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# Spinocerebellar Ataxia Type 1

Synonym: SCA1

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## Summary

### Clinical characteristics

Spinocerebellar ataxia type 1 (SCA1) is characterized by progressive cerebellar ataxia, dysarthria, and eventual deterioration of bulbar functions. Early in the disease, affected individuals may have gait disturbance, slurred speech, difficulty with balance, brisk deep tendon reflexes, hypermetric saccades, nystagmus, and mild dysphagia. Later signs include slowing of saccadic velocity, development of upgaze palsy, dysmetria, dysdiadochokinesia, and hypotonia. In advanced stages, muscle atrophy, decreased deep tendon reflexes, loss of proprioception, cognitive impairment (e.g., frontal executive dysfunction, impaired verbal memory), chorea, dystonia, and bulbar dysfunction are seen. Onset is typically in the third or fourth decade, although childhood onset and late-adult onset have been reported. Those with onset after age 60 years may manifest a pure cerebellar phenotype. Interval from onset to death varies from ten to 30 years; individuals with juvenile onset show more rapid progression and more severe disease. Anticipation is observed. An axonal sensory neuropathy detected by electrophysiologic testing is common; brain imaging typically shows cerebellar and brain stem atrophy.

### Diagnosis/testing

The diagnosis of SCA1 is established in a proband with characteristic clinical findings and an abnormal CAG repeat expansion in *ATXN1* identified by molecular genetic testing. Affected individuals usually have 39 or more CAG repeats.

### Management

*Treatment of manifestations:* Supportive care including adaptive devices, physical therapy, occupational therapy, avoidance of obesity; intensive rehabilitation (coordinative physiotherapy) may be beneficial; speech therapy and communication devices for dysarthria; video esophagram to help identify the consistency of food least likely to trigger aspiration and feeding devices may be indicated with recurrent aspiration; caloric support for those with weight loss; vitamin supplementation as needed; psychotherapy, neuropsychologic rehabilitation, and/or

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standard psychiatric treatments for cognitive and psychiatric manifestations; pharmacotherapy and/or referral to pain management as needed for pain.

*Surveillance:* Every three to six months: neurologic assessment for progression of ataxia, and physiatry, occupational therapy, and physical therapy assessment for mobility and self-help skills; at each visit: assessment of access to communication, speech needs, aspiration risk, feeding needs, mood, psychiatric manifestations, cognition, and family needs.

*Agents/circumstances to avoid:* Alcohol, medications known to cause nerve damage (e.g., isoniazid, large-dose vitamin B<sub>6</sub>), and circumstances that could lead to physical harm, such as operating machinery or climbing to great heights.

## Genetic counseling

SCA1 is inherited in an autosomal dominant manner. Offspring of an affected individual have a 50% chance of inheriting the expanded allele. Anticipation has been observed in SCA1; expansions are more likely to occur when the pathogenic *ATXN1* allele is paternally transmitted, and contractions are more typical of maternal transmissions. Once an abnormal CAG trinucleotide expansion in *ATXN1* has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

## Diagnosis

The phenotypic manifestations of spinocerebellar ataxia type 1 (SCA1) are not specific, and no formal clinical diagnostic criteria exist.

## Suggestive Findings

SCA1 **should be suspected** in individuals with the following clinical findings and family history.

### Clinical findings

- Progressive cerebellar ataxia
- Dysarthria
- Eventual deterioration of bulbar functions

**Family history** is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of SCA1 **is established** in a proband with suggestive findings and a heterozygous abnormal CAG trinucleotide expansion in *ATXN1* identified by molecular genetic testing (see Table 1).

### Allele sizes

- **Normal alleles**
  - **6-35 CAG repeats.** These normal alleles have been found to have CAT trinucleotide repeat interruption(s) and are considered non-mutable.
  - **36-44 CAG repeats.** Pathogenicity of alleles in the 36-44 range depends on the presence or absence of CAT trinucleotide repeats that interrupt the CAG repeats. Alleles in the 36-44 CAG repeat range are considered normal if they have CAT interruptions; if they do not, they may be in the mutable normal (36-38 CAG repeats) or full-penetrance (>39 CAG repeats) range.

