ATAXIA GLOBAL INITIATIVE 1ST AGI REGIONAL CONFERENCE: LATIN AMERICA

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DISCLOSURE:

HAGT has received grants from educacional activities with:

- **Biogen, Knight, and Teva.**

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OBJECTIVE:

- **The meeting aims to highlight the perspectives of leading clinical investigators from Latin America, sharing their experiences in the study and management of hereditary ataxias, and discussing how AGI can further support clinical trial development in Latin America and the Caribbean.**

OUTLINE

Introduction

History of Hereditary Ataxia Outpatient Clinic (Hospital de Clínicas, The Federal University of Paraná)

Hereditary cerebellar ataxias research

- **Collaborative studies in hereditary cerebellar ataxias**

Future perspectives

INTRODUCTION

Hereditary Ataxias Outpatient Clinic of the Neurology Service of the Department of Internal Medicine of the Hospital de Clínicas of the Federal University of Paraná (Curitiba, Paraná, Brazil):

- **The Hereditary Ataxias Outpatient Clinic attends 16 patients per week, with:**
  - **Clinical assessment protocols, for autosomal recessive cerebellar ataxias (ARCAs), autosomal dominant cerebellar ataxias (SCAs), X-linked and mitochondrial cerebellar ataxias**
  - **Routine MR imaging**
  - **Molecular genetic exams (in collaboration with other national and international centers)**
  - **Symptomatic treatment**
  - **-Genetic counseling**

HISTORY

The Hereditary Ataxias Outpatient Clinic was founded in 1989, at the Hospital Clinics of the Federal University of Paraná in the city of Curitiba, Paraná, Brazil, with Drs. Walter Olesckho Arruda and Hélio A. Ghizoni Teive:

Arq Neuropsiquiatr 2007;65(4-A):965-968

THE HISTORY OF SPINOCEREBELLAR ATAXIA TYPE 10 IN BRAZIL

Travels of a gene

Hélio A.G. Teive[1], Walter O. Arruda[2], Salmo Raskin[3], Tetsuo Ashizawa[4], Lineu César Werneck[1]

ABSTRACT - The authors report the history of spinocerebellar ataxia 10 (SCA10), since its first report in a large Portuguese-ancestry Family with autosomal dominant pure cerebellar ataxia, till the final identification of further families without Mexican ancestry. These families present a quite different phenotype from those SCA10 families described in Mexico.

KEY WORDS: spinocerebellar ataxia, spinocerebellar ataxia type 10, "pure" cerebellar ataxia.

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1st August 1994

Dear Dr. Arruda,

We are still working on the da Luz family in terms of linkage analysis. They do not appear to map to chromosome 14 (where the Machado-Joseph locus is) but we are still working on chromosome 12. We are rather low on DNA from some individuals as there was not much in the original tubes. I wonder if you have any left from the original extractions. If there is some I would be very grateful to receive it.

With best wishes,

Yours sincerely,

Anita Harding MD FRCP
PROFESSOR OF CLINICAL NEUROLOGY

Dr. W.O. Arruda
Rua Goncalves Dias 713
80240-340 Curitiba PR
Brasil

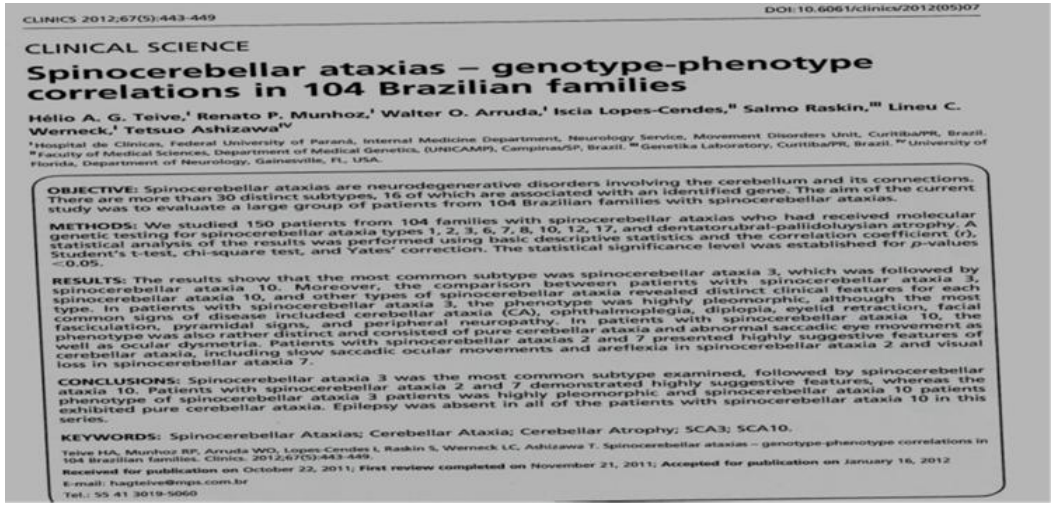
Figure. Anita Harding's letter reporting the results of genetic studies in the first described family with SCA type 10 in Brazil (W.O. Arruda, 1988).

HEREDITARY ATAXIAS RESEARCH- SCAS:

› Neurology. 1996 Jan;46(1):214-8. doi: 10.1212/wnl.46.1.214.

