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A novel autosomal dominant spinocerebellar ataxia (SCA22) linked to chromosome 1p21-q23

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Summary

The autosomal dominant cerebellar ataxias (ADCA) are a clinically, pathologically and genetically heterogeneous group of disorders. Ten responsible genes have been identified for spinocerebellar ataxia types SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12 and SCA17, and dentatorubral pallidoluysian atrophy (DRPLA). The mutation is caused by an expansion of a CAG, CTG or ATTCT repeat sequence of these genes. Six additional loci, *SCA4*, *SCA5*, *SCA11*, *SCA13*, *SCA14* and *SCA16* have also been mapped. The growing heterogeneity of the autosomal dominant forms of these diseases shows that the genetic aetiologies of at least 20% of ADCA have yet to be elucidated. We ascertained and clinically characterized a four-generation Chinese pedigree segregating an autosomal dominant phenotype for cerebellar ataxia. Direct mutation analysis, linkage analysis for all known SCA loci and a genome-wide linkage study were performed. Direct mutation analysis excluded *SCA1*, *2*, *3*, *6*, *7*, *8*, *10*, *12*, *17* and *DRPLA*, and genetic linkage analysis excluded SCA4, 5, 11, 13, 14 and 16. The genome-wide linkage study suggested linkage to a locus on chromosome 1p21-q23, with the highest two-point LOD score at D1S1167 (Zmax = 3.46 at θ = 0.00). Multipoint analysis and haplotype reconstruction traced this novel SCA locus (SCA22) to a 43.7-cM interval flanked by D1S206 and D1S2878 (Zmax = 3.78 under four liability classes, and 2.67 using affected-only method). The age at onset ranged from 10 to 46 years. All affected members had gait ataxia with variable features of dysarthria and hyporeflexia. Head MRI showed homogeneous atrophy of the cerebellum without involvement of the brainstem. In six parent–child pairs, median onset occurred 10 years earlier in offspring than in their parents, suggesting anticipation. This family is distinct from other families with SCA and is characterized by a slowly progressive, pure cerebellar ataxia.

Keywords: autosomal dominant spinocerebellar ataxia; spinocerebellar ataxia type 22; linkage analysis; haplotype analysis; mutation analysis

Abbreviations: ADCA = autosomal dominant cerebellar ataxia; CASI = cognitive abilities screening instrument; DRPLA = dentatorubral pallidoluysian atrophy; MMSE = mini-mental state examination; PCR = polymerase chain reaction; SCA = spinocerebellar ataxia

Introduction

The autosomal dominant cerebellar ataxias (ADCAs) are a heterogeneous group of disorders (Harding, 1982, 1993) with variable onset and different clinical and neuropathological features, reflecting the degree of cerebellar and brainstem dysfunction. Molecular genetic analyses have revealed genetic loci for sixteen ADCA subtypes, including spinocerebellar ataxia (SCA) types 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 16, 17, and dentatorubral pallidoluysian atrophy (DRPLA) (Stevanin *et al*., 2000). The specific mutations for 10 of the 16 ADCA have been identified; most of the mutational mechanisms are expansion of short tandem repeats of three (CAG or CTG) or five (ATTCT for *SCA10*) nucleotides (Orr *et al*., 1993; Nagafuchi *et al*., 1994; Imbert *et al*., 1996; Pulst *et al*., 1996; Sanpei *et al*., 1996; Kawaguchi *et al*., 1994; David *et al*., 1997; Zhuchenko *et al*., 1997; Koob *et al*., 1999; Matsuura *et al*., 2000; Holmes *et al*., 1999; Nakamura *et al*., 2001). However, the genetic loci for at least 20% of familial ADCAs have yet to be identified, implying the presence of other unidentified responsible genes (Takano

