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AFG3L2-Related Neurologic Disorders

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Summary

Clinical characteristics. *AFG3L2*-related neurologic disorders comprise four phenotypes. Spinocerebellar ataxia type 28 (SCA28), the most common phenotype, is characterized by young adult onset (26.5 ± 17.2 years); the onset range is from birth to 74 years of a cerebellar syndrome manifesting initially as very slowly progressive gait and limb ataxia resulting in incoordination and balance problems. Less frequently, ptosis/ophthalmoplegia, dysarthria, or upper-limb incoordination may occur as the initial finding. Pyramidal syndrome (increased and brisk reflexes, extensor plantar reflex, and spasticity) is commonly observed in individuals with longer disease duration. Although cognitive impairment, spasticity, and ophthalmologic signs can occur with disease progression, most individuals remain ambulatory and fully independent throughout their lives.

Spastic ataxia type 5 (SPAX5), reported in 14 individuals to date, ranges from severe neurodegeneration with microcephaly, poor weight gain, developmental delay, developmental regression around age nine months, and death as early as age 2.5 years. Milder presentations range from onset in infancy to an early-onset complex cerebellar ataxia with myoclonic epilepsy.

AFG3L2-related autosomal recessive spinocerebellar ataxia (*AFG3L2*-SCAR), reported in two individuals to date, is a late-onset ataxia with a clinical phenotype closely resembling that of SCA28.

Optic atrophy type 12 (OPA12) manifests as decreased visual acuity (variable but frequently ranging from 0.2/10 to 2/10), photophobia, and impaired color vision. Ophthalmologic findings are optic nerve pallor and highly reduced retinal nerve fiber layer on optical coherence tomography. Although affected individuals do not present with ataxia, some may exhibit sensorineural hearing loss, neurodevelopmental disorders, dystonia, and spasticity.

Diagnosis/testing. The diagnoses of SCA28 and OPA12 are established in a proband with suggestive findings and a heterozygous pathogenic variant in *AFG3L2* identified by molecular genetic testing.

The diagnoses of SPAX5 and *AFG3L2*-SCAR are established in a proband with suggestive findings and biallelic pathogenic variants in *AFG3L2* identified by molecular genetic testing.

Management. *Treatment of manifestations:* Supportive care to improve quality of life, maximize function, and red complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields includ neurologists (to address pharmacologic treatment of myoclonic epilepsy, spasticity, movement disorders); occupational therapists (to optimize activities of daily living and home safety); physiatrists and physical therapists (to

help maintain independence and mobility); nutritionists and feeding therapy programs (to assess the risks of aspiration and need for gastrostomy tube placement for those with dysphagia); speech-language therapists (to address communication for individuals who have expressive language difficulties), ophthalmologists (to consider surgery for ptosis); low vision clinics (for those with optic atrophy); and social workers and psychologists (depending on any cognitive or psychologic manifestations).

Surveillance: Routinely scheduled follow-up appointments with treating clinicians are recommended to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations.

Agents/circumstances to avoid: Alcohol consumption and sedatives such as benzodiazepines that may worsen gait ataxia and coordination. Carbamazepine and phenytoin may exacerbate myoclonus in SPAX5.

Genetic counseling. SCA28 and OPA12 are inherited in an autosomal dominant manner. *AFG3L2*-SCAR and SPAX5 are inherited in an autosomal recessive manner.

Autosomal dominant inheritance: Most individuals diagnosed with SCA28, and some individuals diagnosed with OPA12, have an affected parent. Some individuals diagnosed with an autosomal dominant *AFG3L2*-related neurologic disorder have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with an autosomal dominant *AFG3L2*-related neurologic disorder has a 50% risk of inheriting the pathogenic variant. If the reproductive partner of an individual with an autosomal dominant *AFG3L2*-related neurologic disorder also has an *AFG3L2* pathogenic variant, offspring are at risk of inheriting biallelic pathogenic variants and having an autosomal recessive *AFG3L2*-related neurologic disorder. Once the *AFG3L2* pathogenic variant has been identified in an affected family member, predictive testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Autosomal recessive inheritance: The parents of a child with an autosomal recessive *AFG3L2*-related neurologic disorder are presumed to be heterozygous for an *AFG3L2* pathogenic variant. If both parents are known to be heterozygous for an *AFG3L2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *AFG3L2* pathogenic variants. Heterozygous family members of an individual with an autosomal recessive *AFG3L2*-related neurologic disorder are typically asymptomatic and the risk of developing an *AFG3L2*-related neurologic disorder appears to be low. Once the *AFG3L2* pathogenic variants has been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

***AFG3L2*-Related Neurologic Disorders: Included Phenotypes** [1]
• Spinocerebellar ataxia type 28 (SCA28) • Spastic ataxia type 5 (SPAX5) • *AFG3L2*-related autosomal recessive spinocerebellar ataxia (*AFG3L2*-SCAR) • Optic atrophy type 12 (OPA12)

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

No consensus clinical diagnostic criteria for *AFG3L2*-related neurologic disorders have been published.

