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Spinocerebellar Ataxia Type 37

Synonyms: SCA37

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Summary

Clinical characteristics

Spinocerebellar ataxia type 37 (SCA37) is characterized by adult onset, dysarthria, slowly progressive gait and limb ataxia with severe dysmetria in the lower extremities, mild dysmetria in the upper extremities, dysphagia, and abnormal ocular movements (dysmetric vertical saccades, irregular and slow vertical smooth pursuit, slow vertical optokinetic nystagmus, and oscillopsia (visual disturbance in which objects appear to oscillate). In most individuals, the initial signs/symptoms include falls, dysarthria, or clumsiness followed by a complete cerebellar syndrome. A distinctive clinical feature is the presence of altered vertical eye movements in early stages of the disease, even preceding ataxia symptoms. Clinical progression is slow and affected individuals usually become wheelchair bound between ten and 33 years after disease onset.

Diagnosis/testing

The diagnosis of SCA37 is established in a proband by identification of a heterozygous ATTTC repeat insertion within *DAB1* by molecular genetic testing. All affected persons have 31-75 ATTTC repeats, flanked on both sides by polymorphic ATTTT repeats over 58 units.

Management

Treatment of manifestations: Currently, no treatment reverts the course of the disease. Speech therapy to improve communication and ameliorate dysphagia; thickness modification of food and fluids to prevent aspiration; physical therapy to train balance; use of external devices (e.g., canes or walkers) when needed to avoid falls; occupational/behavioral therapy.

Surveillance: Scale for the Assessment and Rating of Ataxia (SARA) score annually; electrooculographic tests may be performed every two years (cooperation required); brain MRI volumetry every two years.

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Genetic counseling

SCA37 is inherited in an autosomal dominant manner. All individuals diagnosed to date with SCA37 have an affected parent. Each child of an individual with SCA37 is at a 50% risk of inheriting the intronic ATTTC repeat insertion within *DAB1*. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the ATTTC repeat insertion within *DAB1* has been identified in an affected family member.

Diagnosis

The phenotypic manifestations of spinocerebellar ataxia type 37 (SCA37) are not specific and no formal diagnostic criteria exist; thus, the diagnosis of SCA37 rests on molecular genetic testing. However, if autosomal dominant inheritance is apparent, or if pure cerebellar ataxia with adult onset, initial dysarthria, and dysmetric vertical saccades are seen in a simplex case, SCA37 should be suspected.

Suggestive Findings

SCA37 **should be suspected** in individuals with the following clinical and imaging findings.

Clinical findings

- Dysarthria (scanning speech), often preceding other cerebellar signs
- Altered vertical and horizontal eye movements (e.g., dysmetric saccades, slow and irregular smooth pursuit, and slow optokinetic nystagmus). Abnormalities restricted to the vertical axis may be an initial and predominant feature.
- Progressive cerebellar gait ataxia (severe dysmetria in the lower extremities, mild in the upper extremities and trunk)
- Late eye movement abnormalities: nystagmus, oscillopsia, asymptomatic saccadic intrusions
- Late additional clinical findings: hand tremor, dysphagia
- Family history of similarly affected individuals

Imaging findings on brain MRI examination. Initial vermis atrophy rapidly evolving to diffuse cerebellar atrophy with sparing of the brain stem [Serrano-Munuera et al 2013]

Establishing the Diagnosis

The diagnosis of SCA37 **is established** in a proband with suggestive neurologic findings and a heterozygous ATTTC pentanucleotide repeat insertion within an ATTTT repeat, in a 5' UTR intron of *DAB1*, identified by molecular genetic testing [Seixas et al 2017, Corral-Juan et al 2018] (see Table 1).

Allele Sizes

Normal alleles have a repetitive ATTTT stretch of 7-400 units, which is not interrupted by ATTTC units, though 3% may be interrupted by AT-rich motifs; most (93%) bear ≤30 ATTTT repeats [Loureiro et al 2019].

