

Clinical phenotype of Brazilian families with spinocerebellar ataxia 10

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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.

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The disease-causing mutation of spinocerebellar ataxia type 10 (SCA10) is a large expansion of a pentanucleotide (ATTCT) repeat located in an intron of a gene of unknown function, *SCA10* (also known as *E46L*), on chromosome 22q.¹ Clinically, SCA10 is a predominantly cerebellar syndrome commonly accompanied by seizures.^{2–5} All reported families had at least 25% of affected members with the ataxia-epilepsy combination, although the frequency of the epileptic phenotype varied among different SCA10 families.^{2–5} A report of four families included some patients with additional clinical features, such as clinical and electrophysiologic signs of polyneuropathy, neuropsychological disturbances, and hepatic dysfunctions.⁴ Subsequent studies demonstrated that SCA10 is rare in populations other than Mexicans.^{6,7} We present five new unrelated Brazilian families with the SCA10 mutation and characterize their clinical phenotype.

Patients and methods. *Patients and clinical investigations.* We studied 28 patients from 5 families with SCA10, which were extracted from >100 Brazilian SCA families identified at the Federal University of Paraná in Curitiba, Brazil. Signed informed consent was obtained under a protocol approved by the Institutional Ethics Committee of the Federal University of Paraná. In this southern Brazilian series of SCA families, a mutation was identified in two-thirds of the cases. SCA3 (Machado-Joseph disease) is the most frequent (73.5%). SCA10 represents the second most common (11.8%), followed by SCA2 (7.4%), SCA7 (4.4%), SCA1 (2.9%), and SCA6 (1.5%; Teive, unpublished data). All patients were evaluated by at least one neurologist (H.T. and/or W.O.A., Y.C.N., and T.A.). History, physical examination, and routine laboratory tests, including complete blood count, blood urea nitrogen, creatinine, electrolytes, glucose, and liver function tests, were obtained. Detailed family history of each patient was obtained and cross-checked for consistency with information obtained from other patients or relatives. The following studies were also performed: CSF studies in 5 patients (marked by “F” in figure

1), brain CT in 17 patients (“C”), brain MRI in 9 patients (“M”), EEG in 11 patients (“E”), nerve conduction velocity with EMG in 10 patients (“N”), and neuropsychological tests in 7 patients (“P”). The neuropsychological tests comprised Wechsler (Wechsler Adult Intelligence Scale III, Wechsler Memory Scale III) and Controlled Oral Word Association Test instruments, the Mini-Mental State Examination (MMSE), and the Hamilton test.

DNA analysis. DNA was extracted from whole blood by conventional methods. Analysis of the ATTCT repeat region in the *SCA10* gene was performed by PCR amplification using primers attct-L (5'-AGAAAACAGATGGCAGAATGA-3') and attct-R (5'-GCCTGGGCAACATAGAGAGA-3') as described previously.¹ Patient DNA samples that showed a single normal *SCA10* allele by PCR underwent Southern blot analysis to assess large expansions.¹

Results. We identified 74 affected members from five Brazilian families and examined 28 of these 74 (figure 1). The genealogic histories and physical characteristics of these patients suggested an admixture of Portuguese and South American Indian ancestry in all five families. In the affected members we examined, the female-to-male sex ratio was 1:1; the age at onset was 34.8 ± 7.7 years (range, 23 to 46 years); and the duration of the disease was 13.7 ± 12.7 years. All patients had a cerebellar syndrome (gait ataxia, dysarthria, dysmetria, dysidiadochokinesis, and nystagmus).

None of these patients had seizures. Only four patients (Patient III-7 of Family 2 and Patients IV-11, IV-14, and V-1 of Family 3; see figure 1) had hyperreflexia, and two patients (Patients IV-11 and IV-14 of Family 3) showed an equivocal spasticity. There were no other abnormalities on neurologic and general physical examination. Brain MRI or CT showed cerebellar atrophy in 27 of 28 patients. One of the 27 patients (Patient III-7 of Family 2) also showed equivocal brainstem atrophy. The remaining one (Patient IV-1 of Family 3) had normal CT. Routine laboratory tests (including complete blood count, sedimentation rate, serum glucose, creatinine, electrolytes, Venereal Disease Re-