Suggestive Findings

The diagnosis of an *AFG3L2*-related neurologic disorder **should be considered** in probands with the following clinical and imaging findings and family history.

Clinical findings

- Onset generally in young adulthood (range: 0-76 years)
- Neurologic examination demonstrating any of the following:
  - Progressive cerebellar ataxia
  - Slowly progressive gait disorder
  - Slowly progressive limb ataxia
  - Cerebellar dysarthria
  - Hyperreflexia or brisk deep tendon reflexes, increased muscle tone in the lower limbs (spasticity), extensor plantar responses
  - Oculomotor abnormalities including smooth pursuit abnormalities, dysmetric and slow saccades, ophthalmoparesis, and gaze-evoked nystagmus
  - Dystonia and/or chorea
  - Parkinsonism
  - Myoclonic epilepsy
  - Mild cognitive impairment and/or neurodevelopmental delay
  - Axonal peripheral sensorimotor neuropathy
- Ophthalmologic examination demonstrating findings of any of the following:
  - Ptosis
  - Optic nerve atrophy and decreased thickness of the retinal nerve fiber layer identified on optical coherence tomography
  - Pale optic discs

Imaging. Brain MRI demonstrating findings of any of the following:

- Cerebellar atrophy predominantly of the superior vermis, with sparing of the brain stem
- Abnormal signal in the globus pallidus

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) or autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of spinocerebellar ataxia type 28 (SCA28) or optic atrophy type 12 (OPA12) **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *AFG3L2* identified by molecular genetic testing (see Table 1).

The diagnosis of *AFG3L2*-related autosomal recessive spinocerebellar ataxia (*AFG3L2*-SCAR) or spastic ataxia type 5 (SPAX5) **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *AFG3L2* identified by molecular genetic testing (see Table 1).

Note: (1) Per American College of Medical Genetics and Genomics / Association for Molecular Pathology variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of *AFG3L2* variants of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: Single-gene testing (sequence analysis of *AFG3L2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended, as the associated phenotypes are not pathognomonic for this gene.

Option 1

A multigene panel that includes *AFG3L2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of pathogenic variants and variants of uncertain significance in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *AFG3L2* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

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 *AFG3L2*-Related Neurologic Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
AFG3L2	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% to date [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Smets et al [2014] reported a deletion of exons 14-16, which likely truncates the protein, in two Belgian families (likely related) with autosomal dominant transmission. This deletion was also identified in another Belgian family [G Coarelli & C Mouraux, unpublished

data]. Further, a 5.3-Mb deletion including the entire gene has been reported in an individual with SCA28 [Myers et al 2014].

Clinical Characteristics

Clinical Description

To date, hundreds of individuals have been identified with an *AFG3L2*-related neurologic disorder [Cagnoli et al 2006, Cagnoli et al 2010, Eskandrani et al 2017, Caporali et al 2020, Charif et al 2020, Dosi et al 2020, Cunha et al 2023, Zheng et al 2025]. The following description of the phenotypic features associated with these conditions is based on these reports and highlights the four distinct clinical presentations associated with *AFG3L2*-related neurologic disorders.

Spinocerebellar Ataxia Type 28 (SCA28)

Age of onset and progression. The usual age at onset is early adulthood (26.5 ± 17.2 years); the range is from birth to 74 years, although infantile presentation is rare. The disease course is slowly progressive with or without slight impairment of functional autonomy even decades after onset. Most individuals remain ambulatory throughout life.

Presentation. In most individuals, SCA28 presents as loss of coordination of lower limbs (unsteadiness, gait ataxia). Less frequently, ptosis/ophthalmoplegia, dysarthria, upper-limb incoordination, or spasticity in lower limbs may occur as the initial finding.

Cerebellar syndrome

- Gait and limb ataxia
- The severity of dysarthria varies between individuals and tends to change with the progression of the disorder. During the early stages of the disease, speech may be mildly impaired but remains easy to understand. As the condition progresses, speech often becomes increasingly slurred, making it difficult to understand.

Oculomotor abnormalities

- Nystagmus, observed in approximately 50% of individuals, may cause oscillopsia, a disabling subjective sensation of visual motion.
- Ophthalmoparesis, observed in approximately 50% of individuals, manifests as limited horizontal and vertical gaze, which can worsen balance disturbance due to ataxia.

Ptosis, observed in approximately 30% of individuals, results in visual field obstruction when pronounced. Surgical correction such as blepharoplasty may be warranted.

Pyramidal syndrome. Increased and brisk reflexes, extensor plantar reflex, and spasticity are commonly observed in individuals with longer disease duration.

