



Review

Spinocerebellar ataxia type 10 – A review

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ABSTRACT

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant inherited ataxia caused by an expanded ATTCT pentanucleotide repeat in intron 9 of the *ATXN10* gene, on chromosome 22q13.3. SCA10 represents a rare form of SCA, until now only described in Latin America, particularly in Mexico, Brazil, Argentina and Venezuela. In Mexico and Brazil SCA10 represents the second most common type of autosomal dominant cerebellar ataxia. The phenotype described in Mexico, is characterized by the association of cerebellar ataxia with epilepsy, while in Brazil the SCA10 phenotype is that of a pure cerebellar ataxia. As yet unidentified genotypic variables may account for this phenotypic difference.

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1. Introduction

Autosomal dominant cerebellar ataxias, currently collectively known as spinocerebellar ataxias (SCAs), represent a heterogeneous group of neurodegenerative disorders primarily affecting the cerebellum and both its afferent and efferent connections, particularly brainstem, and spinal cord [1,2]. The classical clinical findings

of SCAs are progressive gait and limb cerebellar ataxia, associated with nystagmus, dysarthria, and ophthalmoparesis. SCAs may also include varying degrees of additional nervous system signs: other movement disorders (dystonia, parkinsonism, tremor, and, myoclonus), spasticity, peripheral neuropathy, cognitive impairment, epilepsy, autonomic disturbances, optic atrophy and retinopathy. Magnetic resonance imaging (MRI), has proved useful in demonstrating cerebellar atrophy with or without brainstem involvement and occasionally whole brain atrophy depending on the form of SCAs [2,3].

The prevalence of SCAs varies widely mainly according to ethnic distribution in most areas of the world where it has been studied.

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Table 1
Clinical and genetic aspects of SCA10 and other SCAs.

Clinical and genetic aspects	SCA10	ADCA-I ^a	ADCA-II ^a	ADCA-III ^a
Mean age of onset (years)	36	36	35	40 (SCA6 = 52)
Mutations	(ATTCT) ^b	SCAs 1–3, 12, 17 & DRPLA ^c : (CAG) ^{ex} SCAs 13, 27, 28:	SCA7: (CAG) ^{ex}	SCA6:(CAG) ^{ex} SCA8:(CTG/CAG) ^{ex} SCA31:(TGAA) ^{ex} SCAs 4, 5, 11, 14,15 (16) ^d
Correlation between size of repeats and age of onset	Inverse correlation	Inverse correlation for (CAG) ^{ex} disorders	Inverse correlation	Inverse correlation in SCA6; no correlation in SCA8
Cerebellar ataxia	100%	100%	100%	100%
Pyramidal signs	Mild	Often present except in SCA2	Often present	Mostly absent
Extrapyramidal signs	Exceptional	Occasional with SCAs 1–3, 7, 12, 17, 27 & DRPLA	Often present	Absent (young SCA14 patients may have axial myoclonus)
Epilepsy	Frequent in Mexico but exceptional in Brazil	Infrequently seen with SCAs 1–3, 13 & 17 Myoclonus epilepsy is common in DRPLA	Some patients	Absent
Peripheral neuropathy	Frequent in Mexico but absent in Brazil	Often present in SCAs 1–3, 17 & 27	Absent	Present and causes sensory ataxia in SCA4; Minor neuropathy in SCA6&8
Ethnic origin (by history)	Latin Americans of Amerindian admixtures	Worldwide DRPLA prevalent in Japan	Worldwide	Mostly mixed, but SCA31 exclusively in Japan

^a Autosomal dominant cerebellar ataxia (ADCA) classification by Harding [36], in which ADCA-I is associated with extracerebellar signs (optic atrophy/ophthalmoplegia/dementia/extrapyramidal features/amyotrophy); ADCA-II is associated with pigmentary retinal degeneration; and ADCA-III is characterized by pure cerebellar ataxia. Here ADCAs with peripheral neuropathy without extracerebellar CNS features (such as SCA4) are included in ADCA-III.

^b Ex: expansion of the repeat with the unit in preceding parentheses.

^c DRPLA: dentatorubral–pallidoluysian atrophy.