Frequency of spinocerebellar ataxia type 1, dentatorubropallidoluysian atrophy, and Machado-Joseph disease mutations in a large group of spinocerebellar ataxia patients

I Silveira [1], I Lopes-Cendes, S Kish, P Maciel, C Gaspar, P Coutinho, M I Botez, H Teive, W Arruda, C E Steiner, W Pinto-Júnior, J A Maciel, S Jerin, G Sack, E Andermann, L Sudarsky, R Rosenberg, P MacLeod, D Chitayat, R Babul, J Sequeiros, G A Rouleau



CLINICS 2012;67(5):443-449 DOI:10.6061/clinics/2012(05)07

CLINICAL SCIENCE

Spinocerebellar ataxias – genotype-phenotype correlations in 104 Brazilian families

Hélio A. G. Teive,[I] Renato P. Munhoz,[I] Walter O. Arruda,[I] Iscia Lopes-Cendes,[II] Salmo Raskin,[III] Lineu C. Werneck,[I] Tetsuo Ashizawa[IV]

[I]Hospital de Clínicas, Federal University of Paraná, Internal Medicine Department, Neurology Service, Movement Disorders Unit, Curitiba/PR, Brazil. [II]Faculty of Medical Sciences, Department of Medical Genetics, (UNICAMP), Campinas/SP, Brazil. [III]Genetika Laboratory, Curitiba/PR, Brazil. [IV]University of Florida, Department of Neurology, Gainesville, FL, USA.

OBJECTIVE: Spinocerebellar ataxias are neurodegenerative disorders involving the cerebellum and its connections. There are more than 30 distinct subtypes, 16 of which are associated with an identified gene. The aim of the current study was to evaluate a large group of patients from 104 Brazilian families with spinocerebellar ataxias.

METHODS: We studied 150 patients from 104 families with spinocerebellar ataxias who had received molecular genetic testing for spinocerebellar ataxia types 1, 2, 3, 6, 7, 8, 10, 12, 17, and dentatorubral-pallidoluysian atrophy. A statistical analysis of the results was performed using basic descriptive statistics and the correlation coefficient (r), Student's t-test, chi-square test, and Yates' correction. The statistical significance level was established for *p*-values <0.05.

RESULTS: The results show that the most common subtype was spinocerebellar ataxia 3, which was followed by spinocerebellar ataxia 10. Moreover, the comparison between patients with spinocerebellar ataxia 3, spinocerebellar ataxia 10, and other types of spinocerebellar ataxia revealed distinct clinical features for each type. In patients with spinocerebellar ataxia 3, the phenotype was highly pleomorphic, although the most common signs of disease included cerebellar ataxia (CA), ophthalmoplegia, diplopia, eyelid retraction, facial fasciculation, pyramidal signs, and peripheral neuropathy. In patients with spinocerebellar ataxia 10, the phenotype was also rather distinct and consisted of pure cerebellar ataxia and abnormal saccadic eye movement as well as ocular dysmetria. Patients with spinocerebellar ataxias 2 and 7 presented highly suggestive features of cerebellar ataxia, including slow saccadic ocular movements and areflexia in spinocerebellar ataxia 2 and visual loss in spinocerebellar ataxia 7.

CONCLUSIONS: Spinocerebellar ataxia 3 was the most common subtype examined, followed by spinocerebellar ataxia 10. Patients with spinocerebellar ataxia 2 and 7 demonstrated highly suggestive features, whereas the phenotype of spinocerebellar ataxia 3 patients was highly pleomorphic and spinocerebellar ataxia 10 patients exhibited pure cerebellar ataxia. Epilepsy was absent in all of the patients with spinocerebellar ataxia 10 in this series.

KEYWORDS: Spinocerebellar Ataxias; Cerebellar Ataxia; Cerebellar Atrophy; SCA3; SCA10.

Teive HA, Munhoz RP, Arruda WO, Lopes-Cendes I, Raskin S, Werneck LC, Ashizawa T. Spinocerebellar ataxias – genotype-phenotype correlations in 104 Brazilian families. Clinics. 2012;67(5):443-449.

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› Clin Neurol Neurosurg. 2019 Sep;184:105427. doi: 10.1016/j.clineuro.2019.105427. Epub 2019 Jul 10.

Spinocerebellar ataxias in Southern Brazil: Genotypic and phenotypic evaluation of 213 families

Fábio A Nascimento [1], Vinícius O R Rodrigues [2], Fernando C Pelloso [3], Carlos Henrique Ferreira Camargo [4], Adriana Moro [5], Salmo Raskin [6], Tetsuo Ashizawa [7], Hélio Afonso Ghizoni Teive [8]

Affiliations + expand

PMID: 31323545 DOI: 10.1016/j.clineuro.2019.105427

Abstract

Objectives: To describe and correlate the genotype and phenotype of patients diagnosed with SCAs in southern of Brazil.

Patients and methods: Data were collected from the records of our ataxia outpatient clinic. We included 460 patients from 213 families, who were divided into four groups: SCA3, SCA10, Other SCAs and Undetermined.

Results: The most frequent type was SCA3 (45.7%), followed by SCA10 (18.3%), SCA2 (6.5%), SCA1 (4.3%), SCA7 (1.8%), and SCA6 (0.65%). The Undetermined group represented 22.8% of all patients. We observed a high frequency of SCA10 when compared to data from other studies, which can be explained by a founder effect in our region. Statistically significant differences were found for several symptoms when comparing SCA groups, especially lid retraction ($p < 0.001$), ophthalmoplegia ($p < 0.001$), visual loss ($p < 0.001$) and slow saccades ($p < 0.001$) which may help clinically differentiate SCAs and allow neurologists to request the right confirmatory genetic test and define prognosis. Also, the prevalence of epilepsy in SCA10 patients was lower than usual (4.8%), suggesting a genetic variation of the disease.

