Prevalence of Autosomal Dominant Cerebellar Ataxia in Aomori, the Northernmost Prefecture of Honshu, Japan

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Abstract

Objective The frequency of autosomal dominant cerebellar ataxia (ADCA) varies between different regions of Japan. This is the first report on the prevalence of ADCA subtypes in Aomori, Japan.

Methods and Patients Sixty-five familial spinocerebellar ataxia (SCA) patients and 15 sporadic SCA patients were genetically examined. For only the SCA2 patients (n = 8), the magnetic resonance imaging (MRI) data were analyzed in detail.

Results Spinocerebellar ataxia (SCA) type 6 was often observed (77.7% of cases), with SCA2 (10.6% of cases) being the next most common form. Among the 15 sporadic SCA patients, genetic mutations for SCA2, SCA6, SCA17, and SCA31 were identified, indicating that ADCAs should be considered in sporadic cases of ataxia. Furthermore, in SCA2 cases, brainstem atrophy, pontine midline linear hyperintensity, and atrophy of the frontal lobes were frequently observed using MRI.

Conclusion The present data indicate that the prevalence of ADCA in Aomori differs from other prefectures in the Tohoku District. MRI findings are very similar between SCA2 and multiple system atrophy (MSA), and thus care must be taken to prevent the misdiagnosis of sporadic SCA2 as MSA.

Key words: Aomori, autosomal dominant cerebellar ataxia, Japanese, multiple system atrophy, SCA2


Introduction

Autosomal dominant cerebellar ataxias (ADCAs) are included in a heterogeneous group of hereditary neurodegenerative disorders characterized by a combination of cerebellum, brainstem, spinal cord, and peripheral nervous system dysfunction. More than thirty genomic loci have been associated with ADCAs (Search OMIM for SCA, URL http://www.ncbi.nlm.nih.gov/), and the responsible genes have been identified for sixteen subtypes (1). Of these, many possess CAG trinucleotide expansions leading to the expression of proteins with abnormally long poly-glutamine tracts, which appear to mediate neuronal cell death through a combination of toxic gain-of-function and loss-of-function mechanisms. The frequency of ADCAs is known to vary between different regions of Japan, and this has implications for the local management of these diseases. To further understand regional variations in SCA prevalence, we undertook genetic analysis of patients from Aomori Prefecture.

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Subjects and Methods

Subjects

Over a period of 26 months (11/1/2007-12/31/2009), after receiving written informed consent, blood samples were obtained from 65 familial spinocerebellar ataxia (SCA) patients (30 females and 35 males from 57 families) and 15 sporadic SCA patients (eight females and seven males) (Table 1). All patients were Japanese and from Aomori Prefecture (Fig. 1). Patients diagnosed with probable multiple system atrophy (MSA) employing current clinical criteria (2) were excluded from the study. Magnetic resonance imaging (MRI) was conducted in all SCA2 cases using a 1.5-T MR scanner, and axial T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images were assessed. Brainstem atrophy, pontine midline linear hyperintensity (PMH), ‘hot cross bun’ sign (HCBS), and atrophy of the frontal lobes were evaluated by visual inspection. The study was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine.

Genetic testing

Genomic DNA was isolated employing a QIAamp DNA Blood Mini Kit (QIAGEN, Tokyo, Japan) according to the manufacturer’s protocol. Screening for mutations associated with SCA1 (MIM 164400) (3), SCA2 (MIM 183090) (4), SCA3 (MIM 109150) (5), SCA6 (MIM 183086) (6), SCA7 (MIM 164500) (7), SCA8 (MIM 608768) (8), SCA17 (MIM 607136) (9), dentatorubral-pallidoluysian atrophy (DRPLA) (MIM 607462) (10, 11), and SCA31 (MIM 117210) (12) was performed according to previous reports (3-7, 10, 11, 13, 14). Briefly, the regions spanning CAG or CAG/CAA repeats in the ataxin-1 gene, ataxin-2 gene, ataxin-3 gene, CACNA1A gene, ataxin-7 gene, TATA-binding protein gene, and atrophin 1 gene or the CTA/CTG repeats in the SCA8 gene were amplified by the polymerase chain reaction (PCR). The PCR products were resolved by electrophoresis on a 4% agarose gel and stained with ethid-
Table 2. Results of Genetic Testing in 80 Cases of Spinocerebellar Ataxia

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Familial</th>
<th>Sporadic</th>
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<tbody>
<tr>
<td></td>
<td>Case numbers</td>
<td>Case numbers</td>
</tr>
<tr>
<td>SCA1</td>
<td>1</td>
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</tr>
<tr>
<td>SCA2</td>
<td>6</td>
<td>6</td>
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<td>52</td>
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<td>SCA7</td>
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<tr>
<td>SCA8</td>
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<td>SCA17</td>
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<tr>
<td>SCA31</td>
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<td>1</td>
</tr>
<tr>
<td>DRPLA</td>
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<td>0</td>
</tr>
<tr>
<td>Diagnosed case numbers</td>
<td>—</td>
<td>65</td>
</tr>
<tr>
<td>Undiagnosed case numbers</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total numbers</td>
<td>57</td>
<td>65</td>
</tr>
</tbody>
</table>

The numbers in parenthesis indicate percentage of each disease from diagnosed cases.

