Mapping of Autosomal Dominant Cerebellar Ataxia Without the Pathogenic PPP2R2B Mutation to the Locus for Spinocerebellar Ataxia 12

Kazunori Sato, MD; Ichiro Yabe, MD, PhD; Yoko Fukuda, PhD; Hiroyuki Soma, MD, PhD; Yasuo Nakahara, MD, PhD; Shoji Tsuji, MD, PhD; Hidenao Sasaki, MD, PhD

Objectives: To map the disease locus and to identify a gene mutation in a Japanese family with autosomal dominant cerebellar ataxia.

Design: A genome-wide linkage analysis was performed using the Affymetrix genome-wide human single-nucleotide polymorphism array containing 909,622 single-nucleotide polymorphisms. Direct nucleotide sequencing of a candidate gene was performed.

Setting: Hokkaido University Graduate School of Medicine and Tokyo University Graduate School of Medicine.

Patients: Four affected and 6 healthy individuals in a family with autosomal dominant cerebellar ataxia.

Results: One locus on chromosome 5q had a multipoint logarithm of odds score of 2.408, the theoretical maximum. This locus was flanked by markers rs681591 and rs32582 and includes PPP2R2B (protein phosphatase 2, regulatory subunit B, beta isoform), the causative gene of autosomal dominant spinocerebellar ataxia 12 (SCA12). However, unlike SCA12, no CAG repeat expansions in the promoter region and no nucleotide substitution or insertion-deletion mutations in the exons of the PPP2R2B gene were found.

Conclusion: Autosomal dominant cerebellar ataxia mapping to 5q31-q33.1 has no CAG repeat expansion or other mutations of the PPP2R2B gene.

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Spinocerebellar ataxias (SCAs) are hereditary neurodegenerative disorders that mainly affect the cerebellum and spinal cord. However, they are clinically and genetically heterogeneous entities. Although almost 30 gene loci have been described, the causative genes have been identified in nearly half. Spinocerebellar ataxia 29 has been registered with the Online Mendelian Inheritance in Man database; however, the disease locus and causative gene have not been identified in many autosomal dominant cerebellar ataxias (ADCA).

Previously, linkage analysis for the mapping of disease loci has been performed using polymerase chain reaction–based microsatellite markers. This approach has been powerful, especially in mapping mendelian single-gene disorders such as ADCA. However, these markers are sparse in genomic DNA (approximately 10 cM) and therefore have been underpowered in limited pedigree structure. After the discovery of single-nucleotide polymorphisms (SNPs), more than 3.1 million SNPs have been identified in humans to date. Although SNPs are biallelic and have lower heterozygosity than microsatellite markers, they exist at a greater density throughout the genome and are associated with lower genotyping error than microsatellite markers. It has been calculated that a map of 700 to 900 SNPs is equivalent to the current 300 to 400 microsatellite marker sets.

Recent technological advances have permitted the use of microarray-based, high-throughput genotyping for genome-wide linkage analysis using almost 1 million SNPs. This method not only markedly reduces genotyping time and cost, but it extracts considerably more information and offers greater power than sparse maps of conventional microsatellite markers in linkage analysis and is also useful in small families.

Since 1985, we have followed up a small Japanese family with ADCA. For screening of disease loci in this family, we performed 2-point linkage analysis using maps of about 400 microsatellite markers and obtained a maximum logarithm of odds (LOD) score of 2.39 between D5S436 and D5S2014 on chromosome 5q using the Likelihoods in Pedigrees program (data not shown). However, another lesion could not be excluded completely because of sparse mapping of the microsatellite markers. Therefore, to investigate more precisely the disease loci and causative gene of the ADCA in this family, we performed a ge-
A summary of clinical features is shown in the Table. Pure cerebellar ataxia with very slow progression is the common feature in all 5 affected individuals. They had been in good health, except for mild hypertension in one (II-5), until the onset of gait disturbance and/or speech difficulty at unstable gait, slow speech, and poor handwriting and died of stroke at 59 years of age. Four siblings (II-4, II-5, II-7, and II-8) and an offspring of individual II-8 (III-1) are also affected. We examined other siblings (II-1, II-2, II-3, II-6, and II-9) and confirmed that they had no symptoms. Individual III-1 was not included in the genetic analysis because informed consent was not obtained.