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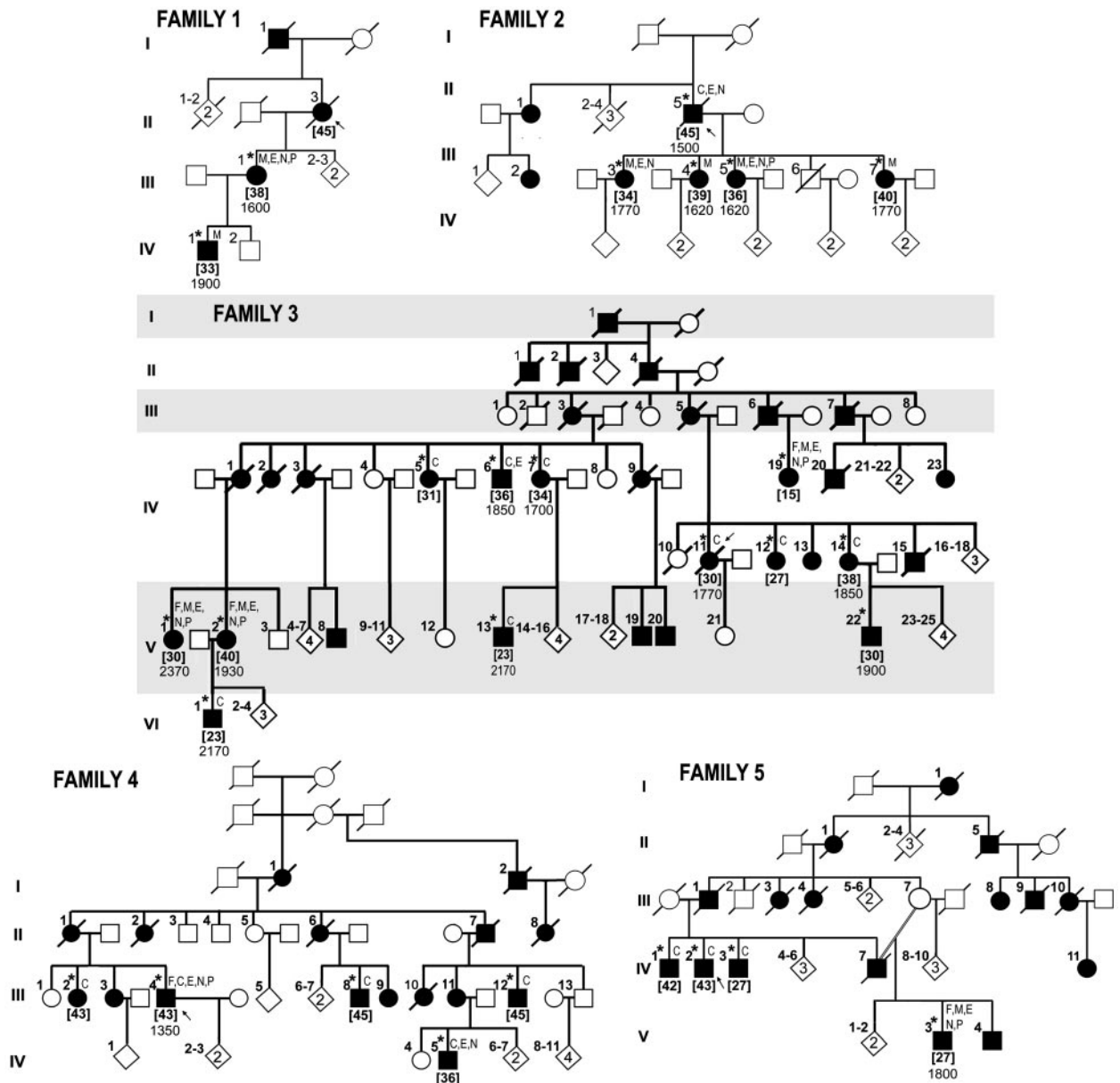


Figure 1. Five Brazilian families with spinocerebellar ataxia type 10: ○ = unaffected female; □ = unaffected male; ● = affected female; ■ = affected male; and ◇ = subject(s) with unspecified gender (a number within this symbol, ◇, indicates the number of siblings of unspecified gender). A diagonal line 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.

search Laboratory, and thyroid and hepatic functions) were normal. EEG was normal in 10 of 11 patients examined, although 1 patient (Patient III-1 of Family 1) had temporal slow activities. Nerve conduction studies/EMG (n = 10) and CSF (n = 5) examination were also normal. Neuropsychological tests were normal, except for one patient (Patient IV-14 of Family 3) with a low IQ of 73 and mild memory difficulties. The Hamilton test and MMSE were normal in all tested patients.

