura et al 1997, Matsuyama et al 1997, Riess et al 1997, Stevanin et al 1997, Schols 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 pathologic *CACNA1A* expansion in the United Kingdom to be 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 [Schols et al 1998] and 43% in another [Geschwind et al 1997]; however, premature death of parents may have hindered complete ascertainment of all cases (see Ataxia Overview).

Differential Diagnosis

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

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 Ataxia Overview).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with spinocerebellar ataxia type 6 (SCA6), the following evaluations are recommended:

- Medical history
- Neurologic examination, including use of a rating scale to be used annually to assess progression
- Brain MRI to gauge the extent of atrophy of cerebellum or other structures

Treatment of Manifestations

Management is supportive.

- Vitamin supplements are recommended, particularly if caloric intake is reduced.
- Acetazolamide may eliminate episodes of ataxia, but does not delay or slow the overall progression.
- Vestibular suppressants can reduce vertigo.
- Although neither exercise nor physical therapy stems the progression of incoordination or muscle weakness, affected individuals should maintain activity.
- Canes and walkers help prevent falling. Modification of the home with such conveniences as grab bars, raised toilet seats, and ramps to accommodate motorized chairs may be necessary.
- Speech therapy and communication devices such as writing pads and computer-based devices may benefit those with dysarthria.
- Weighted eating utensils and dressing hooks help maintain a sense of independence.
- Weight control is important because obesity can exacerbate difficulties with ambulation and mobility.
- When dysphagia becomes troublesome, video esophagrams can identify the consistency of food least likely to trigger aspiration.
- Speech disturbances occasionally occur and may be managed as in other settings.
- Clonopin may be used for REM sleep disorders unless sedative effects increase imbalance in the morning.
- Continuous positive airway pressure may be used for sleep apnea.

Surveillance

Affected individuals should be followed annually or semiannually by a neurologist, with consultations as needed by physiatrist and physical and/or occupational therapist.

Agents/Circumstances to Avoid

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

Testing of Relatives at Risk

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

Therapies Under Investigation

Gazulla & Tintore (2007) suggested gabapentin and pregabalin as potential therapeutic agents.

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

Other

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

Patients and their families should be informed about natural history, treatment, mode of inheritance, genetic risks to other family members, and consumer-oriented resources.

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

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA6 have an affected parent.
- A proband with SCA6 may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* gene mutations is unknown.
- 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.

Note: 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.

Sibs of a proband

- The risk to the sibs of an affected individual depends on the genetic status of the proband's parents.
- If one parent has an expanded *CACNA1A* allele or another mutation, the risk to each sib of inheriting the disease-causing *CACNA1A* allele is 50%.
- When the parents do not have a disease-causing *CACNA1A* allele, the risk to the sibs of a proband appears to be low.
- If neither parent of the proband has a disease-causing *CACNA1A* allele detectable in DNA, it is presumed that the proband has a *de novo* gene mutation and the risk to the sibs of the proband depends on the probability of germline mosaicism. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Offspring of affected individuals have a 50% chance of inheriting the altered *CACNA1A* gene.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent has the disease-causing *CACNA1A* allele, his or her family members are at risk.

Related Genetic Counseling Issues

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. 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.

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 evidence of the disorder, it is possible 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 adults at risk for SCA6 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. When testing at-risk individuals for SCA6, an affected family member should be tested first to confirm the diagnosis of SCA6. Testing for the disease-causing mutation in the absence of definite symptoms or signs 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 SCA6, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems that 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 and evaluations.

Testing of at-risk asymptomatic 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 under 18 years of age 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. 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 (pdf; Genetic Testing).

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. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal testing for pregnancies at 50% risk for SCA6 is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling at approximately ten to 12 weeks' gestation. An affected family member should be tested first to confirm the diagnosis of SCA6 and identify the expansion or mutation of the *CACNA1A* allele.

