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Spinocerebellar Ataxia Type 36 – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Asidan/SCA36, Costa da Morte Ataxia, SCA36

Manuel Arias, MD, PhD,[1] Beatriz Quintáns, PhD,[2] María García-Murias, MS,[2] and Maria J Sobrido, MD, PhD[2]

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Summary

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Clinical characteristics

Spinocerebellar ataxia type 36 (SCA36) is characterized by a late-onset, slowly progressive cerebellar syndrome typically associated with sensorineural hearing loss. Other common features are muscle atrophy and denervation, especially of the tongue, as well as pyramidal signs, thus overlapping with motor neuron disorders. Mild frontal-subcortical affective and cognitive decline may be present as the disease progresses. Brain MRI shows atrophy of the cerebellar vermis in initial stages, later evolving to a pattern of olivopontocerebellar atrophy.

Diagnosis/testing

The diagnosis is suspected based on clinical findings in the absence of primary causes of cerebellar dysfunction. It is supported by a family history consistent with autosomal dominant inheritance, which can include simplex cases (i.e., a single occurrence in a family). Confirmation of the diagnosis relies on detection of an abnormal hexanucleotide GGCCTG repeat expansion in *NOP56*. Affected individuals typically have alleles with 650 or more repeats. Such testing detects virtually 100% of affected individuals.

Author Affiliations: 1 Neurogenetics Group, Instituto de Investigación Sanitaria (IDIS), Department of Neurology, Complexo Hospitalario Universitario, Santiago de Compostela, Spain; Email: manuel.arias.gomez@sergas.es. 2 Neurogenetics Group, Instituto de Investigación Sanitaria (IDIS), Centro de Investigación Biomédica en red de Enfermedades Raras (CIBERER), Santiago de Compostela, Spain; Email: beatriz.quintans.castro@sergas.es; Email: maria.garcia.murias@usc.es; Email: ssobrido@telefonica.net.

Management

Treatment of manifestations: Treatment of SCA36 involves multidisciplinary specialists and focuses on routine exercise and physical therapy with attention to gait and balance, weight control, and walking aids to facilitate ambulation and mobility. Occupational therapy aids fine movement coordination; speech therapy and communication devices for those with dysarthria. Hearing loss may require hearing aids or cochlear implants, together with audiologic rehabilitation. Emotional and cognitive decline can be addressed in cognitive therapy, treatment of depression, and psychological support. Living space may need to be adapted to help with accessibility.

Prevention of secondary complications: Dietary assessment and feeding therapy programs can improve dysphagia and reduce the risk of aspiration.

Surveillance: At least annual evaluation by a neurologist or more frequently if manifestations are progressing. Annual or biannual evaluation by an otolaryngologist to monitor possible hearing loss. Surveillance of speech and ambulation.

Agents/circumstances to avoid: Alcohol and medications known to affect cerebellar function, as well as those affecting the inner auditory function. Avoidance of acoustic trauma (e.g., use of headphones, noisy environments).

Genetic counseling

SCA36 is inherited in an autosomal dominant manner. Penetrance is complete, although age-dependent. Offspring of affected individuals have a 50% chance of inheriting the *NOP56* pathogenic variant. Prenatal testing is possible for pregnancies at increased risk if the pathogenic variant has been identified in an affected family member.

Diagnosis

Suggestive Findings

The clinical suspicion of spinocerebellar ataxia type 36 (SCA36) is based on the presence of the following nonspecific findings:

- Midline cerebellar ataxia of late onset (usually between ages 40 and 60 years) and slow progression
- Dysarthria and appendicular ataxia generally following the gait imbalance
- Slowly progressive sensorineural hearing loss (SNHL) with onset usually a few years after the cerebellar manifestations
  - A drop of ≥40 dB in frequencies beyond 2500 Hz can be recorded through pure tonal audiometry.
  - Brain stem auditory evoked potentials are characterized by absence or reduced amplitude of waves I and II, consistent with a sensorineural hearing loss [García-Murias et al 2012, Ikeda et al 2013].
- Tongue atrophy and fasciculations, additional signs of motor neuron degeneration in some cases [García-Murias et al 2012, Ikeda et al 2012].