Age-dependent penetrant alleles have an insertion of 31-75 ATTTC repeats [Seixas et al 2017, Corral-Juan et al 2018]. The ATTTC repeats are flanked by ATTTT repeats larger than 31 units on both sides. Both the ATTTT and ATTTC repeats appear to not be interrupted [Loureiro et al 2019]. Alleles of this size or larger are associated with presumed development of SCA37, assuming a normal life span.

There are no known alleles of **incomplete penetrance**.

Single-Gene Testing

Targeted analysis for the heterozygous ATTTC repeat insertion in *DAB1* should be performed by a PCR-based assay, followed by determination of the fragment size and sequencing.

- Long-range PCR followed by Sanger sequencing has performed reliably to unequivocally identify and size the pathogenic ATTTC repeat insertion. For very large ATTTT/ATTTC alleles size could be estimated by automated electrophoresis.
- Repeat-primed PCR (RP-PCR) may not be specific for pathogenic SCA37 ATTTC alleles and it is not recommended, due to the potential for false negative results.

Note: The intronic ATTTC repeat insertion is not detected by multigene panel analysis with next-generation sequencing because of the type and size of the repeat insert and its intronic noncoding localization within an Alu element in *DAB1*.

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 37

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DAB1	Targeted analysis for pathogenic variants [3]	100% [4]

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. Long-range PCR combined with Sanger sequencing has been shown to be a reliable method to detect and characterize the ATTTC repeat insertion (see Single-Gene Testing). Repeat-primed PCR (RP-PCR) may not be specific for pathogenic SCA37 ATTTC alleles and is not recommended, since it also has the potential for negative results.
4. Insertion of a variable number of ATTTC repeats flanked by two stretches of non-pathogenic polymorphic $(ATTTT)_n$ repeats in *DAB1* is the mutational mechanism in all families with SCA37 examined to date [Seixas et al 2017, Corral-Juan et al 2018].

Clinical Characteristics

Clinical Description

Spinocerebellar ataxia type 37 (SCA37) is characterized by a pure cerebellar ataxia phenotype [Serrano-Munuera et al 2013]. A distinctive clinical feature is initial dysarthria and the presence of altered vertical eye movements in early stages of the disease [Serrano-Munuera et al 2013, Corral-Juan et al 2018].

Age of onset and progression. In four Spanish kindreds, onset reported was typically in the fifth decade (mean age of onset: 43.3 years ± 9.9; range 25-64 years) and the mean disease duration was 49.5 years [Serrano-Munuera et al 2013, Corral-Juan et al 2018]. Clinical progression was slow and affected individuals usually became wheelchair bound between ten and 33 years after disease onset. A single individual with rapid progression has been reported to date. In 30 individuals with SCA37 of Portuguese descent, the mean age of onset was 35.7 years (range: 18-58 years) and the mean disease duration was 20 years (range: 3-54 years) [Seixas et al 2017].

Presentation. For most affected Spanish individuals, the initial symptoms included falls, dysarthria, and/or clumsiness, followed by a complete cerebellar syndrome. As a distinct clinical feature, abnormal vertical eye movements were detected in early stages of the disease [Serrano-Munuera et al 2013, Corral-Juan et al 2018]. Dysarthria was the first symptom identified in most of the affected individuals from the Portuguese kindreds, albeit with no reported data on vertical eye movements [Coutinho et al 2013, Seixas et al 2017].

Baseline MRI of the brain revealed general cerebellar atrophy with sparing of the brain stem in the individuals studied [Serrano-Munuera et al 2013]. Brain stem auditory evoked potentials yielded normal results. Electrocardiography, echocardiography, transcranial magnetic stimulation tests, and nerve conduction studies all were normal [Serrano-Munuera et al 2013].

Gait and limb ataxia

- Severe dysmetria in the lower extremities
- Mild dysmetria in the upper extremities, mainly irregular fast alternating movements and dysmetria with the left hand, and mild trunk ataxia. Hand postural and action tremor variably appear with disease progression [Corral-Juan et al 2018].

Dysphagia is usually noted about five years after onset of SCA37.