^d SCA15&16 are the same disorder. Mutations are unknown for SCA18–26, 29 & 30, and they are not listed in this table.

One epidemiological study from the Netherlands suggested that the prevalence of SCAs is 3/1000.00 [4] and another from Norway 4.2/100.000 [5]. The increasing number of SCA subtypes has reached up to 30 distinct loci with the most common being types 1–3 (Machado-Joseph disease), 6, and 7. SCA 3 is the most common subtype worldwide, with some expected geographic variations in prevalence [2,3]. A comparison between the clinical and genetic features of SCAs, using Harding's criteria (autosomal dominant cerebellar ataxias types I, II and III) [6] is shown in Table 1.

SCAs can also be viewed and grouped in regard to their specific molecular pathophysiology. Traditionally this is accomplished by dividing SCAs into three general groups: (i) those due to polyglutamine-coding CAG repeat expansions (SCAs 1–3, 6, 7, 17, and DRPLA); (ii) those due to non-coding repeat expansions (SCAs 8, 10 and 12) or insertion (SCA31), and SCAs caused by point mutations (SCAs 5, 11, 13–15 and 27) [2].

SCA type 10 is exclusively found in regions of Latin America, particularly in Mexico and Brazil, where it is the second most common SCA [7].

2. Spinocerebellar ataxia type 10 (SCA10): an overview

SCA10 is caused by an expansion composed of ATTCT pentanucleotide repeats, localized in intron 9 of the *ATXN10* gene on chromosome 22q13.1 [8]. This and SCA31, a new SCA subtype recently described in Japan, are the only human diseases known to be caused by pentanucleotide repeat mutations, ATTCT repeat expansion in SCA10 and TGGAA repeat insertion in SCA31 [9]. SCA10 gene encodes a protein of 475 KD, of largely undetermined function [8,10].

The number of the ATTCT repeat unit ranges from 10 to 29 in the normal population, whereas in affected SCA10 patients the pathological expanded alleles range from 800 to 4500 repeats (Fig. 1) [8,11]. The large gap between normal and potentially pathogenic repeat lengths opens up the possibility of the existence of an as yet unidentified “premutation” phenotype, [11]. However, a hint of this possibility was the description of an early-onset 14 year-old female patient with ataxia, found to have an SCA10 allele of 280 ATTCT repeats. Her mother carried exactly the same repeat expansion length and was asymptomatic, suggesting that expansions within this range could imply reduced penetrance [11].

Raskin et al. [12] described reduced penetrance associated with early-onset in a Brazilian family with SCA10. A 28-year-old female presented with early-onset cerebellar ataxia and epilepsy; her molecular testing showed an expansion of approximately 850 ATTCT repeats at the SCA10 locus. Similar SCA10 expansions of approximately 850 repeats were identified in 6 of 8 asymptomatic paternal relatives who were examined [12].

Alonso et al. [13] found similar findings in two Brazilian families with mixed Portuguese and Amerindian ancestry with SCA10. In the first, the proband, a 59 year-old woman with ataxia since the age of 50, mild pyramidal signs and axonal peripheral neuropathy, had a 400 ATTCT repeat expansion in the *ATXN10* gene. Two of her unaffected sibs aged 65, 56, and her 90 year-old unaffected father, had alleles of 360 (sibs) and 370 (father), demonstrating instability upon transmission most likely with reduced penetrance. In the second family from this study, the affected 56 year-old son with slowly progressive gait ataxia since the age of 20 inherited an allele of 750 repeats from his affected mother who had 760 repeats and had had symptoms since her teens. Other members of this family need to be examined before determining the penetrance of 750–760 repeats. These findings suggest that the repeat expansion threshold for pathogenesis should be lowered to 280 ATTCTs.