Impaired sense of vibration. Although decreased vibration sense at the ankles is present in approximately 20% of individuals, superficial sensation remains consistently normal.

Other

- Other movement disorders including parkinsonism (mainly rigidity and/or bradykinesia), dystonia, chorea, and myoclonus have been observed in approximately 15% of individuals.
- Mild dysphagia has been reported occasionally [Löbbe et al 2014, Zühlke et al 2015, Szpisjak et al 2017]. Feeding difficulties have not been reported.

Intellectual disability and cognitive difficulties. Although occasionally described, intellectual disability and neurodevelopmental delay are not characteristic features of SCA28.

Cognitive decline, reported in approximately 25% of individuals, frequently co-occurs with psychiatric manifestations [Cunha et al 2023].

Neurobehavioral and psychiatric manifestations, including depression and behavioral disorders, have been reported in approximately 20% of individuals.

Electrophysiologic studies. Although affected individuals may report decreased vibration sense, superficial sensation and nerve conduction studies are typically preserved.

Prognosis. Based on current data, life span is not limited by this condition, and several adults have been reported. Although cognitive impairment, spasticity, and ophthalmologic signs can occur with disease progression, most individuals remain ambulatory and fully independent throughout their lives.

Intrafamilial variability in expressivity has been reported in terms of age of onset and clinical severity in several families affected by SCA28 [Di Bella et al 2010]. To date, no families have been described in which individuals have been diagnosed with both SCA28 and OPA12.

Spastic Ataxia Type 5 (SPAX5)

The phenotypic spectrum of SPAX5 ranges from severe neurodegeneration in infancy to an early-onset complex cerebellar ataxia with myoclonic epilepsy. To date, 14 individuals with SPAX5 have been reported.

The most severe manifestations are microcephaly, severe poor weight gain, and severe developmental delay with developmental regression around age nine months. Death has been reported as early as age 2.5 years [Eskandrani et al 2017].

Milder presentations are often limited to ataxia and epilepsy. However, some individuals may also exhibit spasticity, dystonia, chorea, neuropathy, and optic atrophy.

AFG3L2-Related Autosomal Recessive Spinocerebellar Ataxia (*AFG3L2*-SCAR)

***AFG3L2*-SCAR** is a late-onset ataxia with a clinical phenotype that closely resembles SCA28. To date, only two individuals have been reported. The first individual reported presented with slowly progressive ataxia, ptosis, and dysarthria beginning at age 20 years [Tunc et al 2019]. The second individual had slowly progressive ataxia, ptosis, and ophthalmoparesis beginning at age 55 years [Chiang et al 2021].

Optic Atrophy Type 12 (OPA12)

OPA12, a progressive optic atrophy, typically presents before age 20 years; however, adult onset has also been reported. OPA12 accounts for about 4% of all *OPA1*-negative optic atrophy, with a clinical phenotype indistinguishable from that of *OPA1*-related autosomal dominant optic atrophy.

Ophthalmologic abnormalities include decreased visual acuity (variable but frequently ranging from 0.2/10 to 2/10), photophobia, and impaired color vision. Ophthalmologic examination is characterized by optic nerve pallor and highly reduced retinal nerve fiber layer on optical coherence tomography.

Other findings. Brain MRI is usually normal. Affected individuals do not present with ataxia; some may exhibit sensorineural hearing loss, neurodevelopmental disorders, dystonia, and spasticity [Caporali et al 2020].

Genotype-Phenotype Correlations

Variant locations. Reported phenotype correlations with variant locations to date include the following [Caporali et al 2020]:

- Most reported SCA28-related pathogenic variants affect the proteolytic domain (exons 15 and 16).
- The five SPAX5-related pathogenic variants described to date are in the proteolytic domain (exons 15 and 16).
- SCAR-related pathogenic variants, identified in two individuals to date, are compound heterozygous variants – p.[Tyr616Cys];[p.Val723Met] [Tunc et al 2019] and p.[Arg632Ter];p.[Val723Met] [Chiang et al 2021] – located in the proteolytic domain (exons 15 and 16).
- OPA12-related pathogenic variants cluster in the ATPase domain (exons 9 to 12).

SCA28. Individuals heterozygous for the pathogenic variants p.Met666Arg, p.Glu700Lys, and p.Gly671Arg have early-onset disease (i.e., in infancy/childhood), whereas other SCA28-related heterozygous pathogenic missense variants are mainly associated with onset in the second to fourth decade [Mariotti et al 2008, Cagnoli et al 2010, Edener et al 2010, Szpisjak at al 2017].

Penetrance

SCA28. Based on studies published to date, penetrance appears to be complete [Di Bella et al 2010].

OPA12. Reduced penetrance or subclinical phenotypes are suggested by published data [Caporali et al 2020].

