Short Report

Spinocerebellar ataxia type 17 in Indian patients: two rare cases of homozygous expansions


We screened a cohort of 181 patients with features of primary progressive ataxia and chorea for spinocerebellar ataxias 17 (SCA17) mutation after excluding other known SCAs, Huntington’s disease (HD), dentatorubral–pallidoluysian atrophy (DRPLA), and non-genetic causes. This study included patients with known family history of SCA, those with sporadic onset and cases of uncertain family history. Two unrelated patients with Huntington’s disease-like phenotype and cerebellar signs are described with homozygous expansions of 47 and 48 CAG/CAA repeats. A family member with early signs of ataxia was found to carry 37 and 48 repeats. There were fewer CAA interruptions in the repeat sequences of patients than in the controls. The normal repeat range in controls was 21–42, with 91% of the alleles located between 33 and 39 repeats. This is the first report of rare homozygous SCA17 mutation in Indian patients presenting with HD-like phenotype.

Conflict of interest

The authors declare that there are no conflicts of interests.

Spinocerebellar ataxia 17 (SCA17) is a rare type of autosomal dominant cerebellar ataxia (ADCA) which is characterized by cerebellar ataxia combined with a variety of symptoms including dementia, psychiatric symptoms, pyramidal signs, abnormal movements such as dystonia and chorea, choreoathetosis, Parkinsonism and epilepsy (1). The age at onset varies between 3 and 75 years (1). Differential diagnoses include Huntington’s disease (HD), other types of SCA, dentatorubral–pallidoluysian atrophy (DRPLA), Wilson’s disease and other ataxic or choreic disorders. SCA17 is caused by the expansion of more than 42 CAG/CAA repeat units in the coding region of the TATA-box binding protein (TBP; chromosome 6q27) gene, leading to an abnormal expansion of a polyglutamine stretch in the N-terminal of the corresponding protein (2, 3). SCA17 can occur in a familial, de novo, or sporadic form, with low penetrance; hence, genetic screening is essential (4). So far, less than 100 families with SCA17 have been reported and most belong to the Caucasian and Japanese populations (1). Only one case of SCA17 has been described in an Indian patient from the state of Punjab (5). The aim of this study was to estimate the frequency of SCA17 in Indian patients showing features of cerebellar ataxia and chorea. Both familial and sporadic cases of SCA17 were studied; patients with other known...
SCAs, HD, DRPLA, and non-genetic causes were excluded.

**Material and methods**

**Patients and families**

Data was obtained from collaborating hospitals between 1998 and 2003. Patients with features of primary progressive ataxia and chorea either familial or sporadic were selected. A total of 481 subjects were screened including 181 probands, 300 family members related to 72 patients with ADCA and 109 patients with no obvious family history. All the subjects underwent genetic counseling and provided written informed consent; this study was approved by the ethics committees of the government hospitals. Physical and standard neurological examinations were performed by neurologists. The details of neurological examination, various laboratory tests, family history, ethnicity, geographical location, occupation, addiction, and neuroimaging were collected. Patients were screened for non-genetic causes. Family history and diagnoses were confirmed by review of medical and pathological records, if available, neurological examination of affected relatives, and through personal interview of family members and patients.

**Controls**

In all, 167 healthy unrelated individuals visiting the hospitals for medical checkup with detailed medical history, family history, and ethnicity were approached for a control group. Blood samples were collected from these individuals after obtaining written consent and providing counseling. The ethnic groups of controls were sorted and compared to the patients of matched ethnicity.

**Mutation analysis**

For SCA17 mutation analysis, DNA extracted from the blood samples by the standard methods was polymerase chain reaction (PCR) amplified using CY5-labeled primers and an Eppendorf™ mastercycler (Eppendorf, Hamburg, Germany), as specified by Nakamura et al. (3). The PCR products were analyzed using an automatic laser fluorescent (ALF) express sequencer (Pharmacia Biotech, Uppsala, Sweden) and fragment analysis software version 1.2. The CAG/CAA repeats sequence in the PCR products was confirmed by analyzing sequences using BigDye Terminator Cycle Ready Reaction Kit and ABI 377-18 prism sequencer equipped with genescan analysis software version 3.3.1 (Applied Biosystems, Foster City, CA). The population genetics analyses were performed using popgene software (6).