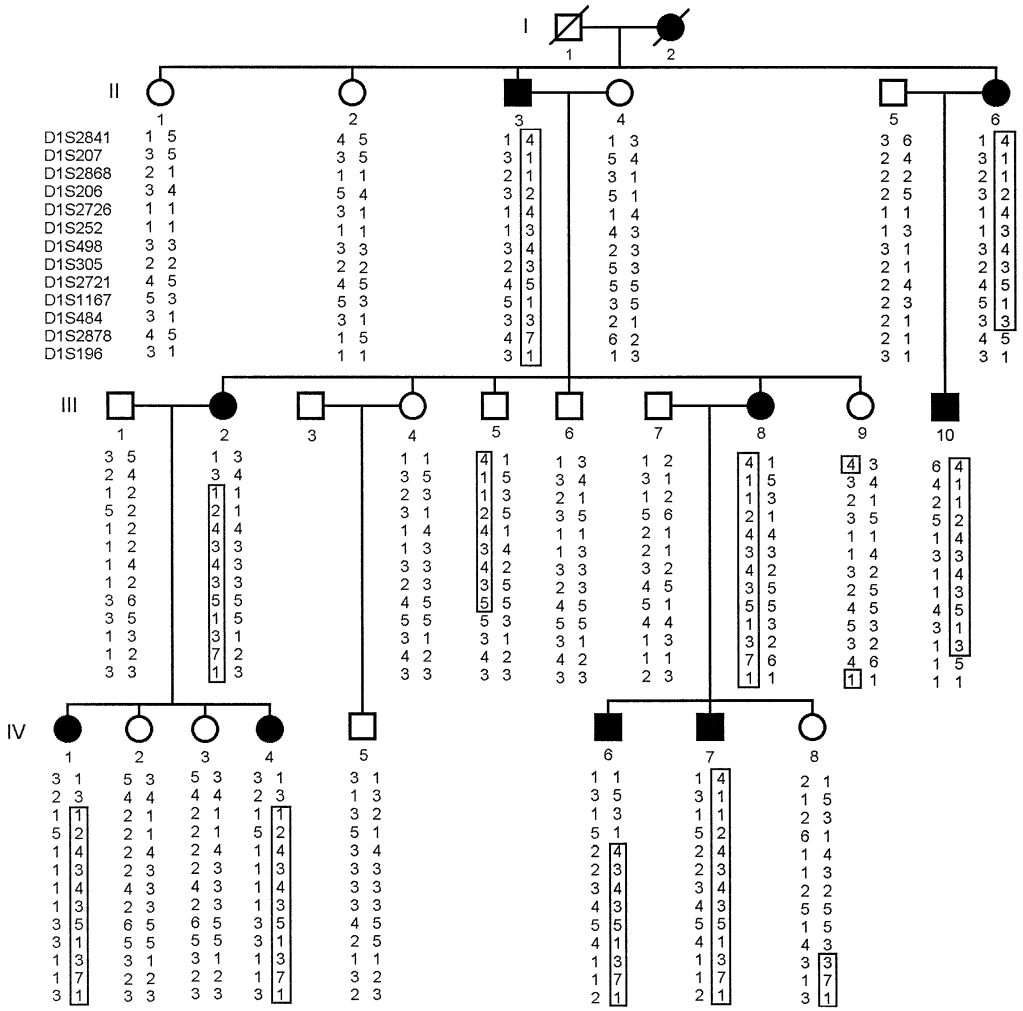

Fig. 1 Partial pedigree structure of the Chinese SCA22 family. Reconstructed haplotypes for thirteen microsatellite markers spanning 75 cM on chromosome 1 in order from the p-terminal to the q-terminal are represented below the symbols. The putative haplotype segregating with the disease is boxed. Recombination events in the disease haplotype suggest that the gene is flanked proximally by D1S206 (IV-6) and distally by D1S2878 (II-6). Open square = male; open circle = female; filled square and filled circle = affected; / = deceased.

et al., 1998; Devos *et al*., 2001; Soong *et al*., 2001). The phenotypes associated with the different loci overlap and vary substantially between and within ADCA families, making clinical classification extremely difficult (Bürk *et al*., 1996; Stevanin *et al*., 2000). Although SCA4, 5, 8, 10, 11, 12, 13, 14, 16 and 17 have not been reported in Chinese individuals, it is highly likely that some Chinese SCA patients have unknown mutations.

Against this background, we performed systematic linkage analysis in a four-generation family with a locus (or mutation) different from those 16 known SCAs, and subsequently mapped the locus to chromosome 1p21-q23. This novel locus was assigned as *SCA22* by the HUGO Gene Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature), while SCA types 18–21 had been registered by other groups, but not yet published. The clinical features of the family and the results of linkage analysis are reported here.

Material and methods

Clinical studies

A four-generation Chinese Han family in which cerebellar ataxia segregates in an autosomal dominant mode was examined by one of the authors (B.S.) (Fig. 1). Twenty-three members from this family, including nine patients, 10 at-risk individuals and four spouses, were enrolled in this study. Those who presented overt cerebellar signs were regarded as affected. An affected male (II-3) was hospitalized for extensive clinical evaluations, including MRI, electrophysiological studies, neuropsychological tests and ophthalmological examinations.