Age at onset was determined by careful history directly taken from 28 patients (see figure 1). The onset was earlier

in the child than the parent by ≥ 5 years in all of the eight parent-child pairs identified. History was indirectly obtained from relatives of additional 18 patients who were deceased or unavailable for direct interview. Although the age at onset information obtained from different relatives was often inconsistent, they agreed on the absence of seizures in all 18 patients.

Eighteen patients from the five families showed expanded alleles ranging from ~1,350 to 2,400 ATTCT repeats (see figure 1). Figure 2 shows representative PCR and Southern blot data from two patients (P1 is Patient

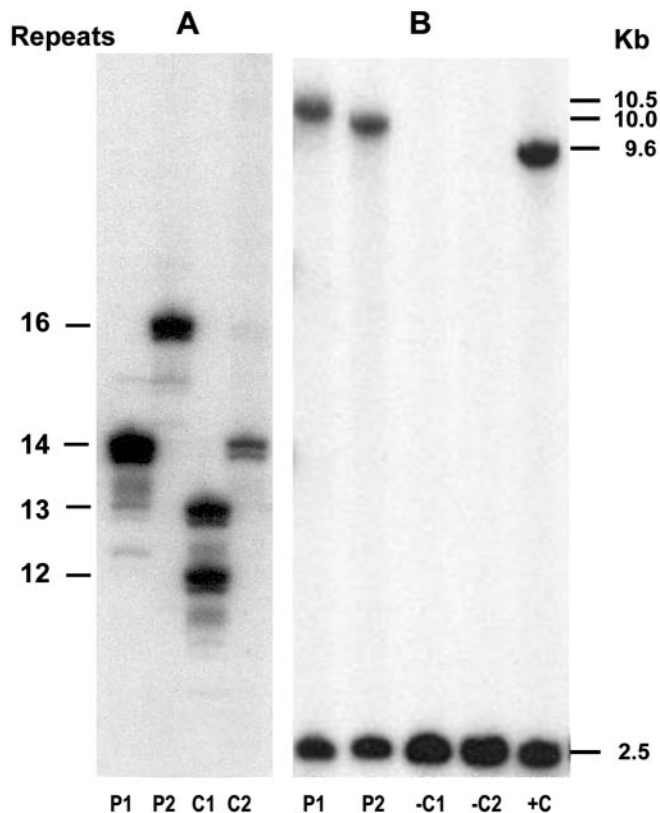


Figure 2. Molecular diagnosis of spinocerebellar ataxia type 10 (SCA10) in Brazilian patients. (A) The PCR analysis showed a single normal allele in two SCA10 patients (P1 and P2). C1 and C2 are normal controls with known genotypes 12/13 and 14/14 SCA10 repeats. (B) The SCA10 expansions were identified 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.

III-1 of family 1, and P2 is Patient II-5 of family 2). These patients demonstrate ATTCT pentanucleotide expansions of ~1,600 and 1,500 repeats. We were able to assess intergenerational changes of the expanded allele length in eight parent-child pairs with known age at onset (see above). The repeat size was larger in the child in all eight pairs. The SCA10 repeat size inversely correlates with the age at onset in our Brazilian SCA10 patients ($r^2 = 0.532$; $p < 0.01$; figure 3).

