U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Opal P, Ashizawa T. Spinocerebellar Ataxia Type 1. 1998 Oct 1 [Updated 2023 Feb 2]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Spinocerebellar Ataxia Type 1

Synonym: SCA1

Puneet Opal, MD, PhD[1] and Tetsuo Ashizawa, MD[2]

Created: October 1, 1998; Updated: February 2, 2023.

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

Author Affiliations: 1 Director, Ataxia Clinic, Department of Neurology, Northwestern Feinberg School of Medicine, Chicago, Illinois; Email: p-opal@northwestern.edu. 2 Director, Neuroscience Research Program, Houston Methodist Research Institute, Houston, Texas; Email: tashizawa@houstonmethodist.org.

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_6), 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 ≥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 [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ATXN1	Targeted analysis for pathogenic variants [3, 4, 5]	100% [6]

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
Ataxia	100% [1]	Not always present at disease onset
Bulbar dysfunction	100% [2]	Almost always present in advanced stages
Ocular manifestations	100% [3]	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±0.37. SCA1 appears to have a faster progression (2.18±0.17 points per year, based on SARA) than SCA2 and SCA3 (1.40±0.11 and 1.61±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±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
Neurologic	Neurologic exam to assess gait, bulbar & ocular manifestations, cerebellar manifestations, & other neurologic features	
	• Video esophagram in those w/dysphagia • Oral feeding assessment by speech or feeding therapist	To determine the consistency of food that is least likely to trigger aspiration
Ophthalmologic	Ophthalmologic exam for abnormal ocular movements, optic nerve atrophy, & macular degeneration	
Cognition	Cognitive assessment	
Pain	Assess for pain secondary to spasms/cramps.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SCA1 to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources; • Social work support; • Home nursing referral.	

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
Ataxia	Care by physiatrist, OT/PT	• Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), & dressing (e.g., dressing hooks). • PT (balance exercises, gait training, & coordinative training should be prioritized over muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL • Inpatient rehab w/OT & PT may improve ataxia & functional abilities. • Weight control to avoid obesity • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)
Dysarthria	Speech/language therapy	Consider alternative communication methods as needed (e.g., writing pads, digital devices).
Dysphagia	• Modify food consistency to ↓ aspiration risk. • Consider feeding device for those w/ recurrent aspiration.	Video esophagram may help define best consistency.
	Nutrition assessment: • Caloric support may be needed in those w/weight loss. • Vitamin supplementation to meet dietary needs	
Cognitive/ Psychiatric	Psychotherapy / neuropsychologic rehab	Consider cognitive behavioral therapy.
	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, & psychosis)	
Pain	• Standard pharmacotherapy for pain control • Referral to pain mgmt specialist as needed	

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
Neurologic	• Neurologic assessment for progression of ataxia, UMN or LMN signs, & history of falls • Monitor ataxia progression w/standardized scale (SARA). • Physiatry & OT/PT assessment of mobility & self-help skills as they relate to ataxia, spasticity, & weakness	Every 3-6 mos

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Dysarthria	Assess need for alternative communication method or speech therapy.	At each visit or as needed
Dysphagia	Assess aspiration risk & feeding methods.	
Cognitive/ Psychiatric	Evaluate mood, signs of psychosis, & cognition to identify need for pharmacologic & psychotherapeutic interventions.	
Family/ Community	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_6) 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
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 601 037 982
  Email: info@fedaes.org
  fedaes.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Spinocerebellar Ataxia Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATXN1	6p22.3	Ataxin-1	ATXN1 database	ATXN1	ATXN1

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

Author History

Tetsuo Ashizawa, MD (2005-present)
Vicki L Brandt; Baylor College of Medicine (1998-2005)
Xi Lin, MD, PhD; University of Texas Medical Branch (2005-2011)
Puneet Opal, MD, PhD (2017-present)
SH Subramony, MD; University of Florida (2011-2017)
Huda Y Zoghbi, MD; Baylor College of Medicine (1998-2005)

Revision History

- 2 February 2023 (sw) Comprehensive update posted live
- 22 June 2017 (ma) Comprehensive update posted live
- 3 July 2014 (me) Comprehensive update posted live
- 20 October 2011 (me) Comprehensive update posted live
- 1 November 2007 (me) Comprehensive update posted live
- 18 July 2005 (me) Comprehensive update posted live
- 18 June 2003 (ca) Comprehensive update posted live
- 29 January 2001 (me) Comprehensive update posted live
- 1 October 1998 (pb) Review posted live
- 26 June 1998 (hz) Original submission

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 1-30-23.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 1-30-23.
- Sequeiros J, Martindale J, Seneca S. EMQN Best Practice Guidelines for molecular genetic testing of the SCAs. European Molecular Quality Genetics Network. Available online. 2010. Accessed 1-30-23.

