

Reduced Penetrance in a Brazilian Family With Spinocerebellar Ataxia Type 10

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Objective: To describe reduced penetrance associated with early onset in a Brazilian family with spinocerebellar ataxia type 10.

Design: Clinical examination and molecular analysis for the ATTCT repeat responsible for spinocerebellar ataxia type 10 in a patient and family members through 3 generations.

Setting: Ambulatory care.

Patients: A 28-year-old female Brazilian patient who presented with early-onset cerebellar ataxia and epilepsy, and her 9 asymptomatic relatives.

Main Outcome Measure: Genotype-phenotype correlation.

Results: Molecular testing on this patient 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 examined.

Conclusion: The stably transmitted pentanucleotide expansion of approximately 850 repeats may represent a mutant SCA10 allele with reduced penetrance that may express an early-onset, severe phenotype.

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SPINOCEREBELLAR ATAXIA TYPE 10 (SCA10) is an autosomal dominant disease caused by an expansion of a pentanucleotide (ATTCT) repeat in an intron of the SCA10 gene on chromosome 22.¹ The ATTCT repeat in SCA10 is polymorphic, ranging in size from 10 to 29 repeats in the normal population. Patients with SCA10 demonstrate expanded mutant alleles ranging from approximately 800 to 4500 repeats.^{1,2} Expanded ATTCT repeats are stable through maternal transmission but unstable through paternal transmission.³ To date, SCA10 has been identified only in Mexican and Brazilian families.⁴ Clinically, the most characteristic feature of SCA10 is a combination of pure cerebellar syndrome and epilepsy.^{1,2,5-8} Epilepsy has been present in approximately 72% of Mexican patients with SCA10, whereas no Brazilian patients with SCA10 have been reported to have epilepsy.^{4,5} Mexican patients with SCA10 also frequently show cognitive impairment, sensory polyneuropathy, and other extracerebellar manifestations.⁵ In this article, we describe a 28-year-old female Brazilian patient who

presented with cerebellar ataxia and epilepsy and had a negative family history of SCA10. Molecular testing on this patient 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 examined, suggesting stable transmission of an approximately 850-repeat expansion and reduced penetrance of this allele for SCA10.

METHODS

We studied a patient with SCA10 and her extended family, which included 8 unaffected members of a 3-generation Brazilian kindred (**Figure 1**). Signed informed consent was obtained under a protocol of Laboratório Genética, Curitiba, Brazil. All of the subjects were evaluated by 3 neurologists (T.A., H.A.G.T., and W.O.A.) and a medical geneticist (S.R.). Detailed history was taken and physical examination and routine laboratory tests were performed. Magnetic resonance imaging of the brain, electroencephalography, and neuropsychological tests were also performed on the affected patient.

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Genomic DNA was extracted from patient blood samples using a commercially available kit (Gentra Puregene; Gentra Systems, Inc, Minneapolis, Minn) based on standard salting-out methods. Analysis of the ATTCT pentanucleotide repeat in the *SCA10* gene was performed by polymerase chain reaction amplification using primers attct-L and attct-R as described previously by Matsuura et al.¹ The DNA samples that showed a single normal allele by polymerase chain reaction analysis were subsequently analyzed by Southern blot to assess large *SCA10* expansions.¹

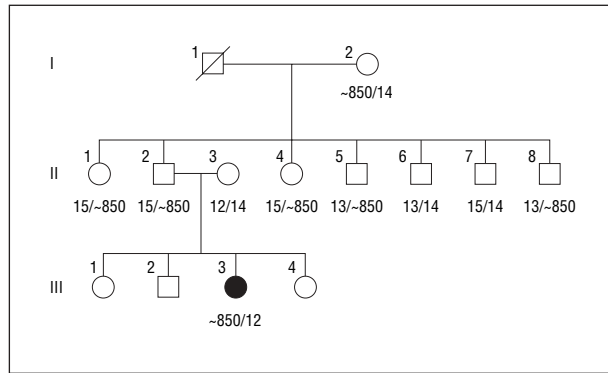


Figure 1. Pedigree of the Brazilian kindred with spinocerebellar ataxia type 10. Numbers below the symbols indicate the ATTCT repeat alleles for genotyped individuals. The allele with approximately 850 repeats was detected in the patient with spinocerebellar ataxia type 10, her asymptomatic father, 2 asymptomatic paternal aunts, 2 asymptomatic paternal uncles, and her asymptomatic paternal grandmother. Open square indicates unaffected male; open circle, unaffected female; filled circle, affected female; and diagonal line, deceased.