Discussion. To date, the literature described SCA10 families with the following characteristic features: 1) all SCA10 families were of Mexican ancestry; 2) affected patients showed cerebellar ataxia frequently accompanied by seizures; and 3) anticipation was observed in these multigenerational families.¹⁻⁵ In contrast, our five families with SCA10 are from Brazil, indicating that SCA10 is not unique to the Mexican population. It remains to be seen

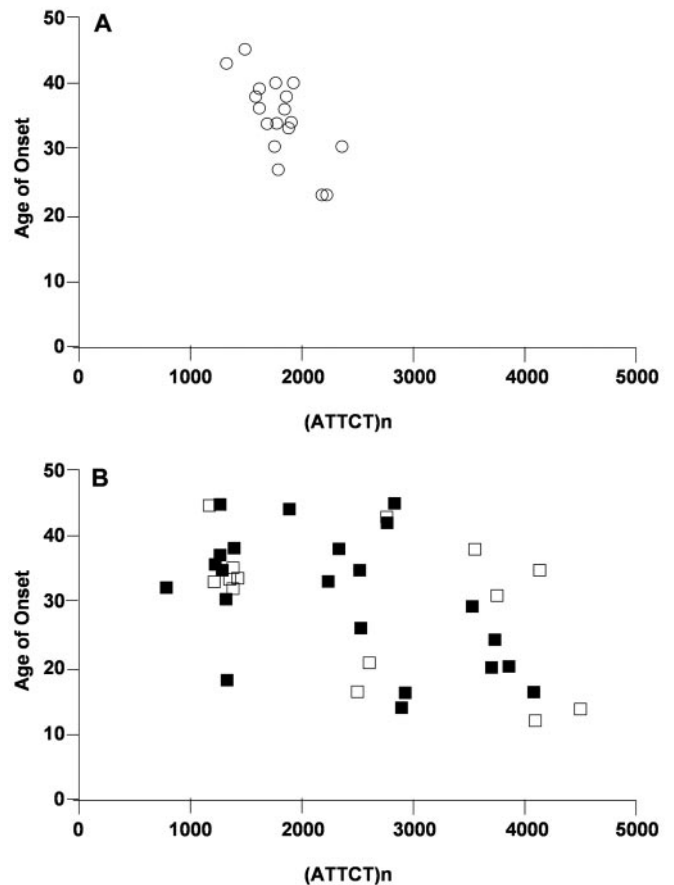


Figure 3. Inverse correlation between the age at onset and the ATTCT repeat expansion size in (A) Brazilian patients with spinocerebellar ataxia type 10 (\circ , $n = 18$; $r^2 = 0.532$; $p < 0.01$), and (B) Mexican patients with (■, $n = 22$) and without (□, $n = 14$) epilepsy (for all 54 patients, $r^2 = 0.264$ 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.

whether the SCA10 mutations identified in Brazilian and Mexican patients share a common ancestral origin.

The clinical features in the Brazilian SCA10 patients differed from those of Mexican SCA10 patients. All Brazilian patients we examined had a cerebellar syndrome, and none of our 43 Brazilian patients had seizures. Conversely, epilepsy was recorded in 24 (60%) of 40 Mexican SCA10 patients reported in the literature. Furthermore, our Brazilian patients exhibited no polyneuropathy and had no hepatic or hematologic abnormalities in contrast to Mexican SCA10 patients.^{4,5} In our patients, neuropsychological testing was normal, and only one patient had a low IQ. Thus, patients in our series could be classified with autosomal dominant cerebellar ataxia type III (pure cerebellar ataxia type) in the Harding classification,⁸ although one of our patients

had mild brainstem atrophy, and a few patients showed equivocal corticospinal tract signs.

Differences in SCA phenotypes across ethnic groups have also been described. Chinese SCA2 patients⁹ and African-American SCA3 patients¹⁰ often show an L-dopa-responsive parkinsonian phenotype, whereas the parkinsonian phenotype is rare in white patients with these SCAs. The Chinese SCA2 patients had relatively shorter expansion of the CAG repeat than white SCA2 patients.⁹ We cannot explain the phenotypic difference between Mexican and Brazilian patients based on the ATTCT repeat expansion size because the repeat size overlapped between the two SCA10 populations, and the epilepsy phenotype in the Mexican patients was associated with a wide range of the repeat size (see figure 3). Careful epidemiologic studies and investigations of *cis*- and *trans*-acting genetic modifiers would be of interest.

Previously reported Mexican SCA10 families showed variable anticipation.²⁻⁵ Our preliminary data hinted at the presence of anticipation in our Brazilian SCA10 families. A long-term prospective study of asymptomatic offspring of affected members will be valuable for further investigation of anticipation in Brazilian SCA10 families.

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