Ocular findings

- Abnormal ocular movements including dysmetric vertical saccades, irregular and slow vertical smooth pursuit, and slow vertical optokinetic nystagmus
- Individuals with long-standing disease showed these abnormalities also in the horizontal axis [Serrano-Munuera et al 2013, Corral-Juan et al 2018].
- Nystagmus
- Oscillopsia (visual disturbance in which objects appear to oscillate)

Individuals described with SCA37 to date do not have sensory deficits, extensor plantar reflexes, fasciculations, epileptic seizures, or cognitive impairment [Serrano-Munuera et al 2013, Corral-Juan et al 2018].

Life span is apparently not shortened.

Neuropathology. Postmortem neuropathology of two individuals with SCA37 showed severe loss of Purkinje cells with abundant astrogliosis, empty baskets, occasional axonal spheroids, and hypertrophic fibers by phosphorylated neurofilament immunostaining in the cerebellar cortex [Corral-Juan et al 2018]. The remaining cerebellar Purkinje neurons showed loss of calbindin immunoreactivity, aberrant dendrite arborization, nuclear pathology including lobulation, irregularity, and hyperchromatism, and multiple ubiquitinated perisomatic granules immunostained for DAB1. A subpopulation of Purkinje cells was found ectopically mispositioned within the cerebellar cortex. No significant neuropathologic alterations were identified in other brain regions, in accord with a pure cerebellar syndrome.

Genotype-Phenotype Correlations

A significant inverse correlation between ATTTC insertion size and age of onset is demonstrated in SCA37 [Seixas et al 2017, Corral-Juan et al 2018], with a sex-specific contribution of the ATTTC repeat size to the age of onset in male ($r = -0.96$; $p<0.0001$; $n = 9$), but not female transmissions ($r = -0.09$; $p<0.75$; $n = 14$) [Corral-Juan et al 2018].

Moreover, affected females presented at a significantly younger age of onset (average = 40.4 years; average number of ATTTC repeats = 51.9) than males (average = 49.0 years; average number of ATTTC repeats = 52.7) ($n = 23$; $p<0.021$) [Corral-Juan et al 2018].

In six Portuguese kindreds, the mean age at onset reported was 33.76 (range 18-58) in 21 females and 40.33 (range 27-57) in nine affected Portuguese males [Seixas et al 2017]. In these, a sex difference in the correlation of onset age with size of the ATTTC repeat insertion was not noted, though only approximately 46% of that variability (from late adolescence to the early 60s) was accounted for by ATTTC repeat size [Seixas et al 2017]. The average disease duration reported was 19.38 years (range 3-54) in 21 females and 21.44 years (range 5-40) in nine Portuguese males [Seixas et al 2017].

Penetrance

Lifelong penetrance in SCA37 was 100% in all described families, but penetrance is age dependent [Seixas et al 2017, Corral-Juan et al 2018].

Anticipation

No evidence of anticipation in the age at onset was identified in the three generations for which data are available from one large Spanish family [Serrano-Munuera et al 2013].

Intergenerational instability with increase in length of the ATTTC repeat (by 2-12 repeats) was reported in all seven paternal transmissions, but in only 9/16 (56%) of the maternal transmissions in Portuguese families [Seixas et al 2017]. In contrast, smaller increments of 2-5 ATTTC repeat units were reported in four of six transmissions in the Spanish families [Corral-Juan et al 2018]. In these families, none or smaller increments were observed when the mother was the transmitting parent. No ATTTC repeat contractions have been reported.

Thus, the $(ATTTC)_n$ insertion appears unstable, and even more so when the father is the transmitting parent.

Prevalence

To date, 66 affected individuals and seven asymptomatic individuals with the ATTTC repeat insertion within *DAB1* have been reported in ten kindreds from the south of the Iberian Peninsula [Serrano-Munuera et al 2013, Seixas et al 2017, Corral-Juan et al 2018]. A common geographic origin in all ten families is suggestive of a founder effect. To date, no individuals with SCA37 from other geographic areas have been reported. The estimated prevalence of SCA37 has been reported in Portugal as 0.20/100,000 (95% CI: 0.13-0.31) [Coutinho et al 2013].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DAB1*.

