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ORIGINAL ARTICLE

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A −16C>T substitution in the 5′ UTR of the *puratrophin-1* gene is prevalent in autosomal dominant cerebellar ataxia in Nagano

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Abstract The molecular bases of autosomal dominant cerebellar ataxia (ADCA) have been increasingly elucidated, but 17–50% of ADCA families still remain genetically undefined in Japan. In this study we investigated 67 genetically undefined ADCA families from the Nagano prefecture, and found that 63 patients from 51 families possessed the −16C > T change in the *puratrophin-1* gene, which was recently found to be pathogenic for 16q22-linked ADCA. Most patients shared a common haplotype around the *puratrophin-1* gene. All patients with the −16C > T change had pure cerebellar ataxia with middle-aged or later onset. Only one patient in a large, −16C > T positive family did not have this change, but still shared a narrowed haplotype with, and was clinically indistinguishable from, the other affected family members. In Nagano, 16q22-linked ADCA appears to be much more prevalent than either SCA6 or dentatorubral-pallidoluysian atrophy (DRPLA), and may explain the high frequency of spinocerebellar ataxia.

Keywords Autosomal dominant cerebellar ataxia · 16q22-linked ADCA · *puratrophin-1* · Nagano

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Introduction

Autosomal dominant cerebellar ataxia (ADCA) is genetically heterogeneous (Margolis 2003; Schols et al. 2004). The most updated GeneTests (8 November 2005) and HUGO Gene Nomenclature Committee (25 November 2005) cover at least 27 different ADCA subtypes including SCA28. Among these, a coding CAG (or CAA, both coding glutamine) repeat expansion has been found in seven subtypes: SCA1, 2, 3/Machado-Joseph disease (MJD), 6, 7, and 17, and dentatorubral-pallidoluysian atrophy (DRPLA) (Banfi et al. 1994; 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; Koide et al. 1999; Nakamura et al. 2001). A non-coding repeat expansion occurs in three subtypes: SCA8, 10, and 12 (Holmes et al. 1999; Koob et al. 1999; Matsuura et al. 2000; Fujigasaki et al. 2001), and a missense mutation in two of them: SCA14 and 27 (Chen et al. 2003; van Swieten et al. 2003). Several reports regarding 16q22-linked ADCA have been released (Nagaoka et al. 2000; Takashima et al. 2001; Li et al. 2003; Hirano et al. 2004), and a single nucleotide substitution (−16C > T) in the 5′

UTR in the *puratrophin-1* gene was recently identified in all patients from 52 unrelated Japanese families sharing a common haplotype at 16q22.1 (Ishikawa et al. 2005).

In Japan, the incidence of spinocerebellar degeneration/ataxia (SCD/SCA) including multiple-system atrophy (MSA) is 15.68 in 100,000. Although SCA6, SCA3/MJD, and DRPLA are the three most prevalent subtypes, their frequencies quite differ from region to region (Maruyama et al. 2002; Sasaki et al. 2003). We previously showed that the incidence of SCA, excluding MSA, was higher (22 in 100,000) in Nagano than in other parts of Japan. In 86 unrelated ADCA families from Nagano, SCA6 (19%) and DRPLA (10%) were common, while SCA3/MJD (3%), SCA1 (2%), and SCA2 (1%) were infrequent (Shimizu et al. 2004). More importantly, the majority of families (65%) were genetically undefined; such families make up 17–50% of the ADCA families in other parts of Japan (Maruyama et al. 2002; Sasaki et al. 2003; Shimizu et al. 2004). A common haplotype of 16q22-linked ADCA reported by Li et al. (2003) was not confirmed in our series (Shimizu et al. 2004).

We hypothesized that there may be distinct ADCA subtypes in Nagano because it is relatively isolated by steep mountains. A genome-wide linkage study was performed in undefined ADCA families to identify possibly new ADCA loci. The −16C > T substitution in *puratrophin-1* was also investigated.

Materials and methods

Subjects

A total of 105 individuals (83 affected and 22 unaffected) from 67 ADCA families originating from the Nagano prefecture were recruited to this study. All affected individuals were examined by at least one experienced neurologist according to the standard clinical criteria. Dominant inheritance was presumed when affected individuals were recognized in at least two generations. Three families (SCAF9, SCAF25, and SCAF41) with several affected members were used for linkage studies. Genomic DNA was isolated from peripheral leukocytes using a PUREGENE DNA purification kit (Gentra Systems, Minneapolis, MN, USA). SCA 1, 2, 3/MJD, 6, 7, 12, and 17, and DRPLA were ruled out after confirming the (CAG)n length by PCR as previously described (Shimizu et al. 2004). This research protocol was approved independently by the Ethical Committee of Shinshu University School of Medicine and by the Committee for Ethical Issues at Yokohama City University School of Medicine.