- **Mutable normal (intermediate) alleles.** 36-38 CAG repeats without CAT interruptions. Mutable normal alleles have not been associated with symptoms but can expand into the abnormal range on transmission to offspring.
- **Reduced-penetrance alleles.** A woman with 44 CAG repeats with CAT repeat interruptions had an affected father but was herself asymptomatic at age 66 years [Goldfarb et al 1996]; thus, she may be an example of reduced penetrance.
- **Full-penetrance alleles**
  - 39-44 CAG repeat alleles must be uninterrupted by CAT repeats to be considered abnormal and are likely to be associated with symptoms [Menon et al 2013, Gardiner et al 2019]. However, there is an inverse correlation between the size of the expansion and the age at onset.
  - 46-70 uninterrupted CAG repeats with CAT interruptions and additional CAGs (e.g., a measured 62-CAG repeat allele with 51 uninterrupted CAGs) have been reported [Menon et al 2013].
  - Complex alleles may occur. One individual with symptomatic SCA1 with a 58-CAG repeat sequence interrupted by two CAT repeats has been reported [Matsuyama et al 1999]; however, this person had an uninterrupted 45-CAT repeat stretch. In individuals with interrupted alleles, correlation with age at onset may be more appropriate if the uninterrupted CAG stretch alone is considered. While interrupted alleles that included a stretch of  $\geq 45$  uninterrupted CAGs may have caused the disease, further studies are needed to determine the precise minimum number of uninterrupted CAGs associated with pathogenicity.

The European Molecular Genetics Quality Network (EMQN) has published best practice guidelines for the genetic testing of the spinocerebellar ataxias including SCA1 [Ramos et al 2016] (see [full text](#)). The guidelines improve the accuracy of genetic testing, although the exact number of repeat units may still vary [Ramos et al 2016].

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

- **Single-gene testing.** Targeted analysis for the heterozygous CAG repeat number in *ATXN1* should be performed first and should include additional evaluation for the presence of CAT trinucleotides that interrupt the CAG repeat tract.
- **A multigene panel** that includes *ATXN1* CAG repeat analysis and other genes of interest (see [Differential Diagnosis](#)) may be considered to identify the genetic cause of the condition 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 1

| Gene <sup>1</sup> | Method   | Proportion of Pathogenic Variants <sup>2</sup><br>Detectable by Method |
|-------------------|--|--|
| <i>ATXN1</i>      | Targeted analysis for pathogenic variants <sup>3, 4, 5</sup> | 100% <sup>6</sup>  |

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See [Molecular Genetics](#) for information on variants detected in this gene.

3. Typically, the number of CAG repeats is determined by standard PCR and fragment length analysis.

4. Distinguishing normal, mutable normal, and pathogenic alleles with 39-44 CAG repeats requires additional evaluation for the presence of CAT trinucleotides that interrupt the CAG repeat tract. Methods may vary (e.g., *Sfa*NI restriction analysis [Chung et al 1993], dual-fluorescence labeled PCR-restriction fragment length analysis [Lin et al 2008], sequencing the PCR product of the CAG repeat region).

5. In some individuals with infantile- or childhood-onset SCA1, direct amplification of the *ATXN1* CAG repeat may not detect large repeat lengths in the hundreds. Southern blot analysis, long-range PCR, or CAG triplet repeat-primed PCR analysis can be used to quantify the CAG repeat number when infantile-onset SCA1 is suspected.

6. Expansion of the number of CAG trinucleotide repeats in *ATXN1* is the mutational mechanism in all individuals with SCA1 examined to date [Orr & Zoghbi 2001].

## Clinical Characteristics

### Clinical Description

Spinocerebellar ataxia type 1 (SCA1) is characterized by ataxia, dysarthria, and eventual deterioration of bulbar functions [Donato et al 2012]. Olmos et al [2022] reviewed extracerebellar effects of SCA. Onset is typically in the third or fourth decade, although early onset in childhood has been documented [Schöls et al 1997]. In adult-onset SCA1, the duration of illness from onset to death ranges from ten to 30 years; individuals with juvenile-onset disease (whose symptoms appear before age 13 years) show more rapid progression and more severe disease and die before age 16 years [Zoghbi et al 1988].

**Table 2.** Spinocerebellar Ataxia Type 1: Frequency of Select Features

| Feature                      | % of Persons w/Feature | Comment   |
|------------------------------|------------------------|---|
| <b>Ataxia</b>                | 100% <sup>1</sup>      | Not always present at disease onset                                       |
| <b>Bulbar dysfunction</b>    | 100% <sup>2</sup>      | Almost always present in advanced stages                                  |
| <b>Ocular manifestations</b> | 100% <sup>3</sup>      | Hypermetric saccades, irregular pursuit, & nystagmus are frequently seen. |

1. Jacobi et al [2022]

2. Yang et al [2020]

3. In early stages of SCA1, most if not all individuals show ocular manifestations [Stephen & Schmahmann 2019].

**Ataxia.** The majority of affected individuals initially present with difficulties in gait. They may first notice problems of balance in going downstairs or making sudden turns; athletic individuals may notice difficulties at an earlier stage of disease in the course of activities that require a high degree of control, such as skiing or dancing.

