Spinocerebellar ataxia 1 (SCA1) in the Japanese in Hokkaido may derive from a single common ancestry

Akemi Wakisaka, Hidenao Sasaki, Akio Takada, Toshiyuki Fukazawa, Yoshihiro Suzuki, Takeshi Hamada, Kiyoshi Iwabuchi, Kunio Tashiro, Takashi Yoshiki

Abstract

Spinocerebellar ataxia 1 (SCA1) is caused by expansion of an unstable CAG triplet repeat located on the short arm of chromosome 6. Precise mapping has shown a positional relationship to closely linked markers in the order of D6S109-D6S274-D6S288-SCA1-AM10GA-D6S89-EDN1 from centromere to telomere. The haplotype which cosegregated with the disease was determined in 12 Japanese pedigrees with SCA1. Although the alleles of the SCA1 haplotype varied from pedigree to pedigree, depending on the distance from the SCA1 locus, the affected and pre-symptomatic subjects carried the same alleles at D6S288 and D6S274. All the families with SCA1 had migrated from either Miyagi or Yamagata Prefectures, neighbouring areas in the Tohoku District, the northern part of Honshu which is the main island of Japan. It seems highly likely that SCA1 in the Japanese, at least those residing in Hokkaido, derives from a single common ancestry.

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The dominantly inherited spinocerebellar ataxies are a cluster of genetically heterogeneous neurodegenerative disorders. Recent advances in molecular genetics have led to the identification of loci and specific gene abnormalities. Six different gene loci have been determined: SCA1 on chromosome 6p24-p23, SCA2 on 12q23-q24, SCA3 or Machado-Joseph disease (MJD) on 14q24-32, SCA4 on 16q24-ter, SCA5 on 11q and dentato-rubropallidoluysian atrophy (DRPLA) on 12p. Among these disorders, abnormal expansions of the CAG trinucleotide repeat have been identified in patients with SCA1, DRPLA, and most recently with MJD. The gene locus for SCA1 was first assigned on the basis of linkage with HLA. After demonstration of a tight linkage with D6S89, SCA1 was precisely mapped to chromosome 6p24-p23. The order of the gene is defined as D6S109-D6S274-D6S288-SCA1-AM10GA-D6S89-EDN1 from centromere to telomere.

Based on linkage analysis and the CAG triplet repeat causing SCA1 when expanded, SCA1 was considered to be a major disorder in dominant OPCA in the Japanese. Most SCA1 pedigrees in Hokkaido originate from the same area, Miyagi and Yamagata Prefectures, thereby suggesting a common origin, and we searched for haplotypes carrying the SCA1 gene in each pedigree. A comparison of these haplotypes with those of healthy populations suggested that SCA1 in the Japanese, at least those who migrated to Hokkaido from these Prefectures, may derive from a single common ancestry.

Materials and methods

SCA1 pedigrees

Of the 12 pedigrees studied, 10 families were living in Hokkaido and two were from Yamagata Prefecture (table 1). The former are descendants of Japanese who migrated from Honshu, the main island of Japan. The original residence in Honshu could be traced in six of 10 Hokkaido pedigrees. In each pedigree, affected subjects of either gender were distributed over successive generations. There were 46 affected subjects, 56 at risk subjects, and 23 spouses. Although the number of mem-

Table 1 SCA1 pedigrees

<table>
<thead>
<tr>
<th>Family No</th>
<th>Subjects sampled</th>
<th>Affect.</th>
<th>At risk</th>
<th>Spouses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>P4</td>
<td>4</td>
<td>2 (1)*</td>
<td>2</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>P9</td>
<td>4</td>
<td>3 (0)</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>P10</td>
<td>16</td>
<td>25 (7)</td>
<td>5</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>P11</td>
<td>7</td>
<td>2 (0)</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>P13</td>
<td>2</td>
<td>1 (0)</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>P16</td>
<td>4</td>
<td>4 (0)</td>
<td>4</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>P36</td>
<td>2</td>
<td>2 (1)</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>P38</td>
<td>2</td>
<td>1 (0)</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>P39</td>
<td>1</td>
<td>3 (0)</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>P51</td>
<td>5</td>
<td>6 (2)</td>
<td>2</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>P52</td>
<td>2</td>
<td>4 (1)</td>
<td>2</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>P61</td>
<td>2</td>
<td>3 (1)</td>
<td>1</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>56 (13)</td>
<td>23</td>
<td>126</td>
<td></td>
</tr>
</tbody>
</table>

* Figures in parentheses indicate number of presymptomatic subjects.

bers of some pedigrees was insufficient to prove linkage with the disease locus, 13 of 56 at risk people were regarded as being presymptomatic, as they had inherited the SCA1 chromosome from affected parents. The diagnosis was confirmed by evidence that all the patients and the presymptomatic subjects carried a mutant SCA1 gene, that is, CAG triplets with more than 39 repeats. The sizes of CAG repeats in each pedigree are given in table 2.

