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NLM Citation: Cleary JD, Subramony SH, Ranum LPW. Spinocerebellar Ataxia Type 8. 2001 Nov 27 [Updated 2021 Apr 22]. 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 8

Synonym: SCA8

John Douglas Cleary, PhD,[1] SH Subramony, MD,[2] and Laura PW Ranum, PhD[3]

Created: November 27, 2001; Updated: April 22, 2021.

Summary

Clinical characteristics

SCA8 is a slowly progressive ataxia with onset typically in the third to fifth decade but with a range from before age one year to after age 60 years. Common initial manifestations are scanning dysarthria with a characteristic drawn-out slowness of speech and gait instability. Over the disease course other findings can include eye movement abnormalities (nystagmus, abnormal pursuit and abnormal saccades, and, rarely, ophthalmoplegia); upper motor neuron involvement; extrapyramidal signs; brain stem signs (dysphagia and poor cough reflex); sensory neuropathy; and cognitive impairment (e.g., executive dysfunction, psychomotor slowing and other features of cerebellar cognitive-affective disorder in some). Life span is typically not shortened.

Diagnosis/testing

The diagnosis of SCA8 is established in a proband with suggestive findings and a heterozygous abnormal $(CTG{\cdot}CAG)_n$ repeat expansion in the two overlapping genes *ATXN8OS/ATXN8* identified by molecular genetic testing.

Management

Treatment of manifestations: Canes and walkers to help prevent falls; modification of the home (e.g., grab bars, raised toilet seats, ramps for motorized chairs) as needed; speech therapy and communication devices for those with dysarthria; weighted eating utensils and dressing hooks to maintain some independence; feeding evaluations to reduce risk of aspiration from dysphagia; physical activity to maintain muscular and cardiopulmonary conditioning.

Surveillance: Routine follow up by the multidisciplinary care team including neurology to assess disease progression; physiatry and occupational and physical therapy to assess mobility and self-help skills; speech and

Author Affiliations: 1 Center for NeuroGenetics Department of Molecular Genetics & Microbiology College of Medicine University of Florida Gainesville, Florida; Email: john.cleary@ufl.edu. 2 Department of Neurology University of Florida Gainesville, Florida; Email: s.subramony@neurology.ufl.edu. 3 Center for NeuroGenetics Department of Molecular Genetics & Microbiology Department of Neurology Genetics Institute College of Medicine University of Florida Gainesville, Florida; Email: ranum@ufl.edu.

language specialists to assess need for alternative communication method or speech therapy; feeding team to assess nutrition, aspiration risk, and feeding methods; and mental health professionals.

Agents/circumstances to avoid: Alcohol can exacerbate incoordination.

Genetic counseling

SCA8 is inherited in an autosomal dominant manner with reduced penetrance. To date, all individuals diagnosed with SCA8 whose parents have been evaluated with molecular genetic testing have one parent with an *ATXN8OS/ATXN8* $(CTG{\cdot}CAG)_n$ repeat expansion. The transmitting parent may or may not have clinical manifestations of SCA8. If a parent of the proband is known to have a $(CTG{\cdot}CAG)_n$ repeat expansion, the risk to each sib of inheriting the repeat expansion is 50%. The $(CTG{\cdot}CAG)_n$ repeat expansion is highly unstable and almost always changes in size on transmission: the repeat expansion is more likely to become larger when maternally transmitted and more likely to contract with paternal transmission. Sibs who inherit a $(CTG{\cdot}CAG)_n$ repeat expansion may or may not develop clinical manifestations of SCA8. Once an SCA8 $(CTG{\cdot}CAG)_n$ repeat expansion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Spinocerebellar ataxia type 8 (SCA8) **should be suspected** in individuals with the following findings.

Clinical findings include slowly progressing cerebellar ataxia with onset typically in the third to fifth decade (age range: <1 to >60 years) AND the following associated clinical features:

- Gait and limb ataxia
- Scanning dysarthria characterized by a drawn-out slowness of speech
- Eye movement abnormalities (e.g., nystagmus, abnormal pursuit and abnormal saccades)
- Often "extracerebellar signs" including:
  - Upper motor neuron findings (e.g., brisk tendon reflexes, spasticity, and Babinski sign)
  - Extrapyramidal signs (e.g., tremor, dystonia and occasionally parkinson-like features)
  - Brain stem signs (e.g., dysphagia and poor cough reflex)
  - Sensory neuropathy (e.g., loss of sensation and loss of tendon reflexes in distal limbs)
  - Cognitive features (e.g., executive dysfunction, psychomotor slowing, and other features of cerebellar cognitive-affective disorder in some)

Family history. SCA8 is an autosomal dominant disorder (i.e., the phenotype can be expressed in heterozygotes); however, because of reduced penetrance, the family history of an affected individual may appear to be consistent with autosomal recessive inheritance (with multiple affected family members in a single generation) or an affected individual may represent a simplex case (i.e., the only affected family member).