**Bulbar dysfunction.** Slurred speech is common at presentation. Mild dysphagia, indicated by choking on food and drink, may occur early in the disease. Atrophy of facial and masticatory muscles, perioral fasciculations, and severe dysphagia leading to frequent aspiration become prominent in the final stages of the disease. Affected individuals eventually develop respiratory failure, which is the main cause of death.

**Ocular manifestations.** Affected individuals may display hypermetric saccades and nystagmus in the early stages of disease [Matilla-Dueñas et al 2008, Donato et al 2012]. As the disease progresses the saccadic velocity slows and an upgaze palsy develops. Nystagmus often disappears with evolving saccadic abnormalities. Optic

nerve atrophy and variable degrees of ophthalmoparesis may be detected in some individuals. Occult or clinically significant maculopathy has been noted in some individuals [Lebranchu et al 2013, Vaclavik et al 2013, Oertel et al 2020].

**Cognitive dysfunction.** Individuals with SCA1 experience impaired executive function, speed, attention, and theory of mind. The cognitive spectrum is broader and cognitive decline more rapid in individuals with SCA1 than in those with SCA2, SCA3, or SCA6 [Klinke et al 2010, Fancellu et al 2013, Ma et al 2014, Moriarty et al 2016].

**Psychiatric manifestations.** Individuals with SCA1 have an increased incidence of depression and negative symptoms as assessed by Scales for Assessment of Negative and Positive Symptoms and Hamilton Depression and Anxiety Scales [Fancellu et al 2013].

**Other cerebellar signs** such as brisk deep tendon reflexes, dysmetria, dysdiadochokinesia, and hypotonia become apparent as the ataxia worsens.

**Pain.** Although prevalence of pain in individuals with SCA1 has not been specifically reported, a large multicenter study including individuals with several types of SCA reported pain/discomfort in approximately half of all individuals with SCA [Moro et al 2019]. Spasticity may cause painful spasms/cramps, but they are generally not severe in individuals with SCA1.

**Disease progression.** Muscle atrophy, decreased or absent deep tendon reflexes, and loss of proprioception or vibration sense may occur in the middle or late stages of the disease [van de Warrenburg et al 2004]. Sensorimotor, mixed (i.e., axonal and demyelinating) polyneuropathy occurs in 82% of individuals with SCA1 [Linnemann et al 2016].

Non-ataxia signs measured by the Inventory of Non-Ataxia Signs (INAS) increase in number with time and correlate with the CAG repeat size until the increase reaches a plateau [Schmitz-Hübsch et al 2008, Schmitz-Hübsch et al 2010, Jacobi et al 2011, Jacobi et al 2015]. Extrapyramidal signs are found in 37.5% of persons with SCA1 (less common than in those with SCA2 and SCA3), and include staring look (53.3%), dystonia and bradykinesia (33.3% for each), and postural tremor (26.7%) [Jhunjhunwala et al 2014].

Individuals with SCA1 who have gait ataxia as the initial manifestation (comprising two thirds of affected individuals [Globas et al 2008]) typically have slower disease progression than those whose initial manifestations did not include gait ataxia [Luo et al 2017].

Large-scale natural history studies of some of the common SCAs (including SCA1) using validated neurologic rating scales and timed measures of motor function have been in progress in many countries. The annual increase in the Scale for Assessment and Rating of Ataxia (SARA) score (which quantifies various aspects of appendicular and limb ataxia – a score of 40 indicates maximum dysfunction [Schmitz-Hübsch et al 2010]) for SCA1, SCA2, SCA3, and SCA6 combined in a one-year follow-up study was  $1.38 \pm 0.37$ . SCA1 appears to have a faster progression ( $2.18 \pm 0.17$  points per year, based on SARA) than SCA2 and SCA3 ( $1.40 \pm 0.11$  and  $1.61 \pm 0.12$ , respectively), an observation that has been reproduced by studies in the US [Jacobi et al 2011, Ashizawa et al 2013, Jacobi et al 2015].

**Juvenile-onset SCA1** is characterized by severe brain stem dysfunction in addition to cerebellar symptoms. The brain stem dysfunction occurs rapidly, leading to death within four to eight years of symptom onset.

