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Spinocerebellar Ataxia Type 38

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Summary

Clinical characteristics

Spinocerebellar ataxia type 38 (SCA38) is characterized as a pure cerebellar ataxia with symptoms typically manifesting in the fourth decade of life. The most common presenting features are nystagmus and slowly progressive gait ataxia. As the disease progresses, cerebellar symptoms (limb ataxia, dysarthria, dysphagia, diplopia on the horizontal line) may emerge, and affected individuals may experience sensory loss. In the later stages of the condition, ophthalmoparesis followed by ophthalmoplegia may occur. Features that distinguish SCA38 from other spinocerebellar ataxias include *pes cavus* without paresis, hyposmia, hearing loss, and anxiety disorder. Dementia and extrapyramidal signs are not common features of SCA38. Brain imaging typically demonstrates cerebellar atrophy mainly affecting the vermis without atrophy of the cerebral cortex and a normal appearance of the brain stem. With disease progression, nerve conduction velocities and electromyography demonstrate a sensory and motor axonal polyneuropathy in all four extremities. Life span is apparently not decreased.

Diagnosis/testing

The diagnosis of SCA38 is established in a proband with progressive gait ataxia and a heterozygous pathogenic variant in *ELOVL5* identified by molecular genetic testing.

Management

Treatment of manifestations: Management remains supportive and may include physical therapy to ameliorate coordination difficulties; crutches and walkers; home adaptations to avoid falls or accommodate motorized chairs; speech/language therapy; weighted utensils; hearing aids for those with hearing loss; and standard therapy for anxiety.

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Prevention of secondary complications: Weight control, as obesity can exacerbate difficulties with ambulation and mobility; vitamin supplements for those with reduced caloric intake.

Surveillance: Annual examination by a physician who is experienced in movement disorders and ataxia.

Agents/circumstances to avoid: Alcohol and medications known to affect cerebellar function.

Therapies under investigation: Docosahexaenoic acid (DHA) supplementation (600 mg/day) may improve clinical symptoms and cerebellar hypometabolism; no data on the effectiveness of DHA in postponing signs and symptoms of SCA38 in asymptomatic individuals with a heterozygous pathogenic variant in *ELOVL5* have been published.

Genetic counseling

Spinocerebellar ataxia type 38 (SCA38) is inherited in an autosomal dominant manner. All reported individuals diagnosed with SCA38 have an affected parent. The offspring of an affected individual are at 50% risk of inheriting the *ELOVL5* pathogenic variant. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant in the family is known; however, requests for prenatal diagnosis of adult-onset diseases are uncommon and require careful genetic counseling.

Diagnosis

Formal clinical diagnostic criteria for spinocerebellar ataxia 38 (SCA38) have not been established.

Suggestive Findings

Spinocerebellar ataxia type 38 (SCA38) **should be suspected** in individuals with the following clinical and brain MRI findings.

Clinical findings

- Slowly progressive gait ataxia with onset in adulthood (3rd-5th decade)
- Nystagmus in the lateral and vertical gaze
- *Pes cavus*
- Hyposmia

Brain imaging findings

- Cerebellar atrophy (sometimes referred to as cerebellar hypometabolism when visualized on PET scan) mainly affecting the vermis without atrophy of the cerebral cortex
- Normal appearance of the brain stem

Establishing the Diagnosis

The diagnosis of SCA38 **is established** in a proband with progressive gait ataxia and a heterozygous pathogenic variant in *ELOVL5* identified by molecular genetic testing (see Table 1).

Because the phenotype of SCA38 is indistinguishable from many other inherited disorders with SCA, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *ELOVL5*) is rarely useful and typically NOT recommended unless there is a known familial pathogenic variant.

- **A spinocerebellar ataxia multigene panel** including *ELOVL5* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost. This approach limits the identification of variants of uncertain significance and pathogenic variants in genes not related to the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. **Exome array** (when clinically available) may be considered if exome sequencing is not diagnostic, particularly when evidence supports autosomal dominant inheritance.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 38

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ELOVL5	Sequence analysis [3]	4/4 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Only two pathogenic variants have been identified to date: c.689G>T (p.Gly230Val) and c.214C>G (p.Leu72Val) [Di Gregorio et al 2014]. See Table 4.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Spinocerebellar ataxia type 38 (SCA38) is characterized as a pure cerebellar ataxia with symptoms typically becoming apparent in the fourth decade of life (age range 26-50 years) [Borroni et al 2016].

- The most common presenting features are nystagmus (21/21; 100%) and slowly progressive gait ataxia (20/21; 95%).
- With disease progression, cerebellar symptoms such as limb ataxia, dysarthria, dysphagia, and diplopia on the horizontal line may develop.

- In the later stages, ophthalmoparesis followed by ophthalmoplegia may become apparent.

  However, visual evoked potentials performed in eight affected individuals were unremarkable [Borroni et al 2016].

- Peripheral nervous system involvement is present in the last phase of disease with sensory loss.
- Dementia or extrapyramidal signs are not detected.