Interstitial deletions encompassing chromosome region 1p32.1-1p32.3 including *DAB1* have been identified in individuals with microcephaly and multiple congenital anomalies [Kehrer et al 2015].

Structural variants within the *DAB1* chromosome region have been associated with intellectual disability, autism, and dysmorphic features [Mulatinho et al 2008, Li et al 2013].

Differential Diagnosis

The ataxic gait and the overall clinical picture in persons with spinocerebellar ataxia type 37 (SCA37) are indistinguishable from those seen in other adult-onset inherited or acquired pure cerebellar ataxias. Nevertheless, initial dysarthria and early altered vertical eye movements may be suggestive of SCA37, particularly when consistent within the same family. When the family history suggests autosomal dominant inheritance, all other autosomal dominant spinocerebellar ataxias (SCAs) need to be considered (see Hereditary Ataxia Overview). SCAs commonly reported to show a pure cerebellar phenotype may be first investigated (e.g., SCA5, SCA6, SCA11, SCA26, SCA30, SCA31). SCA6 is the most common of these (see Table 2). Other SCAs with a complex phenotype may present also as a pure cerebellar ataxia, particularly at an early stage. As with other hereditary diseases, examination of multiple affected relatives at different stages of evolution may be helpful for differential diagnosis.

Table 2. SCAs with a Pure Cerebellar Phenotype to Consider in the Differential Diagnosis of SCA37

Disorder	Gene	Phenotype	Comments
SCA5 (OMIM 600224)	*SPTBN2*	• Pure slowly progressive cerebellar syndrome • Onset age range: 10-68 yrs; congenital & infantile onset also reported • Downbeat nystagmus, impaired smooth pursuit, & gaze-evoked nystagmus	Slower progression than in SCA37; persons w/ SCA5 remain ambulatory despite long disease duration.
SCA6	*CACNA1A*	• Adult-onset slowly progressive ataxia • Mild vibratory sensory loss • Occasional dysphagia • Horizontal & vertical nystagmus • Abnormal vestibuloocular reflex • Rare oculomotor findings in presymptomatic persons: ◦ Low-amplitude horizontal gaze-evoked nystagmus ◦ Significantly ↓ eye velocity for upward saccades ◦ Abnormal frequency of square-wave jerks ◦ ↓ gain for pursuit tracking	• Positional vertigo, downbeat nystagmus, & external ophthalmoplegia also reported in SCA6; not reported in SCA37. • Persons w/presymptomatic SCA37 may also have ↓ gain for pursuit tracking, but in SCA37 saccade velocity is normal & eye movement abnormalities initially affect the vertical axis.
SCA11	*TTBK2*	Relatively pure form of SCA	
SCA26 (OMIM 609306)	*EEF2*	• Pure SCA • Irregular visual pursuit movements	Dysmetric ocular saccades, slow optokinetic nystagmus, & anticipation not reported in SCA26
SCA30 (OMIM 613371)	Unknown [1]	• Relatively pure, slowly progressive SCA • Hypermetric saccades (typically horizontal & into downgaze) • Normal vestibuloocular reflex gain	Phenotype overlaps w/SCA37.
SCA31 (OMIM 117210)	*BEAN1*	• Pure cerebellar syndrome • Variable hearing loss of cochlear origin	Hearing loss of cochlear origin was reported in 1 person w/SCA37 but did not appear related to SCA37.

SCA = spinocerebellar ataxia
1. SCA30 was linked to 4q34.3-q35.1; the gene and molecular defect remain unknown.