**Electrophysiologic studies.** Persons with SCA1 often show abnormal nerve conduction [Schöls et al 2008] in addition to abnormal visual evoked potentials (41%), median somatosensory evoked potentials (41%), and brain stem auditory evoked response (73%) [Chandran et al 2014].

Visual evoked potentials and motor evoked potentials following transcranial magnetic stimulation are abnormal in most individuals with SCA1. Oculomotor recordings reveal eye movement abnormalities in a quantitative fashion.

**Neuroimaging.** Brain CT and MRI examinations show pontocerebellar atrophy [Döhlinger et al 2008]. Although MRI can provide better imaging of the posterior fossa than CT and quantitative MRI studies have documented minor motor dysfunction and loss of cerebellar and brain stem gray matter in presymptomatic persons with SCA1 [Jacobi et al 2013], conventional MRI has limited sensitivity at the presymptomatic stage [Ragno et al 2005].

Voxel-based morphometry show volume loss in the cerebellum and brain stem involving both gray and white matter [Guerrini et al 2004, Ginestroni et al 2008, Goel et al 2011]. Spinal cord atrophy may also be seen [Pedroso & Barsottini 2013].

Regional damage to white matter in individuals with SCA1 has been repeatedly demonstrated by diffusion tensor imaging [Guimarães et al 2013, Park et al 2020].

While positron emission tomography studies have demonstrated hypometabolism in presymptomatic individuals with an *ATXN1* trinucleotide expansion, measurements of metabolites such as N-acetylaspartate and myoinositol by MR spectroscopy revealed evidence of neuronal loss in the cerebellum, pons, and even the supratentorial structures [Oz et al 2010, Emir et al 2013].

Minor motor dysfunction and loss of cerebellar and brain stem gray matter by quantitative imaging studies have been documented in presymptomatic persons known to have an *ATXN1* trinucleotide expansion [Jacobi et al 2013].

**Neuropathology.** Neuropathologic studies reveal cerebellum and brain stem atrophy [Iwabuchi et al 2022]. In the cerebellum, the Purkinje cells are severely depleted, and the vermis may be maximally affected; the flocculonodular lobe is relatively spared [Robitaille et al 1997]. There is some loss of dentate neurons, some of which may show "grumose" degeneration [Yamada et al 2008]. Granule cells are moderately lost, and torpedoes may be seen [Genis et al 1995]. Calbindin immunocytochemistry reveals reduced dendritic arbors [Genis et al 1995]. The brain stem shows loss of basis pontis neurons and olivary neurons. There is loss of afferent fibers in middle and inferior cerebellar peduncles leading to loss of myelin stain reactivity, as well as neuronal loss in the oculomotor nuclei and the ninth and tenth cranial nerve nuclei. The spinal cord shows loss of anterior horn cells and neurons from the Clarke's column, and there is loss of fibers in the posterior column.

Systematic studies have shown that SCA1 neuropathology can involve components of the cerebello-thalamocortical loop, the basal ganglia-thalamocortical loop, the visual system, the nuclei of the auditory system, the somatosensory system at many levels, the vestibular nuclei, both infranuclear and supranuclear oculomotor neurons, several brain stem nuclei, the midbrain dopaminergic system, and the basal forebrain and midbrain cholinergic systems [Rüb et al 2013].

## Genotype-Phenotype Correlations

**Probands.** A strong correlation exists between the number of CAG repeats and severity of disease: the larger the CAG repeat, the earlier the onset and more severe the disease. However, the correlation is broad: only 36%-70% of age-at-onset variance can be explained by CAG repeat size [Orr et al 1993, Schöls et al 1997, Stevanin et al 2000, Globas et al 2008, Whaley et al 2011, Ashizawa et al 2013, Tezenas du Montcel et al 2014a]. Routine testing does not determine the presence of interruptions if the expansion is longer than 44 repeats; however, the presence of interruptions in such alleles delays the age at onset beyond that predicted by the total repeat size [Menon et al 2013]. In a large European study of 317 individuals with SCA1, the size of both the expanded and



normal alleles were significant determinants in the prediction of the age at onset of symptoms [Tezenas du Montcel et al 2014b].

The largest expansions of the CAG repeat tract are found in individuals with infantile- or juvenile-onset SCA1, who typically experience more rapid disease progression and are most commonly the offspring of affected males.

Some clinical signs (facio-lingual atrophy, dysphagia, skeletal muscle atrophy, and possibly ophthalmoparesis) are more common with larger repeat size, independent of disease duration.

Individuals who have biallelic pathogenic *ATXN1* alleles do not appear to develop disease that is more severe than what can be predicted by the larger of their two alleles.

