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

Karen N. McFarland[1,2], **Jilin Liu**[1,2], **Ivette Landrian**[1,2], **Desmond Zeng**[1,2], **Salmo Raskin**[3], **Mariana Moscovich**[1,2,4], **Emilia M. Gatto**[5,6], **Adriana Ochoa**[7], **Hélio A. G. Teive**[4], **Astrid Rasmussen**[8], and **Tetsuo Ashizawa**[1,2,¶]

[1]Department of Neurology, University of Florida, Gainesville, FL 32610 USA

[2]Evelyn F. & William L. McKnight Brain Institute at The University of Florida, Gainesville, FL 32610 USA

[3]Core for Advanced Molecular Investigation, Graduate Program in Health Sciences, Center for Biological and Health Sciences, University of Paraná, Imaculada Conceição St 1155 - CCBS/ PPGCS, Prado Velho, CEP 80215-901 Curitiba, Paraná, Brazil

[4]Movement Disorders Unit, Neurology Service, Hospital de Clínicas, Federal University of Paraná, Centro, Curitiba, PR 80060-150, Brazil

[5]Departamento de Neurología, Sanatorio de la Trinidad Mitre, Buenos Aires, Argentina

[6]Instituto de Neurosciencias Buenos Aires, INEBA, 1428 Buenos Aires, Argentina

[7]Department of Neurogenetics, Instituto Nacional de Neurologia y Neurocirugia Manuel Velasco Suarez, Mexico City, DF, Mexico

[8]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104 USA

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 confers 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

[¶]Corresponding author: Tetsuo Ashizawa, 1149 S Newell Drive, PO Box 200136, Gainesville, FL 32610, Phone: (352) 273-5550, Fax: (352) 273-5575.

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; seizure; 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 noncoding pentanucleotide repeat (ATTCT) expansion in the ninth intron of *Ataxin 10* (*ATXN10*) [1]. The ATTCT repeat can range from 9 to 32 repeats in normal individuals [2]; however, the disease allele can expand from 800 up to 4500 repeats [1] in length with intermediate allele sizes ranging from 280 to 850 repeats [3–5].

All SCA10 patients present with cerebellar ataxia; however, a proportion of patients also present with extracerebellar symptoms including epileptic seizures. These additional disease phenotypes were originally noted to correlate with the patient's ancestral origin [6]. For SCA10 patients of Mexican ancestry, the prevalence of seizures ranges from 25 to 80% while this rate is much lower, 3.75%, in Brazilian SCA10 patients [7–11]. Seizures in SCA10 patients are typically complex partial with occasional secondary generalization and significantly contribute to the morbidity and mortality of the disease.

Previous studies on the SCA10 expansion suggested that repeat purity may influence disease phenotypes. Our recent study of SCA10 expansions containing these penta-(ATCCT and ATCCC) and heptanucleotide (ATATTCT and ATTTTCT) interruptions, the "ATCCT" interruption motif, found that germline transmission of these expansions underwent large contractions, most striking in the paternal germline, yet still conferred an earlier age at onset of ataxia symptoms—a direct contradiction of the concept of genetic anticipation [12]. Our earlier study speculated that the repeat interruption may also affect the expression of the epilepsy phenotype [3]. However, this was based on data of members of only one family with the repeat interruptions.

For this study, we analyzed a large cohort of 31 SCA10 families, five of which carry ATCCT interruption motifs within their expansion, and tested whether this 5′ repeat impurity correlates with disease phenotype, specifically epileptic seizures.

Materials and Methods

DNA samples

Members from SCA10 families were studied and included individuals from Mexican, Brazilian and Argentinean families, previously described [12]. Blood samples were collected after obtaining informed consent under protocols approved by local institutional

review boards. Genomic DNA was extracted from peripheral blood leukocytes using conventional methods.

SCA10 expansion screening

Individuals were screened for the presence of normal SCA10 alleles using protocols as described [1] with described modifications [13]. Samples that showed two normal alleles were excluded from further analyses. The remaining samples were tested by repeat primed PCR (RP-PCR) [14], and RP-PCR-positive samples were subjected to Southern blot analysis to determine the size of the repeat expansion as previously described [1]. The presence of ATCCT repeat interruptions was determined by PCR using ATCCT-PCR as described [12].

