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Spinocerebellar Ataxia Type 4

Synonyms: SCA4, Spinocerebellar Ataxia 4

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Summary

Clinical characteristics

Spinocerebellar ataxia type 4 (SCA4) is a progressive neurologic disease characterized by cerebellar involvement (gait ataxia, balance disturbances, eye movement abnormalities), brain stem involvement (dysarthria, dysphagia), sensory neuropathy, motor neuron involvement (muscle wasting and spasticity), autonomic dysfunction (especially orthostatic hypotension), and cognition and/or behavior manifestations. Age of onset ranges from 12 to 65 years. In the approximately 10% of individuals whose onset is before age 25 years disease manifestations are more severe and often different from those with later-onset disease. As the disease progresses, particularly in those with early-onset disease, eye movement abnormalities, dysarthria, dysphagia, sensory neuropathy, upper and lower motor neuron involvement, and orthostatic hypotension can further aggravate balance and gait problems. Most individuals eventually require a walker or wheelchair. Reduced life expectancy in individuals with earlier-onset severe SCA4 is associated with weight loss, infections, and cardiac arrhythmia. Life expectancy is normal or near normal in individuals with later-onset SCA4.

Diagnosis/testing

The diagnosis of SCA4 is established in a proband with suggestive findings by the identification of a heterozygous abnormal trinucleotide GGC repeat expansion in the terminal exon of *ZFHX3* by molecular genetic testing.

Management

Treatment of manifestations: Multidisciplinary care by neurologists (possible pharmacologic treatment of ataxia); physical therapists (maintain mobility and function); occupational therapists (optimize activities of daily living); speech-language therapists (optimize communication, including augmentative and alternative communication as needed); neuro-ophthalmologists (counsel to minimize impact of eye movement abnormalities); nutritionists and occupational therapists (manage dietary needs and consider need for gastrostomy tube placement);

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neurologists and neurorehabilitation specialist (manage autonomic dysfunction); and mental health specialists (manage mood disorders and changes in cognition and/or behavior).

Surveillance: Monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations via routine evaluations as recommended by the treating clinicians.

Agents/circumstances to avoid: Medications that (1) further reduce cerebellar function, including drinking alcohol and use of sedating drugs; and (2) exacerbate orthostatic hypotension such as large carbohydrate-rich meals and dehydration.

Genetic counseling

SCA4 is inherited in an autosomal dominant manner. Most individuals diagnosed with SCA4 have an affected parent. As anticipation is common in SCA4, the affected parent frequently has milder disease with a later age of onset than their affected offspring. Each child of an individual with SCA4 has a 50% chance of inheriting an abnormal GGC repeat expansion in *ZFHX3*. Once a pathogenic *ZFHX3* GGC repeat expansion has been identified in an affected family member, predictive testing for at-risk family members and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus diagnostic criteria for spinocerebellar ataxia type 4 (SCA4) have been published.

Suggestive Findings

Spinocerebellar ataxia type 4 (SCA4) **should be considered** in probands with the following clinical and imaging findings and family history [Maschke et al 2005, Wictorin et al 2014, Chen et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a].

Clinical Findings

Age of onset ranges from 12 to 65 years. About 10% of individuals have early onset (i.e., before age 25 years).

Progressive cerebellar / brain stem involvement

- **Gait ataxia with balance disturbance** (present in all individuals) is the most common presenting feature.
- **Limb ataxia** (present in all individuals) may be present from symptom onset or only become evident later.
- **Slow and/or hypometric ocular saccades, gaze restriction, or other eye movement abnormalities** (present in all individuals)
  - Although affected individuals may report dizziness when walking and difficulty in rapidly directing their gaze in different directions (such as when crossing a street as a pedestrian), this concern often is only elicited on specific questioning (as these issues are often attributed to cerebellar and sensory involvement and gait disturbances). Examination usually reveals the ability to slowly direct the gaze vertically and/or horizontally in a normal or restricted range. With long-standing disease horizontal, vertical, or total gaze restriction may occur.
  - Other eye movement abnormalities include head eye lag, saccadic pursuit, saccadic intrusions, hypermetric saccades, and, in a few individuals, nystagmus or impaired suppression of vestibulo-ocular reflex.
- **Dysarthria** (in nearly all individuals) can be cerebellar type with imprecise articulation and scanning speech.
- **Dysphagia** (in ~65% with disease progression). Discoordination of oral musculature and pharyngeal retention are typically seen on swallowing examination [A Puschmann, personal observation].

Sensory neuropathy

- Rarely, distal extremity sensory impairment can be the presenting manifestation or the one that predominates early in the disease course. Almost all individuals develop sensory neuropathy with disease progression.
- Examination reveals reduced vibration sense in all individuals and reduction in other sensory modalities (pinprick, temperature, light touch, proprioception) in some. Romberg test may be positive.
- Neurophysiologic signs (a reduction in amplitude or complete loss of sensory nerve action potentials) may predate the onset of balance and gait impairment or of other clinical manifestations [Wictorin et al 2014].

Upper motor neuron (UMN) and/or lower motor neuron (LMN) involvement

- Examination reveals UMN involvement including extensor plantar reflexes in about 85%.
- Signs and symptoms of LMN involvement occur in 30%-100% of individuals with disease progression and can include weakness and muscle wasting that is often mild. Tendon reflexes are absent or diminished in most individuals when balance and gait disturbances become manifest.

Autonomic dysfunction. Signs and symptoms that are rare early in the disease course but can become pronounced with disease progression, especially in persons with early-onset disease, include severe orthostatism, urinary urgency and/or incontinence, and constipation or diarrhea.

Weight loss and/or muscle wasting can be present in more advanced disease stages.

Imaging Findings

Brain MRI usually reveals mild-to-moderate cerebellar atrophy. The atrophy progresses over time and may be predominantly in the anterior cerebellar lobe. Atrophy of the brain stem, pons, and medulla oblongata can be seen in some individuals. Thinning of the spinal cord may be visible on MRI with disease progression.