Literature Cited

Ashizawa T, Figueroa KP, Perlman SL, Gomez CM, Wilmot GR, Schmahmann JD, Ying SH, Zesiewicz TA, Paulson HL, Shakkottai VG, Bushara KO, Kuo SH, Geschwind MD, Xia G, Mazzoni P, Krischer JP,

Cuthbertson D, Holbert AR, Ferguson JH, Pulst SM, Subramony SH. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. Orphanet J Rare Dis. 2013;8:177. PubMed PMID: 24225362.

Ashizawa T, Öz G, Paulson HL. Spinocerebellar ataxias: prospects and challenges for therapy development. Nat Rev Neurol. 2018;14:590–605. PubMed PMID: 30131520.

Cabaraux P, Agrawal SK, Cai H, Calabro RS, Casali C, Damm L, Doss S, Habas C, Horn AKE, Ilg W, Louis ED, Mitoma H, Monaco V, Petracca M, Ranavolo A, Rao AK, Ruggieri S, Schirinzi T, Serrao M, Summa S, Strupp M, Surgent O, Synofzik M, Tao S, Terasi H, Torres-Russotto D, Travers B, Roper JA, Manto M. Consensus paper: ataxic gait. Cerebellum. 2022. Epub ahead of print.

Chandran V, Jhunjhunwala K, Purushottam M, Jain S, Pal PK. Multimodal evoked potentials in spinocerebellar ataxia types 1, 2, and 3. Ann Indian Acad Neurol. 2014;17:321–4. PubMed PMID: 25221404.

Chen HK, Fernandez-Funez P, Acevedo SF, Lam YC, Kaytor MD, Fernandez MH, Aitken A, Skoulakis EM, Orr HT, Botas J, Zoghbi HY. Interaction of akt-phosphorylated ataxin-1 with 14-3-3 mediates neurodegeneration in spinocerebellar ataxia type 1. Cell. 2003;113:457–68. PubMed PMID: 12757707.

Chong SS, McCall AE, Cota J, Subramony SH, Orr HT, Hughes MR, Zoghbi HY. Gametic and somatic tissue-specific heterogeneity of the expanded SCA1 CAG repeat in spinocerebellar ataxia type 1. Nat Genet. 1995;10:344–50. PubMed PMID: 7670474.

Chung MY, Ranum LP, Duvick LA, Servadio A, Zoghbi HY, Orr HT. Evidence for a mechanism predisposing to intergenerational CAG repeat instability in spinocerebellar ataxia type I. Nat Genet. 1993;5:254–8. PubMed PMID: 8275090.

Cummings CJ, Orr HT, Zoghbi HY. Progress in pathogenesis studies of spinocerebellar ataxia type 1. Philos Trans R Soc Lond B Biol Sci. 1999;354:1079–81. PubMed PMID: 10434309.

Cummings CJ, Sun Y, Opal P, Antalffy B, Mestril R, Orr HT, Dillmann WH, Zoghbi HY. Over-expression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice. Hum Mol Genet. 2001;10:1511–8. PubMed PMID: 11448943.

Cvetanovic M, Kular RK, Opal P. LANP mediates neuritic pathology in spinocerebellar ataxia type 1. Neurobiol Dis. 2012;48:526–32. PubMed PMID: 22884877.

Cvetanovic M, Patel JM, Marti HH, Kini AR, Opal P. Vascular endothelial growth factor ameliorates the ataxic phenotype in a mouse model of spinocerebellar ataxia type 1. Nature Med. 2011;17:1445–7. PubMed PMID: 22001907.

Döhlinger S, Hauser TK, Borkert J, Luft AR, Schulz JB. Magnetic resonance imaging in spinocerebellar ataxias. Cerebellum. 2008;7:204–14. PubMed PMID: 18418677.

Donato SD, Mariotti C, Taroni F. Spinocerebellar ataxia type 1. Handb Clin Neurol. 2012;103:399–421. PubMed PMID: 21827903.