Genetic studies and linkage analysis

After written informed consent was obtained from each subject, blood samples were drawn and DNA was extracted

from peripheral blood leukocytes following a standard protocol (Sambrook and Russell, 2001). Exclusion of currently known genetic types of ADCAs was performed in the following two stages.

Exclusion of known ADCA genotypes

Direct mutational analysis for CAG, CTG or ATTCT repeat expansions of *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *SCA8*, *SCA10*, *SCA12, SCA17* and *DRPLA* genes was performed by previously described methods (Orr *et al*., 1993; Kawaguchi *et al*., 1994; Nagafuchi *et al*., 1994; Imbert *et al*., 1996; Pulst *et al*., 1996; Sanpei *et al*., 1996; David *et al*., 1997; Zhuchenko *et al*., 1997; Holmes *et al*., 1999; Koob *et al*., 1999; Matsuura *et al*., 2000; Nakamura *et al*., 2001). Linkage analyses were performed to exclude the possibility of SCA4, 5, 11, 13 and 14. Two-point linkage with correction for age-dependent penetrance was analysed for candidate intervals using 18 microsatellite markers: D16S514, D16S397, D16S398 and D16S512 for the *SCA4* locus at 16q22.1 (Flanigan *et al*., 1996); D11S935, D11S905, D11S1385 and D11S913 for the *SCA5* locus at 11p12-q12 (Ranum *et al*., 1994); D15S968, D15S994, D15S1039 and D15S123 for the *SCA11* locus at 15q14-21.3 (Worth *et al*., 1999); D19S412, D19S606 and D19S867 for the *SCA13* locus at19q13.3-13.4 (Herman-Bert *et al*., 2000); and D19S924, D19S418 and D19S926 for the *SCA14* locus at 19q13.3-qter (Yamashita *et al*., 2000). Exclusion of SCA16 at 8q was carried out while performing whole genome scanning.

Genome-wide scanning

After excluding known SCA mutations, we performed a systematic genome-wide search for the disease locus. An ABI PRISM™ Linkage Mapping Set MD-10 (version 2) (Applied Biosystems, Foster City, CA, USA) was used for screening. This contained 400 dinucleotide-repeat markers covering the entire human genome, with an average interval of 10-cM between markers. An additional three microsatellite markers from the 13.8-cM interval between D1S498 and D1S484 (D1S305, D1S2721, D1S1167) were selected to confirm and refine the genetic location of SCA22. A polymerase chain reaction (PCR) was performed in 7.5 μl reaction mixture containing 7.5 ng of genomic DNA, 0.333 μM of each primer, 2.5 mM $MgCl_2$ and 0.1875 U of Ampli*Taq* Gold DNA polymerase (Applied Biosystems) in 200 μM of dNTPs and 1× PCR buffer II supplied with the enzyme. The PCR conditions consisted of an initial denaturation at 95°C for 12 min, followed by 30 cycles of denaturation at 94°C for 1 min, annealing at 55°C for 1 min, extension at 72°C for 1 min, and a final extension at 72°C for 60 min on MJ Research PTC-100 thermal cyclers (MJ Research, Inc., Watertown, MA, USA) or ABI PRISM 9700 thermal cyclers (Applied Biosystems). The pooled PCR products with internal size standard, GS-ROX400-HD (Applied Biosystems) were analysed with an ABI PRISM 377 automated DNA sequencer (Applied Biosystems) and GeneScan (version 2.1) (Applied Biosystems). The genotypes were defined and edited using the Genotyper (version 2.0) program (Applied Biosystems).

Linkage analysis

Two-point and multipoint linkage analyses were performed with MLINK and LINKMAP modules (both version 5.10), respectively, from the FASTLINK (slow version 4.1P) of the LINKAGE program (Cottingham *et al*., 1993; Schaffer *et al*., 1994). All allele frequencies were assumed equal for each of the markers. The disease prevalence was set at 1 in 100 000. Four age-dependent liability classes were assigned for at-risk, currently unaffected individuals based on the age of onset in the pedigree: 0.3 for under 20 years; 0.5 for 21–30 years; 0.7 for 31–40 years; and 0.9 for >40 years of age. The genetic distance between adjacent markers was determined based on the Marshfield comprehensive human genetic maps (Broman *et al*., 1998). In these maps, the Kosambi map function was used to transform the recombination fraction to the genetic distance. In addition, a multipoint analysis was performed for all autosomes using Genehunter (version 1.2) (Kruglyak *et al*., 1996) and the 'affected-only method' in which only affected individuals ($n = 9$), two unaffected individuals (II-1 and II-2) older than 70 years, and four spouses (II-4, II-5, III-1, and III-7) were analysed at a penetrance of 0.95. Under such conditions, the highest possible maximal LOD score (Zmax) for a five-allele locus was 2.67 based on 200 simulations using the ISIM program of SLINK (version 2.65) (Ott, 1989; Weeks *et al*., 1990).