Family History

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Of note, anticipation (earlier disease onset in successive generations) is commonly observed. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of SCA4 **is established** in a proband with suggestive findings by the identification of a heterozygous abnormal exonic trinucleotide GGC repeat expansion in the terminal exon (exon 10 of 10 in MANE transcript NM_006885.4) of *ZFHX3* by molecular genetic testing (see Table 1 and Table 6). (For more information on MANE transcripts, see www.ncbi.nlm.nih.gov/refseq/MANE.)

Note: Pathogenic GGC repeat expansions in *ZFHX3* **are not reliably detected** by standard sequence-based multigene panels, exome sequencing, or genome sequencing and may require specific bioinformatic methods for their detection (see Molecular Genetics, ***ZFHX3* technical considerations**).

Repeat sizes. To date, *ZFHX3* GGC repeat lengths have been reliably characterized by long-read sequencing in 35 persons with SCA4 [Chen et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a, Wallenius et al 2024b] and by PCR fragment analysis in nine unrelated individuals with SCA4 [Dalski et al 2024]; thus, the repeat ranges provided here will likely be modified as molecular tools and detection methods evolve.

- **Normal:** Fewer than 31 GGC repeats (most common length: 21 repeats, including non-GGC interruptions)

- **Intermediate:** Range from 31 to 41 GGC repeats. Note: To date, there is insufficient evidence that intermediate repeats are pathogenic.
- **Pathogenic (high penetrance):** 42 or more GGC repeats (no interruptions). Note: To date, the smallest number of GGC repeats that is pathogenic has not been well defined.

Note: (1) Normal alleles always contain interruptions in the regularly repeated GGC sequence that encodes glycine. The most common normal allele includes one AGT triplet (encoding serine, or a "serine interruption") and two GAC triplets (also encoding glycine); however, many different variations have been observed in normal alleles [Wallenius et al 2024a, Table S5]. Together, these interruptions are referred to as "non-GGC interruptions." (2) Intermediate alleles have been observed in only a few individuals to date; thus, no conclusions about their composition can be drawn. (3) Pathogenic alleles are composed of pure GGC repeats and do not contain non-GGC interruptions to date.

Molecular genetic testing relies on specific tools to characterize the size and purity of *ZFHX3* GGC repeat expansions. Based on current knowledge and molecular methods, the authors propose a two-tiered testing approach:

1. Short-read whole-genome sequencing. Short-read whole-genome sequencing-based tools developed for the detection of nucleotide repeat expansions have led to the identification of exonic GGC repeats in the terminal exon of *ZFHX3* [Ibañez et al 2022, Chen et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a].
2. Long-read sequencing or PCR fragment analysis. Long-read sequencing is likely the most reliable method for the detection of *ZFHX3* GGC repeat expansions [Figueroa et al 2024, Wallenius et al 2024b], especially if SCA4 cannot be ruled out by analysis of short-read data or if the exact number of expanded repeats needs to be determined. Recently, PCR fragment analysis was described as an orthogonal method to detect pathogenic repeat expansions in *ZFHX3* and determine their length [Dalski et al 2024].

For further information, see Molecular Genetics, ***ZFHX3* technical considerations**.

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 4

Gene [1]	Method	Proportion of Pathogenic Variants Identified by Method
ZFHX3	Long-read sequencing [2]	100% (35/35)
	PCR fragment analysis [3]	100% (10/10)
	Short-read whole-genome or exome sequencing with gene-specific analysis of GGC expansions & non-GGC interruptions [4]	Detects presence or absence of expanded repeat (in 100%) but cannot accurately determine repeat length

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

2. Long-read sequencing can detect the presence of a pathogenic repeat expansion and has accurately quantified repeat length for all repeat expansions identified to date [Chen et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a, Wallenius et al 2024b]. Whole-genome long-read sequencing may be used as well as the targeted (adaptive) long-read sequencing assay that has been established [Chen et al 2024]. Detailed evaluation of all data available from single-molecule long-read sequencing suggests that the exact length of expanded repeats may differ slightly between blood cells of an individual with SCA4 [Chen et al 2024, Figueroa et al 2024, Wallenius et al 2024a, Wallenius et al 2024b], making it impossible to state one single repeat length for an individual; thus, one individual may have a range of repeat lengths in a blood sample. Because this range is relatively narrow, it was possible to determine clearly in all 35 individuals with SCA4 analyzed by long-read sequencing to date if repeats were pathogenically expanded or not (see Molecular Genetics, ***ZFHX3* technical considerations**).

3. Dalski et al [2024]

4. GGC repeat expansions in *ZFHX3* underlying SCA4 have been identified using short-read (conventional) exome or genome sequencing when specific analytic tools for the detection of repeat expansions were used [Ibañez et al 2022, Figueroa et al 2024, Wallenius et al 2024a]. Although such testing detects or rules out the presence of a pathologically expanded GGC repeat, it cannot accurately determine the number of repeats of most pathologically expanded repeat lengths [Wallenius et al 2024a] (See Molecular Genetics, ***ZFHX3* technical considerations**).

Clinical Characteristics

Clinical Description

Spinocerebellar ataxia type 4 (SCA4) is a progressive neurologic disease characterized over time by cerebellar / brain stem involvement, sensory neuropathy, upper and lower motor neuron involvement, and autonomic dysfunction as well as less common signs and symptoms including weight loss.

To date, more than 200 affected individuals have been identified in families with SCA4. For many reports only historical information is available; however, several publications have provided information on modern genetic studies and more detailed clinical information on individuals and kindreds described previously [Flanigan et al 1996, Hellenbroich et al 2003, Maschke et al 2005, Hellenbroich et al 2006, Wictorin et al 2014]. Recently, clinical assessments on more than 50 individuals have been reported [Chen et al 2024, Dalski et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a]. Among these reports, the extent of the assessments and descriptions of disease signs and symptoms differ. The following description of the phenotypic features of SCA4 is based on these reports.

