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Spinocerebellar Ataxia Type 3

Synonyms: Machado-Joseph Disease, SCA3

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Summary

Clinical characteristics

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is characterized by progressive cerebellar ataxia and variable findings including pyramidal signs, a dystonic-rigid extrapyramidal syndrome, significant peripheral amyotrophy and generalized areflexia, progressive external ophthalmoplegia, action-induced facial and lingual fasciculations, and bulging eyes. Neurologic findings tend to evolve as the disorder progresses.

Diagnosis/testing

The diagnosis of SCA3 is established in a proband with suggestive findings and a heterozygous abnormal CAG trinucleotide repeat expansion in *ATXN3* identified by molecular genetic testing.

Management

Treatment of manifestations: Management is supportive as no medication slows the course of disease. The goals of treatment are to maximize function and reduce complications. It is recommended that each individual be managed by a multidisciplinary team of relevant specialists such as neurologists, occupational therapists, physical therapists, physiatrists, orthopedists, nutritionists, speech therapists, social workers, and psychologists. Various manifestations may respond to pharmacologic agents. Regular physical activity is recommended, including combined physical and occupational therapy focused on gait and coordination. Canes and walkers help prevent falling; motorized scooters, weighted eating utensils, and dressing hooks help to maintain independence. Speech therapy and communication devices may benefit those with dysarthria, and dietary modification those with dysphagia. Other recommendations include home adaptations to prevent falls and improve mobility, dietary supplements if caloric intake is reduced, weight control to facilitate ambulation and mobility, and caution with general anesthesia.

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Surveillance: Annual assessments (or more frequently as needed) of neurologic findings (e.g., dysarthria, dysphagia, bladder dysfunction, neuropathic pain, cognitive and psychiatric manifestations), weight and nutritional status, and social support.

Genetic counseling

SCA3 is inherited in an autosomal dominant manner. Each child of an affected individual has a 50% chance of inheriting the *ATXN3* CAG repeat expansion.

Once the CAG 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 an *ATXN3* CAG repeat expansion cannot be used to accurately predict onset, severity, type of symptoms, or rate of progression of SCA3.

Diagnosis

Suggestive Findings

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), **should be suspected** in individuals with the following clinical findings and family history [Lima & Coutinho 1980, D'Abreu et al 2010].

Clinical findings. Progressive cerebellar ataxia often and variably associated with:

- Pyramidal signs
- A dystonic-rigid extrapyramidal syndrome
- Significant peripheral amyotrophy and generalized areflexia
- Progressive external ophthalmoplegia
- Action-induced facial and lingual fasciculations; bulging eyes

Family history. Consistent with autosomal dominant inheritance (i.e., multiple affected family members in successive generations or a single occurrence in a family). Absence of a family history of SCA3 does not preclude this diagnosis.

Establishing the Diagnosis

The diagnosis of SCA3 **is established** in a proband with suggestive findings and a heterozygous abnormal CAG trinucleotide repeat expansion in *ATXN3* identified by molecular genetic testing (see Table 1).

Note: Pathogenic $(CAG)_n$ repeat expansions in *ATXN3* **cannot be detected by** sequence-based multigene panels, exome sequencing, or genome sequencing.

Repeat sizes [Costa Mdo & Paulson 2012 and references therein]:

- **Normal.** 12 to 44 CAG repeats. Overall, 93.5% of normal alleles have fewer than 31 CAG repeats.
- **Intermediate.** CAG repeat size ranges between clearly normal and full penetrance. The smallest unstable repeat size is 45 CAG repeats [Padiath et al 2005]. Some intermediate alleles are not associated with classic clinical features of SCA3 [Costa Mdo & Paulson 2012 and references therein].
- **Pathogenic (full penetrance).** ~60 to 87 [Kawaguchi et al 1994, Costa Mdo & Paulson 2012 and references therein]. The smallest full-penetrance allele is not well defined.

Molecular genetic testing relies on targeted analysis to characterize the number of *ATXN3* CAG repeats (see Table 7).

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 3

Gene [1]	Method [2, 3]	Proportion of Probands with a Pathogenic Variant Detectable by Method
ATXN3	Targeted analysis for CAG trinucleotide expansions	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 CAG repeats in *ATXN3*.
3. Note: Sequence-based multigene panels, exome sequencing, and genome sequencing cannot detect pathogenic repeat expansions in this gene.