  Note: Peripheral nerve conduction velocities, both motor and sensory, are usually within normal range. Somatosensory evoked potentials may show mild abnormalities after stimulation in the lower limbs [García-Murias et al 2012].
- Other clinical features variably present: gaze-evoked nystagmus, eyelid ptosis, decreased vibration sense, and cognitive impairment

- On brain MRI: atrophy of the superior vermis in initial stages, global cerebellar atrophy in intermediate stages, and olivopontocerebellar atrophy in advanced stages
  - Cerebellar atrophy is a constant finding, usually starting in the upper vermis and progressing to the hemispheres.
  - Involvement of the pons and medulla with subcortical atrophy and dilatation of the fourth ventricle is present later on with a pattern of olivopontocerebellar degeneration; however, the "cross sign" brain stem T_2-weighted signal characteristic of other neurodegenerative diseases was not observed in SCA36.
  - White matter abnormalities are generally not a feature of this disease.
  - Cortical brain atrophy (especially of frontal areas) may be seen in advanced cases [Abe et al 2012, García-Murias et al 2012, Ikeda et al 2012].
- Family history consistent with autosomal dominant inheritance. Of note, the disease may not be recognized in previous generations because of late onset and/or mild manifestations. Thus, SCA36 should also be considered in simplex cases (i.e., single occurrence in a family) with undiagnosed ataxia, especially in geographic regions where families with SCA36 have been observed (see Prevalence) [García-Murias et al 2012, Sugihara et al 2012].

Establishing the Diagnosis

To establish the diagnosis of SCA36 in a proband requires identification of a **pathogenic (full-penetrance)** 6-bp (GGCCTG)n repeat located in intron 1 of *NOP56*. See Table 1.

Allele sizes

- **Normal alleles.** 3-14 GGCCTG repeats. Only a few population screenings have been published to date. The following may be a population-specific difference, but could also reflect different genotyping protocols.
  - The number of GGCCTG repeats varies from three to 14, with the nine-repeat allele being the most frequent in persons of northern European background [García-Murias et al 2012, Sarto et al 2013, Figley et al 2014].
  - Kobayashi et al [2011] reported a normal allele size of three to eight repeats in Japanese controls.
- **Alleles of uncertain significance.** Whether alleles of 15 to 650 repeats are large normal, expansion-prone, or pathogenic needs to be elucidated.
- **Pathogenic (full-penetrance) alleles.** 650 or more GGCCTG repeats. The largest pathogenic alleles reported to date are estimated to comprise about 2500 hexanucleotide repeats [Kobayashi et al 2011, García-Murias et al 2012].

Molecular Genetic Testing

Molecular genetic testing is performed as targeted analysis for pathogenic variants to determine the number of GGCCTG hexanucleotide repeats (see Molecular Genetics for details).

- **Normal alleles** are detected by conventional PCR with primers flanking the GGCCTG repeat region.
  - The presence of two normal-sized *NOP56* alleles rules out the diagnosis of SCA36.
  - If only one allele is detected, additional testing by repeat-primed PCR (RP-PCR) is required to determine if a second *NOP56* allele that is too large to detect by this method is present.
- **Pathogenic full-penetrance alleles** are detected by RP-PCR analysis specific for the GGCCTG hexanucleotide sequence.
  - The diagnosis of SCA36 is ruled out if one allele is detected by conventional PCR and RP-PCR does not detect an expanded allele.

- Although RP-PCR is highly sensitive, it does not determine the number of GGCCTG repeats [Kobayashi et al 2011]. Southern blot analysis of genomic DNA is necessary to determine the number of GGCCTG repeats in a pathogenic allele; however, exact sizing is not routinely necessary for unequivocally expanded alleles.

- **Alleles of uncertain significance** (15-650 repeats) are detected by the same two methods.
  - At the smaller end of the range (e.g., 15 to ~50 repeats) conventional PCR is appropriate.
  - Larger alleles can only be detected by RP-PCR and/or Southern blot analysis of genomic DNA.

Note: Beyond the normal allele range, no clear clinical utility has been demonstrated to date from knowing the exact repeat number; thus, estimation of allele size by Southern blot or other methods is not performed on a routine basis.

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 36

Gene [1]	Method	Variants Detected	Proportion of Probands with a Pathogenic Variant Detectable by Method
NOP56	Targeted analysis for pathogenic variants [2, 3]	Expanded (GGCCTG)n hexanucleotide repeats [4]	100%

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants.
2. Conventional PCR analysis detects normal-sized alleles (3-14 GGCCTG repeats) and expanded alleles in the lower range of alleles of uncertain significance.
3. Only RP-PCR and/or Southern blot analysis of genomic DNA can detect the presence or absence of a large expanded pathogenic GGCCTG hexanucleotide repeat.
4. Pathogenic allele size is ~650 to ≥~2500 GGCCTG repeats.

Clinical Characteristics

Clinical Description

The first clinical observations proposing the existence of a distinctive new type of spinocerebellar ataxia – later designated spinocerebellar ataxia type 36 (SCA36) – were reported independently by Ohta et al [2007] in Japan, and Arias and collaborators in families from Galicia (northwestern Spain) [Arias et al 2008]. The main features of SCA36 were detailed in the Galician patients [Arias et al 2012, García-Murias et al 2012] as well as in Japanese families in whom the molecular defect was first reported [Kobayashi et al 2011, Ikeda et al 2012]. Further knowledge of the clinical manifestations of SCA36 came more recently with thorough characterization of additional cases from Japan, Spain, and Italy [Sugihara et al 2012, de Fábregues et al 2013, Sarto et al 2013].