Age of onset of initial manifestations of SCA4 reported to date ranges from 12 to 65 years. Compared to individuals with milder, later-onset disease, those with early-onset disease (i.e., before age 25 years) develop more severe and often different manifestations.

Cerebellar / Brain Stem Involvement

Balance and gait disturbances affect all individuals with SCA4 and are the most frequent presenting disease manifestations. The main and predominant cause is cerebellar dysfunction in most individuals; however, sensory ataxia may contribute early in the disease course, and in some it can be a prominent component. As the disease progresses, particularly in those with early-onset disease, upper and lower motor neuron involvement and orthostatic hypotension can further aggravate balance and gait problems. Most individuals eventually require a walker or wheelchair.

Cerebellar ataxia of the limbs develops in all individuals.

Eye movement abnormalities can cause difficulty in rapidly directing the gaze in different directions, causing the sensation of dizziness when walking. Over time, restriction of horizontal or vertical gaze or all eye movements may occur.

While the range of reported eye movement abnormalities is compatible with radiologic and neuropathologic evidence that the disease process affects both the cerebellum and the brain stem, it may also reflect differences in the assessment or reporting of neuro-ophthalmologic findings.

Dysarthria, occurring in most individuals over time, can be cerebellar type with imprecise articulation and scanning speech. Some individuals depend on augmentative and alternative means of communication (AAC).

Some individuals may have a predominantly nasal or hypernasal speech [A Puschmann, personal observation].

Dysphagia, affecting many individuals over time, often causes longer-than-usual times to eat a meal or an inability to eat sufficient meals, contributing to the marked involuntary weight loss observed in many persons. Some individuals need to depend on gastrostomy tube placement to assure adequate caloric intake.

Sensory Neuropathy

Paresthesias with tingling or burning sensations in the feet or hands are common, with a distal-to-proximal gradient; symptoms of restless legs also occur. Affected individuals may experience worsening of their balance and gait disturbances in darkness, as observed in sensory ataxia [Wallenius et al 2024a].

Neurophysiologic signs (a reduction in amplitude or complete loss of sensory nerve action potentials) may predate the onset of balance and gait impairment or other clinical manifestations [Wictorin et al 2014].

Upper Motor Neuron (UMN) and/or Lower Motor Neuron (LMN) Involvement

UMN involvement, observed in about 85% of individuals, includes extensor plantar reflex responses usually without foot clonus or spasticity.

Later in the disease course, LMN involvement, including weakness and muscle wasting that occurs in 30%-100% of individuals, may contribute to difficulties standing and walking [Maschke et al 2005, Wictorin et al 2014]. Fasciculations have been reported.

Autonomic Dysfunction

In individuals with earlier-onset disease or in advanced disease stages, autonomic dysfunction can become very disabling.

Orthostatic hypotension of variable degree affects most persons during their disease and is often symptomatic.

In individuals with more severe disease, orthostatic hypotension can become so pronounced that in extreme cases, individuals cannot be erect or even in a sitting position (despite intensive pharmacologic treatment) because marked drops in blood pressure cause fainting [Wictorin et al 2014, Wallenius et al 2024a].

In individuals with later-onset disease, orthostatic hypotension may remain subclinical and may not cause impairment because affected individuals tend to start using a wheelchair when their gait and balance problems occur, thus avoiding the frequent postural changes that occur in individuals who are ambulatory.

Other manifestations of autonomic dysfunction can include the following:

- Neurogenic urinary bladder disturbances often lead to urinary incontinence.
- Increased bowel movements may cause diarrhea; decreased bowel movements may cause constipation. Both can be either mild or severe. When severe either can cause significant distress.
- Esophageal hypomobility and atony may occur [Dalski et al 2024].
- Erectile dysfunction has been reported; the authors suspect that similar dysfunction occurs in females.
- Abnormal sweating or hot flashes may either be an independent phenomenon or due to decreases in blood pressure.
- Sleep disturbances and acrocyanosis have been reported in some.
- Cardiac arrhythmias, a cause of death in severely affected individuals, may be related to cardiac autonomic denervation.

Other Findings

Unintended weight loss. With disease progression many individuals develop unintended, marked weight loss likely caused by a combination of underlying disease processes (e.g., dysphagia, muscle wasting due to LMN disease, immobility, diarrhea, or possible changes in appetite) or mild behavioral or cognitive changes that possibly make some individuals opt against gastrostomy tube placement despite considerable cachexia [Wictorin et al 2014; K Wictorin & A Puschmann, personal observations].

Fasciculations. Faciolingual and tongue fasciculations, myokymia, and twitching of facial muscles have been described [Maschke et al 2005, Chen et al 2024, Figueroa et al 2024, Paucar et al 2024], as well as involuntary overflow/dystonic oromandibular movements when persons with very slow ocular saccades direct their gaze to the side [Wictorin et al 2014].

Movement disorders, observed in individuals with SCA4 but probably not yet fully characterized, include the following:

- Dystonia manifesting as cervical or exercise-induced dystonia, foot or limb dystonia, or affecting the diaphragm, eyelids, or larynx (i.e., laryngospasm)
- Mirror movements of the hands
- Overflow movements in which ipsilateral facial grimacing accompanies attempts to lateral gaze
- Tremor, choreatic movements, and myoclonic jerks

Parkinsonism has not been reported to date.

Learning difficulties and/or neurobehavioral/psychiatric manifestations. Most individuals do not show clinically relevant cognitive or behavioral abnormalities; however, exceptions such as the following have been observed:

- Learning difficulties and manifestations of autism spectrum disorder were evident in one individual with very early onset at age 15 years [Wallenius et al 2024a].
- One individual with very severe disease declined to see a neurologist for unknown reasons. Other individuals declined gastrostomy tube placement for feeding despite worsening severe weight loss [Wictorin et al 2014; K Wictorin & A Puschmann, personal observations].
- Some of the most severely affected individuals develop depression, whereas other persons with SCA4 do not [A Puschmann, personal observations].

