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Spinocerebellar Ataxia Type 2

Synonym: SCA2

Stefan M Pulst, MD[1]

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Summary

Clinical characteristics

Spinocerebellar ataxia type 2 (SCA2) is characterized by progressive cerebellar ataxia, including nystagmus, slow saccadic eye movements, and in some individuals, ophthalmoparesis or parkinsonism. Pyramidal findings are present; deep tendon reflexes are brisk early on and absent later in the course. Age of onset is typically in the fourth decade with a ten- to 15-year disease duration.

Diagnosis/testing

The diagnosis of SCA2 rests on the use of molecular genetic testing to detect an abnormal CAG trinucleotide repeat expansion in *ATXN2*. Affected individuals have alleles with 33 or more CAG trinucleotide repeats.

Management

Treatment of manifestations: Management is supportive. Affected individuals should maintain activity. Canes and walkers help prevent falls; 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. When dysphagia becomes troublesome, video swallowing studies can identify the consistency of food least likely to trigger aspiration.

Prevention of secondary complications: Vitamin supplements are recommended; weight control helps minimize difficulties with ambulation and mobility.

Surveillance: Annual examination by a physician experienced in movement disorders and ataxia.

Agents/circumstances to avoid: Alcohol and medications known to affect cerebellar function.

Author Affiliation: 1 Department of Neurology University of Utah Salt Lake City, Utah; Email: stefan.pulst@hsc.utah.edu.

Genetic counseling

SCA2 is inherited in an autosomal dominant manner. Offspring of an affected individual have a 50% chance of inheriting the causative CAG trinucleotide repeat expansion. The repeat may expand significantly, especially when transmitted by the father. Prenatal testing for a pregnancy at increased risk is possible if the diagnosis has been established by molecular genetic testing in an affected family member.

Diagnosis

Suggestive Findings

Spinocerebellar ataxia type 2 (SCA2) **should be suspected** in individuals with the following:

- Slowly progressive ataxia and dysarthria
- Nystagmus and slow saccadic eye movements
- Family history consistent with autosomal dominant inheritance

Establishing the Diagnosis

The diagnosis of SCA2 **is established** in a proband with a heterozygous pathogenic variant in *ATXN2* (see Table 1). The clinical features of SCA2 do not allow diagnosis with certainty; thus, diagnosis depends on molecular genetic testing.

Allele sizes

- **Alleles not causing SCA2.** Alleles with 31 or fewer CAG repeats
- **Alleles of uncertain clinical significance.** Alleles with 32 repeats are uncommon; correlation with clinical findings and family history may be helpful.
- **Alleles predisposed to meiotic instability (longer normal alleles)** have a CAG length-dependent increased instability [Almaguer-Mederos et al 2018]. Precise risk estimates based on large numbers of affected individuals from different ethnic groups are not available. In a small number of observations, presence of an uninterrupted (pure CAG) repeat structure increases risk of expansion and conversely, CAA interruptions appear to stabilize the repeat in transmissions.
- **Amyotrophic lateral sclerosis-risk alleles.** Alleles with 30, 31, or 32 repeats [Neuenschwander et al 2014]
- **Recessive SCA2-causing alleles.** Homozygous 31/31 repeat alleles [Tojima et al 2018]
- **Dominant SCA2-causing alleles.** Alleles with 33 or more CAG repeats (see Note) [Pulst et al 1996, Charles et al 2007]. Persons who have an SCA2-causing allele are considered at risk of developing SCA2 in their lifetime. SCA2-causing alleles are further classified as follows:
  - **Reduced-penetrance SCA2-causing alleles.** 33-34 CAG trinucleotide repeats. An individual with an allele in this range is at risk for SCA2 but may not develop symptoms. Alleles of 33 CAG repeats are considered "late onset" (age >50 years). An older asymptomatic individual with 34 CAG repeats has been reported [Riess et al 1997].
  - **Full-penetrance SCA2-causing alleles.** The most common disease-causing alleles have 37 to 39 repeats. Extreme CAG repeat expansion (>200) has been reported [Babovic-Vuksanovic et al 1998] (see Anticipation).

Note: Interruption of a CAG expanded allele by a CAA repeat does not mitigate the pathogenicity of the repeat size because both CAG and CAA code for glutamine [Costanzi-Porrini et al 2000]; however, the interruption may enhance the meiotic stability of the repeat [Choudhry et al 2001]. Conversely, the lack of CAA interruption in some expanded alleles may increase the instability of the expansion and therefore increase the risk of transmission of a larger expansion to offspring, who may become symptomatic.