The absence of an autosomal dominant family history of disease should not be used to rule out a diagnosis of SCA8.

Note: Affected individuals homozygous for repeat expansions have also been reported in the literature, suggesting that two expansion alleles may further increase risk.

Establishing the Diagnosis

The diagnosis of SCA8 **is established** in a proband with suggestive findings and a heterozygous abnormal $(CTG{\cdot}CAG)_n$ repeat expansion in the two overlapping genes *ATXN8OS/ATXN8* identified by molecular genetic testing (see Table 1).

Note: Pathogenic $(CTG{\cdot}CAG)_n$ repeat expansions in *ATXN8OS/ATXN8* **cannot be detected by** sequence-based multigene panels, exome sequencing, or genome sequencing.

Repeat Sizes

Note: Although it is the $(CTG{\cdot}CAG)_n$ portion of the repeat tract that expands in affected individuals, the reference ranges are based on the combined total length of the flanking $(CTA{\cdot}TAG)_n$ repeat and the $(CTG{\cdot}CAG)_n$ repeat.

- **Normal.** 15 to 50 $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats
- **Reduced penetrance** occurs for $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats of all sizes [Ranum et al 1999; Authors, unpublished data].
- **Pathogenic (higher penetrance).** 54 to 250 $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats are most often seen in individuals with ataxia; however, repeat sizes ranging from 71 to more than 1300 repeats have been found both in individuals who develop ataxia and in those who do not [Authors, unpublished data].

Molecular Genetic Testing

Molecular genetic testing relies on targeted analysis to characterize the number of *ATXN8OS/ATXN8* $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats (see Table 7).

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 8

Genes [1]	Method [2, 3]	Proportion of Probands with a Pathogenic Variant Detectable by Method
ATXN8OS/ATXN8	Targeted analysis for $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat expansions [4]	~100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Table 7 for specific methods to characterize the number of (CTA·TAG)n(CTG·CAG)n combined repeats in *ATXN8OS/ATXN8*. While the (CTA·TAG)n portion of the repeat can be polymorphic, it is the (CTG·CAG)n portion of the repeat that expands.
3. Note: Sequence-based multigene panels, exome sequencing, and genome sequencing cannot detect pathogenic repeat expansions in these genes.
4. Trinucleotide repeat expansion located within two overlapping genes: an untranslated portion of *ATXN8OS* and a short open reading frame for *ATXN8*.

Clinical Characteristics

Clinical Description

SCA8 is a slowly progressive ataxia with onset typically in adulthood (range: neonatal period to age 73 years) [Day et al 2000, Ikeda et al 2000, Juvonen et al 2000, Silveira et al 2000, Felling & Barron 2005, Maschke et al 2005, Whaley et al 2011]. Disease progression is typically over decades regardless of the age of onset. Common initial manifestations are dysarthria and gait instability; life span is typically not shortened [Day et al 2000, Juvonen et al 2000].

Persons with adult onset typically exhibit cerebellar signs (e.g., nystagmus, abnormal pursuit and saccadic eye movement) and gait and limb ataxia indicated by a broad-based gait and abnormal finger-to-nose, finger-chase,

and heel-to-shin maneuvers. These are often associated with additional neurologic signs [unpublished data and Gupta & Jankovic 2009].

Dysphagia can be a significant complication [Zeman et al 2004, Kim et al 2013].