The authors suspect these behaviors might indicate cognitive changes; however, this has not been studied in more detail. Nonetheless, these findings in some individuals suggest cognitive or neurobehavioral/psychiatric manifestations, perhaps within the cerebellar cognitive affective syndrome [Schmahmann & Sherman 1998].

Prognosis. Reduced life expectancy in individuals with earlier-onset severe SCA4 was associated with weight loss, infections, and cardiac arrhythmia. Life expectancy was normal or near normal in individuals with later-onset SCA4 [Paucar et al 2024, Wallenius et al 2024a].

Genotype-Phenotype Correlations

Genotype-phenotype correlations to date are preliminary as data are only available on 35 individuals with SCA4 whose repeat sizes have been studied by long-read sequencing [Chen et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a, Wallenius et al 2024b] and 26 individuals studied with PCR fragment analysis [Dalski et al 2024].

Age of onset correlates inversely with the GGC repeat size; however, the correlation is not perfect, suggesting that unidentified additional genetic or non-genetic factors may also affect the age of onset.

- The longest pathogenic repeat, 74 GGC repeats, was observed in an individual whose balance disturbances started at age 15 years.
- The shortest pathogenic repeat, 44 GGC repeats, was observed in an individual whose disease onset was at age 60 years.

Larger GGC repeat sizes are associated with more severe disease manifestations, faster disease progression, poorer outcome, and shorter life expectancy. Exact cutoffs for large GGC repeat size causing severe manifestations has not been determined; however, it is likely that a gradual increase in disease severity is observed with increasing repeat sizes.

Some disease manifestations have only been observed in individuals with younger-onset disease who have longer repeat expansions, including very severe orthostatic hypotension that make erect or seated positions impossible, clinically relevant cognitive or behavioral changes that may remain mild or might include autism spectrum disorder [Wallenius et al 2024a], and reduced life expectancy.

Penetrance

To date, *ZFHX3* repeats with 42 or more GGC triplets have only been found in individuals with SCA4, whereas more than 46,000 alleles from individuals without SCA4 had at the most 30 GGC triplets, suggesting high, possibly complete, penetrance of expanded repeats with 42 triplets or more.

Penetrance is age dependent, with onset between ages 12 and 65 years in all individuals with SCA4 reported to date.

Intergenerational Instability

Anticipation (earlier disease onset in successive generations) has been observed in many families; however, some children developed disease manifestations at a later age than their affected parents [Chen et al 2024, Dalski et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a].

In five families for which individual-level data on age at onset was published, affected children developed manifestations of SCA4 one to 30 years earlier (mean: 10.1 years; standard deviation: 7.5 years) than their affected parents; two children developed manifestations seven and nine years later than their affected parent [Wallenius et al 2024a]. In other reports, affected children developed manifestations of SCA4 an average of 5.2 years [Flanigan et al 1996], 11 years [Dalski et al 2024, Paucar et al 2024], or 21.6 years earlier than their affected parents. Ascertainment or reporting biases may have affected these observations.

No difference in anticipation between maternal and paternal transmission was observed.

Increasing repeat length with parent-to-child transmission has been described in several instances [Dalski et al 2024, Figueroa et al 2024, Wallenius et al 2024b] and likely explains the tendency of the disease to manifest at a younger age in children of affected parents (anticipation). Future studies may be able to determine the degree of intergenerational instability more accurately (see Molecular Genetics).

Nomenclature

SCA4 was previously referred to as "spinocerebellar ataxia, autosomal dominant, with sensory axonal neuropathy" or "autosomal dominant cerebellar ataxia with slow ocular saccades, neuropathy and orthostatism." These terms are no longer in use.

Prevalence

To date, *ZFHX3* repeat expansions have been described in more than 200 affected individuals from 26 families or kindreds [Chen et al 2024, Dalski et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a]. While these studies included evaluation of several large and previously described pedigrees, at least 18 probands or smaller families were identified in a relatively short time after the disease-causing genetic variants became known.

To date, all reported families with *ZFHX3* GGC repeat expansions have originated from Sweden (many from the limited geographic area of Skåne, the southernmost region of Sweden) or Germany (particularly northern Germany), suggesting a founder event [Chen et al 2024, Dalski et al 2024, Figueroa et al 2024, Wallenius et al 2024a]. Likely, the founder event is the (successive) loss of the non-GGC interruptions by spontaneous mutational events over many generations [Wallenius et al 2024a]. This is compatible with the inability to establish genealogical links between the families described despite intense attempts [A Puschmann, personal observations] and the fact that members in the oldest generations of several known pedigrees remained clinically unaffected.

No pathogenic *ZFHX3* GGC repeats were found in 76 persons with undiagnosed ataxia from Brazil or in 258 persons with unexplained ataxia and 411 persons with multiple system atrophy from Hokkaido, Japan [Matsushima et al 2024, Novis et al 2024, Shirai et al 2024], indicating that SCA4 is rare in these populations.

To date, no pathogenic *ZFHX3* GGC repeats have been identified in datasets of individuals with ataxia in other populations; however, information is lacking on the exact population background of these individuals.

Genetically Related (Allelic) Disorders

Pathogenic predominantly *de novo* variants in *ZFHX3* (e.g., truncation, nonsense, and missense variants), whole-gene deletions, and contiguous gene deletions involving *ZFHX3* have been reported in individuals with autism spectrum disorder, neurodevelopmental phenotypes, and/or epilepsy. Ataxia and neuropathy have not been described in individuals with these phenotypes.