Results

Clinical features of the SCA family

The index patient (II-3) was evaluated for the first time at the age of 68 years (Fig. 1) in the Neurology Department at the Taipei Veterans General Hospital. He was a right-handed man of Chinese descent with a 23-year history of slowly progressive clumsiness of gait associated with upper limb ataxia. Cerebellar testing disclosed gait and limb ataxia that still allowed him to walk with two canes. Hypo-reflexia and dysarthria with scanning speech and dysphagia were also noted. Further examination revealed no cognitive impairment, long tract signs, myoclonus, tremors, sensory loss or cogwheel rigidity. The ophthalmological examination showed intermittent microsaccadic pursuits, normal saccadic velocity and gaze-directed horizontal nystagmus, without visual loss, retinopathy or ophthalmoplegia. Neuropsychological examination disclosed a normal cognitive function with a Cognitive Abilities Screening Instrument (CASI) score of 93 and a Mini-Mental State Examination (MMSE) score of 28. Electromyography and nerve conduction studies were normal. Somatosensory and auditory brainstem evoked potentials were abnormal, suggesting impaired conduction

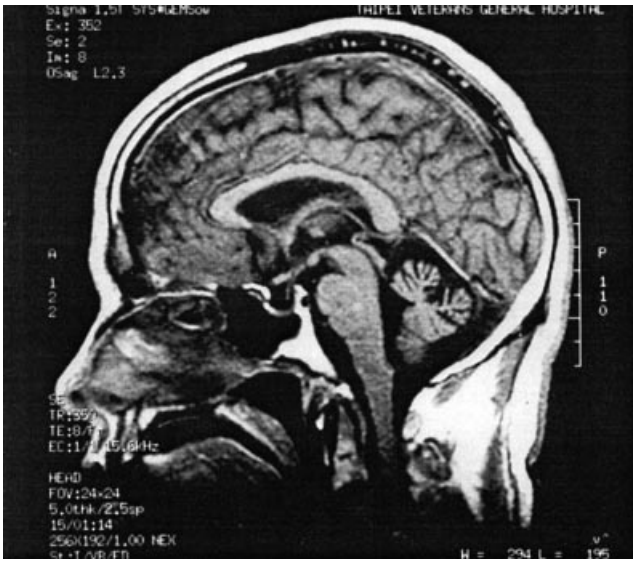

Fig. 2 Cerebral MRI of patient III-10 at age 48 years. The T_1-weighted [TR (repetition time) = 350 ms; TE (echo time) = 8 ms] mid-sagittal image shows distinct atrophy of the cerebellar vermis with no lesion in the brainstem or the cerebral cortex.

in the brainstem and spinal cord. Cranial MRI study revealed a homogeneous cerebellar atrophy including the vermis and cerebellar hemispheres, but sparing the pons (Fig. 2).

In the nine affected individuals, none of them, by history, had evidence of episodic cerebellar dysfunction. The mean age at onset was 40.5 years (range 35–46 years) for generation II (n = 2), 20.7 ± 4.0 years (range 17–25 years) for generation III (n = 3), and 12.5 ± 2.1 years (range 10–15 years) for generation IV (n = 4). The mean age at examination was 35.9± 22.4 years (range 12–69 years) and the mean duration since onset was 14.6 ± 11.6 years (range 1–31 years).

The initial symptom was gait ataxia in all of the members (Table 1). The progression was remarkably slow but varied. So far, only II-3, with an international cooperative ataxia rating score of 57 (Trouillas *et al*., 1997), needed help for walking 20 years after the disease onset. The cardinal clinical features were relatively pure cerebellar signs including ataxia of the trunk and limbs, dysarthria and cogwheel pursuits of the eyes. No cogwheel rigidity, myoclonus, tremors or akinesia was observed in any patient. None of the affected patients had motor or sensory deficits, extensor plantar reflexes, fasciculations, epileptic seizures or cognitive impairment.