Significant loss of abilities of daily living is reported only after 20 years of disease. In a study by Borroni et al [2016] of 21 affected individuals from three families, the following was reported:

- All affected individuals were able to participate in activities of daily living during the first decade after symptom onset.
- During the second decade of symptoms, of 13 affected individuals:
  - Nine (70%) had difficulties with ambulation that required the use of a cane.
  - Four (30%) required assistance with washing and dressing.
- During the third decade of symptoms, of eight affected individuals:
  - Seven (87%) required the use of a wheelchair and required assistance with activities of daily living.
  - Four (50%) required assistance with feeding.
  - Four (50%) developed dysphagia.
  - One (12%) developed incontinence.

Features that help distinguish SCA38 from other spinocerebellar ataxia conditions are *pes cavus* without paresis (14/17; 82%) and hyposmia (13/17; 76%).

Other signs and symptoms may include the following:

- Hearing loss (7/21; 33%), the basis of which has not been systematically studied

  Auditory evoked potentials were abnormal in 11/12 (92%) of individuals assessed.

- Anxiety disorder (7/21; 33%)

Brain imaging usually documents cerebellar atrophy with sparing of the cerebral cortex and no white matter disease.

Electrophysiology. With disease progression, nerve conduction studies and electromyography typically demonstrate a sensory and motor axonal polyneuropathy in all four extremities [Borroni et al 2016].

Prognosis. Data on life expectancy are limited. In three affected individuals, the mean time from symptom onset to death was 41 years (range 20-52 years), with the youngest person succumbing at age 70 years [Borroni et al 2016].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Penetrance

Disease penetrance appears to be complete in both males and females but is age dependent. In individuals with the c.689G>T (p.Gly230Val) pathogenic variant, SCA38 was fully penetrant by age 50 years [Borroni et al 2016].

Prevalence

This disease is likely extremely rare. A study of 346 individuals with spinocerebellar ataxia in China found no individuals with a pathogenic variant in *ELOVL5* [Liu et al 2015]. No further cases beyond those described by Di Gregorio et al [2014] have been reported to date.

Anticipation

Anticipation has not been observed in families with SCA38.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ELOVL5*.

Differential Diagnosis

The inherited spinocerebellar ataxias (SCAs) are a heterogeneous group of neurologic disorders that defy easy differentiation on the basis of clinical criteria alone [Klockgether et al 2019]. For most individuals with SCA, inter- and intrafamilial variability is too great to permit definitive classification without molecular genetic testing. See also Hereditary Ataxia Overview.

- The most commonly occurring SCAs – those caused by polyglutamine expansions (i.e., SCA1, SCA2, SCA3, SCA7, SCA17, and DRPLA) – usually present with signs and symptoms before age 30 years, are more rapidly progressive, and demonstrate brain stem involvement on brain MRI.
- SCA6 is characterized by adult-onset slowly progressive ataxia and gaze-evoked nystagmus, findings that overlap with those of SCA3.
- Friedreich ataxia and ataxia with oculomotor apraxia type 1 and type 2 (AOA1 and AOA2) are autosomal recessive and more rapidly progressive than SCA38. They usually have childhood onset and severe peripheral involvement (polyneuropathy).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 38 (SCA38), the evaluations in Table 2 are recommended if they have not already been completed.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with Spinocerebellar Ataxia Type 38

System/Concern	Evaluation	Comment
Neurologic	Neurologic evaluation	Incl scales to evaluate severity of cerebellar ataxia & to allow standardized follow up
	Brain MRI	To assess degree of cerebellar atrophy
Eyes	Ophthalmologic evaluation	To assess for diplopia & ophthalmoparesis/ophthalmoplegia
Ears	Baseline audiology evaluation	To assess for hearing loss
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	

Treatment of Manifestations

Management of individuals remains supportive, as no known therapy to delay or halt the progression of the disease exists.

The American Academy of Neurology has developed guidelines for the treatment of motor dysfunction in individuals with ataxia [Zesiewicz et al 2018].

Table 3. Treatment of Manifestations in Individuals with Spinocerebellar Ataxia Type 38

Manifestation/ Concern	Treatment	Considerations/Other
Ataxia	Physical therapy to ameliorate coordination difficulties, especially w/ walking	Although no clinical evidence of benefit has been offered thus far, individuals should maintain activity.
	Crutches (less often canes) & walkers	To prevent falls
	Home adaptations incl grab bars for bathtub or shower chairs, raised toilet seats, & ramps to accommodate motorized chairs, as needed	
Dysarthria	Speech/language therapy	Communication devices incl writing pads & computer-based devices may be of benefit.
	Video esophagram can identify consistency of food least likely to trigger aspiration.	Weighted eating utensils & dressing hooks help maintain a sense of independence.
Hearing loss	Hearing aids may be helpful in selected cases.	Consider referral to audiologist.
Anxiety	Standard treatment	
Family/ Community	• Appropriate social work involvement to connect families w/ local resources, respite, & support • Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies	Ongoing assessment for need of home nursing

Prevention of Secondary Complications

Weight control is important because obesity can exacerbate difficulties with ambulation and mobility.

Vitamin supplements may be recommended, particularly if caloric intake is reduced.