Figure 1. Modified pedigree, genotypes, and haplotype construction using single-nucleotide polymorphism (SNP) markers on centromeric and teromeric boundary areas. Circle indicates female individual; square, male; open diamond, unaffected age-at-risk individual; and slash, deceased. Solid symbols show affected individuals. The SNP markers (rs codes) are given in the left column in consecutive order (centromeric q-arm on top). Genotypes are described numerically in the boxes, and the haplotypes are shaded with different colors. The genotypes and haplotypes of individual I-1 are deduced from those of other family members. Based on logarithm of odds (LOD) scores from pairwise parametric analysis, the centromeric and teromeric boundary of the candidate locus defined by the recombination between adjacent SNPs is shown with the rs codes in blue lettering. The haplotype segregating with the disease is shaded in red. Because individual I-1 has homozygous genotypes in the boundary areas (boxed sections), the recombination site in the same areas in offspring II-4 and II-9 could not be identified. Therefore, the precise boundaries of the candidate locus could not be determined by haplotype analysis.
Table. Clinical Features of Affected Family Members

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>II-4</th>
<th>II-5</th>
<th>II-7</th>
<th>II-8</th>
<th>III-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At examination</td>
<td>40</td>
<td>39</td>
<td>34</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>At symptom onset</td>
<td>35</td>
<td>35</td>
<td>28</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>Symptoms at onset</td>
<td></td>
<td>Difficulty walking, poor handwriting</td>
<td>Difficulty walking</td>
<td>Difficulty walking</td>
<td>Head tremor</td>
</tr>
<tr>
<td>SARA score (DD, y)a</td>
<td>Not obtained</td>
<td>14.5 (26)</td>
<td>13.0 (28)</td>
<td>12.5 (26)</td>
<td>4.0 (5)</td>
</tr>
<tr>
<td>Ocular overshoot</td>
<td>Equivocal</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Saccadic pursuit</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Gaze nystagmus</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Reflexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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</tr>
<tr>
<td>Lower limb</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Gait ataxia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lower limb</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Muscle tone</td>
<td>Spasticity</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Involuntary movement</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Head tremor</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dementia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MRI findings</td>
<td>CA</td>
<td>CA, mild ischemic lesion in DWM</td>
<td>CA</td>
<td>CA</td>
<td>CA</td>
</tr>
<tr>
<td>Other complications</td>
<td>–</td>
<td>Hypertension</td>
<td>MALT lymphoma of the duodenum</td>
<td>–</td>
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</tr>
<tr>
<td>CAG repeats in PPP2R2B gene</td>
<td>16/17</td>
<td>16/17</td>
<td>16/17</td>
<td>16/17</td>
<td>Not obtained</td>
</tr>
</tbody>
</table>

Abbreviations: CA, cerebellar atrophy; DD, disease duration; DWM, deep white matter; MALT, mucosa-associated lymphoid tissue; MRI, magnetic resonance imaging; SARA, Scale for the Assessment and Rating of Ataxia; +, present; –, absent.

a Higher SARA scores indicate greater severity of ataxia (maximum, 40 points).

All procedures used in this study were approved by the Hokkaido University Ethics Committee. After written informed consent was obtained from each individual (I-2 and II-1 through II-9), blood samples were collected and genomic DNA was extracted from the leukocytes. Using methods described previously, we excluded abnormal expansion of CAG/CTG repeats or reported mutations in each gene of SCA1, SCA2, Machado-Joseph disease/SCA3, SCA5, SCA6, SCA7, SCA8, SCA10, dentatorubral-pallidoluysian atrophy, SCA12, SCA13, SCA14, SCA17, and SCA27 in each individual.9 The C→T change in the 5’ untranslated region of the puratrophin 1 gene with linkage disequilibrium for 16q22.1-linked ADCA was also examined and excluded using previously described methods.9 DNA SAMPLING AND EXCLUSION OF KNOWN SCA GENOTYPES