Linkage to chromosome 1p21-q23

After the candidate regions for *SCA4*, *SCA5*, *SCA11*, *SCA13* and *SCA14* were excluded based on a LOD score of ⩽–2, a total of 382 microsatellite markers distributed from chromosome 1 to 22 were analysed for a systematic genome-wide search. The first suggestive evidence for linkage of the disease locus was obtained at D1S498, for which MLINK yielded a maximal LOD score of 2.76 at a recombination rate of 0.00, as well as several flanking loci with a Zmax greater than 1.5 (Table 2). Additional microsatellite markers around this region were subjected to tandem testing for linkage. A maximum LOD score of 3.46 at recombination (θ) = 0.00 was obtained for marker D1S1167 (Table 2).

A five-point analysis was performed over the intervals of D1S206—(21.7 cM)—D1S498—(12.7 cM)—D1S1167—(9.3 cM)—D1S2878. A maximal multipoint LOD score of 3.78 was obtained close to the marker D1S1167 (Fig. 3). Multipoint analyses of all 22 autosomes using the 'affected only method' with Genehunter supported this conclusion with a maximal LOD score of 2.67 at D1S498 (data not shown). Although the highest possible Zmax for a five-allele locus was 2.67 based on 200 simulations using the ISIM program of SLINK (Ott, 1989; Weeks *et al*., 1990), the robustness of prior linkage analysis could still be demonstrated.

Table 1 *Summary of the clinical profile of the nine patients with SCA22*

Symptoms/signs	Incidence (%)
Trunkal ataxia	100
Appendicular ataxia	100
Dysarthria	89
Hypo-reflexia	89
Nystagmus	67
Pyramidal sign	0
Extrapyramidal signs	0
Myoclonus	0
Tremors	0
Dementia	0
Ophthalmologic abnormalities	0
Autonomic dysfunction	0

Haplotype analysis

Recombination events, visualized by haplotype reconstruction, confirmed the results obtained from linkage analysis in this family (Fig. 1). The centromeric boundary of the candidate interval was defined by an obligate recombination event observed between D1S206 and D1S2726 in individual IV-6. The telomeric boundary was currently defined by another recombination event observed between D1S484 and D1S2878 in individuals II-6. These two critical recombination events delimited the disease gene within a 43.7-cM interval flanked by D1S206 and D1S2878. All the affected individuals share the same haplotype for this candidate interval. There exists an additional recombination event between markers D1S2721 and D1S1167 in individual III-5, who is currently unaffected and is >40 years old. His affection status might help to narrow down further the candidate region as being either telomeric to D1S2721 (in case remaining unaffected) or centromeric to D1S1167 (in case becoming affected).

Table 2 *Two-point LOD scores for the SCA22 locus and 13 chromosome 1 markers*

	Recombination fraction (θ)						
Marker	0.00	0.05	0.10	0.20	0.3	Zmax	θmax
D1S2841	–11.98	–0.72	–0.17	0.24	0.30	0.30	0.28
D1S207	–11.54	0.08	0.52	0.68	0.52	0.69	0.18
D1S2868	–5.03	–0.32	–0.02	0.17	0.17	0.19	0.24
D1S206	2.49	2.36	2.17	1.68	1.08	2.49	0.00
D1S2726	1.77	1.58	1.39	0.97	0.54	1.77	0.00
D1S252	1.29	1.25	1.15	0.87	0.50	1.29	0.00
D1S498	2.76	2.60	2.39	1.85	1.20	2.76	0.00
D1S305	1.94	1.85	1.71	1.31	0.82	1.94	0.00
D1S2721	0.68	0.68	0.64	0.48	0.28	0.68	0.00
D1S1167	3.46	3.15	2.83	2.14	1.38	3.46	0.00
D1S484	0.58	0.51	0.44	0.29	0.16	0.58	0.00
D1S2878	–3.66	1.77	1.79	1.49	1.02	1.81	0.08
D1S196	0.70	0.64	0.56	0.39	0.21	0.70	0.00

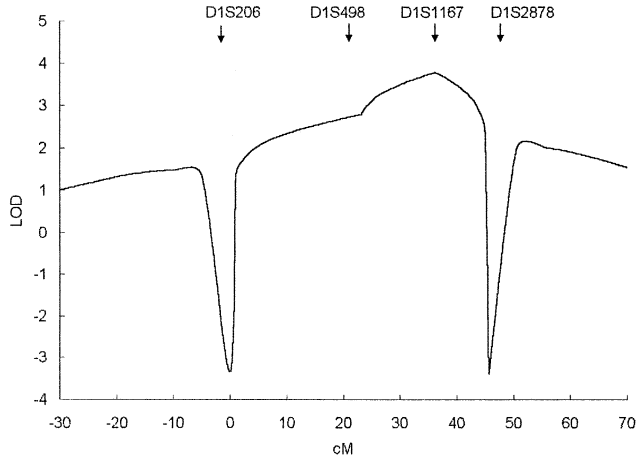

Fig. 3 Multipoint linkage analysis of the D1S206-D1S498-D1S1167-D1S2878 interval. Markers D1S206 and D1S2878 flank the candidate region of SCA22.