Emamian ES, Kaytor MD, Duvick LA, Zu T, Tousey SK, Zoghbi HY, Clark HB, Orr HT. Serine 776 of ataxin-1 is critical for polyglutamine-induced disease in SCA1 transgenic mice. Neuron. 2003;38:375–87. PubMed PMID: 12741986.

Emir UE, Brent Clark H, Vollmers ML, Eberly LE, Öz G. Non-invasive detection of neurochemical changes prior to overt pathology in a mouse model of spinocerebellar ataxia type 1. J Neurochem. 2013;127:660–8. PubMed PMID: 24032423.

Fancellu R, Paridi D, Tomasello C, Panzeri M, Castaldo A, Genitrini S, Soliveri P, Girotti F. Longitudinal study of cognitive and psychiatric functions in spinocerebellar ataxia types 1 and 2. J Neurol. 2013;260:3134–43. PubMed PMID: 24122064.

Fernandez-Funez P, Nino-Rosales ML, de Gouyon B, She WC, Luchak JM, Martinez P, Turiegano E, Benito J, Capovilla M, Skinner PJ, McCall A, Canal I, Orr HT, Zoghbi HY, Botas J. Identification of genes that modify ataxin-1-induced neurodegeneration. Nature. 2000;408:101–6. PubMed PMID: 11081516.

Gardiner SL, Boogaard MW, Trompet S, de Mutsert R, Rosendaal FR, Gussekloo J, Jukema JW, Roos RAC, Aziz NA. Prevalence of carriers of intermediate and pathological polyglutamine disease-associated alleles among large population-based cohorts. JAMA Neurol. 2019;76:650–6. PubMed PMID: 30933216.

Genis D, Matilla T, Volpini V, Rosell J, Dávalos A, Ferrer I, Molins A, Estivill X. Clinical, neuropathologic, and genetic studies of a large spinocerebellar ataxia type 1 (SCA1) kindred: (CAG)n expansion and early premonitory signs and symptoms. Neurology. 1995;45:24–30. PubMed PMID: 7824128.

Ginestroni A, Della Nave R, Tessa C, Giannelli M, De Grandis D, Plasmati R, Salvi F, Piacentini S, Mascalchi M. Brain structural damage in spinocerebellar ataxia type 1: a VBM study. J Neurol. 2008;255:1153–8. PubMed PMID: 18438695.

Globas C, du Montcel ST, Baliko L, Boesch S, Depondt C, DiDonato S, Durr A, Filla A, Klockgether T, Mariotti C, Melegh B, Rakowicz M, Ribai P, Rola R, Schmitz-Hubsch T, Szymanski S, Timmann D, Van de Warrenburg BP, Bauer P, Schols L. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. Mov Disord. 2008;23:2232–8. PubMed PMID: 18759344.

Goel G, Pal PK, Ravishankar S, Venkatasubramanian G, Jayakumar PN, Krishna N, Purushottam M, Saini J, Faruq M, Mukherji M, Jain S. Gray matter volume deficits in spinocerebellar ataxia: An optimized voxel based morphometric study. Parkinsonism Relat Disord. 2011;17:521–7. PubMed PMID: 21600833.

Goldfarb LG, Vasconcelos O, Platonov FA, Lunkes A, Kipnis V, Kononova S, Chabrashvili T, Vladimirtsev VA, Alexeev VP, Gajdusek DC. Unstable triplet repeat and phenotypic variability of spinocerebellar ataxia type 1. Ann Neurol. 1996;39:500–6. PubMed PMID: 8619528.

Guerrini L, Lolli F, Ginestroni A, Belli G, Della Nave R, Tessa C, Foresti S, Cosottini M, Piacentini S, Salvi F, Plasmati R, De Grandis D, Siciliano G, Filla A, Mascalchi M. Brainstem neurodegeneration correlates with clinical dysfunction in SCA1 but not in SCA2. A quantitative volumetric, diffusion and proton spectroscopy MR study. Brain. 2004;127:1785–95. PubMed PMID: 15240431.

Guimarães RP, D'Abreu A, Yasuda CL, França MC Jr, Silva BH, Cappabianco FA, Bergo FP, Lopes-Cendes IT, Cendes F. A multimodal evaluation of microstructural white matter damage in spinocerebellar ataxia type 3. Mov Disord. 2013;28:1125–32. PubMed PMID: 23553599.