Clinical Characteristics

Clinical Description

Spinocerebellar ataxia type 3 (SCA3) is characterized by progressive cerebellar ataxia and variable findings including pyramidal signs, a dystonic-rigid extrapyramidal syndrome, significant peripheral amyotrophy and generalized areflexia, progressive external ophthalmoplegia, action-induced facial and lingual fasciculations, and bulging eyes. Neurologic findings tend to evolve as the disorder progresses.

Table 2. Select Features of Spinocerebellar Ataxia Type 3

Feature	Frequency			Comment
	Nearly all	Common	Infrequent	
Cerebellar ataxia	●			Limb & gait ataxia
Dysarthria	●			Cerebellar & hypokinetic dysarthria
Ophthalmologic involvement	●			Nystagmus; slow saccadic eye movements; ophthalmoparesis, dysconjugate eye movements, & diplopia
Vestibular dysfunction	●			Early sign of disease, noted on head turning
Motor neuron degeneration		●		• Upper motor neuron involvement (hyperreflexia, spasticity) may resemble HSP. • Lower motor neuron involvement (fasciculations, weakness w/muscle wasting, areflexia, distal sensory loss)
Cognitive difficulties			● See footnote 1.	Cerebellar cognitive affective syndrome may incl impairments in executive functioning, visual processing, & some forms of memory.
Mood changes		●		Impaired emotional functioning; depression
Dystonia		●		Dystonia more common in early-onset disease
Parkinsonism		●		• Rigidity is a more reliable indicator than tremor or bradykinesia. • Parkinsonism is often DOPA responsive.
Autonomic dysfunction		●		Bladder disturbances, difficulty w/thermoregulation, & cardiovascular dysautonomia
Sleep disorder		●		Rapid eye movement behavior disorder; periodic limb movements
Restless legs syndrome		●		
Fatigue		●		Assoc w/depression & daytime somnolence
Behavior disorder			●	
Chronic pain		●		Most often lumbosacral

Table 2. continued from previous page.

Feature	Frequency			Comment
	Nearly all	Common	Infrequent	
Respiratory involvement			●	Terminal disease

HSP = hereditary spastic paraplegia
1. Major cognitive decline is infrequent.

Age of onset of SCA3 is highly variable but most commonly in the second to fifth decade. In a large cohort of affected individuals from the Azores, the mean onset was age 37 years. The range of age of onset largely reflects differences in CAG repeat size (see Genotype-Phenotype Correlations) and the specific clinical features can vary greatly, depending largely on CAG repeat length and age of onset [Cancel et al 1995, Maciel et al 1995, Matilla et al 1995, Dürr et al 1996, Matsumura et al 1996, Schöls et al 1996, Vale et al 2010].

Presenting features include gait problems, speech difficulties, clumsiness, and vestibular and oculomotor findings (for review see Mendonça et al [2018], Klockgether et al [2019], and references therein; see also Yoshizawa et al [2004], Rana et al [2016], Wolf et al [2017], and Wu et al [2017]).

Progressive ataxia, nystagmus, diplopia, dysarthria, and hyperreflexia may occur early in the disease. An early sign can be a feeling of unsteadiness on head turning, indicating vestibular dysfunction. Subtle balance issues usually predate hand incoordination.

Upper motor neuron signs often become prominent, and in some families may resemble hereditary spastic paraplegia [Gan et al 2009, Wang et al 2009, Lin et al 2018].

Earlier-onset disease (before age ~25 years) often manifests dystonia [Nunes et al 2015], whereas later-onset disease (after age ~50 years) often manifests peripheral neuropathy and amyotrophy.

SCA3 should also be considered in cases of familial Parkinsonism, especially in individuals with African ancestry [Subramony et al 2002, Lu et al 2004].

Other findings may include the following:

- Autonomic problems, including bladder and thermoregulation disturbances; both cardiovascular and sudomotor dysfunction may be present [Yeh et al 2005, França et al 2010, Takazaki et al 2013].
- Disabling sleep disturbances [Pedroso et al 2016], including rapid eye movement sleep behavior disorder [Friedman 2002, Friedman et al 2003] and restless legs syndrome [Schöls et al 1998, van Alfen et al 2001, D'Abreu et al 2009, Pedroso et al 2011].
- Fatigue that is often associated with depression and daytime somnolence [Martinez et al 2017]. Given the frequency of sleep disturbance in SCA3, evaluation for disruptive sleep disturbance such as obstructive sleep apnea as the cause of fatigue is recommended.
- Impaired executive and emotional functioning, referred to as cerebellar cognitive affective syndrome [Braga-Neto et al 2012, Roeske et al 2013, Tamura et al 2018], as well as depression [Lo et al 2016], that are unrelated to ataxia severity. However, such individuals do not develop dementia [Zawacki et al 2002]. Verbal fluency and visual memory deficits have also been noted [Kawai et al 2004].
- Chronic pain, often in the lumbosacral region [França et al 2007]. The basis for pain can range from dystonia to peripheral neuropathy. Cramps associated with neuropathy can be bothersome.
- Vocal cord paralysis, though uncommon, has been described [Isozaki et al 2002] but is not viewed as a distinctive disease feature.