The most common SCAs are those caused by polyglutamine expansions (e.g., SCA1, SCA2, SCA3/MJD, SCA6, SCA7, SCA17, DRPLA); these should also be considered in the differential diagnosis. However, they usually begin before age 30 years, may progress more rapidly, show brain stem involvement on MRI, and may have a complex clinical presentation with distinctive features (as is the case with retinopathy in SCA7). In simplex individuals or sibships (particularly with consanguineous parents), Friedreich ataxia should not be neglected in the differential diagnosis of any SCA, as it is relatively common and may present on occasion with late onset and "atypical" forms.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 37 (SCA37), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Physical examination

- Neurologic assessment
- Assessment of the full range of symptoms associated with a progressive cerebellar syndrome. Among a range of clinical scoring systems that have been described [Saute et al 2012], the Scale for the Assessment and Rating of Ataxia (SARA) [Schmitz-Hübsch et al 2006] provides a reliable and consistent assessment of most of the clinical features and progression of SCA37.
- Electrooculographic tests may properly assess progression at the onset of disease.
- Specific assessment of the cerebellar cognitive affective syndrome may be considered.
- Brain MRI examination
- Consultation with speech, physical, behavioral, and occupational therapists
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No curative treatment is available for individuals with SCA37. Palliative care includes the following:

- Speech therapy to improve communication and ameliorate dysphagia
- Thickness modification of food and fluids to prevent aspiration
- Physical therapy to train balance
- Use of external devices (e.g., canes or walkers) when needed to avoid falls
- Occupational/behavior therapy

Surveillance

The following are appropriate:

- SARA score annually. Note: SARA may not detect disease progression for the first five to seven years.
- Electrooculographic tests may be performed every two years (cooperation is required).
- Brain MRI volumetry every two years

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 37 (SCA37) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- All individuals diagnosed to date with SCA37 have an affected parent.
- A proven *de novo* ATTTC repeat insertion within the intronic ATTTT repeat in *DAB1* has not been reported to date.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- The family history of an individual diagnosed with SCA37 may appear to be negative because of failure to recognize the disorder in family members, age-related penetrance and early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected and/or is known to have the ATTTC repeat insertion within *DAB1*, the risk to the sibs of inheriting this variant is 50%.
  - An ATTTC repeat allele may expand further in length, resulting in transmission of an allele with a larger ATTTC repeat. While possible, no evidence of anticipation has been yet identified [Serrano-Munuera et al 2013].
  - In sibships with similar ATTTC repeat sizes, female sibs may present at a significantly younger age (see Genotype-Phenotype Correlations).
- However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for SCA37 because of the possibility of age-related penetrance in a parent (or the theoretic possibility of parental germline mosaicism).

Offspring of a proband. Each child of an individual with SCA37 has a 50% chance of inheriting the ATTTC repeat insertion within *DAB1*.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the ATTTC repeat insertion, the parent's family members may be at risk.

Related Genetic Counseling Issues

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

- Predictive testing for at-risk relatives is possible once the pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

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

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.

- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of SCA37, it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored. This scenario has not ever been reported in SCA37.

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the ATTTC repeat insertion within *DAB1* has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **Associação Portuguesa de Ataxias Hereditárias (APAHE)**
  Rua 25 de Abril n.º 82
  Castro Marim 8950-122
  Portugal
  Email: apaheportugal@gmail.com
  www.apahe.pt

- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  www.ataxia.org.uk

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

- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org
- **NCBI Genes and Disease**
  Spinocerebellar ataxia
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 34 983 278 029; 34 985 097 152; 34 634 597 503
  Email: sede.valladolid@fedaes.org; sede.gijon@fedaes.org; sede.bilbao@fedaes.org
  fedaes.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

Molecular Genetics

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

Table A. Spinocerebellar Ataxia Type 37: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
DAB1	1p32.2-p32.1	Disabled homolog 1	DAB1	DAB1

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 37 (View All in OMIM)

603448	DAB ADAPTOR PROTEIN 1; DAB1
615945	SPINOCEREBELLAR ATAXIA 37; SCA37

Molecular Pathogenesis

Spinocerebellar ataxia type 37 (SCA37) is a repeat expansion disorder caused by a heterozygous 5'UTR intronic insertion of 31-75 ATTTC repeats, flanked on both sides by an ATTTT repeat tract with more than 58 units each, in *DAB1*. The complex repeat tract has an overall configuration $(ATTTT)_{60\text{-}79}$ $(ATTTC)_{31\text{-}75}$ $(ATTTT)_{58\text{-}90}$ [Loureiro et al 2019]. Both the ATTTC and the ATTTT repeats are unstable. It is the $(ATTTC)_n$ insertion that is pathogenic, while pure $(ATTTT)_n$ stretches as large as 400 repeats are not [Seixas et al 2017]. Normal alleles can be interrupted by AT-rich motifs, whereas the pathogenic alleles have a pure $(ATTTC)_n$ flanked by ATTTT repeats [Loureiro et al 2019].