Hourez R, Servais L, Orduz D, Gall D, Millard I, de Kerchove d'Exaerde A, Cheron G, Orr HT, Pandolfo M, Schiffmann SN. Aminopyridines correct early dysfunction and delay neurodegeneration in a mouse model of spinocerebellar ataxia type 1. J Neurosci. 2011;31:11795–807. PubMed PMID: 21849540.

Iwabuchi K, Koyano S, Yagishita S. Simple and clear differentiation of spinocerebellar degenerations: overview of macroscopic and low-power view findings. Neuropathology. 2022;42:379–93. PubMed PMID: 35859519.

Jacobi H, Bauer P, Giunti P, Labrum R, Sweeney MG, Charles P, Dürr A, Marelli C, Globas C, Linnemann C, Schöls L, Rakowicz M, Rola R, Zdzienicka E, Schmitz-Hübsch T, Fancellu R, Mariotti C, Tomasello C, Baliko L, Melegh B, Filla A, Rinaldi C, van de Warrenburg BP, Verstappen CC, Szymanski S, Berciano J, Infante J, Timmann D, Boesch S, Hering S, Depondt C, Pandolfo M, Kang JS, Ratzka S, Schulz J, Tezenas du Montcel S, Klockgether T. The natural history of spinocerebellar ataxia type 1, 2, 3, and 6: a 2-year follow-up study. Neurology. 2011;77:1035–41. PubMed PMID: 21832228.

Jacobi H, du Montcel ST, Bauer P, Giunti P, Cook A, Labrum R, Parkinson MH, Durr A, Brice A, Charles P, Marelli C, Mariotti C, Nanetti L, Panzeri M, Rakowicz M, Sulek A, Sobanska A, Schmitz-Hubsch T, Schols L, Hengel H, Baliko L, Melegh B, Filla A, Antenora A, Infante J, Berciano J, van de Warrenburg BP, Timmann D, Szymanski S, Boesch S, Kang JS, Pandolfo M, Schulz JB, Molho S, Diallo A, Klockgether T. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. Lancet Neurol. 2015;14:1101–8. PubMed PMID: 26377379.

Jacobi H, Reetz K, du Montcel ST, Bauer P, Mariotti C, Nanetti L, Rakowicz M, Sulek A, Durr A, Charles P, Filla A, Antenora A, Schöls L, Schicks J, Infante J, Kang JS, Timmann D, Di Fabio R, Masciullo M, Baliko L, Melegh B, Boesch S, Bürk K, Peltz A, Schulz JB, Dufaure-Garé I, Klockgether T. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. Lancet Neurol. 2013;12:650–8. PubMed PMID: 23707147.

Jacobi H, Schaprian T, Beyersmann J, Tezenas du Montcel S, Schmid M, Klockgether T, et al. Evolution of disability in spinocerebellar ataxias type 1, 2, 3, and 6. Ann Clin Transl Neurol. 2022;9:286–95. PubMed PMID: 35188716.

Jhunjhunwala K, Netravathi M, Purushottam M, Jain S, Pal PK. Profile of extrapyramidal manifestations in 85 patients with spinocerebellar ataxia type 1, 2 and 3. J Clin Neurosci. 2014;21:1002–6. PubMed PMID: 24602359.

Jin DK, Oh MR, Song SM, Koh SW, Lee M, Kim GM, Lee WY, Chung CS, Lee KH, Im JH, Lee MJ, Kim JW, Lee MS. Frequency of spinocerebellar ataxia types 1,2,3,6,7 and dentatorubral pallidoluysian atrophy mutations in Korean patients with spinocerebellar ataxia. J Neurol. 1999;246:207–10. PubMed PMID: 10323319.

Keiser MS, Geoghegan JC, Boudreau RL, Lennox KA, Davidson BL. RNAi or overexpression: alternative therapies for spinocerebellar ataxia type 1. Neurobiol Dis. 2013;56:6–13. PubMed PMID: 23583610.

Keiser MS, Monteys AM, Corbau R, Gonzalez-Alegre P, Davidson BL. RNAi prevents and reverses phenotypes induced by mutant human ataxin-1. Ann Neurol. 2016;80:754–65. PubMed PMID: 27686464.

Klinke I, Minnerop M, Schmitz-Hubsch T, Hendriks M, Klockgether T, Wullner U, Helmstaedter C. Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3, and 6. Cerebellum. 2010;9:433–42. PubMed PMID: 20502998.

