Frequency Analysis and Clinical Characterization of Spinocerebellar Ataxia Types 1, 2, 3, 6, and 7 in Korean Patients

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Background: By genetic analysis, the CAG repeat expansion has been established in spinocerebellar ataxia (SCA) types 1, 2, 3, 6, and 7. Despite the genetic differentiation of SCA, the characterization of the phenotypes of various SCAs has been challenging for better clinical diagnosis.

Objective: To analyze the frequencies and the clinical manifestations of SCA1, SCA2, SCA3, SCA6, and SCA7 in Korean patients.

Patients and Methods: We performed genetic analysis in 253 unrelated Korean patients with progressive cerebellar ataxia. We compared the frequencies, inheritance patterns, and various clinical manifestations of patients with genetically confirmed SCA.

Results: Among the 52 patients with expanded CAG repeat, the most frequent SCA type was SCA2, followed by SCA3, SCA6, SCA1, and SCA7. Nine patients (17%) had a negative family history of ataxia, mostly in SCA6. There were characteristic clinical features such as hypotonia and optic atrophy for SCA1; hyporeflexia for SCA2; nystagmus, bulging eye, and dystonia for SCA3; and macular degeneration for SCA7. Interestingly, 4 patients (1 with SCA2, 1 with SCA3, and 2 with SCA6) were misdiagnosed as having multiple-system atrophy because of the absence of family history and the presence of parkinsonism and urinary incontinence.

Conclusions: This study provides a detailed analysis of the clinical characteristics of the genetically defined CAG-repeat SCAs in Korean patients. Although phenotypes were heterogeneous, some clinical features may be helpful for clinical diagnosis. However, genetic studies for SCA are needed despite uncertain family history or the presence of atypical clinical features causing misdiagnosis as atypical parkinsonism.

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The autosomal dominant spinocerebellar ataxias are a clinically and genetically heterogeneous group of neurodegenerative disorders characterized by progressive deterioration in balance and coordination as well as cerebellar ocular disturbance. These disorders are caused by progressive degeneration that affects the cerebellum, brainstem, and spinocerebellar tracts. The cerebellar syndrome is frequently associated with signs of cerebral, pyramidal, extrapyramidal, bulbar, spinal, and peripheral nervous system involvement in highly variable degrees. Several clinical and neuropathologic classifications have been established and the basis of age at onset and degree of involvement of the cerebellum, basal ganglia, spinal cord, and brainstem and the presence of a peripheral neuropathy. To date, 16 different spinocerebellar ataxias (SCAs) have been identified with the linkage analysis. Among these SCAs, the genes for 10 of these loci (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA15, and SCA17) have been cloned, whereas the genes for the SCA4, SCA5, SCA11, SCA13, SCA14, and SCA16 loci have yet to be isolated. The association of CAG repeat expansions in the coding regions of the SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 genes has been firmly established. In contrast, the precise contribution of SCA8, SCA10, SCA12, and SCA15 repeat expansions to the autosomal dominant cerebellar ataxia disease spectrum remains unclear. The value of genetic classification has been highlighted by the striking variability in clinical phenotype observed among family members as well as the broad overlap in clinical phenotypes observed among different genotypes. Jin et al examined the frequency of 6 types of autosomal dominant spinocerebellar ataxia (SCA types 1, 2, 3, 6, and 7 and dentatorubral pallidoluysian atrophy) in Korean patients with...
progressive ataxia with the use of a molecular genetic analysis.

Despite the recent success in genetic differentiation of SCA, it remains unclear whether genetically defined subtypes of SCA present distinct phenotypes for SCA1, SCA2, SCA3, SCA6, and SCA7. The characterization of the phenotypes of various SCAs has been challenging for better clinical diagnosis without molecular genetic analysis. Several studies have attempted to analyze the clinical features of the genetically confirmed individual SCAs or to compare the clinical presentation of SCAs. However, those studies did not recruit all of the subtypes of CAG-repeat SCAs or include some common clinical features such as restless leg syndrome or myoclonus.