Individuals with SCA36 present with findings of midline cerebellar ataxia around age 50 years (mean 53 years, range 29 to 65 years), followed by dysarthria, appendicular ataxia, and impaired hearing. The first symptoms noticed by affected individuals are usually imbalance and lack of stability while walking. Disease progression is slow and most affected individuals are still able to walk unaided ten years after disease onset.

Dysarthria, present in an estimated 90% of affected individuals, is mostly ataxic in nature. However, in advanced disease the voice acquires a mixed quality with associated bulbar and/or pseudobulbar dysfunction.

Appendicular cerebellar signs are also present in virtually all patients, manifesting as dysmetria and dysdiadochokinesis.

Sensorineural hearing loss (SNHL) was observed in approximately 80% of affected individuals from very large Spanish kindreds, suggesting that hearing loss may be a manifestation of SCA36 [García-Murias et al 2012]. Although this was later confirmed in independent studies [Ikeda et al 2013], SNHL appeared to be less common in other SCA36 series [Sugihara et al 2012].

Although the precise onset of SNHL is difficult to establish, hearing deficit is generally noticed by the affected individuals within a decade following gait imbalance. In a few cases, hearing loss may appear before cerebellar symptoms, possibly as a result of additional environmental factors (e.g., acoustic trauma).

The hearing loss typically evolves slowly, from mild to moderate deficit by the sixth to seventh decades of life. In later stages of the disease, hearing loss can be severe, causing a severe disability in verbal communication. Ikeda et al [2013] found a statistically significant correlation between severity of hearing loss and SARA (Scale for the Assessment and Rating of Cerebellar Ataxia) score and the number of years since the onset of disease manifestations.

Nystagmus and/or abnormality of horizontal saccades are present in roughly 50% of persons with SCA36. Approximately 10% have ptosis. Vertical and lateral gaze limitation can also be present [Ohta et al 2007].

Motor neuron degeneration, including both upper and lower motor neuron involvement, is common. Tongue atrophy and fasciculations were observed in up to 60%-70% of individuals in some series [García-Murias et al 2012, Ikeda et al 2012]. Mild or moderate neurogenic dysphagia, mostly for liquids, may be evident, usually in later stages. More prominent bulbar signs have been noticed in some individuals [Ohta et al 2007]. The eventual need for nasogastric or percutaneous feeding is extremely rare, and may be considered in some patients with very advanced disease. This is consistent with the fact that upper neuron involvement (which generally leads to less severe manifestations than lower motor neuron involvement) is more likely the cause of bulbar signs in SCA36 than lower neuron involvement [García-Murias et al 2012, Sugihara et al 2012].

Significant atrophy and fasciculations affecting skeletal muscle of the trunk and limbs were reported in some families from Japan [Ikeda et al 2012]; however, these findings were not evident upon evaluation of other cases [García-Murias et al 2012, Sugihara et al 2012].

Upper motor neuron (pyramidal) features commonly include hyperreflexia and Babinski sign whereas significant weakness and spasticity (velocity-dependent resistance to passive muscle stretch) are rare.

Cognitive decline is usually mild to moderate and has a predominant frontal-dysexecutive pattern.

Mood changes including apathy or depression may also be present.

Other. Sensory disturbance, dysautonomia, and extrapyramidal features were not described in the largest published series of SCA36 and, thus, appear to be rare [García-Murias et al 2012, Ikeda et al 2012, Sugihara et al 2012]; however, in rare cases dystonia and parkinsonism have been reported [Miyashiro et al 2013, de Fábregues et al 2013].

Functional brain imaging. Single photon emission tomography 99mTc-ECD-SPECT studies obtained in a few patients demonstrated cerebellar hypoperfusion in early stages, as well as decline of cortical blood flow in more advanced stages, especially in frontal regions [Abe et al 2012].

Histopathology. Cell loss is observed in the Purkinje layer and dentate nucleus in the cerebellum. Reduced neuronal density is observed in the hypoglossal nucleus and anterior horn of the cervical spinal cord. Bunina-type eosinophilic cytoplasmic inclusions in the motor neurons (as seen in amyotrophic lateral sclerosis) were not detected [Ikeda et al 2012].

Genotype-Phenotype Correlations

Probands. Typically, individuals with the *NOP56* GGCCTG hexanucleotide repeat expansion present a late-onset cerebellar syndrome with or without some additional features (see Natural History). Based on the estimated 100 cases reported so far, SCA36 shows a rather characteristic phenotype with limited variability in its clinical presentation.

Although a tendency to show earlier and more severe symptoms has been observed in individuals with larger hexanucleotide repeat expansions, no statistically significant correlation has been demonstrated to date with:

- Allele size and age at onset [Kobayashi et al 2011, García-Murias et al 2012];
- SARA (Scale for the Assessment and Rating of Cerebellar Ataxia) score [Ikeda et al 2012];
- Cognitive or affective impairment [Abe et al 2012].