MICROSATELLITES AND DNA GENOTYPING

The six microsatellites identified around the SCA1 gene are D6S109, D6S274, D6S288, AM10GA, D6S89, and EDN1. DNA genotypes were determined by PCR amplification, as described elsewhere.

TEST FOR LINKAGE DISEQUILIBRIUM

A chromosome carrying (“SCA1 chromosome”) and not carrying (“normal chromosome”) the disease gene was determined by haplotype segregation analysis in each pedigree. The latter were derived from 23 healthy or unrelated subjects who had married into the family. Data on 73 healthy subjects who had married into the families with ataxia other than SCA1 were incorporated into data on controls. Allele frequencies of each marker on SCA1 and normal chromosomes were calculated by simple counting. For comparison, standardised linkage disequilibrium coefficient (D/Dmax) and Yule’s association coefficient (A) were calculated for each allele of the marker. The p value was calculated by Fisher’s exact probability test. Significance of association for the allele was evaluated by corrected p value (pc), which is the Fisher’s p value multiplied by the number of alleles compared.

Results

HAPLOTYPE SEGREGATION ANALYSIS

To determine the haplotype carrying the SCA1 gene, we reconstituted the haplotype of the six loci (D6S109-D6S274-D6S288-AM10GA-D6S89-EDN1) for each member. SCA1 co-segregated with a single haplotype in a pedigree specific manner, as shown in table 2. Although the alleles of SCA1 haplotypes varied from pedigree to pedigree depending on the distance from the SCA1 gene, all pedigrees shared the same alleles at D6S274 (allele 3) and D6S288 (allele 1). While most SCA1 haplotypes carried an allele 1 at the AM10GA locus, allele switches from 1 to 2 were evident in three of 12 families. The allele switches at AM10GA were always accompanied by those at the next adjacent loci of D6S89 and EDN1.

LINKAGE DISEQUILIBRIUM

We next examined the association (linkage disequilibrium) between the SCA1 gene and the markers. The allele frequencies of the markers were compared between SCA1 and the normal chromosome. A significant positive association with the SCA1 gene was obtained with allele 3 of D6S274 (12/12 in SCA1 chromosome v 56/128 in normal chromosome, A = 1-00, D/Dmax = 0-32, pc = 7-99 × 10^-4), allele 1 of D6S288 (12/12 in SCA1 v 67/180 in normal, A = 1-00, D/Dmax = 0-31, pc = 6-95 × 10^-3), allele 5 of D6S89 (8/12 in SCA1 v 42/182 in normal, A = 0-74, D/Dmax = 0-24, pc = 1-38 × 10^-3), and allele 2 of EDN1 (6/12 in SCA1 v 10/106 in normal, A = 0-81, D/Dmax = 0-36, pc = 1-38 × 10^-3), but not with the other two markers. These findings suggest that they are localised close enough to the SCA1 locus to maintain possible linkage disequilibrium, a result which parallels the finding that all the SCA1 pedigrees shared the same allele at D6S288 and D6S274.
population of Ainu aborigines. Most present day Hokkaido residents are descendants of Japanese who migrated from various areas of Japan during the last 100 years. A variety of hereditary ataxia has been diagnosed in the residents of Hokkaido. When the original residence of these ataxic pedigrees was investigated, it became clear that most subjects with SCA1 were mostly from Miyagi and Yamagata Prefectures, whereas subjects with MJD were from Toiyama and Niigata Prefectures. Since immigration to other areas of Japan was extensively prohibited during the Yedo era (from 1603 to 1868 AD), cultural and human communications were rare. The fact that one specific ataxia is most frequently observed in one specified area reflects this history.

Kwiatkowski et al reported that the alleles of AM10GA showed no recombination with SCA1 and varied among ethnic groups. Since the AM10GA allele of the Japanese patients is not identical to those noted in any other ethnic group, mutations in the SCA1 gene might possibly have occurred independently in each ethnic group. In the Japanese, the mutation may even have occurred in one founder who lived in Miyagi or Yamagata Prefectures. This event may not be in the distant past (about 17 generations ago) because linkage disequilibrium with EDN1, 4cM from SCA1 gene, is still maintained. However, linkage disequilibrium among seven tested markers, including the polymorphic CAG repeats of SCA1, was not observed among normal healthy populations (data not shown).

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