Lasagna-Reeves CA, Rousseaux MW, Guerrero-Munoz MJ, Vilanova-Velez L, Park J, See L, Jafar-Nejad P, Richman R, Orr HT, Kayed R, Zoghbi HY. Ataxin-1 oligomers induce local spread of pathology and decreasing them by passive immunization slows Spinocerebellar ataxia type 1 phenotypes. Elife. 2015;4:e10891. PubMed PMID: 26673892.

Lebranchu P, Le Meur G, Magot A, David A, Verny C, Weber M, Milea D. Maculopathy and spinocerebellar ataxia type 1: a new association? J Neuroophthalmol. 2013;33:225–31. PubMed PMID: 23584155.

Lin JX, Ishikawa K, Sakamoto M, Tsunemi T, Ishiguro T, Amino T, Toru S, Kondo I, Mizusawa H. Direct and accurate measurement of CAG repeat configuration in the ataxin-1 (ATXN-1) gene by "dual-fluorescence labeled PCR-restriction fragment length analysis.". J Hum Genet. 2008;53:287–95. PubMed PMID: 18301861.

Lin X, Antalffy B, Kang D, Orr HT, Zoghbi HY. Polyglutamine expansion down-regulates specific neuronal genes before pathologic changes in SCA1. Nat Neurosci. 2000;3:157–63. PubMed PMID: 10649571.

Linnemann C, Tezenas du Montcel S, Rakowicz M, Schmitz-Hubsch T, Szymanski S, Berciano J, van de Warrenburg BP, Pedersen K, Depondt C, Rola R, Klockgether T, Garcia A, Mutlu G, Schols L. Peripheral neuropathy in spinocerebellar ataxia type 1, 2, 3, and 6. Cerebellum. 2016;15:165–73. PubMed PMID: 26054379.

Luo L, Wang J, Lo RY, Figueroa KP, Pulst SM, Kuo PH, Perlman S, Wilmot G, Gomez CM, Schmahmann JD, Paulson H, Shakkottai VG, Ying SH, Zesiewicz T, Bushara K, Geschwind M, Xia G, Subramony SH, Ashizawa T, Kuo SH. The initial symptom and motor progression in spinocerebellar ataxias. Cerebellum. 2017;16:615–22. PubMed PMID: 27848087.

Ma J, Wu C, Lei J, Zhang X. Cognitive impairments in patients with spinocerebellar ataxia types 1, 2 and 3 are positively correlated to the clinical severity of ataxia symptoms. Int J Clin Exp Med. 2014;7:5765–71. PubMed PMID: 25664104.

Matilla-Dueñas A, Goold R, Giunti P. Clinical, genetic, molecular, and pathophysiological insights into spinocerebellar ataxia type 1. Cerebellum. 2008;7:106–14. PubMed PMID: 18418661.

Matsuura S, Shuvaev AN, Iizuka A, Nakamura K, Hirai H. Mesenchymal stem cells ameliorate cerebellar pathology in a mouse model of spinocerebellar ataxia type 1. Cerebellum. 2014;13:323–30. PubMed PMID: 24242763.

Matsuyama Z, Izumi Y, Kameyama M, Kawakami H, Nakamura S. The effect of CAT trinucleotide interruptions on the age at onset of spinocerebellar ataxia type 1 (SCA1). J Med Genet. 1999;36:546–8. PubMed PMID: 10424816.

Menon RP, Nethisinghe S, Faggiano S, Vannocci T, Rezaei H, Pemble S, Sweeney MG, Wood NW, Davis MB, Pastore A, Giunti P. The role of interruptions in polyQ in the pathology of SCA1. PLoS Genet. 2013;9:e1003648. PubMed PMID: 23935513.

Mieda T, Suto N, Iizuka A, Matsuura S, Iizuka H, Takagishi K, Nakamura K, Hirai H. Mesenchymal stem cells attenuate peripheral neuronal degeneration in spinocerebellar ataxia type 1 knockin mice. J Neurosci Res. 2016;94:246–52. PubMed PMID: 26707550.

Moriarty A, Cook A, Hunt H, Adams ME, Cipolotti L, Giunti P. A longitudinal investigation into cognition and disease progression in spinocerebellar ataxia types 1, 2, 3, 6, and 7. Orphanet J Rare Dis. 2016;11:82. PubMed PMID: 27333979.