To better understand the phenotypes of genetically determined trinucleotide-repeat SCAs, we compared the frequencies, inheritance pattern, and clinical features of Korean patients with genetically confirmed SCAs (SCA1, SCA2, SCA3, SCA6, and SCA7). We also analyzed the correlation between CAG repeat numbers and such clinical manifestations as age at onset and inheritance pattern.

**METHODS**

**PATIENTS**

Our study enrolled 253 unrelated individuals who were manifesting progressive ataxia as a main clinical feature from January 1, 1995, to December 31, 2000. Study participants were recruited on the basis of a diagnosis of ataxia of unknown cause, without regard to inheritance pattern, age at onset, sex, or disease severity, from 14 neurology clinics across South Korea, including our clinic. Some studied patients overlapped with those of our colleagues’ previous study. Criteria used to exclude patients with ataxia of known cause included evaluation of alcohol consumption, thyroid function testing, vitamin B12 and E levels, folate levels, tumor markers, anti–Purkinje cell antibody, serum and urine amino acid levels, very-long-chain fatty acid levels, and brain magnetic resonance imaging. Brain magnetic resonance imaging demonstrated mild to severe atrophy of the cerebellum with or without brainstem involvement. Age at onset and family history were determined on the basis of historical information. Blood was collected from the unrelated affected individuals to investigate the trinucleotide repeat of SCA1, SCA2, SCA3, SCA6, and SCA7 genes. All persons enrolled in the study gave their informed consent before their inclusion in the study.

**MOLECULAR GENETIC ANALYSIS**

Blood samples in EDTA were obtained from all participants. Genomic DNA was isolated from the peripheral-blood leukocytes by means of a genomic DNA purification kit (Promega, Madison, Wis). Polymerase chain reaction was performed with the primers CAG-a and CAG-b for SCA1, SCA2-A and SCA2-B for SCA2, MJD32 and MJD25 for SCA3, S-3-F1 and S-3-R1 for SCA6, and 4U1024 and 4U716 for SCA7. The polymerase chain reaction conditions were as described in each original report. Technical details of molecular genetic analysis were described as reported previously.

**EVALUATION OF CLINICAL FEATURES**

Fifty-two patients with SCA1 (6 patients), SCA2 (17 patients), SCA3 (15 patients), SCA6 (10 patients), and SCA7 (4 patients) were eligible for detailed neurologic examination. The referring neurologists examined the patients by checking off the lists of various clinical findings. The checklist consisted of the following clinical features: cerebellar ataxia (including gait disturbance, limb ataxia, and speech disturbance), hypertonia, disturbance of extraocular movement (including saccade, pursuit, nystagmus, and ophthalmoplegia), optic atrophy, macular degeneration, bulging eyes, tremors (postural and terminal), extrapyramidal symptoms (parkinsonism, chorea, and dystonia), myoclonus, pyramidal signs, ataxia, sensory symptoms, restless leg syndrome, dementia, dysphagia, and urinary incontinence.

**STATISTICAL ANALYSIS**

Statistical analysis was performed with SPSS 10.0 for Windows (SPSS Inc, Chicago, Ill). The results were expressed as mean ± SD. Kruskall-Wallis test and Scheffe post hoc analysis after rank were used to assess the difference in age at onset among the groups. The correlation between the age at onset and the CAG repeat length was evaluated by Spearman correlation test in each group. We used the Mann-Whitney test to compare the age at onset and the CAG repeat number between SCA6 with family history and SCA6 without family history. Fisher exact test was performed to assess the frequency of clinical features among the groups, and the subsequent adjustment of P values with the permutation method was performed for the pairwise comparison as a post hoc test.