Haplotype Analysis

Haplotype analysis was performed with single nucleotide polymorphisms (SNPs), rs5764850 and rs72556348. These two SNPs flank the SCA10 expansion and were used in a prior study [15] and define the C-expansion-GGC SCA10 haplotype (rs5764850, underlined C; rs72556348, underlined G). PCR primers were as described [15]. Following PCR amplification, alleles for SNP rs5764850 and rs72556348 were identified by restriction fragment length polymorphisms (RFLP; TaqI and HhaI, respectively) of the PCR products for each SNP. Test restriction digests of the PCR products were carried out on sequence-confirmed haplotypes to ensure correct digest conditions and confirm expected digest patterns.

Statistical Analysis

For our analyses, we included only SCA10-positive individuals who showed signs of ataxia and did not include asymptomatic carriers. Expansion sizes are expressed throughout the manuscript as mean ± standard deviation. Statistical significance was determined the Student's t-test for unpaired comparison of two groups. Chi-square and odds ratio analysis were performed. Analyses were carried out using Prism 6 for Mac OS X Version 6.0c (GraphPad Software, Inc).

Results

Repeat length does not correlate with epileptic seizures in SCA10

In our cohort of SCA10 families previously described [12], we first determined whether repeat length plays a role in the phenotypic variation between SCA10 patients with or without epilepsy (Figure 1). We found that the expansion size of SCA10 patients that developed epilepsy (mean ± s.d.= 2240 ± 911 repeats, n=37) did not significantly differ from that of patients that did not develop epilepsy (mean ± s.d.= 2041 ± 878 repeats, n = 51; $P = 0.3033$), suggesting that the size of the expanded repeat does not act as a major modifier of the epilepsy phenotype in SCA10 patients.

SCA10 haplotype analysis

We used single nucleotide polymorphisms (SNPs), rs5764850 and rs72556348, which flank the SCA10 expansion and have been used to define a shared C-SCA10 expansion-G SCA10

haplotype in Brazilian and Mexican SCA10 patients [15]. Haplotype analysis in sixteen Mexican, two Brazilian and one Argentinean SCA10 families shows a C-expansion-G haplotype that is consist with the past study and supports the conclusion of a shared haplotype (data not shown).

ATCCT repeat interruptions predict an increased risk of epileptic seizures

We next examined the association between ATCCT interruptions within the SCA10 expansion and the occurrence of epileptic seizures. In an analysis of SCA10 patients from all 31 families, we find that 43 of individuals also developed epilepsy and, of these individuals with both ataxia and epilepsy symptoms, 23 were ATCCT-positive. Conversely, 78 SCA10-positive patients were ataxic but epilepsy-free and, of these, 12 were ATCCT-positive (Table 1). This relationship between ATCCT interruptions within the SCA10 expansion and epileptic seizures is statistically significant (Chi-square analysis: $\chi^2 = 19.58$, df = 1, $p < 0.0001$) and and shows that SCA10-positive individuals that carry ATCCT repeat interruptions have a greater risk of developing epilepsy (odds ratio = 6.3; 95% CI: 2.7 – 14.9). Further analyzing only SCA10-positive individuals with Mexican ancestry reveals similar results (see Table 1; Chi-square analysis: $\chi^2 = 17.84$, df = 1, $p < 0.0001$; odds ratio = 6.2; 95% CI: 2.6 – 15.0). Overall, these results indicate that ATCCT repeat interruptions act as a significant modifier of the SCA10 disease phenotype.

We also make note that there is an obvious genetic component to the epileptic phenotype in these SCA10 families. The majority of SCA10 patients with epilepsy also have a first degree SCA10-positive relative with epilepsy as well (48 out of 43 individuals) whereas SCA10 patients without epileptic symptoms were more evenly distributed between first-degree relatives with or without epilepsy (Table 2; Chi-square analysis: $\chi^2 = 20.80$, df = 1, $p < 0.0001$). Odds ratio analysis reveals that SCA10-positive individuals with epilepsy are at a higher risk of having a first-degree, SCA10-positive family member with epilepsy as well (odds ratio = 8.7; 95% CI: 3.2 – 24.9). Similar results were seen when we performed this analysis with only SCA10 individuals of Mexican ancestry (Table 2; Chi-square analysis: $\chi^2 = 14.97$, df = 1, $p = 0.0001$; odds ratio = 7.8; 95% CI: 2.5 – 24.2).