- Heterozygous *ZFHX3* pathogenic variants were identified in individuals with global developmental delay with learning difficulties and/or mild-to-moderate intellectual impairment, autism spectrum disorder, muscular hypotonia, and feeding difficulties (due to oropharyngeal dysphagia) [Pérez Baca et al 2024].
- Biallelic pathogenic variants were identified in eight (2.1%) unrelated Chinese children with focal (partial) epilepsy and infantile spasms with or without neurodevelopmental features in a group of 378 individuals with focal epilepsy [He et al 2024].
- *De novo* heterozygous *ZFHX3* variants were reported in individuals with autism spectrum disorder and in individuals from a large case series with a broad range of developmental disorders including epileptic encephalopathies [Epi4K Consortium et al 2013, Hashimoto et al 2016, Wang et al 2016, Deciphering Developmental Disorders Study 2017, Kosmicki et al 2017, He et al 2024]. Only limited clinical details were provided in these publications, and the pathogenicity of at least some of the identified variants may still need to be validated.

Differential Diagnosis

Although spinocerebellar ataxia type 4 (SCA4) is characterized by sensory impairment, slow saccades, and autonomic dysfunction, it is difficult and often impossible to distinguish SCA4 from other hereditary ataxias based on clinical examination alone. Molecular genetic testing is highly recommended to make an accurate diagnosis. (See Hereditary Ataxia Overview for a review of the differential diagnosis of hereditary ataxia and causes of hereditary ataxia.)

Table 2 lists a selection of known genetic disorders with ataxia, neuropathy, and/or slow saccades that may form the most common differential diagnoses of SCA4 in clinical practice. (This list is not comprehensive, as many additional genetic disorders may be mistaken for SCA4.)

Table 2. Genetic Disorders with Ataxia, Sensory Neuropathy, and/or Slow or Hypermetric Ocular Saccades in the Differential Diagnosis of Spinocerebellar Ataxia Type 4

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/SCA4	Distinguishing from SCA4
ATXN1	SCA1	AD	• Progressive cerebellar ataxia • Slow or hypermetric ocular saccades • Sensory neuropathy	• Spasticity • More prominent/earlier bulbar dysfunction (speech, swallowing) • Cognitive dysfunction • Usually mixed sensorimotor neuropathy

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/SCA4	Distinguishing from SCA4
ATXN2	SCA2	AD	• Progressive cerebellar ataxia • Slow or hypermetric ocular saccades • Predominantly sensory neuropathy in many persons	• Parkinsonism, tremor • ↓ muscle tone • Not all persons have neuropathy
ATXN3	SCA3	AD	• Progressive cerebellar ataxia • Slow or hypermetric ocular saccades • Predominantly sensory neuro(no)pathy in some individuals • Amyotrophy	• Parkinsonism • Action-induced facial & lingual fasciculations • Bulging eyes • May have motor or sensorimotor neuro(no)pathy
RFC1	*RFC1* CANVAS / spectrum disorder	AR	• Progressive cerebellar ataxia • Sensory neuropathy • Autonomic dysfunction	• Abnormal or absent vestibulo-ocular reflex • Chronic cough • Prominent neuropathic pain
FXN	Friedreich ataxia	AR	• Progressive cerebellar ataxia • ↓ vibration sense • Muscular weakness • Bladder dysfunction • Neuropathy	• Usually sensorimotor neuropathy • Scoliosis • Hearing & vision loss • Cardiomyopathy • Usually earlier onset
TDP1	SCA w/axonal neuropathy type 1	AR	• Progressive cerebellar ataxia • Distal sensory impairment	• More commonly early onset in late childhood to adolescence • Develop motor neuropathy & peripheral weakness • Nystagmus • No saccadic slowing described
TTPA	Ataxia w/vitamin E deficiency	AR	• Progressive ataxia • Upper & lower motor neuron signs • Purely sensory neuropathy in subset of persons	• Manifests more commonly in childhood • Retinopathy • Very low plasma vitamin E concentration • Neuropathy may be purely motor or sensorimotor

Based on Linnemann et al [2016], Jensen et al [2019], Jaques et al [2022], Roberts et al [2022]
AD = autosomal dominant; AR = autosomal recessive; CANVAS = cerebellar ataxia with neuropathy and vestibular areflexia syndrome; MOI = mode of inheritance; SCA = spinocerebellar ataxia

Non-genetic causes of cerebellar disease and slow saccades include Wernicke encephalopathy and anti-GAD antibody syndrome [Jensen et al 2019]. Cerebellar disease, pyramidal signs, and dysautonomia occur in multiple systems atrophy (MSA) [Jaques et al 2022].

Management

No clinical practice guidelines for spinocerebellar ataxia type 4 (SCA4) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SCA4, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Spinocerebellar Ataxia Type 4: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic assessment for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus)	Use clinical neurologic eval & standardized scale to establish baseline for ataxia, such as SARA. [1]
	Assessment for non-cerebellar signs (vibration sense, other sensory modalities, Romberg test / sensory ataxia, weakness, amyotrophy, reflexes, dysphagia, movement disorders, involuntary facial movements)	• Use clinical neurologic eval • Consider nerve conduction studies to establish presence & severity of sensory neuropathy.
	Assessment for symptoms of autonomic dysfunction: • Dizziness, lightheadedness, fainting, falls when standing up • Urinary dysfunction • Sexual dysfunction • Constipation, diarrhea, fecal incontinence • Flushing, abnormal sweating	• Use standardized measurement of orthostatic blood pressure. [2] • Consider tilt table testing. • Consider urology eval. • Consider additional autonomic testing in persons who are symptomatic.
	Ask affected person & family/guardian about depression, learning difficulties, features of ASD, & behavioral changes.	Consider referral to psychiatrist or psychologist for assessment & treatment.
	Brain MRI	Evaluate extent of atrophy of cerebellum & other structures.
Eye movement abnormalities	Consultation w/neuro-ophthalmologist or orthoptist	• Assess saccades, gaze restriction, & smooth pursuit. • Use standardized eye movement exam for ocular pursuit & saccades, apraxia, & gaze restriction. [3] • Consider objective/instrumental recordings of eye movements.
ADL/Musculoskeletal	PT eval	• Assess need for balance exercises, gait training to maintain mobility, & exercises to help prevent falls & maintain function. • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers).
	OT eval	Assess need for adaptive devices to optimize ADL.
Dysarthria	Speech-language pathologist	Assess need for: • Speech-language therapy; • Methods of augmentative & alternative communication.
Dysphagia	• Swallowing eval • Measure & record body weight. • Calculate BMI.	• Consider VFSS to assess risk of aspiration. • Referral to nutritionist & OT