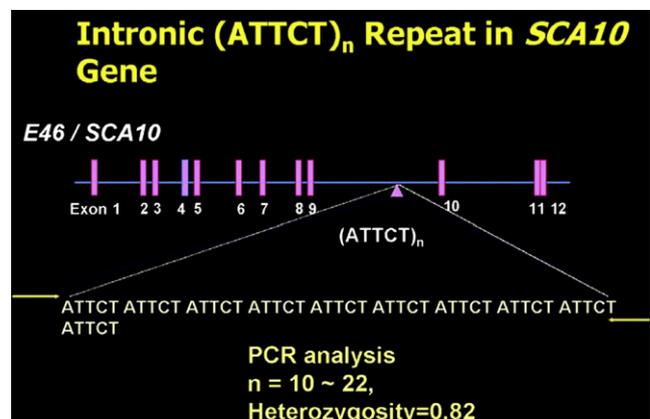


Fig. 1. SCA10 Gene.

cerebellar neurons [24], and over-expression of ataxin-10 results in differentiation and neurite extension of PC12 cells [10].

Current available data suggest that neither a gain nor a loss of physiological function of ataxin-10 is likely to play a major role in the pathogenesis of SCA10. First, the expanded ATTCT repeat is located within an intron, not coding for a protein. Furthermore, the expansion of the ATTCT repeat does not interfere with the transcription and post-transcriptional processing of the mutant *ATXN10* gene [11,26]. Therefore, the expanded ATTCT repeat is transcribed into expanded AUUCU repeats in the unprocessed mutant RNA transcript, and intron 9 containing the expanded AUUCU repeat is correctly spliced out [25]. Consequently, processed mRNA levels remain unaltered in spite of the repeat expansion. Furthermore, *ATXN10* knockout mice show embryonic lethality whereas mice heterozygous for ataxin-10 deficiency exhibit no disease phenotype [26]. Importantly, a recent report described asymptomatic patients with a reciprocal translocation that disrupted intron 2 of the *ATXN10* gene, suggesting that haploinsufficiency of *ATXN10* does not cause SCA10 in humans [27]. White et al. [25] showed that the expanded AUUCU RNA repeat from the mutant *ATXN10* transcript interacts with the nuclear protein hnRNP K, leading to apoptosis via massive translocation of protein kinase C delta to mitochondria, suggesting that SCA10 is likely to be caused by RNA-based gain-of-toxic-function mechanisms.

5. Genotype–Phenotype correlation

Important aspects, commonly related to forms of triplet repeat disorders, have been suggested in SCA10 [14,28]: (i) expanded ATTCT repeats in the *ATXN10* gene are unstable when paternally transmitted, however when transmission is maternal, repeat sizes are relatively stable; (ii) leukocytes, lymphoblasts, oral mucous membrane, and sperm cells show some degree of somatic and germline mosaicism, indicating mitotic and meiotic instability; (iii) the size of expanded ATTCT repeats and the pattern of somatic mosaicism were stable over a 5 year period; (iv) expansion size and age of onset were inversely correlated, however the correlation coefficient can only explain about one-third of the variation in age of onset, implying the existence of other determinants of age of onset; (v) anticipation is sometimes associated with intergenerational contraction rather than expansion as seen on some triplet repeat disorders. *De novo* expansion of the *ATXN10* repeat has not been identified. The patterns of phenotypic expression and instability are variable, both within and between families. One of the proposed mechanisms for these phenomena is that the configuration of the expanded alleles may vary, as shown by Matsuura et al. in 2006 [11]. In this study two SCA10 families were reported with distinct phenotypes with regard to the occurrence of seizures and the correlation of repeat length with age at onset. All patients in one of the families showed pure continuous repeats, whereas those in a second family showed a complex interruption pattern composed of two different septa repeat interruptions, ATTTTCT and ATATTCT. This pattern was similar in all the affected individuals through three generations, although the location of interruptions varied. These findings challenged the conventional wisdom that disease-causing expansions had to be composed of uninterrupted repeats, suggesting that the degree of purity of the expansions may be a disease modifier. This is the case in SCA 1, SCA 2, fragile X syndrome, Friedreich's ataxia, and myotonic dystrophy type 1 where sequence interruptions appear to stabilize repeat tracts, and the loss of interruptions is associated with instability and repeat expansion [8,11,29].

Although this theory remains to be tested it this may also explain the marked variability in frequency of seizures between families from Mexico and Brazil.

The disease severity does not seem to correlate with expansion size, suggesting that family-dependent factors influence disease severity. Also, no correlation between expanded allele size and seizure phenotype has been detected [14,28,30].

Longitudinal clinical data are needed to examine whether repeat size correlates with disease progression.