Table 2. Select Features of Spinocerebellar Ataxia Type 8

Feature	Prevalence of Feature [1]
Gait ataxia	+++
Dysarthria	+++
Limb ataxia	+++
Hyperreflexia	++
Sensory signs	++
Cognitive impairment	++
Extensor plantar response	+
Dysphagia	+

+ ++ = feature present in >80% of individuals; ++ = present in 30%-50% of individuals; + = present in <20% of individuals
1. Baba et al [2005], Factor et al [2005], Felling & Barron [2005], Munhoz et al [2006], Gupta & Jankovic [2009], Ushe & Perlmutter [2012], Kim et al [2013]

Although a number of atypical findings have been reported in individuals with $(CTG{\cdot}CAG)_n$ repeat expansions in *ATXN8OS/ATXN8*, the causative relationship between the $(CTG{\cdot}CAG)_n$ repeat expansion and these other findings remains unknown, given the relatively high frequency of the $(CTG{\cdot}CAG)_n$ repeat expansion in the general population and the reduced penetrance of the disease. These atypical findings can include the following:

- Parkinson-like features [Wu et al 2004, Baba et al 2005, Wu et al 2009, Kim et al 2013]
- Multiple-system atrophy [Factor et al 2005, Munhoz et al 2009, Smetcoren & Weckhuysen 2016]
- Severe childhood onset (<20 years) including neonatal onset with cognitive difficulties associated with ataxia and cerebellar atrophy on brain imaging observed in a proportion of individuals without other identified disorders [Felling & Barron 2005]
- Amyotrophic lateral sclerosis [Baba et al 2005, Kim et al 2013]
- Oromandibular and lingual dystonia (in 1 individual). Persons with oromandibular or lingual dystonia may have increased chewing and swallowing problems.
- Respiratory muscle weakness (uncommon) [Kim et al 2013]
- Seizure-like episodes (highly unusual; reported in 1 individual) [Swaminathan 2019]

Neuroimaging. Brain MRI and CT consistently show cerebellar atrophy, specifically in the cerebellar hemisphere and vermis [Gupta & Jankovic 2009]. Occasionally the imaging studies do not show an abnormality in the presence of clinical ataxia.

In one individual in whom serial MRI scans were performed nine years apart, little progression in the cerebellar atrophy was observed [Day et al 2000].

Mild cerebellar atrophy was observed in an asymptomatic male age 71 years with a $(CTG{\cdot}CAG)_n$ repeat expansion [Ikeda et al 2000].

Genotype-Phenotype Correlations

Expansion repeat size. No correlation between the combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat length and age of onset or disease severity has been observed [Day et al 2000; Gupta & Jankovic 2009; Authors, unpublished data].

Homozygosity for the repeat expansion. Individuals homozygous for the $(CTG{\cdot}CAG)_n$ repeat expansion have been reported more frequently than for other forms of spinocerebellar ataxia caused by nucleotide repeat expansions [Koob et al 1999; Day et al 2000; Stevanin et al 2000; Tazón et al 2002; Izumi et al 2003; Schöls et al 2003; Brusco et al 2004; Corral et al 2005; Juvonen et al 2005; Authors, unpublished data].

Compared to the ages of onset of individuals heterozygous for a $(CTG{\cdot}CAG)_n$ repeat expansion, the ages at onset in most individuals homozygous for $(CTG{\cdot}CAG)_n$ repeat expansions were not obviously accelerated even within a sibship [Day et al 2000].

Penetrance

The true penetrance of the combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat lengths is not understood, as interfamilial differences in penetrance for the same size repeat expansion can be seen. Nevertheless, the following have been observed:

- A number of independent studies have shown that greater than 90 combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats are more often found in individuals with ataxia than in unaffected controls [Izumi et al 2003, Ikeda et al 2004, Zeman et al 2004].
- In a large family (MN-A [Day et al 2000]) with SCA8, individuals with ataxia had longer combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat lengths (mean size: 117) compared to 21 asymptomatic relatives with shorter combined repeat lengths (mean size: 92), demonstrating that repeat length plays a role in disease penetrance [Koob et al 1999, Day et al 2000].

Analysis of additional families showed that the pathogenic repeat expansion range varied substantially among families, and that repeat length could not be used to predict whether an asymptomatic individual would subsequently develop disease manifestations [Ikeda et al 2004; Ikeda et al 2008; Authors, unpublished data].

Anticipation

Maternal transmission. The $(CTG{\cdot}CAG)_n$ portion of the repeat tract is more likely to become larger with maternal transmission [Moseley et al 2000].

Paternal transmission. The $(CTG{\cdot}CAG)_n$ portion of the repeat tract is more likely to contract with paternal transmission, usually resulting in smaller repeats that may fall into the reduced penetrance range [Moseley et al 2000].