**Progression rate.** Longer repeat expansions were associated with faster progression ( $0.06 \pm 0.02$  SARA total score unit per additional repeat unit;  $p=0.0128$ ) [Jacobi et al 2015]. Affected individuals with more than 52 CAG repeats tend to become significantly disabled five years after the onset of disease.

## Penetrance

Penetrance is considered to be greater than 95% but is age dependent. Onset after age 60 years has occasionally been reported [Sasaki et al 1996, van de Warrenburg et al 2004]. A woman with 44 CAG repeats with CAT repeat interruptions had an affected father but was herself asymptomatic at age 66 years [Goldfarb et al 1996], possibly representing reduced penetrance.

## Anticipation

Anticipation (an increase in the severity and earlier onset of the phenotype in progressive generations) has been observed in SCA1 [Zoghbi et al 1988, Whaley et al 2011, Ashizawa et al 2018]. The tendency of the *ATXN1* CAG repeat to expand as it is transmitted provides a biologic explanation for the earlier age of onset in subsequent generations. Expansions are more likely to occur when the pathogenic *ATXN1* allele is paternally transmitted, and contractions are more typical of maternal transmissions [Whaley et al 2011].

## Nomenclature

The nomenclature for the autosomal dominant hereditary ataxias has varied over the years. Terms no longer used to refer to SCA1 include Marie's ataxia, atypical Friedreich's ataxia, and olivopontocerebellar atrophy.

## Prevalence

Approximately one to two individuals in 100,000 develop SCA1.

Worldwide, SCA1 represents approximately 6% of individuals with autosomal dominant cerebellar ataxia; this figure varies considerably based on geographic location and ethnic background. For example, SCA1 has not been identified as a cause of autosomal dominant ataxia in Koreans [Jin et al 1999]; however, in eastern Siberia, SCA1 accounts for essentially 100% of individuals with autosomal dominant ataxia [Platonov et al 2016].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ATXN1*.

## Differential Diagnosis

The inherited spinocerebellar ataxias (SCAs) are a heterogeneous group of neurologic disorders that defy easy differentiation on the basis of clinical criteria alone. See [Hereditary Ataxia Overview](#), [Evaluation Strategies to Identify the Genetic Cause of Hereditary Ataxia in a Proband](#).

Rarely, SCA1 may present with features of hereditary spastic paraparesis [Pedroso et al 2015] (see [Hereditary Spastic Paraplegia Overview](#)).

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual with molecularly confirmed spinocerebellar ataxia type 1 (SCA1), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis in Individuals with Spinocerebellar Ataxia Type 1

| System/Concern                        | Evaluation  | Comment   |
|---------------------------------------|---|---|
| <b>Neurologic</b>                     | Neurologic exam to assess gait, bulbar & ocular manifestations, cerebellar manifestations, & other neurologic features  |   |
|                                       | <ul style="list-style-type: none"> <li>• Video esophagram in those w/dysphagia</li> <li>• Oral feeding assessment by speech or feeding therapist</li> </ul>                           | To determine the consistency of food that is least likely to trigger aspiration   |
| <b>Ophthalmologic</b>                 | Ophthalmologic exam for abnormal ocular movements, optic nerve atrophy, & macular degeneration  |   |
| <b>Cognition</b>                      | Cognitive assessment  |   |
| <b>Pain</b>                           | Assess for pain secondary to spasms/cramps.   |   |
| <b>Genetic counseling</b>             | By genetics professionals <sup>1</sup>  | To inform affected persons & their families re nature, MOI, & implications of SCA1 to facilitate medical & personal decision making |
| <b>Family support &amp; resources</b> | Assess need for: <ul style="list-style-type: none"> <li>• Community or <a href="#">online resources</a>;</li> <li>• Social work support;</li> <li>• Home nursing referral.</li> </ul> |   |

MOI = mode of inheritance; SCA1 = spinocerebellar ataxia type 1

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

### Treatment of Manifestations

There is no known therapy to delay or halt the progression of SCA1.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by a neurologist with consultation from physiatrists, physical and occupational therapists, and other specialists as needed (see Table 4).