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [4]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of SCA4 to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources • Social work involvement for parental support • Home nursing referral

ADL = activities of daily living; ASD = autism spectrum disorder; BMI = body mass index; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; VFSS = videofluoroscopic swallowing study

1. Schmitz-Hübsch et al [2006]

2. See www.cdc.gov/steadi/media/pdfs/STEADI-Assessment-MeasuringBP-508.pdf.

3. Shaikh et al [2022]

4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse, other health practitioners performing genetic counseling in specific health care systems

Treatment of Manifestations

There is no cure for SCA4. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Spinocerebellar Ataxia Type 4: Treatment of Manifestations

Manifestation/Concern	Treatment/Referral	Considerations/Other
Cerebellar ataxia	By PT & OT	• PT to maintain mobility & function [1] • Self-directed exercise as prescribed by PT • OT to optimize ADL • Avoid alcohol intake & strenuous physical activity that may precipitate episodes of ataxia. • Consider adaptive devices to maintain/improve mobility (e.g., canes, walking sticks, walker). • Inpatient rehab w/PT & OT may improve ataxia & functional abilities in persons w/degenerative ataxias. [2] • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)
	By neurologist	• No specific pharmacologic treatment has been studied in SCA4. • Consider treatments (e.g., riluzole) as recommended in published consensus guidelines [1, 2] following local/institutional/national practice.
Dysarthria	By speech-language therapist	Incl methods of augmentative & alternative communication as needed (e.g., writing pads & digital devices)
Eye movement abnormalities	Neuro-ophthalmology consultation	• Counsel on how to minimize impact of slow/limited eye movements in daily life situations. • Consider emerging pharmacotherapies for eye movement disturbances.
Dysphagia / Weight loss	Feeding recommendations by nutritionist/OT	• Consider nutritional & vitamin supplementation to meet dietary needs. • Consider timing of gastrostomy tube placement.

Table 4. continued from previous page.

Manifestation/Concern	Treatment/Referral	Considerations/Other
Autonomic dysfunction	By neurologist / neurorehabilitation specialist	• For orthostatic hypotension, consider ↑ fluid intake, bolus fluid intake, ↑ sodium intake, abdominal & lower extremity compression &/or treatment w/medications (e.g., midodrine, droxydopa, fludrocortisone, or others). [2] • Consider treatment for urinary urgency/frequency (e.g., bladder / pelvic floor muscle training, mirabegron, solifenacin, self-catheterization). [3] • Consider treatment for erectile dysfunction, constipation, diarrhea (loperamide).
Mood disorder	By OT/psychiatrist/ psychologist	Non-pharmacologic: • Exercise as feasible re motor symptoms, stimulation-based OT • Psychodynamic therapy, cognitive behavioral therapy Pharmacologic treatment: • SSRI, buspirone
Learning difficulties / ASD symptoms / Cognitive or behavioral changes	When suspected by care team: psychology/psychiatry consultation	• Non-pharmacologic supportive treatment • Pharmacologic treatment as indicated • Psychological support
Psychological burden of worsening impairments	By psychologist / social worker	Psychological support, social support

ASD = autism spectrum disorder; OT = occupational therapy/therapist; PT = physical therapy/therapist; SSRI = selective serotonin reuptake inhibitor
1. van de Warrenburg et al [2014], Zesiewicz et al [2018]
2. Palma & Kaufmann [2020]
3. Lucas [2019]

Surveillance

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

Table 5. Spinocerebellar Ataxia Type 4: Recommended Surveillance

System/Concern	Evaluation	Frequency
Cerebellar ataxia	• Neurologic eval to assess progression & need for pharmacotherapy • Monitor ataxia progression w/standardized scale (SARA). [1]	Annually or as needed
	PT eval re mobility, need for durable equipment	Per treating PT
	OT eval re ADL, need for safety modifications	Per treating OT
Autonomic dysfunction	Repeat clinical assessment of manifestations of autonomic dysfunction (see Table 3).	At least annually; more often if new symptoms occur
Dysarthria	Eval re need for speech therapy or methods of augmentative & alternative communication	Per symptom progression

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Dysphagia / Weight loss	• Measurement of body weight • Calculation of BMI	• Initially, at least annually • When weight loss occurs, at least every 3 mos
	Assessment of nutrition, aspiration risk, & feeding methods	As needed
Eye movement abnormality	Eval by neurologist or ophthalmologist: • Assess relevant eye movements (see Table 3). • Assess for dizziness when turning head, looking sideways.	Annually or as needed
	Eval by ophthalmologist as needed	Per occurrence of symptoms
Mood/Cognition/ Behavior	Assess for mood & mild cognitive or behavioral changes.	At least annually or as needed
Family/Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

OT = occupational therapy/therapist; PT = physical therapy/therapist; SARA = Scale for the Assessment and Rating of Ataxia
1. Bürk & Sival [2018]

Agents/Circumstances to Avoid

Persons with SCA4 can be advised to avoid the following:

- Drinking alcohol, which can further reduce cerebellar function, especially if excessive
- Sedating drugs, which may reduce cerebellar function
- Any other agents that may impair balance or lower blood pressure
- Large carbohydrate-rich meals, as they may cause postprandial hypotension and exacerbate orthostatic decreases in blood pressure
- Dehydration, especially in high ambient temperatures, as it may exacerbate hypotension

The benefit of the use of diuretics or antihypertensive agents needs to be balanced against the risk of increasing orthostatic hypotension [Wieling et al 2022].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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 4 (SCA4) is inherited in an autosomal dominant manner.

Anticipation (earlier disease onset in successive generations) has been observed in many families and is an important issue to address when counseling family members of individuals with SCA4 (see Intergenerational Instability).