Conclusion: Although SCA3 remains the most common, we observed a high frequency of SCA10 in our region. In addition, some symptoms and signs might help differentiate the SCAs.

HEREDITARY ATAXIAS RESEARCH – SCA3

Review > Arq Neuropsiquiatr. 1991 Jun;49(2):172-9. doi: 10.1590/s0004-282x1991000200010.

[Machado–Joseph disease: description of 5 members of a family]

[Article in Portuguese]

H A Teive [1], W O Arruda, P C Trevisol-Bittencourt

Affiliations + expand

PMID: 1810235 DOI: 10.1590/s0004-282x1991000200010

Abstract

The authors report the clinical and laboratorial findings of 5 affected members (all males) of a family with Machado-Joseph disease. The mode a inheritance was autosomal dominant. The mean onset age was 38 years (range 30-50 years). The clinical picture was pleomorphic and included cerebellar ataxia, external ophthalmoplegia with bulging eyes, extrapyramidal/pyramidal syndromes, amyotrophy with fasciculations and peripheral neuropathy, in variable degrees of severity. In one patient parkinsonian rigidity was greatly improved with the use of trihexaphenidyl and L-dopa. CT scan examinations disclosed a variable degree of cerebellar atrophy, with mild cerebral atrophy in one patient. Brainstem evoked potentials were normal in two patients. EMG showed denervation in three patients. Muscle biopsy (gastrocnemium) with histochemical studies revealed chronic muscle denervation in four cases. Sural nerve biopsy with conventional pathological study was normal in four cases. This family was living in Florianopolis, Santa Catarina, where there is a great number of Portuguese descendants from the Azores Islands. The worldwide presence of the disease seems to result from the genic diffusion of the disease with the Portuguese emigration during the Great Navigations Era and with some later emigratory settlement.

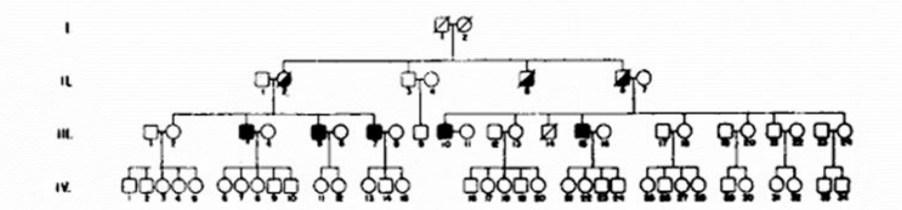
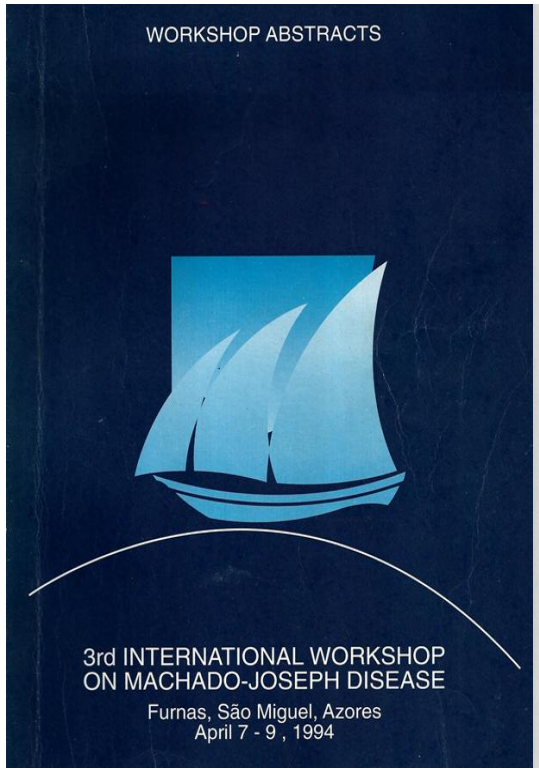


Fig. 1 — Heredograma da família a que se refere o estudo de 5 casos.

Sinais e sintomas	Pacientes III-3	III-5	III-7*	III-10	III-15
Dismetria	+	+			+
Dissdiadococinesia		+	+		+
Disartria		+	+		+
Nistagmo	+		+	+	+
Manobra do rechaço (+)		+			
Tremor			+		
Marcha atáxica	+	+	+	+	+
Oftalmoplegia	+	+			+
Diplopia		+			+
Bulging eyes		+	+		+
Disfagia		+			+
Reflexo do vômito (++)		+			+
Fraqueza muscular		+			+
Fasciculações					
Língua		+		+	
Face					+
Membros		+	+	+	+
Mioquimia					+
Atrofia muscular		+			+
Espasticidade				+	+
Hipotonia		+			
Hiperreflexia					+
Hiporreflexia		+			
Sinal de Babinski					+
Hipoestesia tátil		+			
Hipoestesia dolorosa		+			
Hipopalestesia		+			
Rigidez muscular			+	+	+
Bradicinesia			+		
Postura distônica					+

Tabela 1 — Sinais e sintomas neurológicos nos pacientes estudados.