Disease progression

- Ambulation becomes increasingly difficult, leading to the need for assistive devices (including wheelchair) ten to 15 years following onset.
- Profound ataxia of limbs and gait becomes prominent. Individuals with later adult onset and shorter CAG repeats can manifest a disorder that combines ataxia, generalized areflexia, peripheral neuropathy, and muscle wasting.
- Saccadic eye movements become slow and ophthalmoparesis develops, resulting initially in upgaze restriction. Dysconjugate eye movements result in diplopia.
- At the same time, a number of other "brain stem" signs develop, including temporal and facial atrophy, characteristic action-induced perioral twitches, vestibular symptoms, tongue atrophy and fasciculations, dysphagia, and poor ability to cough and clear secretions.
- Often a staring appearance to the eyes is observed, but neither this nor the perioral fasciculations are specific for SCA3.
- Evidence of a peripheral polyneuropathy [França et al 2009] may appear later, with loss of distal sensation, ankle reflexes, and sometimes other reflexes as well, and with some degree of muscle wasting.
- Parkinsonism that can respond to dopaminergic agents (e.g., levodopa) occurs in a subset of individuals.
- Sitting posture is compromised later in disease, with affected individuals assuming various tilted positions.
- Autonomic dysfunction can sometimes be disabling, but is not always related to severity of motor dysfunction or disease duration.

Late in the disease course, individuals are usually wheelchair bound and have severe dysarthria, dysphagia, facial and temporal atrophy, poor cough, often dystonic posturing and ophthalmoparesis, and occasionally blepharospasm.

Life span. The disease progresses relentlessly; death from pulmonary complications and cachexia occurs from six to 29 years after onset [Sudarsky et al 1992, Sequeiros & Coutinho 1993]. In a study from Brazil, the mean age of onset was 36 years with a 21-year mean survival after onset [Kieling et al 2007].

Subtypes of SCA3. Clinical features can vary greatly, due largely to varying CAG repeat size. Based on this phenotypic variability, Portuguese researchers classified SCA3 into several subtypes in addition to ataxia, including a dystonic-rigid syndrome, a parkinsonian syndrome, and a neuronal amyotrophy syndrome with muscle wasting and peripheral neuropathy [Riess et al 2008]. However, striving to place affected individuals into a specific SCA3 subtype has little clinical value because of the considerable overlap across subtypes, and because one type can evolve into another during the course of disease [Fowler 1984].

Brain MRI most often reveals pontocerebellar atrophy [Bürk et al 1996]. The most commonly observed abnormality is enlargement of the fourth ventricle [Onodera et al 1998], which reflects atrophy of the cerebellum and brain stem. The degree of brain atrophy detectable by MRI varies greatly, consistent with the wide clinical variability observed. In a large European natural history study, clinical dysfunction in SCA3 correlated with the degree of total brain stem atrophy [Schulz et al 2010].

Brain magnetic resonance spectroscopy (MRS) can detect early neurochemical abnormalities in brain regions of SCA3 and similar SCAs [Joers et al 2018]. Efforts are under way to determine whether MRS in select brain regions can be used in clinical trials as an early biomarker of disease state or progression [Ashizawa et al 2018].

Nerve conduction velocity studies often reveal involvement of sensory nerves as well as motor neurons [Lin & Soong 2002, França et al 2009].

Neuropathologic studies have established that degeneration is widespread and not confined to the cerebellum, brain stem, and basal ganglia [Rüb et al 2008]. In general, however, the cerebral cortex is largely spared despite evidence of cognitive dysfunction. While the cerebellum typically shows atrophy (particularly of the deep cerebellar nuclei) in some individuals, Purkinje cells and inferior olivary neurons are relatively spared [Sequeiros & Coutinho 1993].