Prevalence

There are no epidemiologic studies of the frequency of $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat expansions; however, estimates suggest that the prevalence of expansions greater than 50 $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)$ repeats is approximately 1:100 to 1:1200 chromosomes in various populations [Koob et al 1999; Ikeda et al 2000; Juvonen et al 2000; Vincent et al 2000; Ikeda et al 2004; Sułek et al 2004; Zeman et al 2004; Authors, unpublished data] (see Molecular Genetics).

SCA8 is thought to account for 2%-5% of autosomal dominant inherited ataxia. Because of reduced penetrance, the prevalence of SCA8 is far lower than expected based on observed frequency of $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat expansions.

The frequency of expansions greater than ~90 repeats is higher in persons with ataxia than in the general population [Izumi et al 2003, Ikeda et al 2004, Zeman et al 2004].

The prevalence of a $(CTG{\cdot}CAG)_n$ repeat expansion and SCA8 may be especially high in Finland [Juvonen et al 2000, Juvonen et al 2002, Juvonen et al 2005].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* have been shown to be associated with pathogenic variants in *ATXN8OS* or *ATXN8*.

Differential Diagnosis

Individuals with spinocerebellar ataxia type 8 (SCA8) may present with unexplained ataxia that is part of the larger differential diagnosis of hereditary and acquired ataxias (see Hereditary Ataxia Overview).

Ataxia. SCA8 is similar to other SCAs in that it affects coordination, with oculomotor and bulbar involvement and limb and gait ataxia, and it is therefore difficult to distinguish SCA8 from other SCAs based on clinical exam. Although SCA8 is associated with some distinctive features compared to other common SCAs (see following text), molecular genetic testing is highly recommended to make an accurate diagnosis.

- **SCA1.** Disease progression is much slower, with less bulbar involvement than SCA1 [Day et al 2000, Zeman et al 2004, Whaley et al 2011].
- **SCA2.** Saccadic eye movements in SCA8 are not dramatically slowed, in contrast to SCA2 [Whaley et al 2011, Moscovich et al 2015].
- **SCA3.** Unlike SCA3, SCA8 does not typically show marked manifestations suggestive of either lower motor neuron involvement or extrapyramidal involvement.
- **SCA4.** Although sensory nerves are affected, SCA8 does not result in the complete loss of sensory nerve function seen in SCA4 [Hellenbroich et al 2006].
- **SCA5, SCA6.** In contrast to the mainly cerebellar presentations of SCA5 and SCA6, severely affected individuals with SCA8 have spastic dysarthria, tendon reflex hyperactivity, and extensor plantar responses [Ranum et al 1994, Whaley et al 2011].
- **SCA7.** Unlike SCA7, SCA8 does not include retinal degeneration [Whaley et al 2011].
- **SCA10.** Seizures are not common in SCA8, thus, distinguishing it from SCA10.
- **SCA12.** While cognitive decline has been reported in some families with SCA8 [Zeman et al 2004, Baba et al 2005, Lilja et al 2005], it occurs less commonly than in SCA12 [Rasmussen et al 2001]. Although upper limb postural tremor in SCA12 also distinguishes it from SCA8 [Holmes et al 1999], this feature is also present in SCA15 and SCA27.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 8 (SCA8) 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 8

System/Concern	Evaluation	Comment
Neurologic	Neurologist: assess for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit).	Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS). [1]
	UMN dysfunction (spasticity, Babinski signs, hypereflexia)	Clinical neurologic eval
	Refer to neuromuscular clinic (OT/PT / rehab specialist).	To assess gross motor & fine motor skills, ambulation, & need for adaptive devices & PT
Dysarthria	Speech/language eval	
Dysphagia	Swallow eval	Swallow imaging, swallowing rehab
Ocular involvement	Complete eye exam	Assess for nystagmus, saccades & smooth ocular pursuit, gaze limitation
Neuroimaging	Brain MRI or CT	If not performed at initial eval
Cognitive/ Psychiatric	Assess for cognitive dysfunction assoc w/cerebellar cognitive & affective syndrome (executive function, language processing, visuospatial/visuoconstructional skills, emotion regulation).	Consider use of: • CCAS scale [2] to evaluate cognitive & emotional involvement; • Psychiatrist, psychologist, neuropsychologist if needed.
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of SCA8 to facilitate medical & personal decision making
Family support & resources	Assess: • Knowledge & availability of local community support or online resources; • Need for social work involvement for parental support; • Need for home nursing referral.	