HEREDITARY ATAXIAS RESEARCH- SCA3



MACHADO-JOSEPH DISEASE IN SOUTHERN BRAZIL

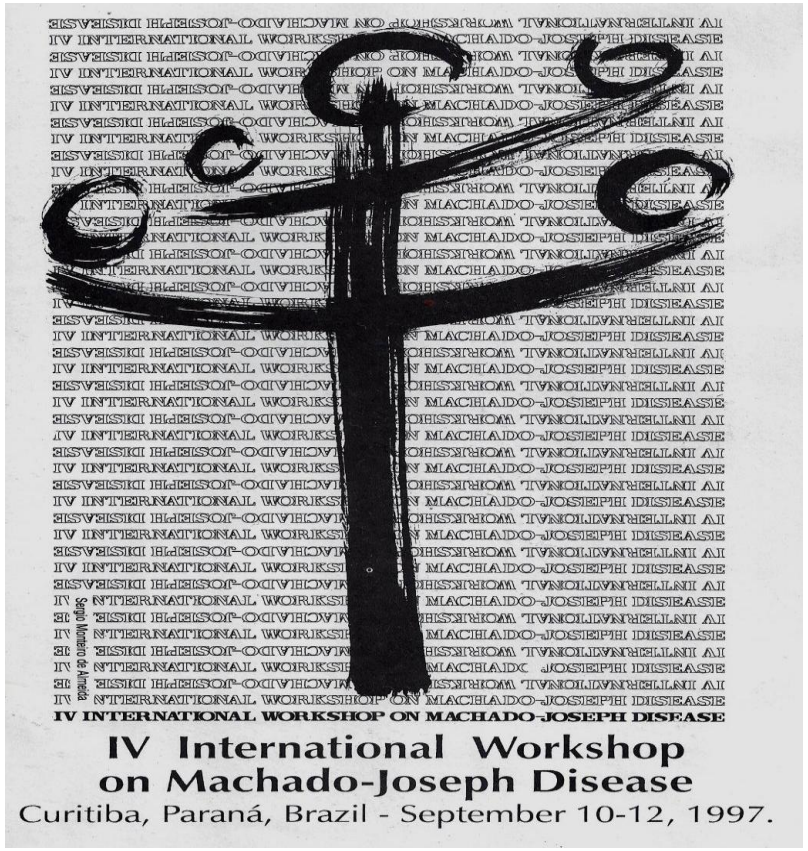
Teive H.A.G., Arruda W.O., Trevisol P.C.B.
Grupo de Estudos de Ataxias Hereditárias, Sociedade Paranaense de Ciências Neurológicas, Curitiba, PR, Brazil

The authors studied 44 patients out of 11 families with late onset cerebellar ataxia (LOCA).

All families live in Southern Brazil, in the states of Santa Catarina and Paraná, and all of them have a Portuguese-Azorean background. The patients were divided into two groups: GROUP 1 - 19 patients with clinical diagnosis of Machado-Joseph disease (MJD), according to the criteria of Lima and Coutinho (types 1, 2 and 3); GROUP 2 - 25 patients with LOCA undergoing investigation, with a clinical picture heralded by cerebellar ataxia and external ophthalmoplegia. Some of these patients will probably turn out to have MJD. The authors reviewed the history of Portuguese/Azorean immigration to Southern Brazil, as well as the clinical, neuroradiological, and neurophysiological data collected from these kindreds.

Professor Paula Coutinho´s group and Hélio Teive, 1994

HEREDITARY ATAXIAS RESEARCH- SCA3



IV International Workshop on Machado-Joseph Disease

Curitiba, Paraná, Brazil September 10-12, 1997.

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HEREDITARY ATAXIAS RESEARCH- SCA10

Clinical phenotype of Brazilian families with spinocerebellar ataxia 10

H.A.G. Teive, MD; B.B. Roa, PhD; S. Raskin, MD, PhD; P. Fang, PhD; W.O. Arruda, MD; Y. Correa Neto, MD; R. Gao, MD; L.C. Werneck, MD, PhD; and T. Ashizawa, MD

Abstract—Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant ataxia caused by an ATTCT repeat expansion in an intron of the SCA10 gene. SCA10 has been reported only in Mexican families, in which the disease showed a combination of cerebellar ataxia and epilepsy. The authors report 28 SCA10 patients from five new Brazilian families. All 28 patients showed cerebellar ataxia without epilepsy, suggesting that the phenotypic expression of the *SCA10* mutation differs between Brazilian and Mexican families.

NEUROLOGY 2004;63:1509–1512

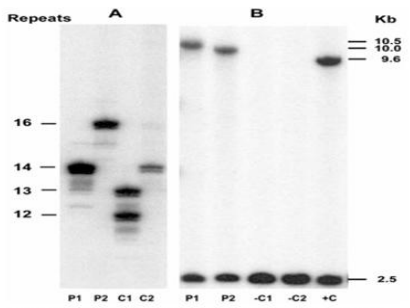


Figure 2. Molecular diagnosis of spinocerebellar ataxia type 10 (SCA10) in Brazilian patients. (A) The PCR analysis showed a single normal allele in two SCA10 patients (P1 and P2). C1 and C2 are normal controls with known genotypes 12/13 and 14/14 SCA10 repeats. (B) The SCA10 expansions were identified by Southern analysis of EcoRI genomic DNA fragments hybridized to a unique probe adjacent to the SCA10 pentanucleotide, which detected one normal allele (2.5 kb) and a large expanded allele in each patient. The SCA10 genotypes for Patient P1 (Patient III-1, Family 1) is 14 and ~1,600 repeats; Patient P2 (Patient II-5, Family 2) has 16 and ~1,500 SCA10 repeats. Lanes containing SCA10 positive (+C) and normal (−C1 and −C2) controls are indicated.