Prevalence

SCA28 accounts for approximately 1%-3% of autosomal dominant cerebellar ataxia (ADCA) in individuals of European origin [Cagnoli et al 2010, Hersheson et al 2012], with an estimated incidence of 0.045 in 100,000 individuals.

OPA12 accounts for approximately 4%-5% of autosomal dominant optic atrophy [Caporali et al 2020, Zheng et al 2025].

The other two *AFG3L2*-related neurologic disorders are extremely rare: to date, only 14 individuals have been reported with SPAX5 and two with *AFG3L2*-SCAR.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *AFG3L2*.

Contiguous gene deletions and duplications involving *AFG3L2* have been reported, including chromosome 18p deletion syndrome (OMIM 146390). The phenotype in individuals with chromosome18p deletion syndrome is more complex than in individuals with an autosomal dominant *AFG3L2*-related neurologic disorder (presumably due to the involvement of additional genes) and typically includes neurodevelopmental manifestations, dysmorphic features, and short stature [Turleau 2008].

Differential Diagnosis

Spinocerebellar ataxia type 28 (SCA28). The ataxic gait of individuals with SCA28 is indistinguishable from that seen in other adult-onset inherited or acquired ataxias. When the family history suggests autosomal dominant inheritance, all other autosomal dominant cerebellar ataxias should be considered (see Hereditary Ataxia Overview).

Spastic ataxia type 5 (SPAX5). The differential diagnosis of SPAX5 should include other spastic ataxias and complex ataxias.

***AFG3L2*-related autosomal recessive spinocerebellar ataxia (*AFG3L2*-SCAR)** presents with a clinical phenotype that closely resembles SCA28; therefore, the differential diagnosis is similar to that of SCA28.

Optic atrophy type 12 (OPA12). Optic atrophy observed in individuals with OPA12 is clinically indistinguishable from that seen in other forms of optic atrophy.

See Table 2 for selected genes of interest in the differential diagnosis of *AFG3L2*-related neurologic disorders.

Table 2.

Genes of Interest in the Differential Diagnosis of *AFG3L2*-Related Neurologic Disorders

Phenotype	MOI	Gene(s)	Disorder	Features of This Disorder / Comment
Spinocerebellar ataxia	AD	*ATN1*	DRPLA	• Polyglutamine expansions • Typically present before age 40 years
	AD	*ATXN1*	SCA1	

Phenotype	MOI	Gene(s)	Disorder	Features of This Disorder / Comment
(See Hereditary Ataxia Overview.)	AD	*ATXN2*	SCA2	• More rapidly progressive than SCA28 & *AFG3L2*-SCAR • Assoc w/brain stem involvement on MRI
	AD	*ATXN3*	SCA3	
	AD	*ATXN7*	SCA7	
	AD	*TBP*	SCA17	
	AD	*CACNA1A*	SCA6	Clinical features (adult-onset, slowly progressive ataxia & gaze-evoked nystagmus) overlap those of SCA28 & *AFG3L2*-SCAR.
	AD	*FGF14*	GAA-*FGF14*-related ataxia (SCA27B)	• Adult-onset ataxia • Typically begins w/episodic ataxia assoc w/downbeat nystagmus
	AR	*APTX*	Ataxia w/oculomotor apraxia type 1 (AOA1) (OMIM 208920)	• AOA1 & AOA2 are childhood-onset disorders characterized by marked peripheral involvement, incl severe polyneuropathy. • They are typically more rapidly progressive than SCA28 & *AFG3L2*-SCAR.
	AR	*SETX*	Ataxia w/oculomotor apraxia type 2 (AOA2)	
	AR	*FXN*	Friedreich ataxia	• Tendon reflexes are often ↓ or abolished. • Other typical findings incl ganglionopathy, scoliosis, cardiopathy, auditory neuropathy, optic neuropathy, & diabetes.
	AR	*RFC1*	*RFC1* CANVAS / spectrum disorder	• Triad of cerebellar ataxia, vestibular dysfunction, & sensory neuropathy • Chronic cough can precede neurologic symptoms by several decades.
Spastic ataxia (SPAX) (OMIM PS108600)	AR	*CHP1*	SPAX9	Spastic ataxia that may present w/childhood onset
	AR	*COQ4*	SPAX10	
	AR	*MARS2*	SPAX3	
	AR	*MTPAP*	SPAX4	
	AR	*NKX6-2*	SPAX8 (See *NKX6-2*-Related Disorder.)	
	AR	*SACS*	ARSACS	
	AD	*TUBA4A*	SPAX11	
	AD	*VAMP1*	SPAX1	