BARS = Brief Ataxia Rating Scale; CCAS = cerebellar cognitive affective syndrome; ICARS = International Co-operative Ataxia Rating Scale; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMN = upper motor neuron

1. Bürk & Sival [2018]

2. Hoche et al [2018]

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

Treatment of Manifestations

There is no specific treatment for SCA8. The goals of treatment are to maximize function and reduce complications.

It is recommended that affected individuals be managed by a multidisciplinary team of relevant specialists such as neurologists, occupational therapists, physical therapists, physiatrists, orthopedists, nutritionists, speech and language therapists, and psychologists depending on the clinical manifestations.

Table 4. Treatment of Manifestations in Individuals with Spinocerebellar Ataxia Type 8

Manifestation/ Concern	Treatment	Considerations/Other
Cerebellar ataxia	PT/OT	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs). • Inpatient rehab w/OT/PT may improve ataxia & functional abilities in those w/degenerative ataxias. [2, 3] • Weight control to avoid obesity • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)
	Pharmacologic treatment	Pharmacotherapy for ataxia is generally disappointing & no approved drugs exist. Anecdotal studies report benefit from drugs incl (e.g.) buspirone, riluzole, & 4-aminopyridine.
	Transcranial magnetic stimulation (TMS)	No data for SCA8, but TMS has shown some promise for other ataxias & could be considered.
UMN involvement (spasticity)	Pharmacologic treatment	Drugs incl baclofen & tizanidine may be considered for severe spasticity.
Eyes	• Abnormal eye movements may respond to 4-aminopyridine, baclofen, or memantine. • Prisms may be used to obviate diplopia.	Expert neuro-ophthalmology consult is useful.
Dysarthria	Speech & language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Feeding therapy programs to improve nutrition & dysphagia & ↓ risk of aspiration	• Video esophagram may help define best food consistency. • Sensory stimulation (e.g., putting an item such as a straw in the mouth) may ↓ involuntary movements & improve articulation, chewing &/or swallowing. [4]
Poor weight gain	Nutrition assessment	Consider nutritional & vitamin supplementation to meet dietary needs.
Cognitive/ Psychiatric	Pharmacologic treatment	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, & psychosis)
	Psychotherapy / neuropsychological rehab	Consider cognitive & behavioral therapy, incl Goal Management Training®. [5]
Dystonia	Consider Botox® for focal dystonia.	
Social support	Social work referral	To assist in identifying sources for in-home &/or local community support

ADL = activities of daily living; OT = occupational therapy/therapist; PT = physical therapy/therapist; UMN = upper motor neuron

1. Martineau et al [2014]
2. Zesiewicz et al [2018]
3. van de Warrenburg et al [2014]
4. Ushe & Perlmutter [2012]
5. Ruffieux et al [2017]

Surveillance

Table 5. Recommended Surveillance for Individuals with Spinocerebellar Ataxia Type 8

System/Concern	Evaluation	Frequency
Neurologic	• Neurologic assessment for progression of ataxia, UMN signs • Monitor ataxia progression w/standardized scale (SARA, ICARS, or BARS). [1] • Physiatry, OT/PT assessment of mobility, self-help skills as they relate to ataxia & spasticity	Annually; more often for an acute exacerbation
Dysarthria	Need for alternative communication method or speech therapy	Per symptom progression
Dysphagia	Assess nutrition, aspiration risk & feeding methods.	
Cognitive/ Psychiatric	Evaluate mood, signs of psychosis, cognitive complaints to identify need for pharmacologic & psychotherapeutic interventions.	Per symptom progression & development of psychiatric symptoms
Social support	Assess needs of affected person, family, & care providers.	Annually

BARS = Brief Ataxia Rating Scale; ICARS = International Co-operative Ataxia Rating Scale; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMN = upper motor neuron

1. Bürk & Sival [2018]

Agents/Circumstances to Avoid

Alcohol should be avoided because it can exacerbate problems with incoordination.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Troriluzole is in a Phase III clinical trial (NCT03701399) for a number of SCAs including SCA8.

Ongoing preclinical studies are being performed in SCA8 animal models to assess possible benefits of therapies that target the pathogenic $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat expansions or the RNA or proteins produced from the pathogenic repeat expansion.

Because it is possible that therapeutic strategies successful for one spinocerebellar ataxia caused by an abnormal nucleotide repeat expansion could apply to other SCAs, it is important to prepare for eventual clinical trial studies by establishing key outcome measures for affected individuals.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

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 8 (SCA8) is inherited in an autosomal dominant manner.