Genotype-Phenotype Correlations

Age of onset inversely correlates with the size of the CAG repeat expansion. Some individuals with the largest reported expansions (86 and 83 repeats) had disease onset at age five years and 11 years, respectively [Zhou et al 1997]. Despite such observations, there is evidence that other nonspecified genetic or non-genetic factors also contribute [van de Warrenburg et al 2005, Globas et al 2008].

Phenotype. A loose correlation exists between the size of the CAG repeat expansion and the clinical phenotype [Cancel et al 1995, Maciel et al 1995, Matilla et al 1995, Sasaki et al 1995, Dürr et al 1996, Lerer et al 1996, Matsumura et al 1996, Schöls et al 1996, Vale et al 2010].

In general, the longest disease-causing CAG repeats cause earlier-onset disease that is more likely to have dystonia as part of the presentation.

In contrast, the shortest disease-causing CAG repeats cause later-onset disease that is more likely to have peripheral manifestations such as neuropathy and weakness. Parkinsonism, which occurs in a subset of affected persons, is not associated with any particular CAG repeat size. Rare intermediate alleles of 45 to about 60 CAG repeats may show variable expressivity; in particular, these rare intermediate alleles can manifest with isolated restless legs syndrome with no other features of disease.

Intrafamilial variation in severity has been reported [Lerer et al 1996, Carvalho et al 2008]. Variation in severity is largely attributed to differences in CAG repeat size.

Homozygosity for the CAG repeat has been associated with more severe disease in a few families [Lerer et al 1996, Carvalho et al 2008]. However, many homozygotes in a Yemeni family were no more severely affected than heterozygotes in other families.

Penetrance

In SCA3, penetrance approaches 100% and is age related.

CAG repeat sizes associated with reduced penetrance of SCA3 are not firmly defined. Of note, an asymptomatic individual age 66 years with 68 CAGs has been reported [van Alfen et al 2001].

Anticipation

Instability of the CAG repeat expansion has been documented in transmission of the repeat from parent to child. Overall, expansion of the repeat is more common than contraction; thus, anticipation (earlier age of onset and more severe disease manifestations in offspring) occurs in SCA3.

Although the probability of CAG repeat expansion may be greater with paternal than with maternal transmission, the paternal bias is not pronounced (as, for example, in Huntington disease) [Souza et al 2016].

Nomenclature

SCA3 is also known as Machado-Joseph disease (MJD) and Azorean ataxia. In fact, this autosomal dominant form of ataxia, which was first described among immigrants from the Portuguese Azorean islands, was initially known as MJD. In the early 1990s the locus for MJD was identified on chromosome 14 and revealed to be a CAG repeat expansion in *MJD1* (now renamed *ATXN3*). During this same time, scientists mapped what was initially thought to be an unrelated ataxia, SCA3, to the same chromosomal region. Once the *ATXN3* CAG repeat expansion underlying MJD was discovered, it soon became clear that SCA3 and MJD were caused by CAG repeat expansions in the same gene.

Prevalence

No accurate data are available regarding the prevalence of SCA3 in the general population, though in many populations SCA3 is the most common of the autosomal dominant ataxias, which overall are rare.

Worldwide, SCA3 is thought to be the most common spinocerebellar ataxia (SCA), comprising 20%-50% of families (reviewed in Klockgether et al [2019]).

Countries in which SCA3 is the most common SCA include Portugal (58%-74%), Brazil (69%-92%), China (48%-49%), the Netherlands (44%), Germany (42%), and Japan (28%-63%).

In contrast, countries in which SCA3 is quite rare include Italy (1%) and South Africa (4%) [Klockgether et al 2019 and references therein].

In the US and Canada, SCA3 is one of several SCAs comprising the most common autosomal dominant ataxias, with SCA3 accounting for 21%-25% of families [Klockgether et al 2019 and references therein].

Origin of the CAG repeat expansion. Haplotype analyses suggest that the CAG repeat expansion arose independently from at least two distinct events, the first occurring in Asia and the second in the Portuguese population [Gaspar et al 1996, Martins et al 2007, Klockgether et al 2019 and references therein]. Most disease worldwide likely resulted from Portuguese emigration.

A large international genetic study showed that a single intragenic haplotype is shared by a majority of the families studied (including those from the Azorean island of Flores), suggesting a single founder variant. However, at least two other haplotypes have been identified in the Portuguese population [Gaspar et al 2001, Verbeek et al 2004].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ATXN3*.