**Results**

The phenotypic features of the patient cohort were cerebellar ataxia (97%) combined with dementia (7%), psychiatric symptoms (26%), pyramidal signs (93%), abnormal movements (56%), e.g. dystonia (23.3%) and chorea (14%), choreoathetosis (30%), Parkinsonism (12%), myoclonus (2.3%) and epilepsy (15%). Only 72 patients presented with positive family history and 12.26% of patients were born of consanguineous marriage of which 4% belonged to ADCAs.

The repeat length in controls was less than 42 repeat units with a skewed distribution of predominant alleles in the range of 29–40 (Fig. 1). In the 334 chromosomes analyzed, the distribution of alleles and modal alleles did not vary significantly with the ethnic groups. Two patients, homozygous for expanded CAG/CAA repeats of 47 and 48 in the TBP gene were identified with a frequency of 1.1% (2 of 181). An affected relative was found to be a heterozygote with genotype 37/48. Interestingly, both the patients presented with HD-like phenotype and were born of consanguineous marriage where the parents were first-degree cousins. The nucleotide sequences of CAG/CAA repeats in the TBP gene of both SCA17 patients were determined and deposited in GenBank (Accession Numbers AY528423, AY368204).

**Case 1**

A 45-year old male (Family A, Fig. 2) presented with a history of slurred speech and dysphagia for 9 years, gait ataxia for 5 years and involuntary limb movements for 1 year. In addition, he had mild memory impairment and occasional aggressive behavior. On examination, he had a mild cognitive decline with mini-mental state examination (MMSE) score of 23/30 showing difficulty in problem solving and memory functions. His saccadic eye movements were slow in initiation and he had broken pursuit. His eye movements were otherwise complete. His speech was markedly dysarthric. The patient had distinct ataxia of both upper and lower limbs with poor tandem gait. There was dystonic posturing of distal parts, with occasional striate toes. The choreiform movements were present in all the limbs, but were predominant on the lower limbs. He had rigidity in both upper and lower limbs. All the deep tendon reflexes were normal.
Fig. 1. Distribution of (CAG/CAA)_n repeats at the spinocerebellar ataxias 17 locus in Indian patients. The filled bars represent the normal chromosomes of controls, and open bars represent the expanded chromosomes of patients. The normal repeat range was 21–42, with 91% of the alleles between 33 and 39. Expanded CAG/CAA repeat units of 47 and 48 were found in the patients. The modal allele of 36 repeats was found in 22% of the chromosomes.

apart from ankle jerks, which were depressed and the plantar response was flexor. There was no sensory dysfunction. Magnetic resonance imaging (MRI) revealed cerebellar degeneration (Fig. S1, supporting information online). On genetic analysis, an expanded SCA17 homozygous genotype of 47/47 CAG/CAA repeats was found in the TBP gene. The patient died at the age of 54 years as a result of complications related to ataxia after remaining in the bedridden state for 1 year. His 21-year old nephew was found to be a heterozygote with the genotype of 37/48 at the SCA17 locus. He had symptoms of early ataxia with age at onset of 19 years. All other affected members of the patient’s family were dead and no accurate information was available. The family belonged to the south Indian state of Kerala.