Phenotype	MOI	Gene(s)	Disorder	Features of This Disorder / Comment
Hereditary spastic paraplegia (HSP) (See OMIM PS303350 & Uncomplicated Hereditary Spastic Paraplegia Overview.)	AR	*AP5Z1*	SPG48	HSPs that may present w/adult-onset cerebellar ataxia
	AR	*ATP13A2*	SPG78 (OMIM 617225)	
	AR	*B4GALNT1*	SPG26 (OMIM 609195)	
	AR	*CAPN1*	SPG76 (OMIM 616907)	
	AR	*CYP7B1*	SPG5	
	AR	*KIF1C*	SPG58	
	AD	*REEP1*	SPG31	
	AR	*SPG7*	SPG7	• SPG7 (which may account for ~5% of all AR HSP) is an adult-onset slowly progressive spastic ataxia w/ophthalmoparesis, ptosis, parkinsonism, cognitive decline, & optic atrophy. • The distinction between *SPG7* & *AFG3L2*-related neurologic disorders cannot be made on clinical exam & requires molecular genetic testing for confirmation.
	AR	*SPG11*	SPG11	HSPs that may present w/adult-onset cerebellar ataxia
	AR	*ZFYVE26*	SPG15 (OMIM 270700)	
	AD [1]	*ATL1*	SPG3A	HSPs that may present w/childhood-onset cerebellar ataxia
	AR	*CYP2U1*	SPG56	
	AR	*DDHD1*	SPG28	
	AR	*ERLIN1*	SPG62	
	AR	*FA2H*	Fatty acid hydroxylase-assoc neurodegeneration (SPG35)	
	AR	*GBA2*	SPG46	
	AD AR	*KIF1A*	SPG30	
	AD	*KIF5A*	SPG10	
	XL	*PLP1*	SPG2 (See *PLP1*-Related Disorders.)	
	AR	*PNPLA6*	SPG39 (See *PNPLA6*-Related Disorders.)	
	AD	*SPTAN1*	SPG91	
	AR	*SVBP*	SPG94 [2]	

Phenotype	MOI	Gene(s)	Disorder	Features of This Disorder / Comment
Optic atrophy (OMIM PS165500)	AR AD	*ACO2* *AFG3L2* *DNM1L* *MCAT* *MECR* *MIEF1* *OPA1* *OPA3* *RTN4IP1* *SSBP1* *TMEM126A* *YME1L1*	Optic atrophy	• OPA1 (caused by pathogenic variants in *OPA1*) is the most frequent type of AD optic atrophy, accounting for ~70% of affected persons. It typically presents in early childhood (age ~5 yrs) & may be assoc w/auditory neuropathy. • Other inherited optic atrophies differ in assoc manifestations.
	MT	mtDNA genes incl: *MT-ND1* *MT-ND4* *MT-ND6*	Leber hereditary optic neuropathy (LHON)	Bilateral, painless, subacute central vision loss in young adults
	AR	*DNAJC30* *NDUFS2*	Leber-like hereditary optic neuropathy (OMIM 619382 & 620569)	Nuclear genes assoc w/LHON-like phenotype
Progressive myoclonic epilepsy	AR	*CSTB*	Progressive myoclonic epilepsy type 1 (Unverricht-Lundborg disease)	Progressive myoclonic epilepsies present w/myoclonus & seizures but differ from SPAX5 in systematic involvement.
	AR	*EPM2A* *NHLRC1*	Progressive myoclonus epilepsy, Lafora type	
	MT	*MT-TF* *MT-TH* *MT-TI* *MT-TK* *MT-TL1* *MT-TP* *MT-TS1* *MT-TS2*	MERRF	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; MT = mitochondrial; mtDNA = mitochondrial DNA; SCA = spinocerebellar ataxia; SCAR = spinocerebellar ataxia, autosomal recessive; SPAX = spastic ataxia; XL = X-linked

1. SPG3A is almost exclusively inherited in an autosomal dominant manner.
2. Launay et al [2025]

Mitochondrial disorders (See Single Large-Scale Mitochondrial DNA Deletion Syndromes and Primary Mitochondrial Disorders Overview.)

- May present with ataxia and spasticity
- May be associated with external ophthalmoplegia and ptosis. *POLG*-related disorders [Reitinger & Mackay 2024] and other mitochondrial disorders may be associated with optic atrophy with variable multisystemic involvement.

Acquired/multifactorial conditions to consider in the differential diagnosis of *AFG3L2*-related neurologic disorders include the following:

- Multiple system atrophy cerebellar type (MSA C-type) presents later in life with cerebellar signs, autonomic dysfunction, and parkinsonism. Disease progression in MSA C-type is more rapid than in SCA28.
- Ataxia can result from alcoholic cerebellar degeneration, paraneoplastic cerebellar degeneration, vitamin E deficiency, and chronic infection.
- Toxic optic neuropathy can be caused by alcohol consumption or nutritional deficiency (e.g., vitamin B_{12} deficiency).
- Multiple sclerosis and associated disorders (i.e., neuromyelitis optica and MOG antibody disorders) may present with optic neuritis. MRI findings including white matter lesions can distinguish these inflammatory diseases from OPA12.