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 diagnosis 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 or early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

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

Molecular Genetics

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

Table A. Molecular Genetics of Spinocerebellar Ataxia Type 6

Gene Symbol	Chromosomal Locus	Protein Name
CACNA1A	19p13	Voltage-dependent P/Q-type calcium channel subunit alpha-1A

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 Spinocerebellar Ataxia Type 6

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

Table C. Genomic Databases for Spinocerebellar Ataxia Type 6

Gene Symbol	Entrez Gene	HGMD
CACNA1A	773 (MIM No. 601011)	CACNA1A

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

Note: HGMD requires registration.

Normal allelic variants: *CACNA1A* consists of 47 exons. A polymorphic CAG repeat in the 3' end of the gene occurs within a portion of the gene previously thought to be only non-coding. The identification of expansions of this CAG repeat associated with autosomal dominant ataxia was accompanied by the recognition of a novel long splice form of the alpha 1A mRNA in which the reading frame includes the CAG repeat translated into glutamine residues. The CAG repeats range from $(CAG)_4$ to $(CAG)_{18}$.

Pathologic allelic variants: Disease-associated CAG-repeat alleles ranging from $(CAG)_{21}$ to $(CAG)_{33}$ have been reported. The most common allele is $(CAG)_{22}$. One individual with a $(CAG)_{20}$ allele has episodic ataxia [Jodice et al 1997].

Normal gene product: The *CACNA1A* gene encodes an alpha-1A subunit that serves as the pore-forming subunit of a voltage-dependent P/Q-type calcium channel (reviewed in Greenberg 1997). Voltage-dependent calcium channels are made up of beta and gamma-s accessory subunits. Alpha-1A subunits are membrane glycoproteins of approximately 2400 amino acids in length in which primary structure predicts the presence of four homologous domains, each consisting of six transmembrane domains and a pore-forming P loop. 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. The alpha1 (2.1), formerlyα1A, subunit is the major pre-forming subunit of the $CaV_{2.1}$ (PLQ type) voltage-gated calcium channel. The *CACNA1A* gene gives rise to several alternatively spliced mRNAs of approximately 7-8 kb [Ophoff et al 1996]. The predicted polypeptides range from 195 to 270 kd and vary in sequence internally and in the carboxy terminus. The discovery of the polymorphic CAG repeat in the 3' end of the gene was associated with the identification of a novel long splice form of the alpha-1A 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 glutamates in length. The function of the different splice forms of the *CACNA1A* gene products remains to be demonstrated, although differences have been measured in phosphorylation acceptor sites.

Abnormal gene product: The expanded CAG repeat in the *CACNA1A* gene in SCA6 codes for an expanded polyglutamine tract in the carboxy terminus of a long splice form of the alpha-1A subunit of a P/Q-type calcium channel [Zhuchenko et al 1997]. Whether the action of the mutant gene product is to perturb calcium channel function or to bind to nuclear-binding proteins remains to be demonstrated.

The allelic disorder, autosomal dominant cerebellar ataxia associated with *CACNA1A* mutations (including p.Gly293Arg in the P loop of the first domain, p.Ala454Thr in the I-II loop, and p.Arg1664Gln), has a very similar phenotype to that of SCA6 associated with CAG-repeat expansions [Yue et al 1997, Tonelli et al 2006, Cricchi et al 2007]. As these mutations are not likely to act via the hypothetical nuclear binding mechanisms or transamination, an effect on calcium channel function is the most likely scenario for either pathogenic allele [Chen & Piedras-Renteria 2007, Kordasiewicz & Gomez 2007, Saegusa et al 2007]. As these

mutations 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.

Resources

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

NCBI Genes and Disease
Spinocerebellar ataxia

Spinocerebellar Ataxia: Making an Informed Choice about Genetic Testing
Booklet providing information about spinocerebellar ataxia
depts.washington.edu/neurogen/SpinoAtaxia.pdf

euro-ataxia (European Federation of Hereditary Ataxias)
Boherboy Dunlavin
Co Wicklow
Ireland
Phone: 045 401218
Fax: 045 401371
Email: mary.kearneyl@euro-ataxia.org
www.euro-ataxia.org

International Network of Ataxia Friends (INTERNAF)
www.internaf.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

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
www.wemove.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

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

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Suggested Readings

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Chapter Notes

Revision History

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