For more information see Molecular Genetics, Molecular Pathogenesis.

At-risk individuals. The age of onset, severity, specific symptoms, and progression of the disease vary and cannot be predicted by family history or *NOP56* GGCCTG hexanucleotide repeat size.

Penetrance

From the families reported to date, penetrance of an *NOP56* GGCCTG hexanucleotide pathogenic allele appears to be complete but age dependent. Although the first manifestations of SCA36 typically appear roughly between age 45 and 55 years, the range may be as broad as age 30 to 65 years.

Sugihara et al [2012] identified the *NOP56* expansion among some simplex cases of ataxia (i.e., single occurrence in a family), and suggested this observation might be explained by reduced penetrance of a pathogenic allele. On the other hand, the *NOP56* expansion was not detected in any general population controls from different studies, including 300 individuals from Japan [Kobayashi et al 2011] and 234 from Spain [García-Murias et al 2012].

Some individuals with SCA36 have reported that their parents lived to a very advanced age without signs of the disease [García-Murias et al 2012]. Although this observation could be explained by anticipation or reduced penetrance, retrospective clinical data from deceased individuals must be interpreted cautiously. Thus, further investigations of multigenerational kindreds with SCA36 are needed in order to address the issue of disease penetrance.

Anticipation

A characteristic of many neurodegenerative disorders caused by abnormal expansion of a nucleotide repeat sequence is genetic anticipation (i.e., an increase in severity and earlier onset of disease manifestations in successive generations). Statistically significant evidence of anticipation in SCA36 was not observed in the few large families with SCA36 in which parent-offspring data were available [Kobayashi et al 2011, García-Murias et al 2012, Ikeda et al 2012]. Although a slightly lower mean age of onset in successive generations (52.4 years versus 56.3 years) was reported in one kindred [García-Murias et al 2012], increased awareness could also have been a confounding factor.

Nomenclature

When Arias et al [2008] described a large number of affected individuals from Galicia and suggested it was a new type of ataxia (subsequently identified as SCA36) they referred to the disease as "Costa da Morte ataxia" after the toponym of that Atlantic region.

Similarly, since many Japanese with SCA36 lived in the western Japan region of Chugoku near the Asida river the authors named this disease "Asidan ataxia" [Abe et al 2012, Ikeda et al 2013].

Prevalence

The prevalence of spinocerebellar ataxia types varies among different countries. In general, SCA3 is the most frequent SCA worldwide [Sequeiros et al 2011], while SCA10 is more prevalent in Mexico [Matsuura et al 2002] and SCA7 is the most common SCA in Scandinavia [Johansson et al 1998]. The few available studies from Spain

showed a similar frequency (between 15% and 30%) for SCA2 and SCA3 among the autosomal dominant spinocerebellar ataxias [Pujana et al 1999, Infante et al 2005].

Fewer than 100 families with SCA36 have been reported to date and studies specifically designed to investigate the prevalence of SCA36 have not been performed. The prevalence of SCA36 appears to vary among different countries, with possible regional clusters of affected families.

In northwestern Spain (Galicia), SCA36 was the most frequent spinocerebellar ataxia, representing 6.3% of unselected persons with adult-onset ataxia, followed by SCA2 with 4.4%, whereas fewer than 2% had SCA1, SCA3, or SCA7. The frequency of SCA36 was as high as 21.3% when only strictly selected index cases were considered with a spinocerebellar syndrome and definitive autosomal dominant inheritance [García-Murias et al 2012]; however, an overestimation is possible, given the strict ascertainment criteria.

This prevalence is especially relevant for South America, given the long history of Galician emigration to Latin American countries. In fact, family members from the kindreds studied by García-Murias et al [2012] had emigrated to Argentina, Uruguay, Chile, and Mexico.

Persons with SCA36 were reported only anecdotally in Spanish regions other than Galicia. The authors are aware of at least three unrelated affected individuals from other areas of Spain, including the individual reported by de Fábregues et al [2013] and as yet unpublished cases [Authors, personal observation]. Whether or not any ancestral relationship exists between these individuals is as yet unknown.

In Japan the frequency of SCA36 found by different authors varied from 0.6% to 3.6% of the spinocerebellar ataxias, depending on whether all individuals with SCA or only those with autosomal dominant SCA were considered [Kobayashi et al 2011, Sugihara et al 2012]. Thus, among Japanese with ataxia, SCA36 has a relatively low frequency, far below that for SCA6 (~14%), SCA3 (~11%), SCA31 (8%-17%), and DRPLA (~5%), and also lower than other SCA types [Sakai et al 2010, Sugihara et al 2012] (see Hereditary Ataxia Overview).