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

- **Single-gene testing.** Targeted analysis for a homozygous or heterozygous *ATXN2* allele with >31 CAG repeats should be performed first.
- **A multigene panel** that includes *ATXN2* CAG-repeat analysis and other genes of interest (see Differential Diagnosis) may also be considered. 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 SCA2

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ATXN2	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. Detects abnormal number of CAG trinucleotide repeats. PCR amplification detects smaller CAG trinucleotide repeat expansions up to ~100 repeats. Southern blotting is required to detect highly expanded CAG trinucleotide repeat expansions (>100 repeats) and may be indicated in symptomatic infants and children [Mao et al 2002].

Note: Testing individuals with a positive family history of ataxia has a much higher yield than testing individuals with ataxia without an obvious family history.

- In the series reported by Riess et al [1997] only two of 842 affected individuals without a family history of ataxia were heterozygous for an *ATXN2* expansion in the pathogenic allele size range.
- In the series reported by Cancel et al [1997] only two of 90 individuals with olivopontocerebellar atrophy without a known family history were heterozygous for an *ATXN2* expansion in the pathogenic allele size range.

Clinical Characteristics

Clinical Description

Spinocerebellar ataxia type 2 (SCA2) is characterized by slowly progressive ataxia and dysarthria associated with the ocular findings of nystagmus, slow saccadic eye movements, and in some individuals, ophthalmoparesis. Tendon reflexes are brisk during the first years of life, but absent later. Mean age of onset is typically in the fourth decade with a ten- to 15-year disease duration. The disease is more rapidly progressive when onset occurs before age 20 years.

In the original study from Cuba, the earliest symptoms included gait ataxia often accompanied by leg cramps [Orozco Diaz et al 1990]. More than 50% of affected individuals developed a kinetic or postural tremor, decreased muscle tone, decreased tendon reflexes, and abnormal eye movements with slowed saccades progressing to supranuclear ophthalmoplegia. Detailed analyses of the eye movement abnormalities have been reported [Engel et al 2004, Velázquez-Pérez et al 2004].

In individuals with molecularly confirmed *ATXN2*, Geschwind et al [1997b] found almost universal presence of cerebellar ataxia and slow saccadic eye movements in affected individuals, as well as a relatively high incidence

of dystonia or chorea (38%) and dementia (37%). Mild, primarily cerebellar symptoms appeared to segregate in some families, whereas others had an early onset with dementia and chorea. Luo et al [2017] described the initial manifestations in SCA2 and other ataxias.

Similar findings were also reported by Cancel et al [1997] in a series of 111 individuals from 32 families of diverse origins. Slow eye movements were seen in 56%, fasciculations in 25%, and dystonia in 9%. The authors also correlated these findings with disease duration and increasing CAG repeat length.

An SCA2 phenotype that includes L-dopa-responsive parkinsonism has been reported [Furtado et al 2002, Payami et al 2003, Charles et al 2007]. In one Alberta family, the phenotype was consistent with autosomal dominant Parkinson disease, with PET scan showing reduced striatal fluorodopa uptake and normal raclopride binding in two affected members [Furtado et al 2002]. Charles et al [2007] proposed that an interrupted repeat structure may lead to differential binding with RNA-binding proteins and thus result in a parkinsonian rather than a cerebellar phenotype.

Neuropathology. Seven postmortem examinations have been reported in the Holguin population of Cuba [Orozco et al 1989]. A marked reduction in the number of cerebellar Purkinje cells was observed. In silver preparations, Purkinje cell dendrites had poor arborization and torpedo-like formation of their axons as they passed through the granular layer. Parallel fibers were scant and granule cells were decreased in number, whereas Golgi and basket cells were well preserved, as were neurons in the dentate and other cerebellar nuclei. In the brain stem, marked neuronal loss in the inferior olive and pontocerebellar nuclei was observed. Six of seven brains also had marked loss in the substantia nigra. In five spinal cords that were available for analysis, marked demyelination was present in the posterior columns and to a lesser degree in the spinocerebellar tracts. Motor neurons and neurons in Clarke's column were reduced in size and number. In the lumbar and sacral segments, anterior and posterior roots were partially demyelinated. Degeneration in the thalamus and reticulotegmental nucleus of the pons has also been reported [Rüb et al 2003, Rüb et al 2004, Rüb et al 2005].