Discussion

In this study, we carried out genetic analysis of SCA patients from Aomori Prefecture of Honshu, the most northerly region of the main island of Japan. This is the first report on the prevalence of ADCA in Aomori, and the results show that SCA6 and SCA2 are the two most common forms of SCA. In contrast, SCA1 and SCA3 are very rare, and, to date, no cases of SCA7 or DRPLA have been identified. On average in Japan, the frequencies of SCA3, SCA6, and DRPLA are high, but SCA1 is relatively rare (2-3%) (16-18). However, the frequency of ADCA in different regions of Japan can be very variable. For example, SCA1 predominantly occurs in northern parts of Japan such as Miyagi Prefecture (19), Yamagata Prefecture (20), and Hokkaido (21) (Fig. 1) with reported frequencies of 24.8, 34, and 10%, respectively (19-21). The fact that the present study shows SCA1 to be rare in Aomori Prefecture (1.3%) is surprising, given it is close to regions which have a high incidence of SCA1 (Fig. 1). Nevertheless, in Akita Prefecture, adjacent to Aomori Prefecture (Fig. 1), the number of SCA1 cases identified is similarly low (1.4% of SCA cases) (22). A study by Kumagai et al also reported on the prevalence of ADCA in Tohoku District. They identified no cases of SCA1 and found that SCA3 (41.3%) and SCA6 (17.2%) were the two most frequent subtypes in Fukushima Prefecture (23). These differences in disease incidence are thought to have arisen from the fact that many people moved around 1870 to Hokkaido from other areas in Japan. Wakisaka et al reported that all SCA1 patients examined in Hokkaido are descendents from individuals from Miyagi or Yamagata Prefecture, and that a single founder may be responsible (24). If this is correct, the rarity of SCA1 in Aomori Prefecture suggests that individuals from Miyagi and Yamagata did not settle in Aomori.

In contrast, SCA6 was found to be the most predominant ADCA subtype (77.7%) in Aomori. The fact that no large family took part in this study and 52 cases of SCA6 were identified from 45 independent families suggests that a single founder may not underlie all cases. However, without...
haplotype analysis, a single founder cannot be ruled out. Instead, the high incidence of SCA6 is likely to be due to the low migration rate in Aomori. This is corroborated by the finding that three individuals were found to be homozygous for the expanded CACNA1A allele, although there is no evidence of consanguinity in any family.

It is still controversial whether or not expansion of the CTA/CTG repeat in the SCA8 gene truly underlies ataxia. In the present study, we identified three cases of ataxia, from two independent families, in which SCA8 repeat expansion was observed but no other known ADCA mutation was identified. Furthermore, the length of SCA8 repeat expansion in all three cases (100-250 repeats) falls within the range thought to be highly penetrant and pathogenic (25). Taken together, these data support the conclusion that the three cases in the current study are due to an expansion in the SCA8 gene.

SCA31, recently shown to be associated with pentanucleotide repeats containing a (TGGAA) stretch (12), is the third most common ADCA subtype, after SCA6 and SCA3, in Japan (26, 27). In fact, in some areas such as South Kyushu and Nagano Prefecture, it has been found to be the most frequent ADCA subtype (27, 28), making it noteworthy that SCA31 is rare (2.6% of cases) in Aomori Prefecture. From the sporadic SCA cases, SCA2, SCA6, SCA17, and SCA31 were diagnosed by genetic analysis. This indicates that even in the absence of a family history, ADCAs should be considered in patients presenting with ataxia. This is especially true in cases involving sporadic SCA2 as they could be clinically misdiagnosed with MSA due to the similarities of clinical symptoms and findings on MRI such as HCBS, PMH, and brainstem atrophy (29, 30). It is worth pointing out that six out of the eight SCA2 cases showed atrophy of the frontal lobes, which is a common feature of MSA (29). The present findings confirm previous reports that atrophy of the frontal lobes could be an important hallmark of SCA2 (31-33). Although Tsuji et al reported that 67.2% of all cases of cerebellar ataxia in Japan are sporadic and only 27.0% have a family history of disease (17), MSA cases were included in their report. In the present study, frequencies of sporadic

![Figure 2. Representative MRI findings in a 36-year-old female with SCA2. The arrow shows a ‘hot cross bun’ sign on T2-weighted images (a), and brainstem and cerebellar atrophy is clear on T1-weighted images (b, T1WI). Note severe atrophy of the frontal lobes as well as cerebellar atrophy in T1WI (c and d).](image-url)
and familial SCA were 15/80 (19%) and 65/80 (81%), respectively. This lower frequency of sporadic SCA cases probably results from the exclusion of all cases with probable MSA.

In summary, the present study shows that SCA6 and SCA2 are the two most common forms of SCA in Aomori Prefecture. Identifying the prevalence of ADCA types in each region of Japan is important for genetic counseling, management, and estimation of the prognosis for patients.

Acknowledgement

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