Differential Diagnosis

Individuals with spinocerebellar ataxia type 3 (SCA3) may present with unexplained ataxia that is part of the larger differential diagnosis of hereditary and acquired ataxias (see Hereditary Ataxia Overview).

Progressive ataxia, often associated with evidence of upper motor neuron dysfunction including brisk tendon reflexes and extensor plantar responses, can be seen in individuals with SCA3 as well as in many other dominantly inherited ataxias. Thus, it is difficult and often impossible to distinguish SCA3 from the other hereditary ataxias (see Hereditary Ataxia Overview).

The presence of dystonia and parkinsonian features, including a beneficial response to levodopa or dopamine agonists, can cause diagnostic confusion with dopa-responsive dystonia and Parkinson disease [Schöls et al 2000]. In SCA3, however, most individuals manifesting with parkinsonian features also have some evidence of cerebellar involvement.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 3 (SCA3), 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 3

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 &/or LMN dysfunction (weakness, spasticity, Babinski signs, hyperreflexia, amyotrophy, fasciculations)	• Brain MRI &/or spinal cord MRI may be indicated to rule out coincident pathologies. • Consider referral to neuromuscular clinic.
	Extrapyramidal features (e.g., dystonia, parkinsonism)	
	Consider referral to OT/PT / rehab specialist.	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices, PT/OT
Eyes	Complete eye exam	• Assess best corrected visual acuity; nystagmus, saccades & smooth pursuit; vertical & horizontal gaze limitation; ptosis. • Consider referral to ophthalmologist for corrective measures incl prisms &/or surgery.
Speech	For those w/dysarthria: speech/language eval	Consider referral to speech/language pathologist.
Feeding	For those w/frequent choking or severe dysphagia, assess: • Nutritional status; • Aspiration risk.	Consider involving a gastroenterology / nutrition / feeding team, incl formal swallowing eval.
Respiratory	For those w/respiratory symptoms or muscular involvement: obtain pulmonary function tests.	Consider involving pulmonary specialist / respiratory therapist.
Autonomic dysfunction	History of difficulty w/thermoregulation, syncope	
Bladder function	History of spastic bladder symptoms: urgency, frequency, difficulty voiding	Referral to urologist; consider urodynamic eval.
Sleep issues	Consider sleep study.	For obstructive sleep apnea
Chronic pain	Assess location, relationship to sleep or body position, & association w/neuropathy or dystonia.	Depending on location & nature of pain, consider EMG or regional MRI to assess cause.
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, or neuropsychologist if needed.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [3]	To inform affected individuals & their families re nature, MOI, & implications of SCA3 to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources; • Social work involvement for parental support; • Home nursing referral.	

BARS = Brief Ataxia Rating Scale; CCAS = cerebellar cognitive affective syndrome; ICARS = International Cooperative Ataxia Rating Scale; LMN = lower motor neuron; MOI = mode of inheritance; 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 SCA3. The goals of treatment are to maximize function and reduce complications. Each individual should be managed by a multidisciplinary team of relevant specialists such as neurologists, occupational therapists, physical therapists, physiatrists, orthopedists, nutritionists, speech therapists, social workers, and psychologists depending on the clinical manifestations.

Management remains supportive as no medication has been proven to slow the course of disease, Excellent reviews include D'Abreu et al [2010], Ashizawa et al [2018], Duarte-Silva & Maciel [2018], Zesiewicz et al [2018], and Klockgether et al [2019].

Table 4. Treatment of Manifestations in Individuals with Spinocerebellar Ataxia Type 3