In addition, Orozco et al [1989] noted severe gyral atrophy, most prominent in the frontotemporal lobes. The cerebral cortex was thinned, but without neuronal rarefaction. The cerebral white matter was atrophic and gliotic. Degeneration in the pallidonigroluysian system mainly involved the substantia nigra. One brain showed patchy loss in parts of the third-nerve nuclei. Adams et al [1997] reported similar findings in one individual.

Seidel et al [2017] studied the distribution of polyQ aggregates in brain stem sections of individuals with SCA2 and found that cytoplasmic aggregates correlated with disease severity.

An affected individual with white matter pathology has been described [Armstrong et al 2005].

Nerve biopsy has shown moderate loss of large myelinated fibers [Filla et al 1995].

Genotype-Phenotype Correlations

Probands. In general, a clear inverse correlation exists between age of onset and CAG repeat length. However, repeat length cannot predict age of onset or disease severity in an individual. About 50% of age-of-onset variance is not explained by CAG repeat length [Figueroa et al 2017].

- The widest range of age of onset is observed among individuals with fewer than 40 CAG repeats. Some individuals with alleles of 33 and 34 repeats have had onset after age 60 years. In one study, the presence of 37 repeats was associated with ages of onset ranging from 20 to 60 years [Pulst et al 1996].
- For larger repeat sizes, the variability in age of onset is less; repeat sizes greater than 45 are almost always associated with disease onset before age 20 years [Imbert et al 1996, Pulst et al 1996, Sanpei et al 1996, Cancel et al 1997, Geschwind et al 1997b, Riess et al 1997, Moretti et al 2004].

Homozygosity for expanded *ATXN2* alleles (2 alleles in the pathogenic range) does not appear to influence age of onset [Sanpei et al 1996].

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

Penetrance

See Establishing the Diagnosis, **Allele sizes** and Genotype-Phenotype Correlations.

Anticipation

Anticipation (i.e., an increase in the severity of the phenotype and earlier age of onset in later generations) has been observed in SCA2. The tendency of the *ATXN2* CAG repeat to expand as it is transmitted provides a biologic explanation for the earlier age of onset in subsequent generations.

Paternal transmission of alleles with full penetrance or reduced penetrance is most likely to demonstrate meiotic instability and result in anticipation, although large expansions can also be seen in maternally inherited alleles [Figueroa et al 2017]. In one case report, a man who had 43 repeats and onset of symptoms at age 22 years had an infant with apnea, hypotonia, and dysphagia and an allele of 202 CAG repeats [Babovic-Vuksanovic et al 1998]. Mao et al [2002] identified large expansions in four individuals using a Southern blot assay.

Nomenclature

Terms used in the past for SCA2 and other hereditary ataxias include Marie's ataxia, OPCA, and *forme fruste* of Friedreich ataxia. These terms are no longer in use.

Prevalence

Geschwind et al [1997b] found that in an ethnically varied population in the University of California Los Angeles ataxia clinic, SCA2 accounted for 13% of the autosomal dominant cerebellar ataxias (ADCAs) compared with 6% for SCA1 and 23% for SCA3. A similar percentage (15%) was reported by Cancel et al [1997] in 184 families from an ethnically and geographically diverse population.

In the Baylor College of Medicine ataxia clinic, SCA2 was the most common ADCA (18%) [Lorenzetti et al 1997]. Moseley et al [1998] reported that SCA2 was common in individuals presenting to an ataxia clinic at an academic medical center, representing 15% of persons from families with autosomal dominant inheritance and 2% of simplex cases (i.e., a single occurrence in a family) [Moseley et al 1998].

In a large series from several ataxia clinics in Germany, SCA2 represented 14% of ADCA pedigrees [Riess et al 1997].

SCA2 is the most common type of ADCA in Korea [Lee et al 2003]. (See also Hereditary Ataxia Overview.)

Genetically Related (Allelic) Disorders

In addition to ataxia, L-dopa-responsive parkinsonism with or without ataxia has been reported in individuals and families with the *ATXN2* CAG trinucleotide repeat expansion.

Differential Diagnosis

It is difficult and often impossible to distinguish spinocerebellar ataxia type 2 (SCA2) from the other hereditary ataxias (see Hereditary Ataxia Overview). The differential diagnosis should also include Parkinson disease and acquired causes of cerebellar ataxia.

SCA2-related *ATXN2* pathogenic variants should be in the differential diagnosis of adult-onset sporadic progressive ataxia, multiple system atrophy (MSA, Shy-Drager syndrome; OMIM 146500), L-dopa-responsive parkinsonism, atypical Friedreich ataxia [Abele et al 2002], and amyotrophic lateral sclerosis [Neuenschwander et al 2014].