In other countries

- **UK.** Screening of 269 individuals with inherited ataxia from the UK without mutation of the other commonly tested genes causing SCA failed to identifiy the *NOP56* expansion that causes SCA36 [Hersheson et al 2012].
- **Portugal.** Interestingly (given the geographic vicinity to Galicia) no individuals with the GGCCTG *NOP56* expansion were observed among some 100 Portuguese families with ataxia who did not have an established molecular diagnosis [Loureiro et al 2013].
- **Italy.** Sarto et al [2013] found that SCA36 accounts for an estimated 3% of families with autosomal dominant ataxia who do not have mutation of the other commonly tested SCA-related genes.
- **Poland.** Five families with SCA36 were identified [Sulek et al 2013].

In summary, the worldwide distribution of SCA36 is still largely unknown. Most families reported to date come either from northwestern Spain or from western Japan, with some possible clusters in other regions such as Italy or Poland, while virtually no cases were observed to date in other countries.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *NOP56*.

Differential Diagnosis

Given its spectrum of cerebellar and non-cerebellar clinical manifestations, spinocerebellar ataxia type 36 (SCA36) needs to be considered in the differential diagnosis of a range of disorders.

Hereditary ataxias

- **Autosomal dominant spinocerebellar ataxias.** SCA36 should be considered among the cerebellar-plus SCAs (Harding ADCA type I), which include SCA1, SCA2, and SCA3. However, unlike other ataxias in this group SCA36 does not generally affect life expectancy.

  In its initial stages SCA36 is more reminiscent of the pure cerebellar SCAs (ADCA type III), including SCA5, SCA6, SCA11, SCA26, SCA30, and SCA31, which should, therefore, be taken into account, especially in geographic areas where SCA36 has not been reported.

  The age of symptom onset of most of the SCAs included in ADCA type III is younger than that of SCA36 [Schöls et al 2004].

  Although sensorineural hearing loss (SNHL) is a cardinal feature of SCA36, it is not specific as it has also been reported in SCA31 [Owada et al 2005], and can be present in other SCAs as well [Hoche et al 2008, Ikeda et al 2011].

- **Late-onset autosomal recessive cerebellar ataxias.** Several typically early-onset ataxias can sometimes present later in life, including Friedreich ataxia (FRDA), ataxia with oculomotor apraxia type 1 and type 2, ataxia-telangiectasia, autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), and cerebrotendinous xanthomatosis.

  Although the autosomal recessive ataxias often have associated peripheral neuropathy, these disorders can also have pyramidal signs [Fogel & Perlman 2007]. While this is especially true for the spastic ataxias, late-onset FRDA can also include spasticity [Berciano et al 2002].

  As in SCA36, Friedreich ataxia can also include abnormal central auditory pathways [Rance et al 2008].

- **X-linked ataxias.** Fragile X-associated tremor/ataxia syndrome (FXTAS; see *FMR1*-related disorders) is another late-onset ataxia that can clinically resemble SCA36. Brain MRI (T_2-weighted sequences) shows a characteristic hyperintense signal in the middle cerebellar peduncles not observed in SCA36 [Berry-Kravis et al 2007].

See also Hereditary Ataxia Overview and Spinocerebellar ataxia: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Non-genetic ataxias. The differential diagnosis of a simplex case of SCA36 (i.e., a single occurrence in a family) is very broad and includes late-onset ataxias of diverse etiology including: toxic (alcohol, drugs), metabolic (vitamin E deficiency, Wernicke encephalopathy), paraneoplastic, and immune (Miller-Fisher syndrome, Bickerstaff encephalopathy, anti-GAD and other antibody-mediated syndromes, gluten ataxia). An acute or subacute onset and appropriate clinical context (e.g., known tumor, chronic intestinal disease), together with characteristic neuroimaging and/or cerebrospinal fluid findings are helpful diagnostic clues.

Mitochondrial cytopathies. Since hearing loss is also a common associated feature in mitochondrial cytopathies, these diseases must be considered in the differential diagnosis of ataxia with deafness (see Mitochondrial Disease Overview). For example, cerebellar signs, hearing impairment, and ophthalmoplegia are within the phenotype spectrum of *POLG*-associated disorders [Horvath et al 2006]. Compared to SCA36, mitochondrial disorders usually show multisystem involvement as well as a broad intrafamilial range in age of onset and clinical manifestations.

Motor neuron diseases. While tongue fasciculations and atrophy are core features in SCA36, significant signs of lower motor neuron involvement in other muscles are less frequently observed. Thus, SCA36 is unlikely when lower motor neuron involvement is the unique or main manifestation. Consistent with this, no instances of expansion of the *NOP56* GGCCTG hexanucleotide repeat were identified in the 154 individuals with

amyotrophic lateral sclerosis (ALS) studied by Kobayashi et al [2011], or in a larger panel of 352 persons with ALS [Figley et al 2014].