After differentiating 14 SCAs, a genome-wide linkage analysis was performed in each of the family members (6 healthy and 4 affected) using the genome-wide human SNP array (Affymetrix, version 6.0; Hitachi, Ltd, Tokyo, Japan) containing 909,622 SNPs according to the manufacturer’s instructions.10 Parametric linkage analysis was performed using Allegro with SNP HiTLink (a high-throughput linkage analysis system).11 The LOD scores were generated by assuming an equal sex recombination rate and an autosomal dominant disease locus with

13 to 38 years of age (mean age, 29.8 years). Two affected siblings (II-5 and II-7) needed cane assistance 22 and 23 years, respectively, after the onset of symptoms. Other individuals (II-8 and III-1) can still walk without assistance. The most recent mean total score on the Scale for the Assessment and Rating of Ataxia7 for these 3 individuals was 11, indicating mild to moderate disability. One affected family member (II-4) has not been examined since 1997 because of a change in his place of residence.

Neurological examination of all affected members showed limb and trunk ataxia. Only 1 family member (III-1) did not have dysarthria (slurred speech) or defects of smooth pursuit. The initial symptom of the other individuals (except for III-1) was gait disturbance and, for individual III-1, an involuntary movement (head tremor). Three individuals (II-4, II-5, and II-7) had brisk deep tendon reflexes in the lower limbs. Furthermore, one of these (II-4) had ankle clonus and equivocal spasticity without an extensor plantar reflex. None of the affected individuals had gaze-evoked nystagmus. At last follow-up, none of them showed obvious dementia, parkinsonism, neuropathy, or autonomic disturbance. One family member (II-7) developed duodenal lymphoma of the mucosa-associated lymphoid tissue at 54 years of age and was successfully treated with radiation therapy.

All affected individuals underwent magnetic resonance imaging, which showed atrophy of the cerebellum, including the vermis and hemisphere, but no abnormalities of the brainstem or supratentorial structures except for mild ischemic lesions in the deep white matter of individual II-5 (Figure 2).
a penetrance of 100% and a gene frequency of 0.001. Allele frequencies were obtained by the analysis of 200 control subjects. The SNP markers were selected on the basis of a Hardy-Weinberg equilibrium of greater than 0.05, with a call rate of 1 and a confidence score of less than 0.02. Markers for which the minor allele frequency was zero were eliminated. To avoid inaccuracies that can be accompanied by an inflated LOD score, the SNP with the highest minor allele frequency in the region between 80 and 120 kilobases (kb) was selected by the minimum-maximum method.11 The chromosomes, including suggested loci, were also analyzed by all markers using MLINK in linkage/FASTLINK.12,13

**DNA SEQUENCING**

On the basis of the linkage analysis results, direct nucleotide sequencing of candidate gene *PPP2R2B* (protein phosphatase 2, regulatory subunit B, beta isoform; OMIM *604325) was performed. Nine exons—including 2 splice variants of exon 1,14 the promoter region, 500 bases upstream from the transcription initiation site, and the exon-intron boundaries of the *PPP2R2B* gene in affected family members—were amplified using standard polymerase chain reaction methods. After treatment with shrimp alkaline phosphatase and exonuclease I, the polymerase chain reaction samples were directly sequenced (Prism BigDye terminator, version 1.1, and 310 Genetic Analyzer; Applied BioSystems, Tokyo, Japan).

**RESULTS**

Multipoint linkage analysis by selected SNP markers identified the following 8 loci on 4 chromosomes with a positive LOD score: 1 locus (called A) on chromosome 1, 4 (B, C, D, and E) on chromosome 5, 1 (F) on chromosome 15, and 2 (G and H) on chromosome 17. All the LOD scores of the remaining loci were less than −2.0. The size of the loci from A to H were 355, 597, 527, and 263 kb; 4.0 megabases; and 621, 406, and 623 kb, respectively, with LOD scores of 1.026, 0.633, 0.633, 1.032, 2.408, 2.214, 1.425, and 1.408, respectively. Because the LOD score of markers adjacent to those with almost positive LOD scores had minus infinity in all loci except for E and because double recombination in this narrow region is extremely rare, it is likely that these 7 loci do not link with a disease locus in this family. The E locus on chromosome 5q had a multipoint LOD score of 2.408, the theoretical maximum that can be obtained in our family, and so was considered a candidate (Figure 3).