**RESULTS**

**FREQUENCIES OF SCA1, SCA2, SCA3, SCA6, AND SCA7 MUTATIONS IN UNRELATED KOREAN PATIENTS**

From molecular genetic analysis, the expansion of CAG repeat was detected in 52 patients (20.6%) of 253 unrelated individuals. Among the 52 patients with expanded CAG repeat, we found SCA1 expansion at a frequency of 12% (6 cases), SCA2 expansion at a frequency of 33% (17 cases), SCA3 expansion at a frequency of 29% (15 cases), SCA6 expansion at a frequency of 19% (10 cases), and SCA7 expansion at a frequency of 8% (4 cases).

**INHERITANCE PATTERN**

Inheritance pattern was determined on the basis of historical information or results of genetic studies from other family members. The inheritance patterns of patients with genetically confirmed SCA are summarized in Table 2. Nine (17%) of 52 patients had a negative family history of ataxia. On the contrary, 7 (3.5%) of 201 patients with negative DNA analyses had a positive family history. One (17%) of 6 patients with SCA1, 2 (12%) of 17 with SCA2, 2 (13%) of 15 with SCA3, 3 (30%) of 10 with SCA6, and 1 (25%) of 4 with SCA7 did not have a family history of ataxia. The frequencies of sporadic SCA6 and SCA7 were higher than those of other subgroups. In the SCA6 group, patients with sporadic SCA6 showed a later onset of symptoms than those with SCA6 with a family history (mean ± SD, 57.7 ± 14.0 years vs 28.7 ± 17.1 years) (P = .02, Mann-Whitney test). However, CAG repeat numbers were
not different between patients with SCA6 with and without a family history ($P = .6$).

**AGE AT ONSET AND CORRELATION WITH CAG REPEAT LENGTHS**

Mean (±SD) age at onset of the examined affected individuals was 36.3 ± 16.6 years in SCA1 (n = 6), 32.8 ± 12.7 years in SCA2 (n = 17), 38.5 ± 9.7 years in SCA3 (n = 15), 37.4 ± 20.8 years in SCA6 (n = 10), and 35.3 ± 6.2 years in SCA7 (n = 4) (Table 1). There was no significant difference in the age at onset among the groups. Mean numbers of expanded CAG repeats were 70.4 ± 25.9 in SCA1, 44.9 ± 5.3 in SCA2, 73.9 ± 4.8 in SCA3, 23.9 ± 3.6 in SCA6, and 48.3 ± 4.3 in SCA7.

Age at onset was inversely correlated with CAG repeat length only in SCA1 and SCA2, but not in SCA3, SCA6, and SCA7 (SCA1: $r = -0.829$, $P = .04$; SCA2: $r = -0.618$, $P = .006$; SCA3: $r = -0.099$, $P = .73$; SCA6: $r = 0.173$, $P = .54$; SCA7: $r = 0.800$, $P = .2$) (Figure).

**COMPARISON OF CLINICAL FEATURES IN SCA1, SCA2, SCA3, SCA6, AND SCA7**

We analyzed the clinical features of genetically confirmed SCA types 1, 2, 3, 6, and 7. The clinical characteristics of the trinucleotide-repeat SCAs are summarized in Table 1. All patients had cerebellar dysfunctions with various degrees of symptoms. Hypotonia was the prominent feature in patients with SCA1 ($P < .05$, Fisher exact test). Nystagmus was characteristic for patients with SCA3 ($P < .05$). Ophthalmoplegia was detected only in patients with SCA1, SCA2, and SCA3. Optic atrophy was the characteristic feature for SCA1 ($P < .05$), while macular degeneration was detected only in patients with SCA7. Pyramidal signs including hyperreflexia and Babinski sign

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**Table 1. Clinical Characteristics of Patients With SCA1, SCA2, SCA3, SCA6, and SCA7**