Manifestation/Concern	Treatment	Considerations/Other
Cerebellar ataxia	• PT & OT • Self-directed exercise	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL, incl use of adaptive devices (e.g., weighted eating utensils, dressing hooks) • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs). • Inpatient rehab w/OT/PT may improve ataxia & functional abilities in patents w/degenerative ataxias. [2, 3] • Weight control to avoid obesity • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) & improve mobility (e.g., ramps to accommodate motorized chairs) • Although neither exercise nor PT slows progression of incoordination or muscle weakness, affected individuals should maintain activity.
	Pharmacologic treatment	Riluzole [2, 4] & valproic acid [2] may be beneficial for ataxia, though not proven in SCA3 clinical trials.
	Transcranial magnetic stimulation	
Upper motor neuron involvement (spasticity)	Pharmacologic treatment	• Oral antispasmodics (baclofen, atropine-like drugs, & hypnotic agents) may yield variable response. • Botulinum toxin [5] or intrathecal baclofen should also be considered.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Lower motor neuron involvement (weakness)		Orthotics
Dystonia	Pharmacologic treatment	• Antispasmodic agents (e.g., anticholinergics, baclofen) or botulinum toxin injections [5] • For generalized dystonia, consider pallidal deep brain stimulation.
Parkinsonism	Pharmacologic treatment	Levodopa or dopamine agonist [6]
Ophthalmologic involvement	Ophthalmologist referral	• Prisms • Corrective surgery for strabismus • Although 4-aminopyridine can ↓ downbeat nystagmus, horizontal nystagmus is much more common in SCA3.
Dysarthria	Speech/language therapy	Consider alternative communication methods as needed (e.g., writing pads, digital devices).
Dysphagia	Feeding therapy programs to improve nutrition & dysphagia & ↓ aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration
Drooling		Baclofen, atropine-like drugs
Weight	Nutrition assessment	• Consider nutritional & vitamin supplementation to meet dietary needs. • Avoid obesity, which can exacerbate difficulties w/ambulation & mobility.
Respiratory		General anesthesia may be problematic; experience w/local anesthesia has been reported [Teo et al 2004].
Sleep issues	REM sleep behavior disorder	Melatonin
	Nocturnal cramps	Stretching exercises, B complex vitamins, verapamil, diltiazem, gabapentin
	Obstructive sleep apnea	Document & treat obstructive sleep apnea.
Fatigue		Daytime fatigue may respond to psychostimulants used in narcolepsy (e.g., modafinil); consider sleep study to rule out sleep disorder.
Autonomic dysfunction		Orthostatic hypotension is not common, but if present consider support hose or, as needed, oral agents (e.g., fludrocortisone).
Bladder dysfunction		• Oral agents for bladder spasticity (anticholinergics, mirabegron) • Percutaneous tibial nerve stimulation
Restless legs syndrome & periodic limb movements of sleep		• Iron replacement if deficient • Levodopa or dopamine agonist [5]
Chronic pain		If present, neuropathic pain can be treated w/standard pharmacologic therapies.
Cognitive/Psychiatric	Pharmacologic treatment	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, psychosis) [7]
	Psychotherapy / neuropsychological rehabilitation	Consider cognitive & behavioral therapy, incl Goal Management Training®. [8, 9]

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Social support	Social work referral	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; REM = rapid eye movement
1. Martineau et al [2014]
2. Ilg et al [2009], Miyai et al [2012], Zesiewicz et al [2018]
3. van de Warrenburg et al [2014]
4. Romano et al [2015]
5. Freeman & Wszolek [2005]
6. Subramony et al [1993], Nandagopal & Moorthy [2004]
7. Cecchin et al [2007]
8. Depression scores improved as a consequence of occupational therapy, underscoring the fact that non-pharmacologic measures may also improve affective disorder in SCA3 [Silva et al 2010].
9. Ruffieux et al [2017]

Surveillance

Table 5. Recommended Surveillance for Individuals with Spinocerebellar Ataxia Type 3

System/Concern	Evaluation	Frequency
Neurologic	• Neurologic assessment for progression of ataxia; UMN or LMN signs; dystonia & parkinsonism; autonomic dysfunction • Monitor ataxia progression w/standardized scale (SARA, ICARS, or BARS). [1]	Annually; more often for an acute exacerbation
	Physiatry, OT/PT assessment of mobility, self-help skills as they relate to ataxia, spasticity, weakness	Annually; more often for an acute exacerbation
Dysarthria	Need for alternative communication method or speech therapy	Per symptom progression
Dysphagia	Assess aspiration risk & feeding methods.	Per symptom progression
Weight / Nutritional status	• Monitor BMI. • Consult a nutritionist. • High-calorie supplementation	Annually
Respiratory	If symptoms, pulmonary function tests	Per symptom progression
Bladder dysfunction	Flow studies & eval by urologist	Per symptom progression
Neuropathic pain	Evaluate need for pharmacologic treatment.	Per symptom progression
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 & caregiver.	Annually

BARS = Brief Ataxia Rating Scale; ICARS = International Co-operative Ataxia Rating Scale; LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMN = upper motor neuron
1. Bürk & Sival [2018]

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Currently, no medication has been proven to slow or halt the progression of SCA3. The recent promise of nucleotide-based gene silencing strategies in other neurodegenerative diseases such as spinal muscular atrophy, coupled with preclinical success of gene silencing therapy in mouse models of SCA3 [McLoughlin et al 2018], suggest that similar nucleotide-based gene silencing strategies for SCA3 may soon be tested in human clinical trials.