The patient is a 28-year-old Brazilian woman (patient III:3 in Figure 1) who had an initial clinical evaluation at age 8 years owing to learning problems. According to her family, she had an unbalanced gait since she was aged 4 years. She repeated the same grade 3 times and was eventually placed in special education classes. The first sign of definitive ataxia manifested by age 14 years as an increasingly unsteady gait and stance with upper limb ataxia. At age 19 years, brain magnetic resonance imaging showed generalized cerebellar atrophy. In contrast to all previously described Brazilian patients with *SCA10*, this patient developed epilepsy at age 23 years, presenting as myoclonic seizures, complex partial seizures, and generalized tonic-clonic seizures with occasional status epilepticus. Interictal electroencephalographic results were abnormal, with diffuse cortical dysfunction with slow, fused, and disorganized activities. By age 24 years, she was wheelchair bound. At age 26 years, she developed a notable deterioration of her cognitive functions. On examination, she was alert but only responded to simple commands. She was mostly mute and unable to communicate with yes or no answers. Cranial nerves were normal except for decreased saccadic velocity, but pursuit eye movements were normal. Motor examination showed normal strength with slightly decreased muscle tone. There were dysmetria, intention tremor,

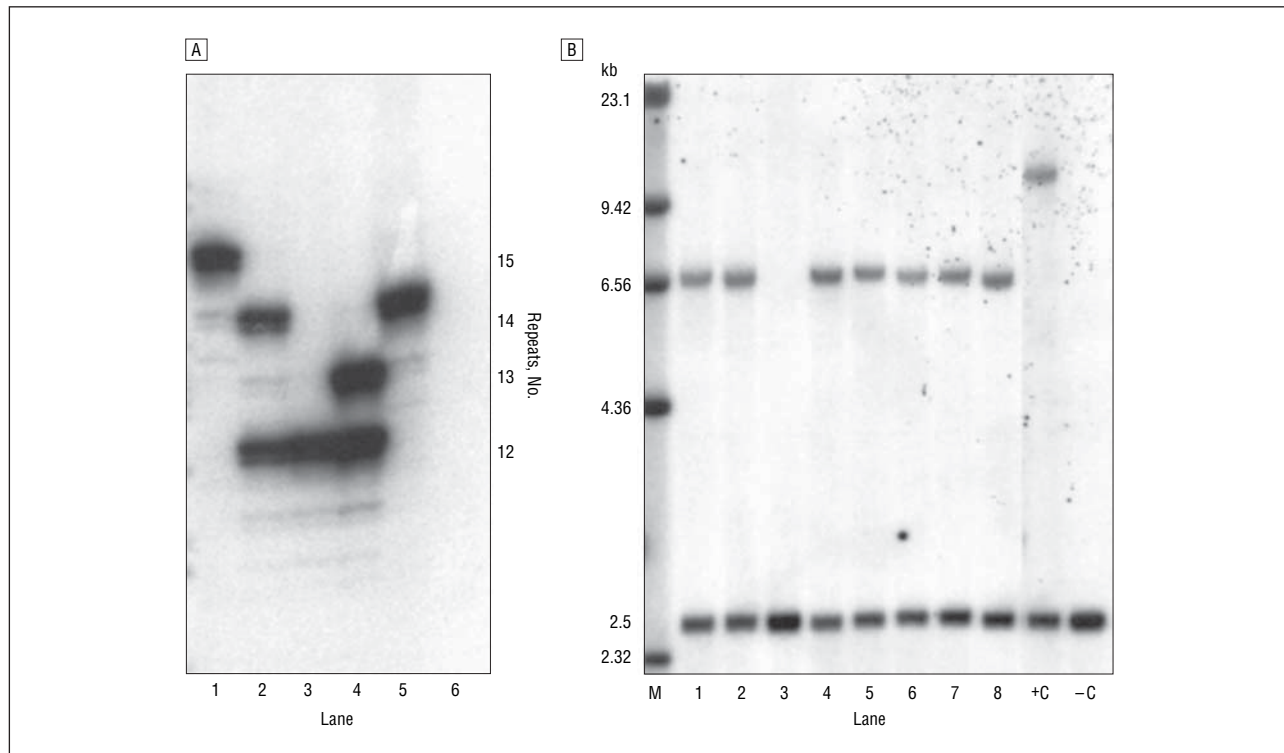


Figure 2. Genotypes of the Brazilian kindred with spinocerebellar ataxia type 10. A, Polymerase chain reaction analysis of the ATTCT repeats in *SCA10*. Normal alleles of the patient with spinocerebellar ataxia type 10 (lane 3), her unaffected mother (lane 2), her unaffected father (lane 1), a negative control with 12 and 13 repeats (lane 4), a positive control with 1 normal allele of 14 repeats (lane 5), and a cloned *SCA10* expansion that is not detectable by polymerase chain reaction (lane 6). B, Southern analysis for *SCA10* expansions. The patient (lane 4) and her unaffected father (lane 2), paternal grandmother (lane 1), paternal uncles (lanes 5 and 6), and paternal aunts (lanes 7 and 8) show a normal *EcoRI* band of approximately 2.5 kilobases (kb), plus a band of approximately 6.6 kb (approximately 850 ATTCT repeats). Her unaffected mother shows only the normal band (lane 3). M indicates marker; +C, control with spinocerebellar ataxia type 10 with an approximately 10.5-kb band (approximately 1600 repeats); and -C, normal control.

and dysdiadochokinesia with trunkal ataxia. She was unable to stand. Reflexes were brisk without pathological reflexes. She responded to pain and vibration.