<table>
<thead>
<tr>
<th></th>
<th>SCA1</th>
<th>SCA2</th>
<th>SCA3</th>
<th>SCA6</th>
<th>SCA7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) affected</td>
<td>6 (12)</td>
<td>17 (33)</td>
<td>15 (29)</td>
<td>10 (19)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Age at onset, mean ± SD, y</td>
<td>36.3 ± 16.6</td>
<td>32.8 ± 12.7</td>
<td>38.5 ± 9.7</td>
<td>37.4 ± 20.8</td>
<td>35.3 ± 6.2</td>
</tr>
<tr>
<td>Expanded CAG repeats, mean ± SD, No.</td>
<td>70.4 ± 25.9</td>
<td>44.9 ± 5.3</td>
<td>73.9 ± 4.8</td>
<td>23.9 ± 3.6</td>
<td>48.3 ± 4.3</td>
</tr>
</tbody>
</table>

**Table 2. Inheritance Patterns of 52 Cases of Genetically Confirmed SCA**

<table>
<thead>
<tr>
<th></th>
<th>SCA1</th>
<th>SCA2</th>
<th>SCA3</th>
<th>SCA6</th>
<th>SCA7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>5 (83)</td>
<td>15 (88)</td>
<td>13 (87)</td>
<td>7 (70)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>No family history</td>
<td>1 (17)</td>
<td>2 (12)</td>
<td>2 (13)</td>
<td>3 (30)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>6 (100)</td>
<td>17 (100)</td>
<td>15 (100)</td>
<td>10 (100)</td>
<td>4 (100)</td>
</tr>
</tbody>
</table>

Abbreviation: SCA, spinocerebellar ataxia.

* $P < .05$ compared with other groups, Fisher exact test.

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Not different between patients with SCA6 with and without a family history ($P = .6$).
were more frequently detected in SCA1 but were not significant. On the other hand, clinical signs of peripheral neuropathy such as decreased sensory and hyporeflexia were the most obvious in patients with SCA2. Dystonia and bulging eye were unique signs of SCA3. Other extrapyramidal symptoms such as parkinsonism and chorea were observed in patients with SCA2, SCA3, and SCA6. Restless leg syndrome, which was more frequent in SCA3, was also observed in SCA2. Dementia was seen in patients with SCA2, SCA3, and SCA6.

As we observed that 3 of the 10 patients with SCA6 had a juvenile onset (before age 20 years), we compared the clinical manifestations of juvenile onset and nonjuvenile onset in the patients with SCA6. Chorea, myoclonus, and hyporeflexia were detected only in the patients with juvenile-onset SCA6. On the contrary, parkinsonism and urinary incontinence were detected only in the patients with nonjuvenile-onset SCA6 (Table 3).

Interestingly, 4 patients (1 with SCA2, 1 with SCA3, and 2 with SCA6) were misdiagnosed as having multisystem atrophy because of the absence of family history and the presence of pyramidal signs, parkinsonism, and autonomic dysfunction such as urinary incontinence.

In our study, we detected 52 patients (20.6%) with expansions of CAG repeats among 253 unrelated Korean individuals manifesting progressive ataxia as the main clinical feature. This frequency of the trinucleotide-repeat SCAs was lower than that of the Japanese group.40 Even though we tried to enroll patients without regard to the inheritance pattern or age at onset, there may have been some selection bias among referring neurologists. Among the 52 patients with expanded CAG repeat, the most frequent SCA type was SCA2 (33%), followed by SCA3 (29%), SCA6 (19%), SCA1 (12%), and SCA7 (8%). As in previous studies,35,37,38,40 our study demonstrated that SCA2 and SCA3 types appeared quite prevalent regardless of the ethnic groups. However, SCA3 is extremely rare in Italy39,41 and in whites in the United Kingdom.42 Spinocerebellar atrophy type 6 is also a relatively common subtype of patients with SCA, with varying frequencies around the world.37,40,43-46 Similar regional differences are reported in Japan, where the SCA6 frequency ranges from 6% to 31% depending on the population studied.47,48