Case 2

A 43-year old male, (Family B, Fig. 2) presented with a 2-year history of slow progressive gait ataxia, followed by dysarthria and dysphagia. On examination, his MMSE score was 20/30. He showed evidence of frontal lobe dysfunction with difficulties in abstract thinking, problem solving and motor sequencing. Fundus examination showed bilateral optic disc pallor. The patient had spasmodic dysphonia. Ataxia was minimal in the upper limbs, but there was rigidity with dystonic posturing in the upper limbs. He had a
broad-based, short-stepped ataxic gait with ignition failure. There was no evidence of tremor, rigidity, bradykinesia, or myoclonus. Sensory examination was normal. Deep tendon reflexes were bilaterally brisk but plantar response was flexor. MRI showed cerebral and cerebellar atrophy with normal brain stem (Fig. S2, supporting information online). Molecular genetic testing revealed SCA17 caused by homozygous CAG/CAA repeat expansions of 48/48 units in TBP gene. The patient died at the age of 47 years, with complications in breathing and swallowing but was not bedridden. All the surviving siblings of the proband were over the age of 50 years, and were unaffected. His son died in an accident. The family members including the daughters of the proband, did not consent for molecular testing. His parents survived till their eighties without exhibiting any psychiatric symptoms; they died of infections unrelated to genetic causes. The proband belonged to a large Maharashtrian family located in western India.

Discussion

The homozygous expansions of 48 and 47 CAG/CAA repeat units in TBP gene were found to be associated with HD-like phenotype in two patients. The expanded repeats differed in both repeat length and sequence configuration from the controls (Table 1). A small proportion of SCA17 patients are found with HD-like phenotype; present in sporadic or in solitary individuals within a family, and in multiple family members (1, 7–10). The prominent features in our patients were ataxia, chorea, Parkinsonism, psychiatric symptoms of slow progressive dementia, cognitive dysfunction and personality changes. Ocular signs such as nystagmus or impaired saccades were not noted. Epilepsy reported in some SCA17 patients (7, 11, 12) was lacking in our cases.

In SCA17 patients, two distinct repeat sequences encoding the polyglutamine stretch have been described: (CAG)₃ (CAA)₃ (CAG)ₙ₁ CAA CAG CAA(CAG)ₙ₂ CAA CAG with expanded (CAG)ₙ₁ and (CAG)₃(CAA₃) (CAG)ₙ₁ CAACAG with expanded (CAG)ₙ₁ (13). As shown in Table 1, the repeat sequence in both patients was similar to the former type but with fewer CAA interruptions at positions IV and position II. The patients with expanded alleles also had 1 CAA repeat at position IV compared to the controls with a CAACAGCAA sequence at the same position. In patients, the increase in the (CAG)₃ repeat number at position I corresponded with the loss of the same number of CAA interruptions at position II compared to the controls, i.e. (CAG)₃ in case 1 and (CAG)₄ in case 2 corresponded to the loss of 1 and 2 CAA interruptions, respectively. The expanded alleles of 47 and 48 CAG/CAA repeats in the homozygous and heterozygous patients in family A was similar in sequence configuration, whereas the normal 37 repeat allele was similar to that of the controls with the same repeat number. -expanded allele.

Table 1. Features of the Indian spinocerebellar ataxias 17 patients with expanded CAG/CAA repeats