We next analyzed whether ATCCT interruptions in the SCA10 expansion correlate with a family history of epilepsy in first-degree, SCA10-positive relatives (Table 3). We find that a significant majority of ATCCT-positive patients (33 out of 35) either have epilepsy or have a SCA10-positive, first-degree family member with epilepsy (Chi-square analysis: $\chi^2 = 17.40$, df = 1, $p < 0.0001$). The presence of the ATCCT repeat interruption confers an increased risk (odds ratio = 13.7, 95% CI: 3.1 – 60.7) of having a family history of epilepsy. A similar analysis in SCA10-positive individuals of Mexican ancestry shows similar results (Table 3; Chi-square analysis: $\chi^2 = 12.85$, df = 1, $p = 0.0003$; odds ratio = 10.5; 95% CI: 2.3 – 47.3).

Discussion

The ATCCT interruptions convey a considerable risk for the epileptic phenotype. We find that ATCCT-positive SCA10 patients have a 6.3-fold (or a 6.2-fold, when considering only SCA10-positive individuals with Mexican ancestry) increased risk of developing epilepsy or

a 13.7-fold (or a 10.5-fold, when considering only SCA10-positive individuals with Mexican ancestry) greater chance of epilepsy within the first-degree family core than those patients that do not carry these interruptions. However, we cannot rule out the possibility that ATCCT-negative SCA10 patients harbor an ATCCT repeat interruption longer than the limits that our PCR assay can detect. Neither can we rule out that these patients repeat interruptions of a different motif as current sequencing capabilities are limited to detecting only the extreme ends of the expansion. Alternatively, other genetic or epigenetic factors may influence the development of epilepsy in those individuals that are ATCCT-negative. Haplotype analysis on these families supports prior studies showing a shared haplotype surrounding the SCA10 expansion.

Interruptions in repeat expansions have been demonstrated for other repeat expansion disorders. In some instances, repeat interruptions are thought to contribute additional phenotypes beyond the typical disease repertoire. In myotonic dystrophy type 1, CCG and GGC repeat interruptions within the 3′ end of the CTG expansion is thought to modify the disease and impart additional phenotypes including neuropathy [16,17]. Additionally, in spinocerebellar ataxia type 2 (SCA2), CAG repeat expansions within *Ataxin 2* containing CAA interruptions are found associated with parkinsonism-predominant forms of SCA2 [18–21]. Furthermore, intermediate allele lengths of *Ataxin 2* expansions with CAA interruptions are found associated with amyotrophic lateral sclerosis [22–25]. On the other hand, interruptions in repeat expansions may mitigate the development of disease phenotypes as seen in spinocerebellar types 1 and 31 (SCA1 and SCA31). In SCA1, expanded alleles containing CAT interruptions within the CAG expansion are either non-pathogenic or lengthen the expected time to age at onset [26–28]. While in SCA31, differences in the repeat motif of the repeat expansion in are hypothesized to underlie its toxicity in the development of SCA31 disease phenotypes [29,30].

In summary, we conclude that ATCCT interruptions act as a strong modifier of the epileptic phenotype in SCA10 patients. This is important information to consider during genetic counseling. As SCA10 is hypothesized to act through an RNA mediated gain-of-function [31–33], further work is needed to understand the impact of these repeat interruptions on pathogenic mechanisms.