Likewise, no *NOP56* pathogenic expansions were identified in 214 Spanish individuals with spastic paraplegia, another group of disorders affecting the upper motor neurons [García-Murias et al 2012].

Degeneration of bulbospinal motor neurons has also been reported in DRPLA [Schöls et al 2004] and in SCA2 [Nanetti et al 2009].

C9orf72-associated neurodegeneration (caused by an intronic hexanucleotide expansion) has a broad phenotypic spectrum, and appears to be the most frequent genetic cause of ALS and frontotemporal dementia (FTD). It can also include cerebellar manifestations [Fogel et al 2012, Cooper-Knock et al 2014], and thus should be considered in the differential diagnosis of individuals who are in the advanced stage of SCA36. See *C9orf72*-Related Amyotrophic Lateral Sclerosis and Frontotemporal Dementia.

Multiple system atrophy, cerebellar type (MSA-C). The cerebellar form of multiple system atrophy (MSA-C) shares clinical similarities with SCA36 in its initial stages. However, other manifestations typical of MSA (dysautonomia, parkinsonism) do not occur or are very uncommon in SCA36 [García-Murias et al 2012].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 36 (SCA36) the following evaluations are recommended:

- Neurologic examination with appropriate scoring protocols:
  - SARA (Scale for the Assessment and Rating of Cerebellar Ataxia) is used to monitor disease severity.
  - The mini-mental state examination (MMSE) may be sufficient for the initial neurologic check-up; however, other cognitive tests more specifically directed to evaluate frontal-subcortical functions may be more appropriate as the disease progresses.
- Examination by an otolaryngologist and audiologist, with emphasis in a comprehensive characterization of degree and anatomic level of hearing dysfunction.
- Clinical genetics consultation and genetic counseling

Additional brain MRI is not necessary following the diagnosis of SCA36; however, it can be used for complementary follow-up evaluation.

Treatment of Manifestations

Specific treatment for SCA36 is currently not available. The therapeutic approach should be multidisciplinary and include the following:

- Physical and occupational therapy to improve gait, balance, and fine motor coordination. Special attention should be paid to activities of daily life.
- Regular physical exercise and weight control to reduce the effect of future balance and walking problems
- Walking aids to facilitate ambulation and mobility. The use of a wheelchair is rare; however, it may be necessary in advanced disease stages. Living space may need to be adapted to help with accessibility.
- Speech therapy and communication devices for those with dysarthria
- Dietary assessment and feeding therapy programs to improve dysphagia and reduce the risk of aspiration
- Depending on the severity of hearing loss and the relative impairment at different levels of the auditory tract, consideration of hearing aids on a case by case basis. The utility of cochlear implants in SCA36 is

unknown; however, they have been proposed for central auditory impairment in other neurodegenerative ataxias [Frewin et al 2013]. Audiologic rehabilitation and speech therapy can help improve the ability to distinguish words and speech patterns from background sounds, while also taking into account the dysarthria in the therapy program.
- Management of emotional and cognitive decline through cognitive therapy, treatment of depression, and psychological support.

Surveillance

The following routine monitoring is recommended after a diagnosis of SCA36 has been confirmed.

- At least annual evaluation by a neurologist or more frequently if symptoms are progressing
- Annual or biannual evaluation by an otolaryngologist to detect or monitor hearing loss
- Surveillance of speech and ambulation

In presymptomatic individuals who tested positive for the *NOP56* expansion, it is appropriate to start surveillance of neurologic status and hearing by age 40-45 years.

Agents/Circumstances to Avoid

Avoid the following:

- Alcohol, as well as drugs with possible side effects on cerebellar function (e.g., phenytoin, carbamazepine, metronidazole, amiodarone, lithium), or the inner ear (e.g., salicilates)
- Environmental noise at work and in everyday life (e.g., listening to loud music or videos directly through headphones)

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 36 (SCA36) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA36 have an affected parent.

- A proband with SCA36 may have the disorder as the result of a *de novo* pathogenic variant. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the pathogenic allele was *de novo*, the proportion of SCA36 caused by *de novo* pathogenic variants is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic allele include molecular genetic testing to determine if a *NOP56* GGCCTG hexanucleotide expansion is present. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation and/or lack of recognition of symptoms of cerebellar disease. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most of individuals diagnosed with SCA36 have an affected parent, the family history 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.

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 or has a *NOP56* GGCCTG hexanucleotide repeat expansion, the risk to the sibs of inheriting the pathogenic allele is 50%.
- The sibs of a proband with clinically unaffected parents are still at increased risk for SCA36 because penetrance is age related.

Offspring of a proband. Each child of an individual with SCA36 has a 50% chance of inheriting the pathogenic allele. On transmission, the GGCCTG hexanucleotide expansion may be longer or shorter than the *NOP56* allele from the affected parent.