Note: Because the penetrance of SCA8 is reduced, it is common for a proband to represent a simplex case (i.e., the only affected family member) or, alternatively, the family history of a proband may appear to be consistent with autosomal recessive inheritance because of multiple affected sibs in a single generation.

Risk to Family Members

Parents of a proband

- To date, all individuals diagnosed with SCA8 whose parents have been evaluated with molecular genetic testing have one parent with an *ATXN8OS/ATXN8* $(CTG{\cdot}CAG)_n$ repeat expansion.
- The transmitting parent may or may not have clinical manifestations of SCA8 depending on the size of the combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat tract and other factors that affect the penetrance of the expanded repeat [Day et al 2000, Juvonen et al 2002, Ikeda et al 2004].
- If neither of the parents of the proband is known to have SCA8, recommendations for the evaluation of parents include targeted analysis for the SCA8 $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat.
- The family history of some individuals diagnosed with SCA8 may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of manifestations, 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 is heterozygous for the $(CTG{\cdot}CAG)_n$ repeat expansion.

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

- If a parent of the proband is known to have a $(CTG{\cdot}CAG)_n$ repeat expansion, the risk to each sib of inheriting the repeat expansion is 50%.
- Sibs who inherit a $(CTG{\cdot}CAG)_n$ repeat expansion may or may not develop clinical manifestations of SCA8. The true penetrance of combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat sizes is not understood, as interfamilial differences in penetrance for the same size repeat expansion can be seen (see Penetrance).
- The $(CTG{\cdot}CAG)_n$ portion of the repeat expansion is highly unstable and almost always changes in size when transmitted from one generation to the next: the repeat expansion is more likely to become larger when maternally transmitted and more likely to contract with paternal transmission (see Anticipation).

Offspring of a proband

- Each child of an individual with a $(CTG{\cdot}CAG)_n$ repeat expansion has a 50% chance of inheriting the repeat expansion. Offspring who inherit a $(CTG{\cdot}CAG)_n$ repeat expansion may or may not develop clinical manifestations of SCA8. The true penetrance of combined $(CTG{\cdot}CAG)_n$ repeat expansion sizes is not understood, as interfamilial differences in penetrance for the same size repeat expansion can be seen (see Penetrance).
- If the proband is female, the $(CTG{\cdot}CAG)_n$ repeat expansion is more likely to become larger when transmitted; if the proband is male, the repeat expansion is more likely to contract when transmitted (see Anticipation).

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or has the $(CTG{\cdot}CAG)_n$ repeat expansion, the parent's family members are at risk.

Related Genetic Counseling Issues

Note: If neither parent of a proband with SCA8 has a $(CTG{\cdot}CAG)_n$ repeat expansion, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- Because of reduced penetrance and disease complexity, the combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat length cannot be used to predict whether or not an individual will develop disease. However, a family history with multiple affected relatives appears to increase the likelihood that an asymptomatic individual with a $(CTG{\cdot}CAG)_n$ repeat expansion will develop ataxia [Author, personal observation].

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

- Predictive testing for at-risk relatives is possible once molecular genetic testing has identified a $(CTG{\cdot}CAG)_n$ repeat expansion in an affected family member:
  - If a $(CTG{\cdot}CAG)_n$ repeat expansion is not detected, the individual is not at risk of developing SCA8.
  - If a $(CTG{\cdot}CAG)_n$ repeat expansion is detected, the individual is at risk for SCA8; however, the test result cannot be used to predict whether an asymptomatic individual will subsequently develop disease manifestations or what the age of onset will be. In addition, the test result cannot be used to predict the severity, features, or rate of progression of SCA8 in individuals who develop disease manifestations.
  - The true penetrance of the combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat length is not understood, as interfamilial differences in penetrance for the same size repeat expansion can be seen (see Penetrance). However, one or more (CCG·CGG) interruptions within the expanded $(CTG{\cdot}CAG)_n$ portion of the repeat have been found more frequently in probands with multiple affected family members compared to probands who represent simplex cases (i.e., a single affected family member). These data suggest that asymptomatic individuals with CCG·CGG interruptions within the $(CTG{\cdot}CAG)_n$ repeat expansion may be at higher risk of developing ataxia [Authors, unpublished data].
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of SCA8, it is appropriate to consider testing of symptomatic individuals regardless of age.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ATXN8OS*/*ATXN8* $(CTG·CAG)_n$ repeat expansion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. (Note: The prenatal finding of a $(CTG·CAG)_n$ repeat expansion cannot be used to accurately predict if a heterozygous family member will develop manifestations of SCA8.)