Acknowledgments

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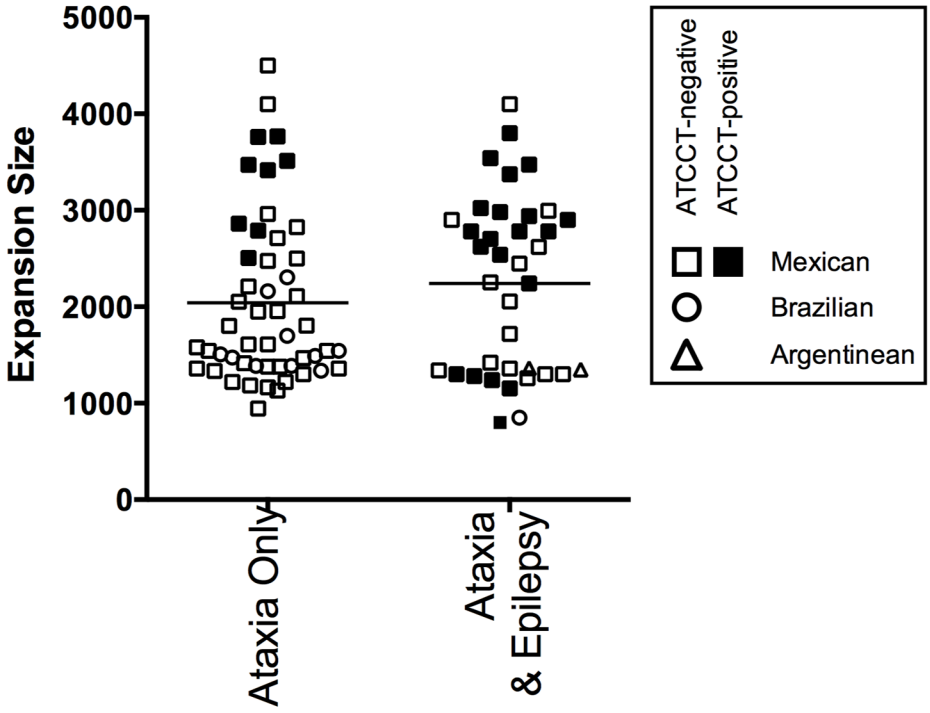

Figure 1.

SCA10 expansion size is not larger in SCA10 patients with epileptic seizures.

Repeat size analysis in SCA10 patient without (mean=2041 ± 877, n=51) and with (mean=2240 ± 911, n=37) epilepsy.

Table 1

Frequency of ATCCT repeat interruptions with the co-occurrence of epilepsy in all SCA10 patients (numbers in **bold**). Frequency of ATCCT repeat interruptions with the co-occurrence of epilepsy in SCA10 patients with Mexican ancestry (numbers in *italics*).

	Ataxia without epilepsy	Ataxia with epilepsy	Totals
ATCCT-negative (all SCA10)	**66**	**20**	**86**
ATCCT-negative (Mexican SCA10 families only)	*55*	*17*	*72*
ATCCT-positive (all SCA10 families)	**12**	**23**	**35**
ATCCT-positive (Mexican SCA10 families only)	*12*	*23*	*35*
Totals (all SCA10 families)	**78**	**43**	**121**
Totals (Mexican SCA10 families only)	*67*	*40*	*107*

Table 2

Familial clustering of epilepsy in all SCA10 patients (numbers in **bold**). Familial clustering of epilepsy in SCA10 patients with Mexican ancestry (numbers in *italics*).

	Ataxia without epilepsy	Ataxia with epilepsy	Totals
SCA10-positive, 1st degree relative *without* epilepsy (all SCA10 families)	**42**	**5**	**47**
SCA10-positive, 1st degree relative without epilepsy (Mexican SCA10 families only)	*31*	*4*	*35*
SCA10-positive, 1st degree relative *with* epilepsy (all SCA10 families)	**36**	**38**	**74**
SCA10-positive, 1st degree relative with epilepsy (Mexican SCA10 families only)	*36*	*36*	*72*
Totals (all SCA10 families)	**78**	**43**	**121**
Totals (Mexican SCA10 families only)	*67*	*40*	*107*

Table 3

Correlation of ATCCT interruptions and epilepsy within the core family (first-degree relatives) in all SCA10 patients (numbers in **bold**). Correlation of ATCCT interruptions and epilepsy within the core family (first-degree relatives) in SCA10 patients with Mexican ancestry (numbers in *italics*).

	SCA10 patients without epilepsy AND no 1st degree relative with epilepsy	SCA10 patients with epilepsy OR a 1st degree relative with epilepsy	Totals
ATCCT-negative (all SCA10)	**39**	**47**	**86**
ATCCT-negative (Mexican SCA10 families only)	*28*	*44*	*72*
ATCCT-positive (all SCA10 families)	**2**	**33**	**35**
ATCCT-positive (Mexican SCA10 families only)	*2*	*33*	*35*
Totals (all SCA10 families)	**42**	**79**	**121**
Totals (Mexican SCA10 families only)	*30*	*77*	*107*