Other family members. The risk to other family members depends on the status of the proband's parents. If a parent has a *NOP56* GGCCTG hexanucleotide repeat expansion and/or is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Testing of asymptomatic adults at risk for SCA36 is possible using the techniques described in Molecular Genetic Testing. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for SCA36, an affected family member should be tested first to confirm the molecular diagnosis of SCA36 in the family.

Testing for the *NOP56* GGCCTG expansion repeat pathogenic allele in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, lifestyle, financial matters, and occupation or career planning. Others may have different motivations including simply "the need to know."

Testing of asymptomatic at-risk adult family members usually involves pretest interviews in which the motives for requesting the test, the individual's knowledge of SCA36, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Another issue to consider is the implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and genetic counseling.

Testing of at-risk asymptomatic individuals younger than age 18 years. Consensus holds that individuals younger than age 18 years at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against such testing are that it removes the individual's choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of an individual with SCA36 has a pathogenic *NOP56* GGCCTG hexanucleotide repeat expansion or clinical evidence of the disorder beyond age 60 years, it is possible that the pathogenic variant is *de novo*. The possibility that a normal- or near-normal-sized *NOP56* allele had expanded to a full mutation cannot be ruled out based on current knowledge. Possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

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

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 Testing

Once a *NOP56* GGCCTG hexanucleotide repeat expansion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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
  www.ataxia.org.uk

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org

- **Galician Ataxia Association (AGA)**
  Centro Municipal Asociativo "Domingo García Sabell"
  Plaza Esteban Lareo, Bloque 17, Sótano
  15008 La Coruña
  Spain
  Phone: 34 981 24 09 85
  Email: ataxias.galicia@gmail.com

- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org
- **NCBI Genes and Disease**
  Spinocerebellar ataxia
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 601 037 982
  Email: info@fedaes.org
  fedaes.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

Molecular Genetics

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

Table A. Spinocerebellar Ataxia Type 36: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
NOP56	20p13	Nucleolar protein 56	NOP56	NOP56

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 36 (View All in OMIM)

614153	SPINOCEREBELLAR ATAXIA 36; SCA36
614154	NOP56 RIBONUCLEAR PROTEIN; NOP56

Molecular Pathogenesis

SCA36 is caused by the pathogenic expansion of a noncoding GGCCTG repeat in the first intron of *NOP56*. This gene encodes a 56-kd protein (nucleolar protein 56, Nop56p) which interacts with *NOP1* and *NOP58* to form the 60S ribosomal subunit. Nop56p belongs to the NOP5/NOP56 protein family involved in ribosomal RNA methylation and pre-rRNA processing [McKeegan et al 2009]. Nop56p is necessary for Myc-induced cell transformation and is hyperactivated in oncogenesis [Cowling et al 2014]. However, the pathogenic mechanisms of SCA36, including whether dysfunction of the Nop56 protein is actually involved, are still unknown.

C9orf72 ALS/FTD syndrome is also caused by a hexanucleotide repeat located in intron 1 of *C9orf72* [DeJesus-Hernandez et al 2011, Renton et al 2011]. The *C9orf72* expansion, which is typically associated with lower motor neuron disease, can also cause cerebellar manifestations [Simón-Sánchez et al 2012, Whitwell et al 2012]; however, this expansion appears to be uncommon among individuals with ataxia [Fogel et al 2012].

The presence of a large expanded pathogenic allele does not appear to change NOP56 transcript or protein levels in cells from individuals in whom novel *NOP56* splicing variants were not detected. Diverse mechanisms leading to a toxic effect of altered RNA metabolism have been proposed for repeat expansion disorders.

- The intronic expansion induces formation of intranuclear RNA foci in lymphoblastoid cell lines, which may disrupt normal transcription through sequestration or inactivation of splicing and other transcription factors [Kobayashi et al 2011]. The presence of RNA foci has also been reported in other SCAs [Daughters et al 2009, Sato et al 2009], in myotonic dystrophies type 1 and type 2, and in Huntington disease-like 2 [Rudnicki et al 2007].
- Another hypothesis regarding possible mechanisms contributing to SCA36 pathogenicity comes from the evidence that microRNA levels can be affected by repeat expansions. Kobayashi et al [2011] found that *MIR1292*, the gene located just downstream of the repeat, is downregulated in patient cells.
- The possibility that abnormal translation products originate from different reading frames on both stands of the elongated repeat (repeat associated non-ATG (RAN) initiated translation) – as suggested for other repeat expansion disorders [Cleary & Ranum 2013] – has not been investigated in SCA36.
- Changes in the local chromatin structure and epigenetic modifications could also be at play [Dion & Wilson 2009], and perhaps affect nearby genes. For instance, just upstream from *NOP56* is *TMC2*, a gene that is mainly expressed in the inner ear and thus may be crucial for auditory function. Pathogenic variants in *TMC1* cause hearing loss [Kurima et al 2002, Tlili et al 2008]. Whether dysfunction of *TMC2* could underlie sensorineural hearing loss in patients with SCA36 is unknown.

