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Bolivian Kindred with Combined Spinocerebellar Ataxia Type 2 and 10

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Abstract

Spinocerebellar ataxias (SCA) are a group of rare hereditary neurodegenerative disorders. Rare cases of two SCA mutations in the same individual have been reported in the literature, however, family descriptions are lacking. Here we present the clinical features and genetic findings of a Bolivian family expressing both SCA2 and SCA10 mutations. The index case and his mother had both SCA2 and SCA10 mutations with a combined clinical phenotype of both disorders, including slow saccades (SCA2) and seizures (SCA10). The uncle of the index case had only a SCA10 mutation. Although the presence of two SCA mutations in the same individuals may be coincidental, the low probability of having both mutations suggests that these mutations might be particularly prevalent in Bolivian population. This is the first description of a family with two SCA mutations with affected subjects having a combined SCA2 and SCA10 phenotype.

Keywords

Ataxia; Hereditary; SCA; Spinocerebellar Ataxia Type 2; Spinocerebellar Ataxia Type 10

Introduction

The spinocerebellar ataxias (SCAs) are a large and heterogeneous group of autosomal dominant hereditary neurodegenerative disorders, characterized mainly by progressive cerebellar degeneration. The mutational mechanisms include repeat expansions of coding and non-coding genes and other mutations (1). SCA2 is one of the most common SCAs worldwide, whereas SCA10 has only been described in American families so far, particularly of Mexican and Brazilian origin (2).

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Conflict of Interest

There is no conflict of interest for any of the author related to this manuscript.

SCA2 is produced by a mutation in the *ataxin-2* (*ATXN2*) gene on chromosome 12q24.1 (3). SCA2 can present as progressive cerebellar syndrome, parkinsonism, or both (3). Slowing of horizontal saccades is a characteristic feature of this disorder (4). SCA10, on the other hand, is caused by a mutation in a non-coding region (intron 9) of the *ataxin-10* (*ATXN10*) gene on chromosome 22q13, producing a pentanucleotide (ATTCT) expansion (2). Full mutation is considered with 700 ATTCT repeats, although a large intermediate range (between 23 and 699 ATTCT repeats) may be encountered in some symptomatic cases. In addition to cerebellar ataxia, some patients with SCA10, particularly those of Mexican origin have also epilepsy (5).

Although the co-existence of two different SCAs in the same individual is exceptionally rare, two cases with combined SCA2 and SCA10 mutations have been described. The first case described was a 54-year old man with Mexican, French and Native American ancestry, he had 38/22 CAG and 962/10 ATTCT repeats in the SCA2 and SCA10 genes, respectively (6). We also described a 38-year old Bolivian man of German ancestry and a combination of SCA2 (44/22 CAG repeats) and SCA10 (1611/13 ATTCT repeats) gene expansions (7). To our knowledge no familial relationship exists between these two subjects and respective families. Both patients had features suggesting combined phenotypic expression of both SCAs types. Despite the importance of this finding, no information regarding the family history of any of these patients was available. Here, we report the clinical and genetic findings of a Bolivian family with combined SCA2 and 10 mutations. The study was approved by the Internal Review Board of the University of Florida and subjects gave written informed consent for genetic studies and clinical evaluations.

Methods

Genomic DNA extraction

Genomic DNA was isolated from whole blood or cultured fibroblast using Qiagen DNeasy Blood & Tissue kit. For genotyping of the index case, the tests were done on dermal fibroblasts. For the other subjects, the tests were done on whole blood DNA.

Southern Blot analysis of SCA10 expansions and SCA2 expansion PCR

Southern blot analysis was done as previously described (2, 8). Briefly, genomic DNA was digested with *EcoRI* to completion. Products were separated on an agarose gel and transferred to a positively charged nylon membrane. The membrane was probed with a 500-bp ³²P-labeled probe that hybridizes upstream the SCA10 expansion. The region containing the SCA2 CAG repeat was PCR amplified as described previously (9). Briefly, PCR was carried out in a final volume of 25 µl, containing 100ng genomic DNA, 0.5 µM forward and reverse primer, and AmpliTaq Gold 360 Master Mix (Life Technologies, #w4398886). Electrophoresis of the PCR products was carried out on a 2% agarose gel.

Clinical assessments

Patients were clinically evaluated with the Scale for the Assessment and Rating of Ataxia (SARA) an 8 item scale ranging from 0-no ataxia to 40-severe ataxia and the modified Rankin scale (mRs).

Family description

The family history strongly suggests an autosomal dominant pattern of inheritance (figure 1). Case I1, the maternal grandfather of the index case was clinically unaffected and died in his 70s of non-neurological causes. Case I2, the maternal grandmother of the index case, had progressive ataxia, but no epilepsy, with an unknown age of onset. She died at the age of 70 due to complications of her neurological disorder. Case II2, the mother of the index case is currently 63 year-old, she has had progressive cerebellar ataxia with prominent dysarthria since her early 40s. She is now bedridden because of severe gait ataxia (SARA score: 33). She has slow horizontal saccades, hyporeflexia and increased tone in the lower extremities without Babinski sign. She has a history of generalized seizures during her 20s. Case II3, the maternal uncle of the index case is 64 year-old, he developed a milder cerebellar syndrome compared to his sister with slower progression since the age of 32 (SARA score: 29). Mild exophthalmos with normal saccades was observed, along with increased tone in the lower limbs with stimulus-sensitive myoclonus, lower limb hyporeflexia, with normal reflexes in the upper limbs, he also showed moderate generalized bradykinesia, but no tremor, no Babinski sign and no history of epilepsy.