6. SCA10: the Brazilian variant

By 2004, all SCA10 patients described were of Mexican or mixed Mexican-American origin presenting with cerebellar ataxia, with seizures being an integral part of the phenotype and anticipation of disease onset in subsequent generations in some pedigrees [8,15,16,19,20]. In that same year, Teive et al. [7] presented the first non Mexican SCA10 cases belonging to five new unrelated Brazilian families and characterized their clinical phenotype and genotype. The study included a total of 74 affected family members, and the authors personally examined 28 of them. All cases had an admixture of Portuguese and Amerindian ancestry with equal gender distribution, and a mean age of onset of 34.8 ± 7.7 years old, ranging from 23 to 46 years. One of the most important findings of this study was the fact that, despite a mean disease duration time of 13.7 ± 12.7 years, all patients had a pure cerebellar phenotype with gait ataxia, dysarthria and nystagmus, only four of the patients had soft pyramidal signs, but, most importantly, none had seizures. Also, these patients did not exhibit clinical or electrophysiological signs of polyneuropathy and hepatic, cardiac, or hematologic abnormalities, in contrast to the Mexican SCA10 patients. Neuroimaging tests (either brain MRI or CT) showed predominantly cerebellar atrophy. From a molecular standpoint, among the eighteen patients from the five families who were genetically tested, the expanded *ATXN10* alleles ranged from 1350 to 2400 ATTCT repeats. The data from this study hinted at the presence of anticipation and the length of ATTCT repeat size inversely correlated with the age of onset in this series of SCA10 patients. More recent data from the same authors looking specifically for the frequency of epilepsy among 60 affected members from 10 SCA10 families found a frequency of seizures of 3.75% (three patients) similar to the expected for the general population of the same age [31]. Two of these patients presented with generalized tonic–clonic seizures, and the third had a complex epileptic syndrome with myoclonic, complex partial, and generalized tonic–clonic seizures. The third patient, who had been published separately [12], also had severe cognitive deficits, in addition to progressive cerebellar ataxia and epilepsy. Brain MRI of these three cases showed predominantly cerebellar atrophy and EEG tracings showed no specific abnormalities.

These findings established the fact that the phenotypic expression of the SCA10 mutation in Brazilian families, with predominantly pure cerebellar ataxia, definitely differs from that of Mexican families, where cerebellar ataxia is accompanied by epilepsy in the majority of cases. The phenotypic difference among these Brazilian and Mexican families cannot be explained in terms of differences in ATTCT repeat expansions as the size of these repeats overlapped [mean 1820 (1350–2400) in the Brazilian and 2838 (800–4500) in the Mexican series] [7,8,15,20].

Finally, another significant issue regarding the Brazilian SCA10 families reported so far is that they have some degree of Amerindian ancestry, in most cases mixed with European ancestry [7,9,13]. However, it should be noted that all Mexican patients also have physical characteristics of Amerindian admixture and a verified family history of seizures tracing back to an Amerindian ancestor in most cases. Thus, the SCA10 ATTCT repeat expansion mutation is likely to have started in an Amerindian population on the American Continent.

7. SCA10 in other South American countries

To date, SCA10 has been exclusively described in patients from Latin America, initially in Mexico and later in Brazil. In these countries, SCA10 represents the second most common SCA, after SCA 2 in Mexico and SCA 3 in Brazil [7,14,15].

In the last 3 years two reports of SCA10 patients from South American countries other than Brazil have been published. The first was from Argentina, published by Gatto et al. [32] in 2007, who reported one family of mixed Spanish and Amerindian origin with six affected members, two of whom were personally assessed and described in the study. These two cases presented with cerebellar ataxia, epilepsy, and cognitive abnormalities, associated with cervical dystonia in one patient and rigid akinetic parkinsonism in the other. Genetic analysis of the *ATXN10* gene revealed a heterozygous expansion of approximately 1100 ATTCT repeats in both cases. The second report, from Venezuela, has so far only been published as an abstract by Gallardo and Soto [33]. The authors described a three generation family with five affected members, one of whom is described in detail. The patient presented with complex partial and secondary generalized seizures, cerebellar ataxia, similar to the Mexican phenotype, plus cognitive dysfunction. Molecular testing on this patient showed an expansion of 4400 ATTCT in the *ATXN10* gene. Among the four remaining family members whose clinical information was described by history, three presented with epilepsy and one had head tremor. The comparison between these Brazilian, Mexican, Argentinean and Venezuelan patients is showed in Table 2 [7,15,32,33]. Interestingly, in these Argentinean and Venezuelan patients, as in Mexican cases with SCA10, the clinical picture is also associated with cerebellar ataxia and epilepsy.