Management

No clinical practice guidelines for *AFG3L2*-related neurologic disorders 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 an *AFG3L2*-related neurologic disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3.

AFG3L2-Related Neurologic Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Cerebellar & extracerebellar	Neurologic exam to assess cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit)	Use standardized scale to establish baseline for ataxia (SARA). [1]
	Evaluate for 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.
	Evaluate for extrapyramidal features (e.g., dystonia, parkinsonism).	Consider referral to movement disorders clinic.
	Consider referral to OT, PT, & rehab specialist.	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices
	Consider EEG to detect myoclonic epilepsy in SPAX5.	Consider referral to epilepsy clinic.

System/Concern	Evaluation	Comment
Eyes	• Ophthalmologist • Oculomotor recording	• Assess best corrected visual acuity. • Assess oculomotor movements for 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/dysphagia: food intake & aspiration risk eval	Consider referral to speech-language pathologist or ENT for formal swallowing eval.
Cognitive/ neurobehavioral/ psychiatric manifestations	• Assess for cognitive dysfunction assoc w/CCAS (executive function, language processing, visuospatial/visuoconstructional skills, emotion regulation). • Assess for cognitive impairment.	• Consider CCAS scale [2] to evaluate cognitive & emotional involvement. • Consider referral to psychiatrist, psychologist, or neuropsychologist if needed.
Genetic counseling	By genetics professionals [3]	To obtain a pedigree & inform affected persons & their families re the transmission risk & implications of *AFG3L2*-related neurologic disorders 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 such as Parent to Parent • Social work involvement for parental support • Home nursing referral

CCAS = cerebellar cognitive affective syndrome; LMN = lower motor neuron; OT = occupational therapy/therapist; PT = physical therapy/therapist; SARA = Scale for the Assessment and Rating of Ataxia; SPAX5 = spastic ataxia type 5; UMN = upper motor neuron

1. Bürk & Sival [2018]
2. Hoche et al [2018]
3. Clinical geneticist, certified genetic counselor, certified genetic nurse, genetics advanced practice provider (nurse practitioner or physician assistant)

Treatment of Manifestations

There is no specific treatment for *AFG3L2*-related neurologic disorders. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by

specialists in relevant fields including neurology, occupational therapy, physical therapy, physiatry, orthopedics, nutrition, speech therapy, social work, and psychology depending on the clinical manifestations (see Table 4).

Table 4.

AFG3L2-Related Neurologic Disorders: Treatment of Manifestations

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). • 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 persons should maintain activity.
Spasticity	Pharmacologic treatment	Antispasmodic agents (e.g., baclofen, tizanidine, clonazepam) or botulinum toxin injections
Parkinsonism	Pharmacologic treatment	• Standard treatment for parkinsonism • Consider referral to movement disorders clinic.
Dystonia	Pharmacologic treatment	Antispasmodic agents (e.g., anticholinergics, baclofen) or botulinum toxin injections
Myoclonic epilepsy (in SPAX5)	Anti-seizure medications (ASMs)	• Consider progressive myoclonic epilepsy treatment guidelines. [1] • Levetiracetam & valproate (avoid in women of childbearing age due to teratogenicity) for mgmt of convulsive seizure & myoclonus control. • Other ASMs incl topiramate, zonisamide, lamotrigine, brivaracetam, piracetam, & perampanel can be used as second-line medication or in case of intolerance.

Manifestation/Concern	Treatment	Considerations/Other
		• Benzodiazepines (clonazepam & clobazam) are used as add-on therapy for myoclonus mgmt.
Ophthalmologic involvement	• Low vision aids such as magnifiers, high-contrast reading materials, adaptative technologies • Photophobia mgmt w/tinted lenses or sunglasses • Consider blepharoplasty surgery if ptosis is disabling.	Per treating ophthalmologist
Dysarthria	Speech-language therapy	Consider eval for alternative means of communication for persons who have expressive language difficulties.
Dysphagia	Feeding therapy programs to improve nutrition & dysphagia & ↓ aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration • Consider gastrostomy tube placement for those at ↑ risk of aspiration.
Weight	Nutrition assessment	• Consider nutritional & vitamin supplementation to meet dietary needs. • Avoid obesity, which can exacerbate difficulties w/ambulation & mobility.
Cognitive/ neurobehavioral/ psychiatric manifestations	Pharmacologic treatment	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, psychosis)
	Psychotherapy / neuropsychological rehab	Consider cognitive & behavioral therapy.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of the need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

1. Cameron et al [2023]

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.