<table>
<thead>
<tr>
<th>Allele and repeat structure</th>
<th>Allele</th>
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<th>III</th>
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<th>VI</th>
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<tbody>
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<td>Geno-type</td>
<td>Age at onset (years)</td>
<td>Age at death (years)</td>
<td>Symptoms</td>
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<td>Control</td>
<td>48/48</td>
<td>Family B</td>
<td>41</td>
<td>47</td>
<td>Ataxia, dysarthria, dysphagia, cognitive decline, Parkinsonism, and chorea</td>
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<td>39</td>
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<td>48*</td>
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<td>47</td>
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The roman letters indicate the regions within the repeat sequence. (CAG₃) indicates the number of CAG repeats. The total CAA interruptions in the expanded alleles of genotype 47/47, 48/48, and 37/48 were compared to the controls with a CAACAGCAA sequence at the same position. In patients, the increase in the (CAG)₃ repeat number at position I corresponded with the loss of the same number of CAA interruptions at position II compared to the controls, i.e. (CAG)₃ in case 1 and (CAG)₄ in case 2 corresponded to the loss of 1 and 2 CAA interruptions, respectively. The expanded alleles of 47 and 48 CAG/CAA repeats in the homozygous and heterozygous patients in family A was similar in sequence configuration, whereas the normal 37 repeat allele was similar to that of the controls with the same repeat number. -expanded allele.
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the repeat sequences found in our patients were different from those described previously and contained fewer CAA interruptions, we were unable to confirm if the repeat configurations influenced the intergenerational instability because the parental genotype was not available for analysis. It is also difficult to conclude whether the loss of CAA interruptions was de novo arising from stable normal or expanded alleles of parents during transmission. In Family A, there is a gain of one repeat unit in the nephew as compared to his uncle. There may be repeat instability because of loss of CAA interruptions in this case. Incomplete penetrance has been suggested for patients carrying 45–49 repeats (7, 9, 14). The inheritance pattern of the patients belonging to Family B with homozygous 48 CAG/CAA repeats suggests a possible case of incomplete penetrance with unaffected parents and siblings who could be healthy heterozygotes as noted in a similar case (12). Isolated homozygous cases with mild or intermediate expanded alleles in the repeat range of 44–47 are affected, whereas heterozygotes carrying one copy of these alleles remain healthy; this poses a question whether copy numbers of such intermediate alleles influence disease condition, onset, and progression.

The patient with 48/48 genotype had the onset at 41 years and died at the age of 47 years, whereas the patient with 47/47 genotype had onset at 36 years and died at the age of 54 years. Therefore, the onset was not earlier for the longer repeat length but increased the severity and disease progression. In the same family, heterozygous individual with 37/48 repeats had an earlier onset than homozygote individual with 47/47 repeats, which further suggests that an increase in copy number of expanded repeats may not influence the age at onset by decreasing it. With only few reports of homozygotes worldwide, the gene dosage effect cannot be concluded. Homozygosity has been shown to lower the age at onset in DRPLA, SCA3 and SCA6, but not in HD, which, however, shows increased severity (17–20). The homozygosity could be most probably because of consanguinity in our patients. Homozygous patients with 47/47 genotype because of partial isodisomy 6 (21) and 48/48 genotype with a history of consanguinity (9) have been reported, but their parental genotypes were not known. The homozygote with 48 repeats reported by Toyoshima et al. (9) had an onset at 39 years and died at the age of 49 years with rapid disease progression. In the partial isodisomy 6 case of 47 repeats, the proband presented with rapidly progressing ataxia associated with dementia and history of over 3 years at the age of 40 years (21).

The homozygous patients in our study did not differ in severity or age at onset as compared to the symptomatic heterozygotes with the same repeat length (3, 12); thereby, our findings also support the gain-of-function hypothesis.

In summary, the frequency of SCA17 patients in Indians is low and can be sporadic, de novo, or familial in nature. We suggest that one mechanism underlying the loss of CAA interruptions may be because of the mutation of CAA to CAG, resulting in smaller increments of repeats which could further partially destabilize the repeat length and introduce errors during replication.

Supporting Information

The following Supporting information is available for this article: Fig. S1. Brain magnetic resonance imaging of proband described in case 1; Family A – T1-weighted sagittal image showing distinct cerebellar atrophy.

Fig. S2. Brain magnetic resonance imaging of proband described in case 2; Family B – T1-weighted sagittal image showing gross cerebellar atrophy and mild cerebral atrophy.

Additional Supporting information may be found in the online version of this article.

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Acknowledgements

We would like to thank the patients who participated in this study and their family members. We also express our gratitude to the neurologists and medical social workers at the collaborating hospitals for their kind help. We wish to thank Drs Sabah Malladi and Ravindra Makde for their critical reading of the manuscript.

References