Using the pairwise LOD scores based on all SNP markers, the centromeric boundary of the candidate locus was determined to be between rs681591 and rs1047729, and the teromeric boundary was between rs741580 and rs32582 (Figure 1). The candidate locus maps to 5q31-q33.1, the location of the *PPP2R2B* gene. The candidate locus in this ADCA is not associated with any of the known SCA loci except for SCA12.

We excluded SCA12 in this family because we found no abnormal expansion of CAG repeats in the promoter region of their *PPP2R2B* gene (16 of 17 repeats in all affected members except for III-1; Table). Direct nucleotide sequence analysis showed no mutations in the 9 exons, including the promoter region and the exon-intron boundaries of this gene.

**COMMENT**

We describe herein a dominant cerebellar ataxia that maps to chromosome 5q and includes the SCA12 locus but without the pathogenic mutations in the promoter region and exons of the *PPP2R2B* gene. Spino cerebellar ataxia 12 is caused by CAG trinucleotide repeat expansions in the promoter region of the *PPP2R2B* gene (55-78 triplets in the mutant alleles and 7-32 in the normal ones).15-17 To date, SCA12 has been reported only in the people of German15 and Indian16-18 descent but not yet in the Japanese population. Besides expansion of CAG repeats, no other mutation has been reported from such SCA12 families, to our knowledge.

Patients with SCA12 typically develop action tremors of the arms or head in the fourth decade of life (100%), then cerebellar ataxia, hyperreflexia, parkinsonism (80%), and anxiety disorders (60%).

![Figure 2](image-url)  
*Midsagittal magnetic resonance image (MRI) (1.5 T; T1-weighted) of the brain of individual II-5 21 years after onset of autosomal dominant cerebellar ataxia.* The MRI study showed marked atrophy of the vermis and cerebellar hemispheres (not shown) without involvement of the brainstem or supratentorial structures.

![Figure 3](image-url)  
*Figure 3. Logarithm of odds (LOD) scores plotted on chromosome 5. The theoretical maximum LOD score in this family was obtained on the E locus (LOD score, 2.408).*
The severity of cerebellar ataxia of SCA12 is milder than that of other dominant SCAs. Brain magnetic resonance imaging and computed tomography of patients with SCA12 show generalized atrophy in the cerebral cortex but less so in the cerebellum. In contrast to these reports, the family in the present study showed slowly progressive, almost pure cerebellar ataxia without any signs of dementia, neuropathy, autonomic failure, or parkinsonism, except for patient III-1, who had head tremor from the initial stage. Such involuntary movement has been described as the major symptom of patients with SCA12. Hyperreflexia was found in 3 patients (60%), a proportion similar to that observed in SCA12. Nystagmus has been found in 30% of patients with SCA12, but not in this family. Magnetic resonance imaging showed atrophy that was restricted to the cerebellum in our family.

Despite several commonalities, the clinical differences between SCA12 and the present family may indicate that these disorders have a different molecular pathogenesis. However, it is difficult to predict from the clinical phenotype in this ADCA family whether the causative gene is different from PPP2R2B because of intrafamilial and interfamilial variability and the phenotypic similarity seen in mutations of different genes in the SCAs. It may also be possible that SCA12 and our example of ADCA are allelic diseases, as has been observed in hemiplegic migraine, episodic ataxia type 2, and SCA6, which are caused by different mutation patterns in the CACNA1A gene encoding the α1 subunit of the P/Q-type voltage-gated calcium channel.