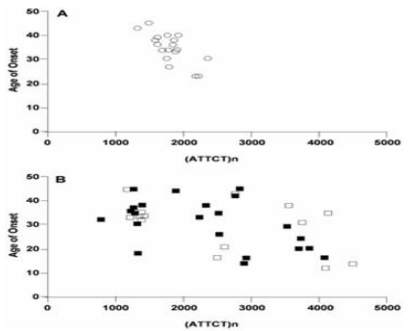


Figure 3. Inverse correlation between the age at onset and the ATTCT repeat expansion size in (A) Brazilian patients with spinocerebellar ataxia type 10 (○, n = 18; $r^2 = 0.532$; $p < 0.01$), and (B) Mexican patients with (■, n = 22) and without (□, n = 14) epilepsy (for all 54 patients, $r^2 = 0.264$ and $p < 0.01$). Note that the expansion size overlaps between the Brazilian patients and the Mexican patients, and the epilepsy phenotype was associated with a wide range of the repeat size and the age at onset among the Mexican patients. Thus, neither expansion size nor age at onset can explain the absence of epilepsy phenotype in Brazilian patients.

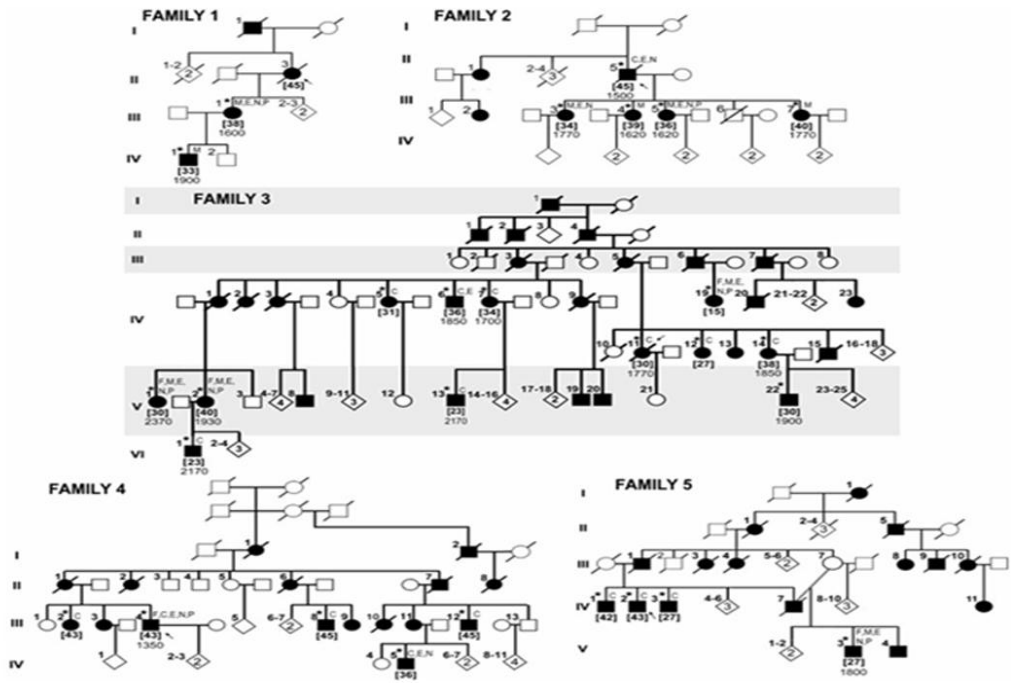


*Figure 1. Five Brazilian families with spinocerebellar ataxia type 10: ○ = unaffected female; □ = unaffected male; ● = affected female; ■ = affected male; and ◇ = subject(s) with unspecified gender (a number within this symbol, ◇, indicates the number of siblings of unspecified gender). A diagonal line across a symbol indicates a deceased individual. Roman numbers show generations within the pedigree. A combination of the Roman generation number and an Arabic number at the left upper corner of a symbol identifies a specific individual within the pedigree. Note that married-in individuals are not assigned numbers in the pedigree. *Specific individuals who were evaluated in this study. The number in brackets ([ ]) indicates the age at onset directly ascertained. Laboratory tests performed for affected subjects are shown as follows: F = CSF; C = CT of the brain; M = MRI of the brain; E = EEG; N = nerve conduction studies and EMG; and P = neuropsychological testing. An arrow (↑) indicates the index patient of the family.*

HEREDITARY ATAXIAS RESEARCH- SCA10

Review › Parkinsonism Relat Disord. 2011 Nov;17(9):655-61.
doi: 10.1016/j.parkreldis.2011.04.001. Epub 2011 Apr 29.

Spinocerebellar ataxia type 10 - A review

Hélio A G Teive [1], Renato P Munhoz, Walter O Arruda, Salmo Raskin, Lineu César Werneck, Tetsuo Ashizawa

Affiliations + expand

PMID: 21531163 DOI: 10.1016/j.parkreldis.2011.04.001

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.