AFG3L2-Related Neurologic Disorders: Recommended Surveillance

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). [1]	Annually or more often for an acute exacerbation
	Physiatry & OT/PT assessment of mobility & self-help skills as they relate to ataxia, spasticity, & weakness	Annually or more often for an acute exacerbation
	EEG & seizure history (in SPAX5)	Every 6 mos or annually; more often for an acute exacerbation
Dysarthria	Assess need for alternative communication method or speech therapy.	Per disease progression
Dysphagia	Assess aspiration risk & feeding methods.	
Weight / Nutritional status	• Monitor BMI. • Consult nutritionist. • High-calorie supplementation	Annually
Ophthalmologic involvement	• Assessment of nystagmus, ophthalmoparesis, & ptosis. • Assessment of visual acuity & photophobia.	
Cognitive/ neurobehavioral/ psychiatric manifestations	Evaluate mood, signs of psychosis, cognitive complaints, & cognitive deterioration (e.g., using CCAS scale) to identify need for pharmacologic & psychotherapeutic interventions.	Per disease progression & development of psychiatric manifestations
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

CCAS = cerebellar cognitive affective syndrome; LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; SPAX5 = spastic ataxia type 5; UMN = upper motor neuron

1. Bürk & Sival [2018]

Agents/Circumstances to Avoid

Alcohol consumption and sedatives such as benzodiazepines may worsen gait ataxia and coordination difficulties.

Carbamazepine and phenytoin may exacerbate myoclonus in spastic ataxia type 5 (SPAX5).

Evaluation of Relatives at Risk

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

Pregnancy Management

When women with SPAX5 have epilepsy, anti-seizure medications should be monitored regularly and adjusted to avoid exposure to teratogenic medications during pregnancy and medications harmful when breastfeeding.

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

AFG3L2-related spinocerebellar ataxia is inherited in an autosomal dominant (spinocerebellar ataxia type 28; SCA28) or autosomal recessive (*AFG3L2*-related autosomal recessive spinocerebellar ataxia; *AFG3L2*-SCAR) manner.

Spastic ataxia type 5 (SPAX5) is inherited in an autosomal recessive manner.

Optic atrophy type 12 (OPA12) is inherited in an autosomal dominant manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA28 have an affected parent. Some individuals diagnosed with OPA12 have an affected parent.
- Some individuals diagnosed with an autosomal dominant *AFG3L2*-related neurologic disorder have the disorder as the result of a *de novo* pathogenic variant. The proportion of probands diagnosed with SCA28 or OPA12 who have the disorder as the result of *de novo* pathogenic variant is unknown. However, such events appear to be rare in SCA28, with only a single individual with a *de novo* pathogenic variant reported to date [Di Bella et al 2010]. A *de novo* pathogenic variant was identified in two of 12 families with OPA12 in one study [Caporali et al 2020].
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.

  Note: A proband may appear to be the only affected family member because of failure to recognize the disorder in family members with milder phenotypes (subclinical OPA12 phenotypes are suggested by published data [Caporali et al 2020]), early death of a parent before the onset of manifestations, or late onset of the disease in an affected parent. Therefore, *de novo* occurrence of an *AFG3L2* pathogenic variant cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the *AFG3L2* pathogenic variant.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.

- The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

  * A parent with somatic and gonadal mosaicism for an *AFG3L2* pathogenic variant may be mildly/minimally affected.

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 pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. The penetrance of SCA28 appears to be complete; however, intrafamilial variability has been reported in age of onset and clinical severity [Di Bella et al 2010]. Reduced penetrance and subclinical manifestations have been reported in heterozygous family members of individuals with OPA12 [Caporali et al 2020].
- If the *AFG3L2* pathogenic variant identified 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 possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *AFG3L2* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for an autosomal dominant *AFG3L2*-related neurologic disorder because of the possibility of reduced penetrance in a heterozygous parent of a proband with OPA12 and the possibility of parental gonadal mosaicism.

Offspring of a proband

- Each child of an individual with an autosomal dominant *AFG3L2*-related neurologic disorder has a 50% risk of inheriting the pathogenic variant.
- If the reproductive partner of an individual with an autosomal dominant *AFG3L2*-related neurologic disorder also has an *AFG3L2* pathogenic variant, offspring are at risk of inheriting biallelic *AFG3L2* pathogenic variants and having an autosomal recessive *AFG3L2*-related neurologic disorder. A child diagnosed with SPAX5 inherited biallelic *AFG3L2* pathogenic variants: one from a parent with OPA12 and one from an unaffected parent with an *AFG3L2* pathogenic variant located in the proteolytic domain [Caporali et al 2020].

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *AFG3L2* pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with an autosomal recessive *AFG3L2*-related neurologic disorder are presumed to be heterozygous for an *AFG3L2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *AFG3L2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:

  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;

- Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.

- Heterozygous family members of an individual with an autosomal recessive *AFG3L2*-related neurologic disorder are typically asymptomatic and the risk of developing an *AFG3L2*-related neurologic disorder appears to be low. However, milder clinical features such as isolated cerebellar atrophy on brain MRI [Tunc et al 2019] or isolated optic atrophy [Caporali et al 2020] have been reported in some heterozygous family members.