In regards to ethnic origin, these Latin American patients also had Amerindian ancestry [7,32–34]. Almeida et al. [35] studied the ancestral origin of the ATTCT repeat expansion in SCA10, concluding that there is an ancestral common origin for SCA10 in Latin America, which might have arisen in an ancestral Amerindian population spreading later into the mixed population of Mexico, Brazil and probably to other Latin American countries.

8. Controversies and future directions in SCA10 research

There are several important unsettled issues regarding SCA10. First, the boundary of the ATTCT repeat number between normal alleles and SCA10 alleles is still uncertain. The allele with 280 ATTCTs has only been described in one affected female with no family history [11]. Therefore, it is possible that she had a sporadic ataxia and the allele with 280 repeats is a normal (non-pathogenic) allele. This would increase the upper boundary of the normal allele from 29 to 280. The same logic may be applicable to the putative reduced penetrance described with 360–370 alleles [13] and 850

repeats [12]. Such coincidental sporadic cases occurring in the indeterminate range of the repeat size would explain why some of these patients had early-onset despite their relatively small repeat expansions. However, alleles in the indeterminate range and sporadic ataxias are both rare. Thus, coincidental occurrences of this combination in multiple cases, support the current interpretation of the reduced penetrance associated with these alleles.

Second, the repeat size instability is not fully understood. While expanded repeats clearly show somatic and male germline instability, tissue examination is limited to blood and sperm. Critical somatic instability may lie in the cerebellum and cerebral cortex, the tissues targeted by the disease. This would be an important issue if the repeat expansion size, as we expect, determines the degree of pathogenicity in the targeted tissues. In addition to tissue-dependent repeat size variability, available data suggest that the somatic mosaicism occurs before patients reach their symptomatic state, but then the repeat appears to stabilize. Studies on genes involved in DNA repair, replicative and transcriptional activities on the repeat DNA, and oxidative stress and other environmental factors that regulate the tissue-specific and temporal variability during the fetal and postnatal development may provide potential targets for therapeutic interventions.

Third, the phenotypic disparity between Brazilian and Mexican families poses scientifically intriguing and clinically important questions. In addition to Mexicans, SCA10 patients in North American Indians, Central Americans and South Americans other than the Brazilians exhibit the seizure phenotype (unpublished data) while the Brazilians mostly have the ADCA-III phenotype. Is it cis elements or trans-acting factors unique to the Brazilians restrict the SCA10 phenotype to the cerebellum?

To date, all the Brazilian SCA10 patients have had strong Portuguese ancestry, except for the 24-year-old Brazilian woman with SCA10 and epilepsy, who had Spanish and Italian ancestries with only remote Portuguese ancestry. If Portuguese chromosomes have phenotype-altering genetic variation(s) in cis or in trans to the SCA10 mutation, identifying such variations could decipher the mechanism of epilepsy in SCA10. Environmental factors are difficult to exclude. However, the Argentinean SCA10 family, whose affected members exhibited the complex phenotype with epilepsy, lived in the region within several hundred kilometers of the State of Paraná, Brazil, site of most SCA10 clusters. Thus we may speculate that macro-geographic factors may not be the major determinants of the phenotypic disparity.

Fourth, data on the genotype–phenotype also pose challenging questions. Why the repeat expansion size does not always correlate with the age of onset; why anticipation in some cases is associated with repeat size contractions? Similar breakdowns of the correlation between the age of onset and the repeat expansion size have been observed in other repeat-expansion diseases and attributed to

Table 2

Clinical and genetic aspects of Brazilian, Mexican, Argentinean and Venezuelan patients with SCA10.