Surveillance

Affected individuals should be examined at least annually by a physician experienced in movement disorders and ataxia.

Agents/Circumstances to Avoid

Alcohol and medications known to affect cerebellar function should be avoided.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

A double-blind, randomized, placebo-controlled study followed by an open-label extension phase demonstrated the usefulness of docosahexaenoic acid (DHA) supplementation (600 mg/day) as a safe and effective treatment for SCA38, showing an improvement of clinical symptoms and cerebellar hypometabolism [Manes et al 2017].

The long-term safety and efficacy of 600 mg/day oral DHA in individuals with SCA38 was further supported by a two-year open-label extension study [Manes et al 2019].

No data on the effectiveness of DHA in postponing the signs and symptoms of SCA38 in asymptomatic individuals who have a heterozygous pathogenic variant in *ELOVL5* are available.

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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Spinocerebellar ataxia type 38 (SCA38) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- All reported individuals diagnosed with SCA38 have an affected parent.
- SCA38 resulting from a *de novo ELOVL5* pathogenic variant has not been reported to date.
- Symptom onset is age dependent (see Penetrance). Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (though theoretically possible, no instances of parental germline mosaicism have been reported).
- The family history of some individuals diagnosed with SCA38 may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected and/or is known to have the *ELOVL5* pathogenic variant identified in the proband, the risk to the sibs is 50%. In reported families, penetrance is 100% by age 50 years with minimal intrafamilial clinical variability.
- If the *ELOVL5* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with SCA38 has a 50% chance of inheriting the *ELOVL5* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ELOVL5* pathogenic variant, his or her 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 the *ELOVL5* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow-up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

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

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

In a family with an established diagnosis of SCA38, it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *ELOVL5* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal 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.

- **Associazione Nazionale SiIndromi Atassiche (A.I.S.A.) O.N.L.U.S.**
  Via Sara 12
  16039
  Italy
  Fax: 39 178 2279678
  www.atassia.it
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  Ataxia UK
  Lincoln House, Kennington Park, 1-3 Brixton Road
  London SW9 6DE
  United Kingdom
  Phone: +44 (0) 207 582 1444
  Email: smillman@ataxia.org.uk
  www.euroataxia.org
- **National Ataxia Foundation**
  2600 Fernbrook Lane
  Suite 119
  Minneapolis MN 55447
  Phone: 763-553-0020
  Email: naf@ataxia.org
  www.ataxia.org
- **NCBI Genes and Disease**
  Spinocerebellar ataxia
- **Spinocerebellar Ataxia: Making an Informed Choice about Genetic Testing**
  Booklet providing information about Spinocerebellar Ataxia
  depts.washington.edu/neurolog/images/neurogenetics/ataxia.pdf

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 38: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

ELOVL5	6p12.1	Elongation of very long chain fatty acids protein 5	ELOVL5	ELOVL5

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 38 (View All in OMIM)

611805	ELONGATION OF VERY LONG CHAIN FATTY ACIDS-LIKE 5; ELOVL5
615957	SPINOCEREBELLAR ATAXIA 38; SCA38

Molecular Pathogenesis

ELOVL5 is a protein that is involved in the elongation of long-chain polyunsaturated fatty acids. It is a membrane protein located in the endoplasmic reticulum and expressed in human cerebellum.

Mechanism of disease causation. Altered function with possible gain of function of the enzyme [Manes et al 2017]; the molecular mechanism of SCA38 is still uncertain. A combination of loss-of-function and gain-of-function mechanisms may be responsible for the disease [Di Gregorio et al 2014, Hoxha et al 2017]. The p.Gly230Val pathogenic change has been shown to cause protein accumulation in the perinuclear area of transfected cells [Di Gregorio et al 2014].

***ELOVL5*-specific laboratory technical considerations.** The chromosome 6:53152683 G>A change (rs150583340) (NP_001229757.1:p.Gln102Ter) is located on an alternative exon of the gene. This alternative transcript was not validated by experiments in several human tissues [Authors, personal communication]. This variant (47/21544 allele in ExAC database) is located in an intronic region of the main transcript and is likely to have no effect on the protein.

Gene structure. The main transcript is NM_021814.4, ELOVL fatty acid elongase 5, transcript variant 1 (7 exons).

Table 4. Notable *ELOVL5* Variants

Variant Classification	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
Benign	NM_001242828.1 [1] NP_001229757.1	c.304C>T	p.Gln102Ter	Variant transcript [1]
Pathogenic	NM_021814.5 [2] NP_068586.1	c.214C>G	p.Leu72Val	Only known pathogenic variants [Di Gregorio et al 2014]
		c.689G>T [3]	p.Gly230Val	

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.
1. Variant transcript with additional in-frame exon compared to predominant transcript
2. Predominant transcript
3. Described in three Italian families

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Author Notes

A Brusco and E Di Gregorio are involved in the study of the genetic bases of spinocerebellar ataxia and the molecular pathogenesis of SCA28 and SCA38.

B Borroni is involved in the study of ataxias and dementia.

All the authors recently worked on the development of a therapy for SCA38 based on DHA administration.

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