Sibs of a proband

- If both parents are known to be heterozygous for an *AFG3L2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *AFG3L2* pathogenic variants.
- Heterozygous family members of an individual with an autosomal recessive *AFG3L2*-related neurologic disorder are typically asymptomatic and the risk of developing an *AFG3L2*-related neurologic disorder appears to be low. However, milder clinical features such as isolated cerebellar atrophy on brain MRI [Tunc et al 2019] or isolated optic atrophy [Caporali et al 2020] have been reported in some heterozygous family members.

Offspring of a proband. Unless an affected individual's reproductive partner also has an *AFG3L2* pathogenic variant, offspring will be obligate heterozygotes for a pathogenic variant in *AFG3L2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *AFG3L2* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *AFG3L2* pathogenic variants in the family.

Related Genetic Counseling Issues

Predictive testing for autosomal dominant *AFG3L2*-related neurologic disorders (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *AFG3L2* 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 for autosomal dominant *AFG3L2*-related neurologic disorders (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.

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 are at risk of having *AFG3L2* pathogenic variant(s).

Prenatal Testing and Preimplantation Genetic Testing

Once the *AFG3L2* pathogenic variant(s) has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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 of prenatal and preimplantation genetic 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 UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk
- **CSC - Connaître les Syndromes Cérébelleux**
  France
  Phone: 33 (0) 9 70 440 451
  csc.asso.fr
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 601 037 982
  Email: info@fedaes.org
  fedaes.org
- **CoRDS Registry**
  Sanford Research
  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.

AFG3L2-Related Neurologic Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AFG3L2	18p11.21	Mitochondrial inner membrane m-AAA protease component AFG3L2	AFG3L2 database	AFG3L2	AFG3L2

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 AFG3L2-Related Neurologic Disorders (View All in OMIM)

604581	AFG3-LIKE MATRIX AAA PEPTIDASE, SUBUNIT 2; AFG3L2
610246	SPINOCEREBELLAR ATAXIA 28; SCA28
614487	SPASTIC ATAXIA 5, AUTOSOMAL RECESSIVE; SPAX5
618977	OPTIC ATROPHY 12; OPA12

Molecular Pathogenesis

AFG3L2 is a nuclear gene that encodes a subunit of the mitochondrial matrix AAA metalloprotease (m-AAA) complex. The AFG3L2 subunit can form homo-oligomeric or hetero-oligomeric protein complexes with the SPG7 protein. The m-AAA complex, located in the inner membrane of the mitochondria, has important functions in proteolysis, protein folding, and membrane trafficking of mitochondrial proteins [Koppen et al 2007, Ghosh Dastidar et al 2024].

Mechanism of disease causation

- **SCA28.** Most pathogenic variants reported to date exert a dominant-negative effect [Di Bella et al 2010]. Nearly all SCA28-associated variants are localized within the central protease loops and are thought to destabilize its structure, which is essential for substrate unfolding and degradation [Puchades et al 2019].
- **SPAX5** is caused by biallelic loss-of-function variants [Pierson et al 2011]. SPAX5-associated variants are close to the protease active site and are involved in substrate cleavage [Puchades et al 2019].
- **OPA12**-associated pathogenic variants are located in the ATPase domain and indirectly disrupt OPA1 processing, leading to mitochondrial fragmentation [Caporali et al 2020].

Table 6.

AFG3L2 Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_006796.1 NP_006787.2	c.1847A>G	p.Tyr616Cys	Pathogenic variants observed in 1 person w/SCAR [Tunc et al 2019]
	c.2167G>A	p.Val723Met	
	c.1894C>T	p.Arg632Ter	Pathogenic variants observed in 1 persons w/SCAR [Chiang et al 2021]
	c.2176G>A	p.Val723Met	
	c.1997T>G	p.Met666Arg	Pathogenic variants specifically assoc w/SCA28 [Cagnoli et al 2010, Edener et al 2010]
	c.2011G>A	p.Gly671Arg	
	c.2098G>A	p.Glu700Lys	

SCA = spinocerebellar ataxia; SCAR = spinocerebellar ataxia, autosomal recessive

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

Dr Giulia Coarelli is actively involved in clinical research at Paris Brain Institute (ICM, https://institutducerveau.org) regarding individuals with spinocerebellar ataxias and spastic paraplegias. She would be happy to communicate with persons who have any questions regarding the diagnosis of these disorders.

Dr Charlotte Mouraux is actively involved in clinical research within the Rare Movement Disorders Research Group (RMD, GIGA CRC Human Imaging, University of Liege, Belgium) regarding individuals with inherited movement disorders. She would be happy to communicate with persons who have any questions regarding diagnosis of these disorders.

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