**Table 4.** Treatment of Manifestations in Individuals with Spinocerebellar Ataxia Type 1

| Manifestation/Concern             | Treatment  | Considerations/Other  |
|-----------------------------------|--|---|
| <b>Ataxia</b>                     | Care by physiatrist, OT/PT   | <ul style="list-style-type: none"> <li>Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), &amp; dressing (e.g., dressing hooks).</li> <li>PT (balance exercises, gait training, &amp; coordinative training should be prioritized over muscle strengthening) to maintain mobility &amp; function<sup>1</sup></li> <li>OT to optimize ADL</li> <li>Inpatient rehab w/OT &amp; PT may improve ataxia &amp; functional abilities.</li> <li>Weight control to avoid obesity</li> <li>Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)</li> </ul> |
| <b>Dysarthria</b>                 | Speech/language therapy  | Consider alternative communication methods as needed (e.g., writing pads, digital devices).   |
| <b>Dysphagia</b>                  | <ul style="list-style-type: none"> <li>Modify food consistency to ↓ aspiration risk.</li> <li>Consider feeding device for those w/ recurrent aspiration.</li> </ul>                  | Video esophagram may help define best consistency.  |
|                                   | Nutrition assessment: <ul style="list-style-type: none"> <li>Caloric support may be needed in those w/weight loss.</li> <li>Vitamin supplementation to meet dietary needs</li> </ul> |   |
| <b>Cognitive/<br/>Psychiatric</b> | Psychotherapy / neuropsychologic rehab   | Consider cognitive behavioral therapy.  |
|                                   | Standard treatment for psychiatric manifestations (e.g., depression, anxiety, & psychosis)   |   |
| <b>Pain</b>                       | <ul style="list-style-type: none"> <li>Standard pharmacotherapy for pain control</li> <li>Referral to pain mgmt specialist as needed</li> </ul>                                      |   |

ADL = activities of daily living; OT = occupational therapy/therapist; PT = physical therapy/therapist

1. Cabaraux et al [2022]

## Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5 are recommended.

**Table 5.** Recommended Surveillance for Individuals with Spinocerebellar Ataxia Type 1

| System/Concern    | Evaluation   | Frequency     |
|-------------------|--|---------------|
| <b>Neurologic</b> | <ul style="list-style-type: none"> <li>Neurologic assessment for progression of ataxia, UMN or LMN signs, &amp; history of falls</li> <li>Monitor ataxia progression w/standardized scale (SARA).</li> <li>Physiatry &amp; OT/PT assessment of mobility &amp; self-help skills as they relate to ataxia, spasticity, &amp; weakness</li> </ul> | Every 3-6 mos |

Table 5. continued from previous page.

| System/Concern                    | Evaluation  | Frequency                  |
|-----------------------------------|---|----------------------------|
| <b>Dysarthria</b>                 | Assess need for alternative communication method or speech therapy.   | At each visit or as needed |
| <b>Dysphagia</b>                  | Assess aspiration risk & feeding methods.   |                            |
| <b>Cognitive/<br/>Psychiatric</b> | Evaluate mood, signs of psychosis, & cognition to identify need for pharmacologic & psychotherapeutic interventions.  |                            |
| <b>Family/<br/>Community</b>      | Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning). | At each visit              |

LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; SARA = Scale for Assessment and Rating of Ataxia; UMN = upper motor neuron

## Agents/Circumstances to Avoid

Affected individuals should avoid alcohol as well as medications known to be neurotoxic such as those that cause neuropathy (e.g., isoniazid, large-dose vitamin B<sub>6</sub>) or those associated with central nervous system toxicity (e.g., diphenylhydantoin).

Circumstances that could lead to physical harm, such as operating machinery or climbing to great heights, should also 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

Riluzole has been shown to provide some symptomatic relief of ataxia in a mixed group of individuals including persons with SCA1 [Ristori et al 2010, Romano et al 2015]; however, further investigation is needed, particularly longer-term disease-specific trials. The number of individuals included with SCA1 was small and did not allow for conclusions regarding treatment efficacy in those with SCA1. Double-blind randomized placebo control trials of riluzole prodrug BHV4157 (troriluzole) are ongoing ([NCT02960893](#), [NCT03408080](#), [NCT03701399](#)), and troriluzole has received Fast Track designation from the FDA.

Intrathecal injection of 3,000 mesenchymal stem cells in SCA1 transgenic mice mitigated the cerebellar neuronal disorganization, atrophy of dendrites, and motor disturbances [Matsuura et al 2014, Nakamura et al 2015]. Investigators at the General Hospital of Chinese Armed Police Forces is recruiting study subjects with hereditary cerebellar ataxia for clinical trials using umbilical stem cell therapy ([NCT01489267](#)).

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.