Ataxia investigators in Europe and in the United States are currently engaged in a collaborative grant application for trial readiness for SCA3 (READISCA) that is seeking to define the natural history of SCA3 and appropriate disease biomarkers [Ashizawa et al 2018].

Troriluzole, a prodrug (i.e., a biologically inactive compound that can be metabolized in the body to produce a drug) of riluzole, is currently being tested as a potential symptomatic treatment for ataxia in several spinocerebellar ataxias including SCA3.

Potassium ion channel modulators have been shown to have symptomatic benefit in animal models of several spinocerebellar ataxias [Bushart et al 2018], but have not yet been evaluated in clinical trials.

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 3 (SCA3) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA3 have an affected parent.
- A proband with SCA3 may have the disorder as the result of expansion of an intermediate *ATXN3* CAG repeat inherited from a parent who does not manifest classic clinical features of SCA3.
- If neither of the parents of the proband is known have SCA3, recommendations for the evaluation of parents include physical examination and consideration of *ATXN3* molecular genetic testing.
- The family history of some individuals diagnosed with SCA3 may appear to be negative because of failure to recognize the disorder in family members, 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 appropriate molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected and/or is known to have an intermediate or pathogenic *ATXN3* CAG repeat expansion, the risk to each sib of inheriting the CAG repeat expansion is 50%. The CAG repeat may

expand on transmission from parent to offspring resulting in an earlier age of onset and more severe disease manifestations in offspring (see Anticipation).
- If an expanded CAG repeat cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the theoretic possibility of parental germline mosaicism.
- If the parents of a proband are clinically unaffected but their genetic status is unknown, sibs are still presumed to be at increased risk for SCA3 because of the possibility of late onset of SCA3 in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an affected individual has a 50% chance of inheriting the *ATXN3* CAG repeat expansion.
- The CAG repeat may expand on transmission from proband to offspring resulting in an earlier age of onset and more severe disease manifestations in offspring (see Anticipation).

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

Related Genetic Counseling Issues

Note: If neither parent of a proband with SCA3 has an *ATXN3* CAG repeat expansion, nonmedical 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.

At-risk individuals. The age of onset, severity, specific manifestations, and progression of SCA3 are variable and cannot be predicted by the family history or results of molecular genetic testing.

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

- Predictive testing for at-risk relatives is possible once molecular genetic testing has identified an *ATXN3* CAG repeat expansion in an affected family member.
- This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.
- Predictive genetic testing has proven beneficial in the Azore Islands, a region with high prevalence of SCA3 [Gonzalez et al 2004].

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 SCA3, it is appropriate to consider testing of symptomatic individuals regardless of age.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ATXN3* CAG repeat expansion has been identified in an affected family member, prenatal and preimplantation genetic testing for SCA3 are possible. (Note: The prenatal finding of an *ATXN3* CAG repeat expansion cannot be used to accurately predict onset, severity, type of symptoms, or rate of progression of SCA3.)

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

Resources

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

- **Ataxia MJD Research Project, Inc.**
  1425 Alvarado Avenue
  Burlingame CA 94010-5547
  Email: info@ataxiamjd.org
  www.ataxiamjd.org
- **NCBI Genes and Disease**
  Spinocerebellar ataxia
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  www.ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167

Email: naf@ataxia.org

www.ataxia.org

- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 34 983 278 029; 34 985 097 152; 34 634 597 503
  Email: sede.valladolid@fedaes.org; sede.gijon@fedaes.org; sede.bilbao@fedaes.org
  fedaes.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

Molecular Genetics

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

Table A. Spinocerebellar Ataxia Type 3: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATXN3		Ataxin-3	ATXN3 database	ATXN3	ATXN3

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 3 (View All in OMIM)

109150	MACHADO-JOSEPH DISEASE; MJD
607047	ATAXIN 3; ATXN3

Molecular Pathogenesis

ATXN3 encodes ataxin-3 (ATXN3), a de-ubiquitinating enzyme that is widely expressed in the brain and throughout the body, existing both in the cytoplasm and nucleus of various cell types. In neurons, ATXN3 is predominantly a cytoplasmic protein but the protein readily shuttles in and out of the nucleus, and tends to concentrate in neuronal nuclei in disease [Paulson et al 1997].