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA4 have an affected parent. As anticipation is common in SCA4, the affected parent frequently has milder disease with a later age of onset than their affected offspring.
- To date, only one individual diagnosed with SCA4 represents a simplex case (i.e., the only affected family member) [Figueroa et al 2024]. Based on data available to date, it is possible that an unaffected parent of a proband with SCA4 may have lost non-GGC interruptions in the regularly repeated *ZFHX3* GGC sequence resulting in GGC repeat instability and expansion; however, this not been observed empirically (see Establishing the Diagnosis).
- A proband may appear to be the only affected family member 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, *de novo* occurrence of an abnormal GGC repeat expansion in *ZFHX3* in the proband cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has an abnormal GGC repeat expansion in *ZFHX3*.

Sibs of a proband. Risk to sibs of a proband depends on the clinical/genetic status of the proband's parents:

- If a parent has an abnormal GGC repeat expansion in *ZFHX3*, the risk to each sib of inheriting an allele with an expanded GGC repeat is 50%. Because anticipation and intergenerational instability have been reported in SCA4, a sib may inherit a *ZFHX3* allele with more GGC repeats than the transmitting parent. Longer repeat expansions are associated with earlier age of onset and a more severe phenotype; however, these correlations are not perfect and additional factors also play a role (see Genotype-Phenotype Correlations).
- If a parent has an intermediate number of repeats (i.e., approximately 31-41 GGC repeats), the parent is not likely to display manifestations of SCA4; however, the repeat size may expand on transmission to offspring and the risk to each sib is increased (see Intergenerational Instability). Note that to date clinical descriptions of individuals with intermediate repeats are not available.
- If the genetic status of the parents is unknown and:
  - There is more than one affected family member, the risk to each sib is presumed to be 50%.
  - The proband represents a simplex case (rare in SCA4 and most likely observed in individuals who develop SCA4 late in their lives), the risk to sibs cannot be quantified but is presumed to be increased.

Offspring of a proband

- Each child of an individual with SCA4 has a 50% chance of inheriting an abnormal GGC repeat expansion in *ZFHX3*.
- The likelihood that an abnormal *ZFHX3* GGC repeat will expand further on transmission from a proband to offspring (resulting in an earlier age at onset in offspring compared with the proband) is much greater than the likelihood of later disease onset in offspring. Differences in repeat sizes between probands and offspring appear to be independent of the affected parent's sex (see Intergenerational Instability).

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent lacks non-GGC interruptions in the repetitive GGC DNA sequence or has a GGC repeat size in the pathogenic range, the parent's family members may be 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 *ZFHX3* GGC repeat size 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, psychological consequences and the perceived 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. Such counseling needs to take into account that there may be wide individual, societal, and legislative differences with regard to which consequences might arise after genetic testing of asymptomatic individuals.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years) for typically adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality should be discussed in the context of formal genetic counseling. The autonomy of the minor is a primary concern and consideration should be given to delay of predictive genetic testing until the at-risk individual is capable of informed decision making.

In a family with an established diagnosis of SCA4, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once a pathogenic *ZFHX3* GGC repeat expansion has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Age of onset, severity, and progression of SCA4 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 and preimplantation genetic testing. While most health care professionals would consider decisions regarding prenatal and preimplantation genetic testing to be the choice of the parents, discussion of these issues is appropriate.

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 Canada**
  Canada
  Phone: 514-321-8684
  Email: ataxia@lacaf.org
  lacaf.org
- **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
- **RaraSwed (National Swedish Registry for Rare Diseases), Swedish Centers for Rare Diseases, CSD i samverkan**
  Sweden
  Phone: 46-(0)46-171000
  Email: csd@skane.se
  csdsamverkan.se/raraswed

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 4: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ZFHX3	16q22.2-q22.3	Zinc finger homeobox protein 3	ZFHX3 database	ZFHX3	ZFHX3

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 4 (View All in OMIM)

104155	ZINC FINGER HOMEOBOX 3; ZFHX3
600223	SPINOCEREBELLAR ATAXIA 4; SCA4

Molecular Pathogenesis

ZFHX3 encodes zinc finger homeobox protein 3 (ZFHX3; previously called ATBF1), a transcription factor that is moderately to highly expressed in the brain, spine, and endocrine tissue (thyroid) and variably expressed in many other tissues. In the nervous system, it has known roles in neuronal differentiation as well as protecting cerebellar neurons from oxidative stress [Ishii et al 2003, Jung et al 2005, Kim et al 2010]. RNA expression is highest in arteries and low in the adult brain; however, prenatally it reaches high expression in several regions in the developing brain [Pérez Baca et al 2024].

ZFHX3 comprises four homeodomains and 23 zinc finger motifs. In its terminal exon (exon 10 of 10 in MANE transcript NM_006885.4), *ZFHX3* has a variable GGC repeat that encodes polyglycine; expansion of this repeat is associated with disease. (For more information on MANE transcripts, see www.ncbi.nlm.nih.gov/refseq/MANE.)

Neuropathologic findings and possible cellular pathomechanisms. Neuropathologic findings, reported in five persons with spinocerebellar ataxia type 4 (SCA4), include cell loss in the cerebellum (particularly of Purkinje cells), brain stem, and spinal alpha motor neurons. Volume loss has also been observed in the posterior columns of the spinal cord and/or spinocerebellar tracts [Hellenbroich et al 2006, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a]. Sensory impairment corresponds to the degeneration of the posterior columns and/or spinocerebellar tracts of the spinal cord observed in nerve conduction studies, MRI, and neuropathology.

Many affected neurons have p62-positive inclusions, mostly in the nucleus but also in the cytoplasm [Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a]. Similar p62-positive inclusions containing polyglycine-rich protein have been found in the other known polyglycine disorders (such as neuronal intranuclear inclusion disease [OMIM 603472], fragile X tremor/ataxia syndrome, or oculopharyngodistal myopathies) [Liufu et al 2022, Zhang et al 2024]. Thus, the polyglycine domains of mutated *ZFHX3* may increase aggregation of ZFHX3. In cell models, GGC expansions increase ZFHX3 protein levels and cause abnormalities in autophagy [Figueroa et al 2024].