SCA10: clinical data	Brazilian patients	Mexican patients	Argentinean Patients	Venezuelan Patients
Number of patients	80	19	5	5
Age of onset (years)	35.5 (22–46)	26.7 (14–44)	35	14 (case report)
Number of ATTCT repeats	1820 (20)	2838	1100	4400
Correlation between size of ATTCT repeats and age of onset	Inverse correlation	Inverse correlation	–	–
Cerebellar ataxia	100%	100%	100%	100%
Pyramidal signs	6(Mild hyperreflexia), 3(mild spasticity)	6 (“Soft” pyramidal signs), 2 (pyramidal signs)	2	–
Epilepsy	3.75%	72.2%	100%	80%
Peripheral neuropathy	0%	66%	–	–
Ethnical origin (by history)	Amerindian ancestry 75%	Amerindian ancestry 100%	Mixed Spanish and Amerindian ancestry	?

(Adapted from reference [30]).

the somatic variability of the repeat size. A similar explanation may be applicable to these SCA10 cases.

Fifth, anticipation is documented, but what is its effect on the gene pool in the general population? Anticipation is a clinical genetic phenomenon in which the age of onset becomes progressively younger in successive generations in a given family with increasingly more severe disease. Anticipation in repeat-expansion disorders is explained by a coinciding progressive increase in repeat expansion size. The endpoint of anticipation is expected to be juvenile, congenital or even prenatal onset of the disease, which severely compromises the reproductive capability of future affected generations. Do we see such a decreased genetic fitness in SCA10? The Mexican neonate who showed hepatic, cardiac and hematological abnormalities [16] could represent such a case. However, if there is reproductive compromise in SCA10 families, then the prevalence of SCA10 cannot be maintained without a permutation gene pool to supply new mutations. In other words, if the prevalence is steady or increasing, there should be *de novo* mutations of the repeat. In other repeat expansion disorders, *de novo* mutations derive from alleles in the upper normal range, which occasionally expand into the full mutation range. Such *de novo* mutations have not been found in SCA10. Thus, issues of limited genetic fitness in anticipation and *de novo* mutations need to be addressed in further investigations.

Sixth, the origin of SCA10 mutation is an intriguing but unsettled question. The exclusive presence of SCA10 in the population with Amerindian admixture in the Americas suggests that SCA10 is a disease of the New World. It is likely that the original mutation occurred in the Amerindian population followed by admixture with European populations. However, whether the SCA10 mutation or putative premutations existed in the Amerindian ancestors before their migration to the Americas is unclear. Haplotype studies suggest that both Mexican and Brazilian SCA10 mutations share the origin of their mutations, and perhaps, the interrupted repeat expansion preceded the pure repeat expansion. It remains to be investigated how these two different expansion patterns developed.

Finally, the pathogenic mechanism triggered by this pentanucleotide repeat expansion is a therapeutically relevant issue. The RNA-mediated toxic gain of function is a convincing model of the pathogenic mechanism of SCA10. However, this model has been examined only in peripheral cells derived from patients with SCA10 and the brain of a transgenic mouse model that expresses the expanded AUUCU repeat transcript. Demonstrating this mechanism in the brain of a patient with SCA10 is imperative before concluding that this is the main pathogenic mechanism of human SCA10. It should also be pointed out that the effect of the toxic RNA accumulation may not be limited to the sequestration of hnRNP K. Other proteins or nucleic acids may interact with the expanded AUUCU repeat and alter neuronal functions. However, alleviation of the mechanism by silencing the expanded AUUCU repeat transcript by RNAi technology raises a hope for therapeutic intervention. It is important to be able to demonstrate that a similar approach to silence the toxic RNA works in the transgenic mouse model which has a robust ataxia and seizure phenotype.

9. Conclusion

Among approximately 30 types of SCAs, SCA10 is, in general, rare. However, in specific geographic regions and ethnic populations, including Mexico, Brazil, (where it represent the second most common type) and possibly other Latin American countries, SCA10 should be considered as a common cause of autosomal dominant cerebellar ataxia. The clinically, characteristic presentation, as described so far, is that of a relatively slowly progressive pure cerebellar ataxia in Brazilian patients, while in Mexico, and in the

single family reports from Argentina and Venezuela, the phenotype is marked by epilepsy as an intrinsic feature of the disease.

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