ATXN3 contains a variable CAG repeat that encodes a polyglutamine tract. Expansion of the CAG repeat is the molecular mechanism underlying the disease. When harboring the polyglutamine expansion encoded by the CAG repeat, ATXN3 is prone to aggregate and mislocalize in neurons [Paulson et al 2017, McLoughlin et al 2020].

SCA3 is one of several SCAs caused by polyglutamine-encoding CAG repeat expansions [Paulson et al 2017, Klockgether et al 2019].

Mechanism of disease causation. Gain of function

Table 6. *ATXN3* Technical Considerations

Technical Issue	Comment [Reference]
Sequence of repeat	CAG
Methods to detect expanded allele (See Table 7.)	Conventional PCR is standard. Triplet-primed PCR (TP-PCR) [Melo et al 2016, Cagnoli et al 2018] & Southern blotting [Kawaguchi et al 1994] have also been described.
Somatic instability	• Alleles w/abnormal number of CAG repeats may display somatic instability of the repeat, appearing as "smeared" expanded alleles w/multiple distinct expansion sizes on PCR & Southern blot analyses [Hashida et al 1997]. • In early studies of the central nervous system, cerebellar tissues tended to have slightly smaller repeat lengths than other brain regions, but higher resolution analysis of somatic expansions employing single cell methods has not been published.
Germline instability	• Typically, spermatozoa contain a larger repeat length than leukocytes in the same individuals [Watanabe et al 1996]. • The probability of repeat expansion is greater w/paternal than w/maternal transmission, though the paternal bias is not pronounced.

Methods to characterize *ATXN3* CAG repeats. Because of the technical challenges of detecting and sizing *ATXN3* CAG repeat expansions, multiple methods may be needed to rule out or detect CAG repeat expansions (see Table 7). Repeats in the normal range (12-44) may be detected by traditional PCR. However, detection of apparent homozygosity for a normal CAG repeat does not rule out the presence of an expanded CAG repeat, thus, testing by triplet-primed PCR (TP-PCR) or Southern blotting is required. In addition, somatic and germline instability of expanded repeats must be considered.

Table 7. Methods to Characterize *ATXN3* CAG Repeats

Interpretation of CAG Repeat Number	Expected Results by Method		
	Conventional PCR	Triplet-primed PCR [1]	Expanded repeat analysis [2]
Normal: 12-44	Detected [3]	See footnote 1.	Expansions can be detected, and repeat size can be approximated. [4, 5]
Intermediate [6]		Expansions may be detected, but repeat size cannot be determined. [7, 8]	
Pathogenic (full penetrance): ~60-97		Expansions are detected, but repeat size cannot be determined. [8]	

1. The design of a triplet-primed PCR (TP-PCR) assay may include conventional PCR primers to size normal repeats and detect expanded repeats in a single assay. The TP-PCR assay itself does not determine repeat size, even alleles in the normal range.
2. Methods to detect and approximate the size of expanded repeats include long-range PCR sized by gel electrophoresis and Southern blotting. The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/or affected individual as a result of competition by the normal allele during amplification.
3. Detection of an apparently homozygous repeat does not rule out the presence of an expanded CAG repeat; thus, testing by TP-PCR or expanded repeat analysis is required to detect a repeat expansion.
4. Southern blotting for the CAG repeat expansion has been described [Kawaguchi et al 1994].
5. Precise sizing of repeats is not necessary as clinical utility for determining the exact repeat number has not been demonstrated.
6. The smallest unstable repeat reported was 45 CAG repeats [Padiath et al 2005]. Some of these alleles are not associated with classic clinical features of SCA3 [Costa Mdo & Paulson 2012 and references therein].
7. TP-PCR for the CAG repeat expansion has been described [Melo et al 2016, Cagnoli et al 2018].
8. Repeats at the lower end of this range may not show the characteristic stutter pattern that indicates an expanded allele.

Table 8. Notable *ATXN3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Repeat Range
NM_004993.5 NP_004984.2	c.886_888CAG[12_44]	p.Gln296[12_44]	Normal
	c.886_888CAG[45_59]	p.Gln296[45-59]	Intermediate
	c.886_888CAG[60_86]	p.Gln296[60_86]	Full penetrance

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

Chapter Notes

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- 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 2-9-23.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 2-9-23.

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