Table 2. Proportion of Individuals with SCA2 Manifesting Phenotypic Features Compared with Individuals with SCA1, SCA3, and SCA6

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%
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 2 (SCA2), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neurologic examination
- Ophthalmologic examination
- Baseline assessment of cognition
- Neuroimaging
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Management of individuals remains supportive as no known therapy to delay or halt the progression of the disease exists.

Although neither exercise nor physical therapy has been shown to stem the progression of incoordination or muscle weakness, individuals should maintain activity.

Canes and walkers help prevent falls.

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.

When dysphagia becomes troublesome, video esophagrams can identify the consistency of food least likely to trigger aspiration.

Improvement of severe tremor with thalamic stimulation has been reported in one individual [Pirker et al 2003]. Another individual showed improvement with stimulation of the subthalamic nucleus [Freund et al 2007].

The American Academy of Neurology has developed guidelines for the treatment of motor dysfunction in patients with ataxia [Zesiewicz et al 2018].

Prevention of Secondary Complications

No dietary factor has been shown to curtail symptoms; however, vitamin supplements are recommended, particularly if caloric intake is reduced.

Weight control is important because obesity can exacerbate difficulties with ambulation and mobility.

Surveillance

Affected individuals should be examined at least annually by a physician experienced in movement disorders and ataxia.

Agents/Circumstances to Avoid

Alcohol and medications known to affect cerebellar function should be avoided.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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 do not work well for cerebellar tremors.

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 2 (SCA2) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA2 have an affected parent.
- A proband with SCA2 may have the disorder as the result of an expansion of a reduced-penetrance allele or a longer normal allele inherited from an unaffected parent.

- Recommendations for the evaluation of apparently asymptomatic parents of a proband include physical examination and consideration of *ATXN2* molecular genetic testing.
- Although most individuals diagnosed with SCA2 have an affected parent or a parent with a longer normal allele, 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 appropriate clinical evaluation and/or 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 a parent of the proband has an *ATXN2* CAG trinucleotide repeat expansion, the risk to the sibs is 50%. However, age of onset, severity, specific symptoms, and progression of the disease are variable and cannot be predicted by the family history or the size of the inherited expansion.
- If an expanded *ATXN2* 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 possibility of germline mosaicism (no instances of germline mosaicism have been reported, although it remains a possibility).

Offspring of a proband

- Each child of an individual with SCA2 has a 50% chance of inheriting an expanded *ATXN2* allele.
- Further *ATXN2* CAG trinucleotide repeat expansion may occur when the expanded *ATXN2* allele is transmitted to offspring. This results in anticipation (an earlier age of onset and more severe disease manifestations in offspring).
- Large expansions are almost exclusively observed when the repeat is passed through the paternal germline [Geschwind et al 1997b, Riess et al 1997] (see Anticipation). Nonetheless, the age of onset, severity, specific symptoms, and progression of the disease are variable and cannot be predicted by the family history or the size of the expansion.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the expanded *ATXN2* 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 the disease 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 an *ATXN2* CAG trinucleotide 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 SCA2, it is appropriate to consider testing of symptomatic individuals regardless of age.

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.

Prenatal Testing and Preimplantation Genetic Testing

Once an *ATXN2* CAG trinucleotide repeat expansion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for SCA2 are possible.

Note: Prenatal testing must take into account the possibility of a highly expanded *ATXN2* allele [Babovic-Vuksanovic et al 1998].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **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
  www.ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org

- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 34 983 278 029; 34 985 097 152; 34 634 597 503
  Email: sede.valladolid@fedaes.org; sede.gijon@fedaes.org; sede.bilbao@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 2: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATXN2	12q24.12	Ataxin-2	alsod/ATXN2 genetic mutations ATXN2 database	ATXN2	ATXN2

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 2 (View All in OMIM)

183090	SPINOCEREBELLAR ATAXIA 2; SCA2
601517	ATAXIN 2; ATXN2

Benign variants. Normal alleles have 31 or fewer CAG repeats. The two normal alleles, which account for more than 95% of alleles in most studies, have 22 and 23 CAG repeats [Pulst et al 1996, Sanpei et al 1996, Riess et al 1997].

Normal alleles typically show one or two CAA trinucleotide repeat interruptions. Because the CAA codon also encodes glutamine, these interruptions do not interrupt the glutamine tract at the protein level. The 5' sequence of the *ATXN2* cDNA is extremely GC rich and two potential ATG initiation codons can be identified. The most 5' ATG is located 78 bp downstream of an in-frame stop codon. Use of this translation initiation site predicts a protein of 140.1 kd. The second ATG, which has a better Kozak consensus sequence, is located just 5' to the CAG repeat region and would result in a protein with a relative molecular weight of 125 kd.