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider 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 for 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.

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

Molecular Genetics

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

Table A. Spinocerebellar Ataxia Type 8: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ATXN8	13q21	Ataxin-8	ATXN8	ATXN8
ATXN8OS	13q21.33	Unknown	ATXN8OS	ATXN8OS

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 8 (View All in OMIM)

603680	ATAXIN 8 OPPOSITE STRAND; ATXN8OS
608768	SPINOCEREBELLAR ATAXIA 8; SCA8
613289	ATAXIN 8; ATXN8

Molecular Pathogenesis

The role of $(CTG{\cdot}CAG)_n$ repeat expansions in *ATXN8OS*/*ATXN8* in disease pathogenesis is supported by findings in families of various backgrounds with ataxia and in mouse models [Ikeda et al 2004; Moseley et al 2006; Daughters et al 2009; Zu et al 2011; Authors, unpublished data].

This repeat sequence is located in both the 3' untranslated region of *ATXN8OS* (CTG orientation) and as part of a short polyglutamine open reading frame in the overlapping gene *ATXN8* (CAG orientation) [Moseley et al 2006]. CTG·CAG and CTA·TAG refer to the forward and reverse sequences, respectively, of two adjacent repeat tracts containing three base pairs of repeat sequences. The CTA·TAG repeat varies modestly in length between families but it is the CTG·CAG portion of the repeat that expands in SCA8.

The CTG·CAG repeat is unstable when transmitted from one generation to the next (see Anticipation). In contrast, the highly polymorphic CTA·TAG repeat adjacent to the CTG·CAG repeat is stable when transmitted from generation to generation [Koob et al 1999, Moseley et al 2000, Ikeda et al 2004, Moseley et al 2006].

Mechanism of disease causation. SCA8 occurs through both toxic RNA and toxic protein gain-of-function mechanisms:

- CUG expansion transcripts (*ATXN8OS)* cause RNA gain-of-function effects [Daughters et al 2009] similar to those found in myotonic dystrophy type 1 and myotonic dystrophy type 2 [Ranum & Cooper 2006]. CUG RNA foci were detected in Purkinje cells, molecular layer interneurons, and Bergmann glia [Daughters et al 2009].
- CAG expansion transcripts (*ATXN8*) express ATG-initiated polyGln protein that accumulates in nuclear aggregates in Purkinje cells [Moseley et al 2006] as well as frontal cortex, pons, and hippocampus [Ayhan et al 2018].
- CAG expansion transcripts (*ATXN8*) have also been shown to express polyalanine [Zu et al 2011] and polyserine [Ayhan et al 2018] expansion proteins, by repeat-associated non-AUG translation. These proteins accumulate in SCA8-affected human and mouse brains [Zu et al 2011, Ayhan et al 2018], with polyserine accumulating in white matter regions that show demyelination and axonal degeneration [Ayhan et al 2018].

Table 6. *ATXN8OS/ATXN8* Technical Considerations

Technical Issue	Comment [Reference]
Sequence of repeat	(CTA·TAG)n(CTG·CAG)n: • CTG·CAG portion of repeat is expanded in disease. • Adjacent CTA·TAG portion of repeat ranges in size from 1 to 21 repeats [Koob et al 1999, Moseley et al 2000]. Sequence variation w/in (CTA·TAG)n(CTG·CAG)n: • Interruptions w/in CTG·CAG expansion by 1 or more CCG·CGG, CTA·TAG, CTC·GAG, CCA·TGG, or CTT·AAG trinucleotides have been observed in full-penetrance repeats [Moseley et al 2006; Authors, unpublished data]. • Persons w/SCA8 have been shown to have both pure CTG·CAG repeats & repeats w/interruptions. Most normal-length repeats do not have interruptions w/in the CTG·CAG expansion [Moseley et al 2006].
Methods to detect expanded allele	Methods to detect (CTA·TAG)n(CTG·CAG)n repeat expansion by RP-PCR & Southern blotting have been described [Koob et al 1999, Tanaka et al 2011].
Somatic instability	The expanded repeat has shown limited somatic mosaicism across tissues from persons w/SCA8 [Martins et al 2005, Moseley et al 2006].
Germline instability	• The (CTG·CAG)n expansion is more likely to become larger when maternally transmitted [Koob et al 1999, Ranum et al 1999, Day et al 2000, Corral et al 2005]. • The (CTG·CAG)n expansion is more likely to contract w/paternal transmission, usually resulting in smaller repeats that may fall into the decreased penetrance size range [Koob et al 1999, Ranum et al 1999, Moseley et al 2000].