Her parents, paternal grandmother, 3 siblings, 2 paternal aunts, and 4 paternal uncles were asymptomatic for ataxia or epilepsy. These relatives had normal neurological examination results, with the exceptions of a paternal uncle (II:5) who has mental retardation due to cerebral palsy and the 77-year-old paternal grandmother (I:2) who showed mild gait disturbance attributable to arthritis. The paternal grandmother (I:2) was a daughter of a woman of Italian descent and a man of mixed ethnic background with Portuguese, Spanish, and South American Indian ancestries.

Molecular genetic testing of this patient showed 1 normal allele of 12 ATTCT pentanucleotide repeats by polymerase chain reaction analysis (**Figure 2A**); Southern analysis showed a normal allele and an expanded allele of approximately 850 repeats (Figure 2B). Because the negative family history in this patient is inconsistent with the autosomal dominant inheritance pattern for SCA10, we decided to genotype both of her clinically unaffected parents. The mother had 2 normal alleles (12 and 14 repeats), whereas the father had a normal allele of 15 repeats and an expanded allele of approximately 850 repeats. Thus, the patient's SCA10 expansion was inherited from her asymptomatic father with no apparent size instability. Among the paternal relatives, 2 uncles, 2 aunts, and the grandmother also showed an expanded allele of approximately 850 repeats. Side-by-side Southern analysis showed a similar-sized allele of approximately 850 repeats in all of the positive family members, with no indication of major SCA10 allele expansions or contractions in transmission through 3 generations (Figure 2B).

COMMENT

Of the 7 individuals who carried the expanded allele of approximately 850 ATTCT repeats in this family, there was only 1 patient (III:3) with an SCA10 phenotype. It is noteworthy that the 77-year-old grandmother (I:2) shows no SCA10 phenotype, suggesting that the allele with approximately 850 ATTCT repeats in individual I:2 did not express the SCA10 phenotype during the average life expectancy (71.7 years) of the Brazilian population.⁹ Despite this apparent reduced penetrance, the allele with approximately 850 ATTCT repeats is unexpectedly associated with an early onset and aggressive progression of the disease in our patient (III:3). This contradicts the inverse correlation between the age at onset and the length of repeat expansions previously observed in SCA10.^{1,4} However, one recent article² described a mother-daughter pair wherein both individuals had an interrupted 280-repeat SCA10 allele; only the daughter showed an ataxia phenotype of childhood onset, raising the possibility that the intermediate SCA10 alleles with reduced penetrance may cause early-onset ataxia. Further stud-

ies are needed to determine whether the early-onset ataxia phenotype in these 2 families is a true SCA10 phenotype or coincidentally associated sporadic ataxia. However, because one of the original families with SCA10 included a patient with approximately 800 ATTCT repeats who presented with the typical SCA10 phenotype with epilepsy,¹ ATTCT repeats in the 800 to 850 range could be considered SCA10 alleles with reduced penetrance.

In contrast to Mexican patients with SCA10, no previously described Brazilian patients with SCA10 had seizures.⁴ Most Brazilian patients also had normal cognitive functions.⁴ Thus, our patient (III:3) may be the first Brazilian patient with SCA10 with epilepsy and impaired cognitive functions. It should be noted that, to our knowledge, this is the first described Brazilian family with SCA10 with Spanish ancestry. Whether a common ancestry with Mexican families with SCA10 played any role in the expression of the complex SCA10 phenotype remains unknown. It is also noteworthy that 2 families with SCA10 with disparate frequencies of seizures have been found to have different sequences of expanded ATTCT repeats.² Thus, sequence structures of our patient's expanded allele could be relevant to her unusual phenotype. Unfortunately, our efforts to sequence this large repeat expansion have been unsuccessful. However, the unusual stability of the approximately 850-repeat allele in our described family through 3 generations is compatible with highly interrupted repeat sequences because it is well established that interrupted repeats are more stable than uninterrupted repeats for most microsatellite repeats.¹⁰

Our data for SCA10 have implications for molecular genetic diagnostics and genetic counseling. Physicians and genetic counselors should be aware that an intermediate expansion of approximately 800 to 850 ATTCT repeats at the SCA10 locus may cause apparently sporadic childhood ataxia that may accompany severe epilepsy and progressive cognitive impairments. Such intermediate expansions may show reduced penetrance wherein family members who carry the same small expansion may not have SCA10 symptoms over a lifetime.

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Author Contributions: Dr Ashizawa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Ashizawa, Teive, Arruda, Fang, and Roa. *Acquisition of data:* Raskin, Teive, Arruda, Fang, Gao, White, Werneck, and Roa. *Analysis and interpretation of data:* Teive, Arruda, Fang, and Roa. *Drafting of the manuscript:* Raskin, Ashizawa, and Teive. *Critical revision of the manuscript for important intellectual content:* Teive, Arruda, Fang, Gao, White, Werneck, and Roa. *Administrative, technical, and material support:* Raskin, Ashizawa, Teive,

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Announcement

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