Future studies with more detailed measures are needed to fully understand genotype-phenotype relationships in SCA36. Limitations to such investigations include:

- Measuring the precise repeat size for large repeat expansions requires labor-intensive, operator-dependent methods such as Southern blot analysis.
- It is not known whether *NOP56* repeat size as measured in peripheral blood cells reflects the actual repeat number in affected tissues.
- Age of onset is difficult to establish and prone to ascertainment bias in slowly progressive neurodegenerative diseases.
- Severity scoring of many neurologic findings (e.g., imbalance, tremor, cognition) is based on clinical scales that can have significant inter-examiner (and other sources of) variability.

Gene structure. *NOP56* comprises 12 exons spanning 5786 bp. The coding region is 1782 bp long (NM_006392.3). Alternatively spliced *NOP56* isoforms have not been fully characterized. The (GGCCTG)n repeat which is pathogenic at more than 650 copies is located in the first intron of *NOP56*. The presence of a 6-bp indel polymorphism (rs28970277) 44 bp upstream from the pathogenic repeat must be taken into account in primer design and genotype interpretation. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Normal alleles are 3 to14 GGCCTG repeats in length; the nine-repeat allele is the most frequent [García-Murias et al 2012, Sarto et al 2013, Figley et al 2014]. Normal alleles are stable on intergenerational transmission.

Alleles of uncertain significance. The clinical implications, if any, of GGCCTG alleles between 15 and 650 repeats remain to be established. Alleles in this size range are not observed in the general population [García-Murias et al 2012, Sarto et al 2013, Figley et al 2014].

Pathogenic variants. Expanded alleles with 650 or more GGCCTG repeats have been described in diverse ethnic background, including individuals from Japan and several European countries (see Prevalence).

No ethnic-specific variants or characteristics of the SCA36 molecular defect have been reported to date.

Repeat-primed PCR (RP-PCR) can detect the presence or absence of an expanded hexanucleotide (GGCCTG) repeat. RP-PCR could also be used to estimate the size of alleles in the range of a few tens of repeats; however, the performance of this technique for allele sizing for SCA36 has not been validated [van der Zee et al 2013]. For

larger alleles, the RP-PCR technique is only useful to determine the existence of a pathogenic allele, not allele size. RP-PCR is a commonly used method of detecting large expansions of nucleotide repeats [Warner et al 1996].

Repeat instability. The size of a large expanded hexanucleotide GGCCTG repeat that is in the definitely pathogenic range (>650) is unstable on intergenerational transmission. Although increase and decrease of the GGCCTG repeat can be observed, increase in repeat size is more common. Thus, the size of the *NOP56* GGCCTG expansion may vary among members of the same family. Whether or how repeat instability may influence the phenotype is unclear.

- The mean increase of allele size reported in the large Galician kindreds studied by García-Murias et al [2012] was 1.8 kb, from ~1230 repeats to ~1530 repeats (i.e. an increase of ~300 repeats), over three successive generations. A larger allele size was noted in the individuals who inherited the variant from their father compared to those who inherited it from their mother [García-Murias et al 2012].
- Decrease in allele size has also been observed especially on maternal transmission [García-Murias et al 2012].

Table 2. *NOP56* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Benign	c.3+71_3+76GGCCTG(3_14) (3-14 GGCCTG repeats)	None	NM_006392.3 NP_006383.2
Pathogenic	c.3+71_3+76GGCCTG(650_?) (>650 GGCCTG repeats)	None	

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.

Normal gene product. Nucleolar protein 56 (also called nucleolar protein 5A) has 594 amino acids (NP_006383.2) and a molecular size of 56 kd. Nop56p belongs to the family of proteins containing a Nop domain, an alpha-helical ribonucleoprotein binding module required for ribosomal biogenesis [Hayano et al 2003, Liu et al 2007]. See Molecular Pathogenesis.

Abnormal gene product. *NOP56* (GGCCTG)n repeat expansions induce RNA foci and sequester the RNA-binding protein SRSF2. In addition, the transcription of *MIR1292*, a microRNA gene located just 19 bp 3' of the GGCCTG repeat, is significantly decreased [Kobayashi et al 2011]. See Molecular Pathogenesis.

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Chapter Notes

Author Notes

The Neurogenetics Group of the Instituto de Investigación Sanitaria de Santiago (IDIS) is a multidisciplinary team of clinical neurologists, geneticists, molecular biologists, and psychologists. The main research interests of the group are:

- Spastic paraplegias, spinocerebellar ataxias, and other movement disorders
- Molecular mechanisms of neurodegenerative and neuromuscular diseases
- Application of genomics, bioinformatics, and databases to understanding genotype-phenotype relationships
- Psychosocial and ethical aspects of translational neurogenetics and genetic counseling

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