Review › Cerebellum. 2025 Apr 15;24(4):86. doi: 10.1007/s12311-025-01838-7.

Spinocerebellar Ataxia Type 10 (SCA 10) in Brazil

Hélio A Ghizoni Teive [1 2 3], Léo Coutinho [4], Carlos Henrique F Camargo [4]

Affiliations + expand

PMID: 40232546 DOI: 10.1007/s12311-025-01838-7

Abstract

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant inherited ataxia caused by the expansion of ATTCT pentanucleotide repeats in intron 9 of the ATXN10 gene. This rare form of SCA has predominantly been observed in individuals of Indigenous American and East Asian descent. Notably, in Mexico and the southern Brazilian states of Paraná and Santa Catarina, SCA10 is identified as the second most prevalent type of spinocerebellar ataxia. Initially, the phenotype described in Mexico featured a combination of cerebellar ataxia and epilepsy-a presentation also observed in other Latin American and Asian countries, as well as some Brazilian states. However, in Paraná and Santa Catarina, the predominant manifestation of SCA10 is pure cerebellar ataxia, which is distinguished from the presentations seen in other regions.

HEREDITARY ATAXIAS RESEARCH- SCA10

› Cerebellum. 2019 Oct;18(5):849-854. doi: 10.1007/s12311-019-01064-y.

Clinical and Genetic Evaluation of Spinocerebellar Ataxia Type 10 in 16 Brazilian Families

Bernardo Machado Dias Domingues [1], Fábio A Nascimento [2], Alex Tiburtino Meira [1], Adriana Moro [3], Salmo Raskin [4], Tetsuo Ashizawa [5], Hélio Afonso Ghizoni Teive [6]

Affiliations + expand

PMID: 31377949 DOI: 10.1007/s12311-019-01064-y

Abstract

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant disorder in which patients have a slowly progressive cerebellar ataxia, with dysarthria, dysphagia, and epilepsy. The aims of this study were to characterize the phenotypic expression of SCA10 and to examine its genotype-phenotype relationships. Ninety-one Brazilian patients with SCA10 from 16 families were selected. Clinical and epidemiological data were assessed by a standardized protocol, and severity of disease was measured by the Scale for the Assessment and Rating of Ataxia (SARA). The mean age of onset of symptoms was 34.8 ± 9.4 years. Sixty-two (68.2%) patients presented exclusively with pure cerebellar ataxia. Only 6 (6.6%) of the patients presented with epilepsy. Patients with epilepsy had a mean age of onset of symptoms lower than that of patients without epilepsy (23.5 ± 15.5 years vs 35.4 ± 8.7 years, p = 0.021, respectively). All cases of intention tremor were in women from one family. This family also had the lowest mean age of onset of symptoms, and a higher percentage of SCA10 cases in women. There was a positive correlation between duration of disease and severity of ataxia (rho = 0.272, p = 0.016), as quantified by SARA. We did not find a statistically significant correlation between age of onset of symptoms and expansion size (r = - 0.163, p = 0.185). The most common clinical presentation of SCA10 was pure cerebellar ataxia. Our data suggest that patients with epilepsy may have a lower age of onset of symptoms than those who do not have epilepsy. These findings and the description of a family with intention tremor in women with earlier onset of symptoms draw further attention to the phenotypic variability of SCA10.

Spinocerebellar Ataxia Type 10: Frequency of Epilepsy in a Large Sample of Brazilian Patients

Hélio A.G. Teive,[1]* Renato P. Munhoz,[1] Salmo Raskin,[1] Walter O. Arruda,[1] Luciano de Paola,[1] Lineu C. Werneck,[1] and Tetsuo Ashizawa[2]

[1]Department of Internal Medicine, Movement Disorders Unit, Neurology Service, Hospital de Clínicas, Federal University of Paraná, Curitiba, Paraná, Brazil; [2]Department of Neurology, University of Florida, Gainesville, Florida, USA