DAB1 functions downstream of reelin, a large glycoprotein secreted by neurons of the developing brain, in a signaling pathway that controls cell positioning in the developing brain and during adult neurogenesis. DAB1 docks to the intracellular part of the reelin very low-density lipoprotein receptor (VLDLR) and apoE receptor type 2 (ApoER2) and becomes tyrosine-phosphorylated following binding of reelin to neurons. In mice, pathogenic variants of Dab1 and Reelin generate highly similar phenotypes; *Dab1* mutation results in the

scrambler and yotari mouse phenotypes [Sheldon et al 1997]. Pathogenic variants in *VLDLR* cause *VLDLR*-associated cerebellar hypoplasia and pathogenic variants in *RELN* cause lissencephaly 2 (OMIM 257320).

Mechanism of disease causation. Several lines of evidence indicate that SCA37-related cerebellar neurodegeneration, like other repeat expansion disorders, occurs through a gain-of-function mechanism [Corral-Juan et al 2018].

The ATTTC insertion creates new putative XBP1 transcription factor binding motifs [Corral-Juan et al 2018]. XBP1 has been implicated in Purkinje cell degeneration in spinocerebellar ataxia type 17 (SCA17) [Yang et al 2014]. Moreover, the ATTTC insertion causes RNA-switch and overexpression of specific RNA isoforms (NCBI/GenBank accession: MK015668) in the SCA37 cerebellar cortex [Corral-Juan et al 2018]. These cerebellar RNA isoforms include exons of *DAB1* that have been implicated in migration deficits of cerebellar Purkinje cells [Yano et al 2010]. As in other spinocerebellar ataxias, such as SCA1 [Sánchez et al 2016], PI3K/AKT signaling has been shown to be altered in SCA37.

***DAB1*-specific laboratory technical considerations.** SCA37 is caused by an intronic insertion of 31 to 75 ATTTC repeats within a polymorphic ATTTT/AAAAT repeat in *DAB1*. Long-range PCR followed by Sanger sequencing analysis has been used to reliably identify and size the pathologic ATTTC repeat insertion (see Establishing the Diagnosis). For very large ATTTT/ATTTC alleles, size could be estimated by automated electrophoresis.

Repeat-primed PCR (RP-PCR) may not be specific for pathogenic SCA37 ATTTC alleles (since it would also show positive with the same amplification pattern of long ATTTT repeats) and has the potential for false negative and positive results; thus, it is not a recommended method.

Non-pathogenic allele. $(ATTTT)_{7–400}$

Pathogenic allele. $[(ATTTT)_{60–79}(ATTTC)_{31–75}(ATTTT)_{58–90}]$

Table 3. Notable *DAB1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Comment [Reference]
MK015668 NM_021080.4	$(ATTTC)_{31-75}$ [1] in an intron within *DAB1* [2]	Located in a 5'UTR intron, flanked by $(ATTTT)_n$ on both sides [Seixas et al 2017, Corral-Juan et al 2018]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. The $(ATTTC)_{31-75}$ insertion causes overexpression of an alternatively spliced transcript (NCBI/GenBank accession: MK015668) in the human cerebellum, the main site of SCA37 pathology [Corral-Juan et al 2018].

Chapter Notes

Author Notes

The authors have been experts on the genetic diagnosis of inherited ataxias since 1990. They have published more than 50 articles on ataxia research, identifying and describing a few novel spinocerebellar ataxia subtypes including SCA37.

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