## 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 1 (SCA1) is inherited in an autosomal dominant manner.

## Risk to Family Members

### Parents of a proband

- Most individuals diagnosed with SCA1 have an affected parent.
- A proband with SCA1 who appears to be the only affected family member may have inherited an expanded allele from a parent with an intermediate expansion. A parent with 36-38 CAG repeats that are not interrupted by CAT trinucleotide repeats is not likely to display any manifestations of SCA1 but does have a "mutable normal" (intermediate) allele that can expand on transmission to offspring (see [Establishing the Diagnosis](#)).
- If the proband appears to be the only affected family member, molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- The family history of some individuals diagnosed with SCA1 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 demonstrated that neither parent has an abnormal CAG trinucleotide expansion in *ATXN1*.

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

- If a parent has an abnormal CAG trinucleotide expansion in *ATXN1*, the risk to each sib of inheriting an expanded *ATXN1* allele is 50%.

Note: If a parent has a mutable normal (intermediate) allele (i.e., 36-38 CAG repeats without CAT interruptions), the parent is not likely to display any manifestations of SCA1, but the allele can expand on transmission to offspring (see [Establishing the Diagnosis](#)).

- Anticipation (an increase in the severity and earlier onset of the phenotype in progressive generations) has been observed in SCA1. Expansions are more likely to occur when the pathogenic *ATXN1* allele is paternally transmitted, and contractions are more typical of maternal transmissions (see [Clinical Characteristics, Anticipation](#)).

### Offspring of a proband

- Each child of an individual with SCA1 has a 50% chance of inheriting an abnormal CAG trinucleotide expansion in *ATXN1*.
- Expanded CAG repeat tracts are unstable: during transmission to offspring they may contract by a few trinucleotides, though they are more likely to expand. Larger intergenerational expansions tend to occur more frequently on paternal than on maternal transmission.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent has an abnormal CAG expansion in *ATXN1*, the parent's family members are at risk.

## Related Genetic Counseling Issues

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

- Predictive testing for at-risk relatives is possible once an abnormal CAG repeat expansion in *ATXN1* has been identified in an affected family member.
- Such testing should be performed in the context of formal genetic counseling and is not useful in reliably predicting age of onset, severity, type of manifestations, 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 younger than 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 SCA1, it is appropriate to consider testing of symptomatic individuals regardless of age.

### **Family planning**

- The optimal time for determination of genetic risk is before pregnancy. Similarly, decisions regarding 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.

## **Prenatal Testing and Preimplantation Genetic Testing**

Once an abnormal CAG trinucleotide expansion in *ATXN1* has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Age of onset, severity, and progression of SCA1 are variable and cannot be reliably predicted by the family history or prenatal molecular genetic testing results.

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. For more information, see the National Society of Genetic Counselors [position statement](#) on prenatal testing in adult-onset conditions.

## **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](#).*

- **MedlinePlus**  
[Spinocerebellar ataxia type 1](#)

- **Associazione Italiana per la lotta alle Sindromi Atassiche (AISA)**  
Via Sara 12  
16039  
Italy  
**Phone:** 39 342 9124574  
**Email:** nazionale@atassia.it  
[www.atassia.it](http://www.atassia.it)
- **Ataxia UK**  
United Kingdom  
**Phone:** 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)  
**Email:** help@ataxia.org.uk  
[ataxia.org.uk](http://ataxia.org.uk)
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**  
United Kingdom  
**Email:** ageorgousis@ataxia.org.uk  
[euroataxia.org](http://euroataxia.org)
- **National Ataxia Foundation**  
**Phone:** 763-553-0020  
**Email:** naf@ataxia.org  
[ataxia.org](http://ataxia.org)
- **Spanish Ataxia Federation (FEDAES)**  
Spain  
**Phone:** 601 037 982  
**Email:** info@fedaes.org  
[fedaes.org](http://fedaes.org)
- **CoRDS Registry**  
Sanford Research  
**Phone:** 605-312-6300  
[CoRDS Registry](http://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 1: Genes and Databases

| Gene         | Chromosome Locus | Protein  | Locus-Specific Databases       | HGMD                  | ClinVar               |
|--------------|------------------|----------|--------------------------------|-----------------------|-----------------------|
| <i>ATXN1</i> | 6p22.3           | Ataxin-1 | <a href="#">ATXN1 database</a> | <a href="#">ATXN1</a> | <a href="#">ATXN1</a> |

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 1 ([View All in OMIM](#))

|        |                                |
|--------|--------------------------------|
| 164400 | SPINOCEREBELLAR ATAXIA 1; SCA1 |
| 601556 | ATAXIN 1; ATXN1                |

## Molecular Pathogenesis

*ATXN1* encodes ataxin-1, a nuclear protein found in a wide variety of cell and tissue types [Servadio et al 1995]. Ataxin-1 has been postulated to have several functions in the nucleus, including transcription regulation and RNA processing. A review provides details of the many proteins that have been found to interact with ataxin-1, including many transcriptional coregulators and proteins involved in RNA binding and metabolism [Matilla-Dueñas et al 2008]. Ataxin-1 also binds corepressors that influence histone acetylation and thereby regulates gene expression [Cvetanovic et al 2012, Venkatraman et al 2014].