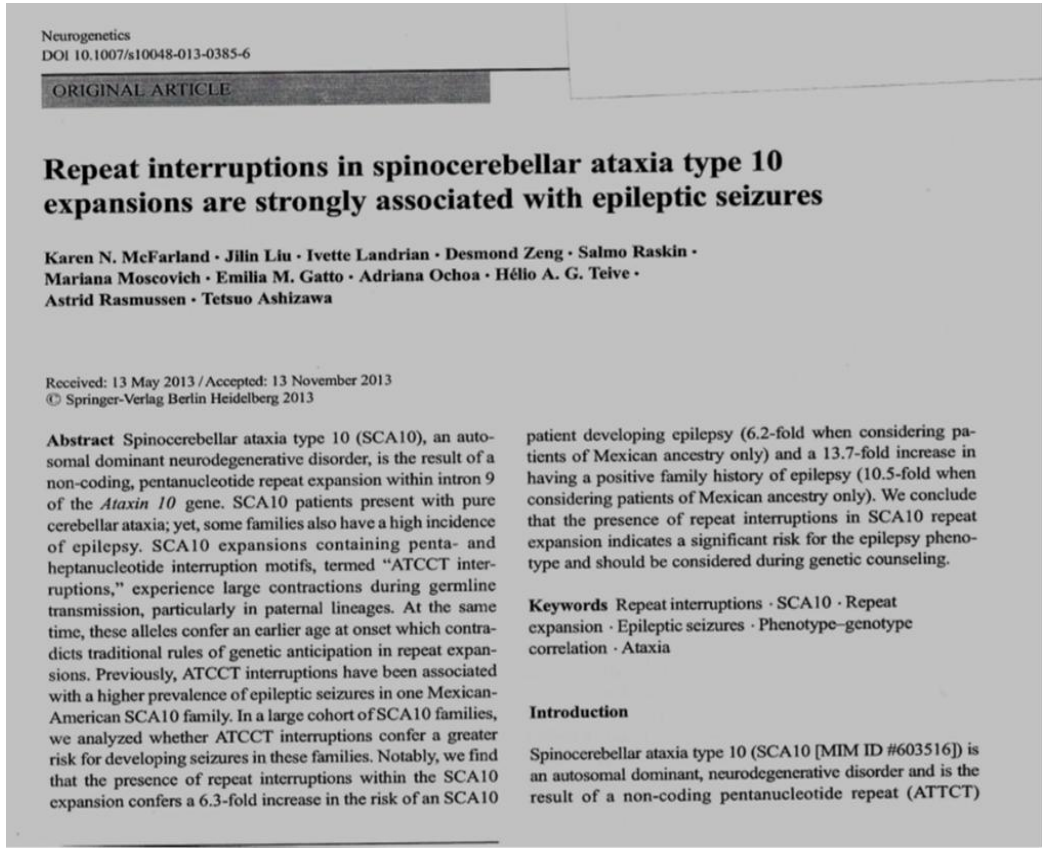
Abstract: **Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant disorder caused by an ATTCT repeat intronic expansion in the SCA10 gene. SCA 10 has been reported in Mexican, Brazilian, Argentinean and Venezuelan families. Its phenotype is overall characterized by cerebellar ataxia and epilepsy. Interestingly, Brazilian patients reported so far showed pure cerebellar ataxia, without epilepsy. Here, authors provide a systematic analysis of the presence, frequency and electroencephalographic presentation of epilepsy among 80 SCA10 patients from 10 Brazilian families. Overall, the frequency of epilepsy was considered rare, been found in 3.75 % of the cases while this finding in populations from other geographic areas reaches 60% of SCA10 cases.** © 2010 Movement Disorder Society

Key words: spinocerebellar ataxia type 10; SCA; autosomal dominant cerebellar ataxia; epilepsy

TABLE 1. *Clinical and genetic aspects of Brazilian, Mexican, Argentinian, and Venezuelan patients with SCA 10*

	Brazilian patients	Mexican patients	Argentinean patients	Venezuelan patients
Number of patients	80	19	5	5
Age of onset (yr)	35.5 (22–46)	26.7 (14–44)	35	14 (case report)
Number of ATTCT repeats	1,820 (20)	2,838	1,100	4,400
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)	Indian ancestry 75%	Indian ancestry 100%	Mixed Spanish and Amerindian	Unknown

HEREDITARY ATAXIAS RESEARCH- SCA10



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ORIGINAL ARTICLE

Repeat interruptions in spinocerebellar ataxia type 10 expansions are strongly associated with epileptic seizures

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Abstract Spinocerebellar ataxia type 10 (SCA10), an autosomal dominant neurodegenerative disorder, is the result of a non-coding, pentanucleotide repeat expansion within intron 9 of the *Ataxin 10* gene. SCA10 patients present with pure cerebellar ataxia; yet, some families also have a high incidence of epilepsy. SCA10 expansions containing penta- and heptanucleotide interruption motifs, termed "ATCCT interruptions," experience large contractions during germline transmission, particularly in paternal lineages. At the same time, these alleles confer an earlier age at onset which contradicts traditional rules of genetic anticipation in repeat expansions. Previously, ATCCT interruptions have been associated with a higher prevalence of epileptic seizures in one Mexican-American SCA10 family. In a large cohort of SCA10 families, we analyzed whether ATCCT interruptions confer a greater risk for developing seizures in these families. Notably, we find that the presence of repeat interruptions within the SCA10 expansion confers a 6.3-fold increase in the risk of an SCA10 patient developing epilepsy (6.2-fold when considering patients of Mexican ancestry only) and a 13.7-fold increase in having a positive family history of epilepsy (10.5-fold when considering patients of Mexican ancestry only). We conclude that the presence of repeat interruptions in SCA10 repeat expansion indicates a significant risk for the epilepsy phenotype and should be considered during genetic counseling.

Keywords Repeat interruptions · SCA10 · Repeat expansion · Epileptic seizures · Phenotype–genotype correlation · Ataxia

Introduction

Spinocerebellar ataxia type 10 (SCA10 [MIM ID #603516]) is an autosomal dominant, neurodegenerative disorder and is the result of a non-coding pentanucleotide repeat (ATTCT)

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The impact of interrupted ATXN10 expansions on clinical findings of spinocerebellar ataxia type 10

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Abstract

Background: Spinocerebellar ataxia type 10 (SCA10), due to an ATTCT repeat expansion in ATXN10, has variable expressivity and the role of presence (ATTCTint +) and absence (ATTCTint-) of interruptions in the repeat is not clear. We aimed to describe the relations between ATTCTint + and age at onset, seizures, and neurologic severity in ataxic and non-ataxic carriers from Brazil.