Case III3, the younger sister of the index case, was examined at the age of 36 years; she had subtle gait ataxia and subtle dysarthria (SARA score: 2), with no history of epilepsy (table). Subjects II1, II4, and III1 were found to be normal. The index case (III2) was examined at the age of 39, he has been described in detail elsewhere, briefly, he had cerebellar ataxia (SARA score: 19), with very slow saccades, prominent tics, and a history of generalized and partial seizures between ages 10 and 13, no parkinsonian or neuropathy signs were noted (7). His brain MRI showed moderate cerebellar and brainstem atrophy.

Genetic tests were carried out in subjects II1, II2, II3, III1 and III2. Subjects II1 and III1 were negative for SCA2 and SCA10 expansions. Southern blot showed expanded alleles for subjects II2, II3 and III2 (figure 1). PCR showed expansions of the SCA2 in subject II2 (index case mother) and in the index case (III2). The expanded allele was confirmed in the index case by sequencing to have pure CAG repeats while the normal allele contains 20 CAG repeats but with two CAA interrupts. These results confirmed combined SCA2 and 10 mutations in the index case and his mother. The sister of the index case (III3) was not available for testing, but her risk of having SCA2 only or SCA10 only is 50%, while the risk of inheriting both SCA2 and SCA10 is 25%.

Discussion

The rare occurrence of two distinct SCAs in the same individual, while coincidental, may influence the clinical expression of the disorder. In our reported family two subjects had combined SCA2 and SCA10 mutations, and showed a “hybrid” phenotype with slow saccades (typical of SCA2) and seizures (described in SCA10). We suspect that the grandmother of the index case also had combined SCA2 and SCA10 mutations, considering that the paternal grandfather was not affected and both mutations appear in the next generation. The uncle of the index case (SCA10 only) showed an interesting phenotype with generalized bradykinesia and increased tone in the lower extremities consistent with parkinsonism, although he tested negative for SCA2. To our knowledge parkinsonism is not

a reported feature of SCA10. He also had lower limb hyporeflexia suggesting neuropathy as reported in 66% of Mexican patients with SCA10 (5).

SCAs are rare hereditary disorders therefore; the co-existence of two SCAs in the same individual is probably coincidental. Rare individuals with different but co-existent SCAs have been described in the last ten years. In one Japanese study, 5 out of 127 (3.9%) families with SCA6, had expanded or intermediate alleles in the SCA8 gene (10). In another study, involving 58 Polish families with SCA1, five (8.6%) had expanded repeats of SCA8 alleles (11). A 31-year-old man with a combination of mutations in SCA3 and SCA8 has been reported (12). In this patient, his asymptomatic mother tested positive only for SCA8, whereas his father with ataxia was not tested (12). The relative over-representation of SCA8 in these “hybrid” individuals may be due to poorly defined phenotype and genotype in SCA8 (13). Interestingly, all previously reported subjects with two SCAs have a mutation in a coding region of a gene with polyglutamine expansion (SCA1, SCA2, SCA3 and SCA6) and mutated genes of a non-coding region (SCA8 and SCA10). Huntington disease, another disorder with expanded CAG repeats, combined with an SCA10 mutation has also been described in a woman with Amerindian ancestry (14).

Since SCA2 is relatively common in Latino populations (the most common in Mexico and Cuba) and SCA10 is the second most common in Brazil after SCA3 and in Mexico after SCA2, the co-occurrence of SCA2 and SCA10 in the same individual may not be so surprising. However, the chance of SCA2 and SCA10 occurring in the same individual is less than 1×10^{-9} in the general population, with the probability of having an SCA10 allele in individuals with SCA2 would be less than 1×10^{-5} suggesting that the prevalence of SCA2 and/or SCA10 might be higher in Bolivians than other populations, although this fact is unknown and worth of further investigations.

In summary, combined SCA2 and SCA10 mutations may present in the same individual, manifesting features of both disorders. Testing for SCA10 may be recommended in SCA2 patients with otherwise unexplained seizures.

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Figure 1.

Family tree. Arrow shows the index case. Results of the southern blot and PCR for the subjects tested. A normal allele, B expanded allele.

Table

Results of the clinical assessments of patients with positive neurological findings from this family.

Case	II2*	II3	III2* (Index case)	III3
Age at evaluation (years)	63	64	39	36
SARA, Item (score range)				
1. Gait (0–8)	8	8	3	1
2. Stance (0–6)	6	6	4	0
3. Sitting (0–4)	4	4	2	0
4. Speech disturbance (0–6)	4	2	3	1
5. Finger chase ^a				
Right hand (0–4)	3	3	1	0
Left hand (0–4)	3	3	1	0
Mean R+L/2	3	3	1	0
6. Nose-finger test				
Right hand (0–4)	2	0	2	0
Left hand (0–4)	2	0	2	0
Mean R+L/2	2	0	2	0
7. Fast alternating hand movements				
Right arm (0–4)	3	3	2	0
Left arm (0–4)	3	3	2	0
Mean R+L/2	3	3	2	0
8. Heel-shin slide				
Right leg (0–4)	3	3	2	0
Left leg (0–4)	3	3	2	0
Mean R+L/2	3	3	2	0
Total SARA score	33	29	19	2
mRS (0–6)	5	4	3	1

* Patients with combined SCA2 and SCA10 mutations.

^a Evaluates kinetic tremor.

SARA: Scale for the Assessment and Rating of Ataxia

mRS: modified Rankin scale: 0- no symptoms; 1- no significant disability; 2-slight disability; 3-moderate disability; 4-moderately severe disability; 5-severe disability; 6-dead.