Mechanism of disease causation. Gain of function

***ZFHX3* technical considerations**

- **Sequence of repeat.** GGC trinucleotide repeat expansion in *ZFHX3* encoding a polyglycine
- **Intergenerational instability.** Non-expanded alleles typically consist of 18 GGC repeats, two synonymous GGT repeats, and a single non-synonymous AGT interruption. The GGT repeats also encode glycine but interrupt the repetitive GGC DNA sequence. Normal alleles therefore result in a protein with 20 glycine residues interrupted by a single serine at position 7 [Wallenius et al 2024a]. Loss of these interruptions within this region is hypothesized to predispose to allele expansion from generation to generation.

  Note: Some of the oldest generations in SCA4 families were not known to have neurologic manifestations (molecular data are not available for these individuals). However, these families are known to share a common founder, suggesting that the founder event may have been the elimination of non-GGC interruptions in *ZFHX3* [Chen et al 2024, Dalski et al 2024, Figueroa et al 2024, Wallenius et al 2024a].

Methods to characterize *ZFHX3* GGC repeats. Due to the technical challenges of detecting and sizing the *ZFHX3* GGC repeat expansions, multiple methods may be needed to rule out SCA4 or to detect and accurately size an expanded *ZFHX3* GGC allele.

- Repeats in the normal range (below 31 GGC repeats) can often be detected in short-read exome and genome data.

- Methods to detect and approximate the size of expanded repeats (42 or more GGC repeats) include the following methods [Chen et al 2024, Dalski et al 2024, Figueroa et al 2024, Paucar et al 2024, Wallenius et al 2024a, Wallenius et al 2024b]:
  - Whole-genome sequencing (short-read sequencing with customized analytic tools)
  - Exome sequencing or sequencing-based multigene panels including *ZFHX3*, if read lengths are sufficient (150 bp) and if appropriate or customized analytic tools are used
  - Long-read sequencing has been shown to reliably detect the presence of a pathogenic repeat expansion and accurately quantify repeat length for all repeat expansions identified to date.
  - PCR fragment analysis has recently been shown to accurately determine repeat lengths [Dalski et al 2024].

Normal-length alleles can be confirmed in whole-genome, exome, and sequence-based multigene panels that include *ZFHX3* (e.g., to rule out SCA4). Pathogenic *ZFHX3* GGC repeat expansions have been identified using short-read exome or genome sequencing when specific analytic tools for the detection of repeat expansions were used [Ibañez et al 2022, Figueroa et al 2024, Wallenius et al 2024a]. The ability of these methods to correctly determine read length depends on the specific methods and analytic tools used by the genetic testing laboratory, and on the length of the individual's GGC repeat. Bioinformatic methods have been developed that either use a sequence with the most common non-GGC interruptions as reference or look for sequences with pure GGC repeats, as in pathologically expanded alleles; these methods can complement each other. Furthermore, visual inspection by a bioinformatician for the presence or absence of non-GGC interruptions can aid in diagnosis [Wallenius et al 2024a].

By contrast, automated analytic pipelines can be insufficient to analyze for *ZFHX3* repeats in short-read data. Pre-test inquiry with the genetic laboratory is recommended when use of short-read (conventional) exome or whole-genome sequencing, or reanalysis of short-read exome or genome data, is considered.

A crucial factor in the detection ability of standard sequencing-based methods is a read length of at least 100 bp or more to ensure accurate mapping of expanded alleles. Although such testing can detect an expanded GGC repeat, it is typically unable to accurately determine the number of repeats. To date, sequencing methods with read lengths below 150 bp have not been able to reliably detect an expansion, although the loss of non-GGC interruptions is reliably detected.

The detection of non-GGC interruptions can probably exclude the diagnosis of SCA4 even when the exact number of repeat units has not been accurately determined. Conversely, lack of non-GGC interruptions may indicate a possible diagnosis of SCA4 and may prompt validation with additional methods.

Detailed evaluation of all available data from single-molecule long-read sequencing suggests that the exact length of expanded repeats may differ slightly between blood cells of an individual with SCA4 (due to either mosaicism or technical reasons). This can make it impossible to define one single repeat length for an individual; rather, one individual may have a range of repeat lengths in a blood sample. However, this range is relatively narrow, and in all 35 individuals with SCA4 analyzed by long-read sequencing to date, it was possible to determine clearly if repeats were pathogenically expanded or not [Chen et al 2024, Figueroa et al 2024, Wallenius et al 2024a, Wallenius et al 2024b].

Table 6. *ZFHX3* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Repeat Range
NM_006885.4 NP_008816.3	$(GGC)_5$ – $(GGC)_{30}$	Normal
	$(GGC)_{31}$ – $(GGC)_{41}$	Intermediate
	$(GGC)_{42}$ – $(GGC)_{74}$	Pathogenic

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

Author Notes

The authors work within the Clinical Neurogenetics Research group at Lund University and Skåne University Hospital in Lund, Skåne, Sweden, where they have identified several families with spinocerebellar ataxia type 4 (SCA4) and continue to follow them clinically and perform genetic analyses. Drs Sorina Gorcenco, Andreas Puschmann, and Klas Wictorin are neurologists, Dr Sigurd Dobloug is a resident in neurology, and Joel Wallenius, MSc, is a bioinformatician.

Dr Andreas Puschmann (andreas.puschmann@med.lu.se) is actively involved in clinical research regarding individuals with SCA4. He would be happy to communicate with persons who have any questions regarding diagnosis of SCA4 or other considerations.

Contact Dr Andreas Puschmann to discuss any findings of intermediate *ZFHX3* GGC repeat expansions, or individuals with other types of *ZFHX3* variants (missense, nonsense, copy number variants) who have ataxia, neuropathy, or dysautonomia.

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