Nine (17%) of 52 patients had a negative family history of ataxia. This relatively large proportion of cases without positive family histories suggests that there was a censor effect or the histories were not taken accurately enough. Thus, further family analysis of these patients with sporadic disease is needed. Consistent with previous reports,37,40,49 the frequency of sporadic SCA6 was higher than that of the other subgroups. This result suggests that the analysis of SCA6 may further contribute to the genetic classification of patients with autosomal dominant cerebellar ataxia, including patients without a clear family history of the disease. As in the previous study,50 patients with sporadic SCA6 showed a later mean age at onset than patients with SCA6 with a family history. However, we could not detect any difference in CAG repeat numbers between the patients with SCA6 with a family history and those without a family history (P = .06).

In terms of age at onset, there was no significant difference among the subgroups. Our study demonstrated that age at onset was not a good differentiating point for classifying the subtypes of SCAs. In general, age at onset of SCA6 appears to be somewhat later than that for other SCAs, and disease progression is less severe.16,34,37,47,51 However, in our study, the mean age at onset of SCA6 was not later than that of the other subgroups. In contrast to a previous study,37 which reported that there was no juvenile-onset case in SCA6, 3 of the 10 patients with SCA6 had a juvenile onset (before age 20 years). CAG repeat numbers were not different between juvenile-onset and nonjuvenile-onset SCA6 (P = .06). However, clinical features were somewhat different between the two. We ob-
served that age at onset was inversely correlated with CAG repeat length only in SCA1 and SCA2, but not in SCA3, SCA6, and SCA7. Consistent with the opinion proposed by Moseley et al., our results indicated that the repeat size could not be used to predict the age at onset for presymptomatic patients.

The clinical features of SCA1, SCA2, SCA3, SCA6, and SCA7 showed a substantial overlap among the subgroups with a large variability within them. Despite the large variability of the phenotypes, there were some combinations of clinical features that seemed to be characteristic of each subtype of SCA, such as hypotonia and optic atrophy for SCA1; hyporeflexia for SCA2; nystagmus, bulging eye, and dystonia for SCA3; and macular degeneration for SCA7. These results regarding clinical characteristics of SCA1, SCA2, SCA3, and SCA7 were consistent with previous reports. In contrast to a previous study, restless leg syndrome was not detected in our cases of SCA1. In contrast to previous studies, which proposed that SCA6 featured pure cerebellar ataxia, in our cases SCA6 had extremely various phenotypes including cerebellar oculomotor signs, pyramidal and extrapyramidal symptoms, myoclonus, dementia, and urinary incontinence. These clinical manifestations varied under the influence of age at onset, for example, parkinsonism and urinary incontinence in nonjuvenile-onset SCA6 vs chorea, myoclonus, and hyporeflexia in juvenile-onset SCA6.

Interestingly, 4 patients (1 with SCA2, 1 with SCA3, and 2 with SCA6) were misdiagnosed as having multiple-system atrophy because of the absence of family history and the presence of pyramidal signs, parkinsonism, and autonomic dysfunction such as urinary incontinence. In regard to urinary incontinence, Soong and colleagues reported that other noncerebellar features such as rigidity, gait abnormality, intellectual impairment, and sphincter disturbances were rarely found in patients with SCA6.

In conclusion, this study provides the first detailed analysis, to our knowledge, of the frequencies and clinical characteristics of the genetically defined CAG-repeat SCAs in Korean patients. These data showed the heterogeneity of phenotypic abnormalities in trinucleotide-repeat SCAs. However, there were some characteristic combinations of phenotypes for each subtype of SCAs, which were also seen in previous studies, and these characteristic clinical features may be helpful for better clinical diagnosis without molecular genetic analysis. Molecular genetic studies of SCA are needed in cases of uncertain family history or the presence of atypical clinical features causing misdiagnosis as atypical parkinsonism.

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