It is believed that the expanded polyglutamine tract resulting from the CAG expansion results in misfolding of ataxin-1, resulting in insoluble aggregates. The abnormal protein accumulates in the nucleus as a single aggregate, often referred to as a nuclear inclusion (NI). NIs affect portions of the cell's protein refolding and degradation machinery (chaperones, ubiquitin, and proteasomal subunits); it is thought that impaired protein clearance underlies the pathogenesis of SCA1. At least three lines of evidence support this hypothesis:

- Neuronal degeneration is accelerated when ubiquitination is impaired in SCA1 transgenic mice [Cummings et al 1999].
- Overexpression of specific chaperones suppresses neurodegeneration in fly and mouse models of polyglutamine disorders [Fernandez-Funez et al 2000, Cummings et al 2001].
- Polyglutamine-expanded ataxin-1 decreases the activity of the proteasome in cell culture [Park et al 2005].

The accumulated toxic species is likely to be oligomers [Lasagna-Reeves et al 2015]. Phosphorylation of p.Ser776 in ataxin-1 is critical for pathogenicity of mutated ataxin-1 [Chen et al 2003, Emamian et al 2003], affecting its clearance through the RAS-MAPK-MSK1 kinase pathway [Park et al 2013]. Substitution to p.Ala776 reduces the toxicity of mutated ataxin-1.

An analysis of the genomic expression profile in SCA1 transgenic mice showed consistently altered levels of mRNA from five genes forming a biologic cohort centered on glutamate signaling pathways in Purkinje cells [Serra et al 2004]. In addition, transcriptional dysregulation of calcium homeostasis genes also appears to be an early feature [Lin et al 2000]. Vascular endothelial growth factor (VEGF), a neurotrophic and angiogenic factor, is also downregulated. Restoring *Vegf* in SCA1 knock-in mice can improve the ataxic phenotype [Cvetanovic et al 2011]. Decreasing the level of ataxin-1 by RNA interference [Keiser et al 2013, Keiser et al 2016] and small molecules that inhibit MSK1 [Park et al 2013] has shown promising results in preclinical studies.

Intracerebroventricular administration of VEGF [Cvetanovic et al 2011], subcutaneous administration of aminopyridines [Hourez et al 2011], and intrathecal administration of mesenchymal stem cells [Matsuura et al 2014, Mieda et al 2016] have also shown therapeutic potential in genetic mouse models of SCA1. Another promising approach is the use of antisense oligonucleotides to reduce ataxin-1 levels, given exciting results in another polyglutamine ataxia, SCA2 [Scoles et al 2017].

**Mechanism of disease causation.** Dominant-negative

### *ATXN1*-specific laboratory technical considerations

- Normal *ATXN1* variants may contain six to 44 CAG repeats and are interrupted with one to three CAT trinucleotides. However, sequencing of cloned alleles has shown that repeat instability can occur even in the presence of interruptions [Menon et al 2013], raising the possibility of such a (rare) occurrence in a clinical sample.
- Mutable normal (intermediate) alleles have 36-38 CAG repeats without CAT interruptions. Mutable normal alleles have not been associated with symptoms but can expand into the abnormal range on transmission to offspring.
- Somatic and meiotic instability has been observed for the *ATXN1* CAG repeats, particularly in tissues that have higher mitotic potential, such as peripheral blood cells and sperm [Chong et al 1995]. The presence



of CAT trinucleotide interruptions within the CAG repeat tract has a demonstrated stabilizing effect in somatic tissues. Comparative analysis of a large normal allele (39 repeats with CAT interruptions) with a small expanded allele (40 uninterrupted repeats) revealed that the interrupted allele was somatically stable, whereas the allele with an uninterrupted CAG tract was unstable [Chong et al 1995].

## Chapter Notes

### Author Notes

- [READISCA](#): Clinical Trial Readiness for SCA1 and SCA3
- [CRC-SCA](#): Clinical Research Consortium for the Study of Cerebellar Ataxia
- [Ataxia Global Initiative](#)
- [Critical Path to Therapeutics for the Ataxias](#)

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