Moro A, Moscovich M, Farah M, Camargo CHF, Teive HAG, Munhoz RP. Nonmotor symptoms in spinocerebellar ataxias (SCAs). Cerebellum Ataxias. 2019;6:12. PubMed PMID: 31485334.

Nakamura K, Mieda T, Suto N, Matsuura S, Hirai H. Mesenchymal stem cells as a potential therapeutic tool for spinocerebellar ataxia. Cerebellum. 2015;14:165–70. PubMed PMID: 25280585.

Oertel FC, Zeitz O, Rönnefarth M, Bereuter C, Motamedi S, Zimmermann HG, Kuchling J, Grosch AS, Doss S, Browne A, Paul F, Schmitz-Hübsch T, Brandt AU. Functionally relevant maculopathy and optic atrophy in spinocerebellar ataxia type 1. Mov Disord Clin Pract. 2020;7:502–8. PubMed PMID: 32626794.

Olmos V, Gogia N, Luttik K, Haidery F, Lim J. The extra-cerebellar effects of spinocerebellar ataxia type 1 (SCA1): looking beyond the cerebellum. Cell Mol Life Sci. 2022;79:404. PubMed PMID: 35802260.

Orr HT, Chung MY, Banfi S, Kwiatkowski TJ Jr, Servadio A, Beaudet AL, McCall AE, Duvick LA, Ranum LP, Zoghbi HY. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat Genet. 1993;4:221–6. PubMed PMID: 8358429.

Orr HT, Zoghbi HY. SCA1 molecular genetics: a history of a 13 year collaboration against glutamines. Hum Mol Genet. 2001;10:2307–11. PubMed PMID: 11673415.

Oz G, Hutter D, Tkác I, Clark HB, Gross MD, Jiang H, Eberly LE, Bushara KO, Gomez CM. Neurochemical alterations in spinocerebellar ataxia type 1 and their correlations with clinical status. Mov Disord. 2010;25:1253–61. PubMed PMID: 20310029.

Park J, Al-Ramahi I, Tan Q, Mollema N, Diaz-Garcia JR, Gallego-Flores T, Lu HC, Lagalwar S, Duvick L, Kang H, Lee Y, Jafar-Nejad P, Sayegh LS, Richman R, Liu X, Gao Y, Shaw CA, Arthur JS, Orr HT, Westbrook TF, Botas J, Zoghbi HY. RAS-MAPK-MSK1 pathway modulates ataxin 1 protein levels and toxicity in SCA1. Nature. 2013;498:325–31. PubMed PMID: 23719381.

Park Y, Hong S, Kim SJ, Kang S. Proteasome function is inhibited by polyglutamine-expanded ataxin-1, the SCA1 gene product. Mol Cells. 2005;19:23–30. PubMed PMID: 15750336.

Park YW, Joers JM, Guo B, Hutter D, Bushara K, Adanyeguh IM, Eberly LE, Öz G, Lenglet C. Assessment of cerebral and cerebellar white matter microstructure in spinocerebellar ataxias 1, 2, 3, and 6 using diffusion MRI. Front Neurol. 2020;11:411. PubMed PMID: 32581994.

Pedroso JL, Barsottini OG. Spinal cord atrophy in spinocerebellar ataxia type 1. Arq Neuropsiquiatr. 2013;71:977. PubMed PMID: 24347021.

Pedroso JL, de Souza PV, Pinto WB, Braga-Neto P, Albuquerque MV, Saraiva-Pereira ML, Jardim LB, Barsottini OG. SCA1 patients may present as hereditary spastic paraplegia and must be included in spastic-ataxias group. Parkinsonism Relat Disord. 2015;21:1243–6. PubMed PMID: 26231471.

Platonov FA, Tyryshkin K, Tikhonov DG, Neustroyeva TS, Sivtseva TM, Yakovleva NV, Nikolaev VP, Sidorova OG, Kononova SK, Goldfarb LG, Renwick NM. Genetic fitness and selection intensity in a population affected with high-incidence spinocerebellar ataxia type 1. Neurogenetics. 2016;17:179–85. PubMed PMID: 27106293.

Ragno M, Perretti AC, Castaldo I, Scarcella M, Acciarri S, Manganelli F, Santoro L. Multimodal electrophysiologic follow-up study in 3 mutated but presymptomatic members of a spinocerebellar ataxia type 1 (SCA1) family. Neurol Sci. 2005;26:67–71. PubMed PMID: 15995822.