Allele of uncertain clinical significance. A 32-CAG repeat is an uncommon allele and information is insufficient to classify it as normal or pathogenic.

Risk alleles. Amyotrophic lateral sclerosis risk alleles have 30, 31, or 32 repeats.

Alleles predisposed to meiotic instability (longer normal alleles) have a CAG length-dependent increased instability [Almaguer-Mederos et al 2018]. Precise risk estimates based on large numbers of affected individuals from different ethnic groups are not available. In a small number of observations, presence of an uninterrupted (pure CAG) repeat structure increases risk of expansion and conversely, CAA interruptions appear to stabilize the repeat in transmissions.

Pathogenic variants. Disease alleles have 33 or more CAG repeats [Pulst et al 2005].

- **Reduced-penetrance SCA2-causing alleles.** 33-34 CAG trinucleotide repeats. An individual with an allele in this range is at risk for SCA2 but may not develop symptoms or only very late in life.
- **Full-penetrance SCA2-causing alleles.** More than 34 CAG trinucleotide repeats. Alleles of this size are associated with development of SCA2 with increased certainty assuming a normal life span. The most common disease-causing alleles have 37 to 39 repeats. Extreme CAG repeat expansion (>200) has been reported [Babovic-Vuksanovic et al 1998] (see Anticipation).

Note: Interruption of a CAG expanded allele by a CAA repeat does not mitigate the pathogenicity of the repeat size because both CAG and CAA code for glutamine [Costanzi-Porrini et al 2000]; however, the interruption may enhance the meiotic stability of the repeat [Choudhry et al 2001]. Conversely, the lack of CAA interruption in some expanded alleles may increase the instability of the expansion and therefore increase the risk of transmission of a larger expansion to offspring, who may become symptomatic.

Table 3. *ATXN2* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Benign	c.496_498CAG(≤31) (≤31 CAG repeats)	p.Gln166(≤31)	NM_002973.3 NP_002964.3
Pathogenic	c.496_498CAG(≥33) (≥33 CAG repeats)	p.Gln166(≥33)	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The *ATXN2* protein product, designated ataxin-2, is typically 1,312 amino acids (with a tract of 22 glutamines) or predicted 1,313 amino acids (with a tract of 23 glutamines) [Imbert et al 1996, Pulst et al 1996, Sanpei et al 1996].

In brains from both unaffected individuals and individuals with SCA2, ataxin-2 has a cytoplasmic localization. It associates with Golgi membranes [Huynh et al 2003]. Using antibodies to ataxin-2, the expression pattern of ataxin-2 was identical in brains of unaffected individuals and those affected with SCA2 [Huynh et al 2000].

Ataxin-2 interacts with a number of proteins (reviewed in Scoles & Pulst [2018]), including an ataxin-2 binding protein designated as RNA-binding protein fox-1 homolog 1 (NP_001135805.1; encoded by *RBFOX1* (NM_001142333.1), which contains RNA-recognition motifs [Figueroa & Pulst 2003]. Interaction of these two proteins suggests a role for ataxin-2 in mRNA translation or transport [Shibata et al 2000]. Ataxin-2-deficient mice do not develop marked neurodegeneration but show obesity, reduced fertility, and changes in hippocampal plasticity [Kiehl et al 2006, Huynh et al 2009]. Subsequent studies have shown additional ataxin-2 interactions most notably with RNA-binding and stress granule proteins including TDP-43 [Becker et al 2017, Paul et al 2018].

Abnormal gene product. Pathogenic alleles of *ATXN2* encode a protein that has an abnormally long stretch of glutamine amino acid residues. The biologic consequence of this abnormal protein is undetermined. Studies of cultured cells, human brains, and transgenic mouse lines showed accumulation of ataxin-2 in the cytoplasm without evidence of intranuclear aggregates Huynh et al [2000]. In vitro expression of an abnormally expanded ataxin-2 caused apoptotic cell death [Huynh et al 2003]. In the *Atxn2* transgenic mouse, ataxin-2 interacted with the inositol-triphosphate receptor type 1, causing abnormally increased Ca^{++} release from intracellular calcium stores that was ameliorated by feeding mice dantrolene prior to onset of symptoms [Liu et al 2009].

References

Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 3-30-22.

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Chapter Notes

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