Methods to characterize *ATXN8OS/ATXN8* $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats. Because of the technical challenges of detecting and sizing $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats within *ATXN8OS/ATXN8*, multiple methods may be needed to rule out or detect an expanded repeat (see Table 7). Repeats in the normal range (15-50 combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeats) may be detected by traditional PCR; however, because detection of an apparent homozygous normal $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat length does not rule out the presence of an expanded $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ allele, testing by RP-PCR or Southern blotting is required.

Table 7. Methods to Characterize *ATXN8OS/ATXN8* $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ Repeats

Interpretation of $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ [1] Repeat Number	Expected Results by Method		
	Conventional PCR	Repeat-primed PCR [2]	Expanded repeat analysis [3, 4]
Normal: 15-50	Detected [5]	See footnote 2.	Expansions can be detected & repeat size can be approximated. [6, 7]
Intermediate [8]	Expansion may be detected depending on allele size. [4, 5]	Expansions may be detected but repeat size cannot be determined. [9, 10]	
Pathogenic: 71-~1300	Not detected	Expansions detected, but repeat size cannot be determined. [9]	

1. CTG·CAG and CTA·TAG refer to the forward and reverse sequences of two adjacent three base-pair repeat sequences.
2. The design of an RP-PCR assay may include conventional PCR primers to size normal repeats and detect expanded repeats in a single assay. The RP-PCR assay itself does not determine repeat size, even alleles in the normal range.
3. Methods of expanded repeat analysis to detect and approximate the size of expanded repeats include long-range PCR sized by gel electrophoresis and Southern blotting.
4. The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/or patient as a result of competition by the normal allele during amplification.
5. Detection of an apparently homozygous normal allele does not rule out the presence of an expanded $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$ repeat; thus, testing by RP-PCR or expanded repeat analysis is required to detect a repeat expansion.
6. Southern blotting for the CAG repeat expansion has been described [Koob et al 1999].
7. Precise sizing of repeats is not necessary as clinical utility for determining the exact repeat number has not been demonstrated.
8. The clinical significance of SCA8 alleles in the 51-70 repeat range is currently unclear but repeats in this range appear to be less likely to result in disease.
9. RP-PCR (referred to as triplet-primed PCR; TP-PCR) for the CAG repeat expansion has been described [Tanaka et al 2011].
10. Repeats at the lower end of this range may not show the characteristic stutter pattern that indicates an expanded repeat.

Chapter Notes

Author Notes

University of Florida Center for NeuroGenetics: neurogenetics.med.ufl.edu

SH Subramony's web page: neurology.ufl.edu/profile/subramony-sub

Laura PW Ranum's web page: neurogenetics.med.ufl.edu/profile/ranum-laura

John Douglas Cleary's web page: neurogenetics.med.ufl.edu/profile/cleary-john

Acknowledgments

We would like to acknowledge all the SCA8 families who have donated time, materials, or knowledge to our work over the years. We would also like to acknowledge previous authors, trainees, and colleagues who have contributed to the understanding of this disorder. Our work has been funded and/or supported by the National Ataxia Foundation, National Institutes of Health, the University of Florida Foundation, and many private donors.

Author History

Fatma Ayhan, BS; University of Florida (2014-2021)
John Douglas Cleary, PhD (2021-present)
Joline C Dalton, MS; University of Minnesota (2001-2021)
John W Day, MD, PhD; Stanford University (2001-2021)

Yoshio Ikeda, MD, PhD; Gunma University Graduate School of Medicine (2001-2021)
Laura PW Ranum, PhD (2001-present)
SH Subramony, MD, PhD (2021-present)

Revision History

- 22 April 2021 (bp) Comprehensive update posted live
- 3 April 2014 (me) Comprehensive update posted live
- 7 February 2007 (me) Comprehensive update posted live
- 15 March 2004 (me) Comprehensive update posted live
- 27 November 2001 (me) Review posted live
- 15 February 2001 (jd) Original submission

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