Ramos A, Raposo M, Milà M, Bettencourt C, Houlden H, Cisneros B, Magaña JJ, Bettencourt BF, Bruges-Armas J, Santos C, Lima M. Verification of inter-laboratorial genotyping consistency in the molecular diagnosis of polyglutamine spinocerebellar ataxias. J Mol Neurosci. 2016;58:83–7. PubMed PMID: 26454745.

Ristori G, Romano S, Visconti A, Cannoni S, Spadaro M, Frontali M, Pontieri FE, Vanacore N, Salvetti M. Riluzole in cerebellar ataxia: a randomized, double-blind, placebo-controlled pilot trial. Neurology. 2010;74:839–45. PubMed PMID: 20211908.

Robitaille Y, Lopes-Cendes I, Becher M, Rouleau G, Clark AW. The neuropathology of CAG repeat diseases: review and update of genetic and molecular features. Brain Pathol. 1997;7:901–26. PubMed PMID: 9217975.

Romano S, Coarelli G, Marcotulli C, Leonardi L, Piccolo F, Spadaro M, Frontali M, Ferraldeschi M, Vulpiani MC, Ponzelli F, Salvetti M, Orzi F, Petrucci A, Vanacore N, Casali C, Ristori G. Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2015;14:985–91. PubMed PMID: 26321318.

Rüb U, Schöls L, Paulson H, Auburger G, Kermer P, Jen JC, Seidel K, Korf HW, Deller T. Clinical features, neurogenetics and neuropathology of the polyglutamine spinocerebellar ataxias type 1, 2, 3, 6 and 7. Prog Neurobiol. 2013;104:38–66. PubMed PMID: 23438480.

Sasaki H, Fukazawa T, Yanagihara T, Hamada T, Shima K, Matsumoto A, Hashimoto K, Ito N, Wakisaka A, Tashiro K. Clinical features and natural history of spinocerebellar ataxia type 1. Acta Neurol Scand. 1996;93:64–71. PubMed PMID: 8825276.

Schmitz-Hübsch T, Coudert M, Bauer P, Giunti P, Globas C, Baliko L, Filla A, Mariotti C, Rakowicz M, Charles P, Ribai P, Szymanski S, Infante J, van de Warrenburg BP, Durr A, Timmann D, Boesch S, Fancellu R, Rola R, Depondt C, Schols L, Zdienicka E, Kang JS, Dohlinger S, Kremer B, Stephenson DA, Melegh B, Pandolfo M, di Donato S, du Montcel ST, Klockgether T. Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms. Neurology. 2008;71:982–9. PubMed PMID: 18685131.

Schmitz-Hübsch T, Fimmers R, Rakowicz M, Rola R, Zdzienicka E, Fancellu R, Mariotti C, Linnemann C, Schöls L, Timmann D, Filla A, Salvatore E, Infante J, Giunti P, Labrum R, Kremer B, van de Warrenburg BPC, Baliko L, Melegh B, Depondt C, Schulz J. Tezenas du Montcel S, Klockgether T. Responsiveness of different rating instruments in spinocerebellar ataxia patients. Neurology. 2010;74:678–84. PubMed PMID: 20177122.

Schöls L, Amoridis G, Büttner T, Przuntek H, Epplen JT, Riess O. Autosomal dominant cerebellar ataxia: phenotypic differences in genetically defined subtypes? Ann Neurol. 1997;42:924–32. PubMed PMID: 9403486.

Schöls L, Linnemann C, Globas C. Electrophysiology in spinocerebellar ataxias: spread of disease and characteristic findings. Cerebellum. 2008;7:198–203. PubMed PMID: 18418678.

Scoles DR, Meera P, Schneider MD, Paul S, Dansithong W, Figueroa KP, Hung G, Rigo F, Bennett CF, Otis TS, Pulst SM. Antisense oligonucleotide therapy for spinocerebellar ataxia type 2. Nature. 2017;544:362–6. PubMed PMID: 28405024.

Serra HG, Byam CE, Lande JD, Tousey SK, Zoghbi HY, Orr HT. Gene profiling links SCA1 pathophysiology to glutamate signaling in Purkinje cells of transgenic mice. Hum Mol Genet. 2004;13:2535–43. PubMed PMID: 15317756.