Discussion

We have mapped a novel locus for ADCA in a Chinese family to a 43.7-cM interval defined by flanking markers D1S206 and D1S2878. This locus, registered as '*SCA22*' with approval from the Human Gene Nomenclature Committee, may be assigned to the chromosome 1p21-q23. In this chromosome 1-linked family, all of the affected individuals showed cerebellar ataxia with no other associated neurological deficits or somatic abnormalities. Harding classified ADCAs into three different groups based on the associated signs: ADCA I includes optic atrophy, ophthalmoplegia, pyramidal and extrapyramidal signs, cognitive impairment or peripheral neuropathy; ADCA II, presence of retinopathy; and ADCA III, absence of associated signs (Harding, 1993). The large family we have described was affected at a variable age of onset (10–46 years) by a cerebellar ataxia that was inherited as an autosomal dominant trait. There were no specific features on the clinical or laboratory examinations distinguishing the kindred from other ADCA families. The marked atrophy restricted to the cerebellum and the slow progression of the disease best fits the category of ADCA III (Schöls *et al*., 1997).

Given that the responsible gene for SCA22 is still unidentified, linkage studies on unassigned pedigrees of ADCA among various ethnic groups with markers on chromosome 1p21–q23 will determine whether SCA22 is prevalent. This novel form of ADCA (SCA22) is relatively rare in the Chinese population. In another study (Soong *et al*., 2001), we investigated the frequency of each subtype of dominant SCAs in Taiwan by genotyping the mutations in 72 patients with ADCA. SCA3 (45%), SCA6 (10.2%) and SCA2 (10.2%) were the three most prevalent disorders, whereas 20% did not have known mutations.

It is always difficult to affirm the presence of anticipation in a single family. Haplotype analysis revealed that individual III-5 carried a portion of the disease haplotype, indicating that he might become affected later. This would modify the mean age at onset calculated for generation III. The possible presence of anticipation in this family suggests that the mutation in *SCA22* gene may also involve a trinucleotide repeat expansion. In SCA types 1, 2, 3, 6, 7, 8, 10, 12, 17 and DRPLA, the responsible genes have been identified. All of them present anticipation and their genetic mutation involves an expansion of the trinucleotide CAG/CTG repeat or the pentanucleotide repeat ATTCT (Matsuura *et al*., 2000). The 43.7-cM candidate region defined by haplotype reconstruction and multipoint analysis is still too large. Additional families with linkage to this locus as well as the development of new markers are needed to refine the candidate interval.

At least three genes containing CAG/polyglutamine tracts have been identified in 1p21-q23, including: *calcium-activated potassium channel, subfamily N, member 3* [*KCNN3*, accession number NM_02249 (two CAG/polyglutamine tracts in this gene)]; *KIAA0476* (accession number

NM_014856); and *trinucleotide repeat-containing 4* (*TNRC4*, accession number NM_007185). However, none of the CAG repeat was expanded in the affected individuals (data not shown) and therefore all these three genes were excluded from being a candidate gene for SCA22. In addition, other neuron-associated genes, e.g. two potassium channel genes (*KCNJ9* and *KCNJ10*, *potassium channel*, *inwardly rectifying, subfamily J, members 9 and 10*) are also mapped to this region. One of these ion channel genes may presumably be the candidate gene for SCA22. Nevertheless, episodic symptoms have not been reported in the affected members of this SCA22 kindred. We are conducting repeat expansion detection analysis and western hybridization experiments with 1C2 antibody to determine whether the mutation in this family is a CAG/polyglutamine-repeat expansion (Trottier *et al*., 1995; Stevanin *et al*., 1996; Zander *et al*., 1998).

In conclusion, we have mapped, on chromosome 1, the locus responsible for a new ADCA, a phenotype that we propose to designate as 'spinocerebellar ataxia type 22 (SCA22)'. Identification of another SCA gene will contribute to the investigation, diagnosis, and genetic counselling of at-risk individuals with ADCAs.

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