Methods: Family, age at onset (AO), and seizures data plus DNA were obtained from symptomatic carriers already diagnosed in Porto Alegre, Curitiba, and São Paulo, Brazil. Patients and their relatives were invited to be evaluated through Scale of Assessment and Rating of Ataxia (SARA) and other clinical scales; a SARA > 2.5 classified subjects as ataxic carriers. Repeat-primed PCR (RP-PCR) defined the expansions with (ATTCTint +) or without (ATTCTint-) interruptions. Comparisons were performed for a p level of 0.05.

Results: Among 78 ataxic carriers, earlier AO ($p = 0.039$) and higher occurrences of epilepsy ($p < 0.0001$) were seen in subjects with ATTCTint + than in those with ATTCTint-. Clinical scales were worse in 34 ataxics than in 7 non-ataxics and 10 related controls ($p = 0.006$) and did not discriminate non-ataxics from controls. The 11 ataxic ATTCTint + carriers had higher SARA scores per year of disease duration than the 23 ATTCTint- carriers ($r = 0.879$, beta = 0.45, $p = 0.0001$).

Discussion: ATTCTint + carriers had worse clinical findings than ATTCTint- carriers: earlier AO, more seizures, and worse ataxia scores. Interruptions in the expanded repeat have a real impact in SCA10 phenotype.

HEREDITARY ATAXIAS RESEARCH- SCA27B

CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Frequency of GAA-*FGF14* Ataxia in a Large Cohort of Brazilian Patients With Unsolved Adult-Onset Cerebellar Ataxia

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Abstract

Objectives

Intronic *FGF14* GAA repeat expansions have recently been found to be a common cause of hereditary ataxia (GAA-*FGF14* ataxia; SCA27B). The global epidemiology and regional prevalence of this newly reported disorder remain to be established. In this study, we investigated the frequency of GAA-*FGF14* ataxia in a large cohort of Brazilian patients with unsolved adult-onset ataxia.

Methods

We recruited 93 index patients with genetically unsolved adult-onset ataxia despite extensive genetic investigation and genotyped the *FGF14* repeat locus. Patients were recruited across 4 different regions of Brazil.

Results

Of the 93 index patients, 8 (9%) carried an *FGF14* $(GAA)_{\geq 250}$ expansion. The expansion was also identified in 1 affected relative. Seven patients were of European descent, 1 was of African descent, and 1was of admixed American ancestry. One patient carrying a $(GAA)_{376}$ expansion developed ataxia at age 28 years, confirming that GAA-*FGF14* ataxia can occur before the age of 30 years. One patient displayed episodic symptoms, while none had downbeat nystagmus. Cerebellar atrophy was observed on brain MRI in 7 of 8 patients (87%).

Discussion

Our results suggest that GAA-*FGF14* ataxia is a common cause of adult-onset ataxia in the Brazilian population, although larger studies are needed to fully define its epidemiology.

Table Clinical Features of Brazilian Patients With GAA-*FGF14*–Related Ataxia

Clinical features	Patient 1.1	Patient 1.2[a]	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Inheritance	AD	AD	Sporadic	AD	AD	Sporadic	Sporadic	Sporadic	AD
Sex	F	M	F	F	M	M	M	M	F
Age at onset	45 y	40 y	67 y	28 y	60 y	59 y	63 y	57 y	60 y
Age at last examination (disease duration)	84 y (39 y)	65 y (15 y)	73 y (6 y)	51 y (23 y)	63 y (3 y)	68 y (9 y)	75 y (12 y)	64 y (7 y)	78 y (18 y)
Episodic symptoms	No	No	No	Yes	No	No	No	No	No
Downbeat nystagmus	No	No	No	No	No	No	No	No	No
Horizontal gaze-evoked nystagmus	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Diplopia/blurry vision/oscillopsia	No	Yes	No	Yes	Yes	Yes	No	Yes	No
Cerebellar dysarthria	No	No	No	No	No	No	No	No	No
Gait ataxia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Apendicular ataxia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vertigo/dizziness	No	No	No	Yes	Yes	Yes	No	Yes	No
Postural tremor	Yes	No	No	No	No	No	No	No	No
SDFS	2	3	3	1	3	3	4	4	6
Cerebellar atrophy on MRI	N/A	Yes (cerebellar vermis)	Yes (global)	Yes (global)	No	Yes (cerebellar vermis)	Yes (cerebellar vermis)	Yes (global)	Yes (cerebellar vermis)
Additional features	Tinnitus, deafness, insomnia, chin tremor	Insomnia, tinnitus	Dysphagia	None	None	Sensory neuropathy	None	Facial and upper limb dystonia, lymphocitic pleocytosis	Parkinsonism, lower limb dystonia, MCI
GAA repeat units	253	268	376	449	363/448	424	303	259	257
Ancestry	EUR	EUR	AMR	EUR	AFR	EUR	EUR	EUR	EUR

FUTURE PERSPECTIVES

Collaborative study with the group of Professor Birgit Schuele (Stanford University, California, USA)

TUPÂ-SCA10

Tracking unique patterns in ataxia

FUTURE PERSPECTIVES

- **Start in 2026 of a collaborative genome sequencing study with the Genetics Laboratory of the Oswaldo Cruz Foundation (FIOCRUZ) in Curitiba, Paraná, Brazil**

- **Maintain and expand collaboration with national and international study groups on hereditary ataxias**

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