Servadio A, Koshy B, Armstrong D, Antalffy B, Orr HT, Zoghbi HY. Expression analysis of the ataxin-1 protein in tissues from normal and spinocerebellar ataxia type 1 individuals. Nat Genet. 1995;10:94–8. PubMed PMID: 7647801.

Stephen CD, Schmahmann JD. Eye movement abnormalities are ubiquitous in the spinocerebellar ataxias. Cerebellum. 2019;18:1130–6. PubMed PMID: 31175630.

Stevanin G, Durr A, Brice A. Clinical and molecular advances in autosomal dominant cerebellar ataxias: from genotype to phenotype and physiopathology. Eur J Hum Genet. 2000;8:4–18. PubMed PMID: 10713882.

Tezenas du Montcel S, Durr A, Bauer P, Figueroa KP, Ichikawa Y, Brussino A, Forlani S, Rakowicz M, Schöls L, Mariotti C, van de Warrenburg BP, Orsi L, Giunti P, Filla A, Szymanski S, Klockgether T, Berciano J, Pandolfo M, Boesch S, Melegh B, Timmann D, Mandich P, Camuzat A, Goto J, Ashizawa T, Cazeneuve C, Tsuji S, Pulst SM, Brusco A, Riess O, Brice A, Stevanin G, et al. Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes. Brain. 2014a;137:2444–55. PubMed PMID: 24972706.

Tezenas du Montcel S, Durr A, Rakowicz M, Nanetti L, Charles P, Sulek A, Mariotti C, Rola R, Schols L, Bauer P, Dufaure-Garé I, Jacobi H, Forlani S, Schmitz-Hübsch T, Filla A, Timmann D, van de Warrenburg BP, Marelli C, Kang JS, Giunti P, Cook A, Baliko L, Melegh B, Boesch S, Szymanski S, Berciano J, Infante J, Buerk K, Masciullo M, Di Fabio R, Depondt C, Ratka S, Stevanin G, Klockgether T, Brice A, Golmard JL. Prediction of the age at onset in spinocerebellar ataxia type 1, 2, 3 and 6. J Med Genet. 2014b;51:479–86. PubMed PMID: 24780882.

Vaclavik V, Borruat FX, Ambresin A, Munier FL. Novel maculopathy in patients with spinocerebellar ataxia type 1 autofluorescence findings and functional characteristics. JAMA Ophthalmol. 2013;131:536–8. PubMed PMID: 23579607.

van de Warrenburg BP, Notermans NC, Schelhaas HJ, van Alfen N, Sinke RJ, Knoers NV, Zwarts MJ, Kremer BP. Peripheral nerve involvement in spinocerebellar ataxias. Arch Neurol. 2004;61:257–61. PubMed PMID: 14967775.

Venkatraman A, Hu YS, Didonna A, Cvetanovic M, Krbanjevic A, Bilesimo P, Opal P. The histone deacetylase HDAC3 is essential for Purkinje cell function, potentially complicating the use of HDAC inhibitors in SCA1. Hum Mol Genet. 2014;23:3733–45. PubMed PMID: 24594842.

Whaley NR, Fujioka S, Wszolek ZK. Autosomal dominant cerebellar ataxia type I: a review of the phenotypic and genotypic characteristics. Orphanet J Rare Dis. 2011;6:33. PubMed PMID: 21619691.

Yamada M, Sato T, Tsuji S, Takahashi H. CAG repeat disorder models and human neuropathology: similarities and differences. Acta Neuropathol. 2008;115:71–86. PubMed PMID: 17786457.

Yang CY, Lai RY, Amokrane N, Lin CY, Figueroa KP, Pulst SM, Perlman S, Wilmot G, Gomez CM, Schmahmann JD, Paulson H, Shakkottai VG, Rosenthal LS, Ying SH, Zesiewicz T, Bushara K, Geschwind M, Xia G, Subramony SH, Ashizawa T, Troche MS, Kuo SH. Dysphagia in spinocerebellar ataxias type 1, 2, 3 and 6. J Neurol Sci. 2020;415:116878. PubMed PMID: 32454319.

Zoghbi HY, Pollack MS, Lyons LA, Ferrell RE, Daiger SP, Beaudet AL. Spinocerebellar ataxia: variable age of onset and linkage to human leukocyte antigen in a large kindred. Ann Neurol. 1988;23:580–4. PubMed PMID: 3165612.

License