Because individual III-1 had a much earlier onset than his father (II-8) and the other affected persons in the family, the presence of anticipation, which is not obvious in SCA12, might be suspected. However, it is difficult to conclude this because of the small number of affected family members and the lack of genetic data for individual III-1.

The PPP2R2B gene encodes a regulatory B subunit of protein phosphatase 2A (PP2A), which is a major class of serine/threonine phosphatases with essential functions in cell growth and signaling. It is postulated that the abnormal expansion of the CAG repeats in SCA12 alters the expression of the PPP2R2B gene and consequently affects PP2A activity, although it remains to be clarified. All affected members of this family with ADCA who underwent genetic examination were heterozygous for CAG repeats in PPP2R2B (16 of 17 repeats). Although the possibility of microdeletion, including this lesion, is not fully excluded, the present family has a disorder that is genetically different from SCA12, which is caused by CAG expansion.

The candidate locus in the present study includes 44 genes. Two of them, HTR4 (5-hydroxytryptamine receptor 4; OMIM *602164) and ADRB2 (adrenergic beta-2 receptor, surface; OMIM +109690), are abundantly expressed in the human brain. The HTR4 gene is highly expressed especially in the limbic system but not in the cerebellum. In contrast, ADRB2 shows expression in the cerebellum, with particularly increased expression in the glial cells of the cerebellum of patients with olivopontocerebellar atrophy. However, there is no report about cerebellar ataxia as a phenotype of ADRB2 transgenic and knockout mice, in which neuroprotection to ischemic injuries and ineffectiveness of antidepressants against neuropathic pain have been shown. Therefore, these genes, including ADRB2, should also be considered candidate genes along with PPP2R2B. Further study is needed to investigate the region surrounding PPP2R2B, including introns and other genes in the candidate locus. Given that the causative gene and responsible mutation have been identified in one family, these findings provide new insights into the pathogenesis of SCA12.

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Correspondence: Hidenao Sasaki, MD, PhD, Department of Neurology, Graduate School of Medicine, Hokkaido University, N15 W7 Kita-ku, Sapporo 060-8638, Japan (h-isasak@med.hokudai.ac.jp).

Author Contributions: Drs Sato, Yabe, and Sasaki had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tsuji and Sasaki. Acquisition of data: Sato, Yabe, Soma, Tsuji, and Sasaki. Analysis and interpretation of data: Sato, Yabe, Fukuda, Soma, Nakahara, Tsuji, and Sasaki. Drafting of the manuscript: Sato, Yabe, Soma, Tsuji, and Sasaki. Critical revision of the manuscript for important intellectual content: Fukuda, Nakahara, and Tsuji. Statistical analysis: Fukuda and Nakahara. Obtained funding: Sasaki. Administrative, technical, and material support: Sato, Yabe, Soma, Tsuji, and Sasaki. Study supervision: Tsuji and Sasaki.

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9. Ishikawa K, Toru S, Tsunemi T, et al. An autosomal dominant cerebellar ataxia linked to chromosome 16q22.1 is associated with a single-nucleotide substitution in the 5′ untranslated region of the gene encoding a protein with spectrin-like or depression (40%), and dementia (20%). However, patients from India differ somewhat from other families with SCA12; they can develop facial myokymia (33%) and subclinical sensory and motor neuropathy (33% to approximately 50%) but lack symptoms of dementia. The severity of cerebellar ataxia of SCA12 is milder than that of other dominant SCAs. Brain magnetic resonance imaging and computed tomography of patients with SCA12 show generalized atrophy in the cerebral cortex but less so in the cerebellum. In contrast to these reports, the family in the present study showed slowly progressive, almost pure cerebellar ataxia without any signs of dementia, neuropathy, autonomic failure, or parkinsonism, except for patient III-1, who had head tremor from the initial stage. Such involuntary movement has been described as the major symptom of patients with SCA12. Hyperreflexia was found in 3 patients (60%), a proportion similar to that observed in SCA12. Nystagmus has been found in 30% of patients with SCA12, but not in this family. Magnetic resonance imaging showed atrophy that was restricted to the cerebellum in our family.

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