Linkage analysis

A large family, SCAF41, consisting of 7 affected and 15 unaffected members, was analyzed using 400 polymorphic markers (ABI PRISM Linkage Mapping Set version 2.5-MD10; Applied Biosystems, Foster City, CA, USA). Furthermore, an additional 21 polymorphic markers mapped to 16q21–16q23.1 (*D16S3111*, *D16S3050*, *D16S3021*, *D16S3043*, *D16S3019*, *TAGA02*, *TTCC01*, *D16S3086*, *GATA01*, *D16S421*, *TA001*, *GA001*, *TTTA001*, *CATG003*, *17msm*, *D16S3085*, *D16S3025*, *CTTT01*, *D16S3067*, *GT01*, and *D16S3018*) were used for the study of three families, SCAF9, SCAF25, and SCAF41. Primer sequences are described elsewhere (Hirano et al. 2004; Ishikawa et al. 2005). PCR was cycled 40 times at 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s in a 10-μl mixture containing 10 ng genomic DNA, 0.5 μM of each primer, 0.2 mM each of dNTP, 10× PCR buffer (TaKaRa, Ohtsu, Japan), and 0.25 U of Takara Ex Taq DNA polymerase (TaKaRa). PCR products were analyzed by an ABI 3100 Genetic analyzer (Applied Biosystems), and their product sizes were determined using the GeneMapper Software version 3.5 (Applied Biosystems). Two-point linkage analysis was carried out using the LINKAGE Program Package (FASTLINK software, version 5.1). The allele frequencies of the markers were set as equal when they were unknown. The disease gene frequency was assumed to be 0.00001. The possibly affected individuals were scored as unknown. LOD scores were corrected by age-dependent penetrance established based on the cumulative age at onset (penetrance 0 for persons aged 39 years and younger, 0.08 for those aged 40–49 years, 0.37 for those aged 50–59 years, 0.79 for those aged 60–69 years, and 0.99 for those aged 70 years or older).

Analysis of a single nucleotide substitution (−16C > T) in the 5′ UTR of *puratrophin-1*

Primer sequences have been described elsewhere (Ishikawa et al. 2005). PCR was cycled 35 times at 94°C for 30 s, 65°C for 30 s, and 72°C for 30 s in a 20-μl mixture containing 30 ng genomic DNA, 0.5 μM of each primer, 0.2 mM each of dNTP, 10× PCR buffer (TaKaRa), and 0.25 U of Takara Ex Taq DNA polymerase (TaKaRa). PCR products were purified with ExoSAP-IT (USB, Cleveland, OH, USA) and sequenced by a standard protocol using BigDye terminator (Applied Biosystems) on an ABI PRISM 3100 Genetic analyzer (Applied Biosystems). Nucleotide substitution was confirmed using the SeqScape software version 2.0 (Applied Biosystems), and by *Eco*NI RFLP designed by Ishikawa et al. (2005). All patients were genotyped for at least nine markers: *16S3086*, *GATA01*, *D16S421*, *TA001*, *GA001*, *TTTA001*, *CATG003*, *17msm*, and *D16S3085*, to confirm haplotypes.

Results

Genome-wide linkage analysis using 400 markers in SCAF41 did not give any locations of maximum LOD scores of three or more. Although several locations with

relatively high scores were identified, including *D1S2785* on 1q43 (LOD, 1.18 [$\theta = 0$]), *D8S549* on 8p22 (LOD, 1.43 [$\theta = 0$]), *D16S515* on 16q23.1 (LOD, 1.03 [$\theta = 0$]); thus, the initial screening failed to reveal a specific locus for the disease.

During this study, the single nucleotide substitution (−16C > T) in the 5′ UTR of the *puratrophin-1* gene was identified as a possible pathological change for 16q22-linked ADCA (Ishikawa et al. 2005). We found this substitution in 11 out of 12 affected and 2 out of 22 unaffected individuals in SCAF9, SCAF25, SCAF41 (Fig. 1), and 16q22-focused linkage analysis in these three families using additional 21 markers gave a maximum LOD score at *TAGA02* of 2.42 ($\theta = 0$). Haplotype analysis demonstrated a common haplotype (1-3-2-T-1-2-5-1-2-2 at *D16S3086 −GATA01 −D16S421* − [−16C/T of *puratrophin-1* {*Q9H7K4*}] *−TA001 −GA001 −TTTA001 −CATG003 −17msm −D16S3085*) in all affected members except SCAF41-21 and two young unaffected members, SCAF41-10 (40 years old) and SCAF25-5 (41 years old), who may be obligate carriers. It is noteworthy that SCAF41-21 (59 years old) did not have the −16C > T change, but shared only a narrowed haplotype (1-3-2 at *D16S3086 −GATA01 −D16S421*) as it is assumed that a recombination happened between *D16S421* and *Q9H7K4*. While her clinical symptoms were still mild, a slowly progressive gait ataxia and clumsiness in the hands were evident.

Further analysis of nine markers (*D16S3086*, *GATA01*, *D16S421*, *TA001*, *GA001*, *TTTA001*, *CATG003*, *17msm*, and *D16S3085*), as well as the −16C > T change, was performed in the other 71 patients from 64 families (Fig. 2). We found that 53 patients from 48 families carried the −16C > T substitution and their phenotypes were compatible with pure cerebellar ataxia. Their average age of disease onset was 60.2 ± 9.3 years (mean ± 1 SD), while the average age of onset for 18 patients from 16 families without the substitution was 37.9 ± 20.8 years and most of them showed juvenile-onset cerebellar ataxia, or extracerebellar neurological symptoms such as parkinsonism, dementia, and/or involuntary movements. Genetic anticipation was observed in two families. Five out of 16 families without the −16C > T change showed late-onset, pure cerebellar ataxia indistinguishable from that of typical patients with the −16C > T change in the *pura-*

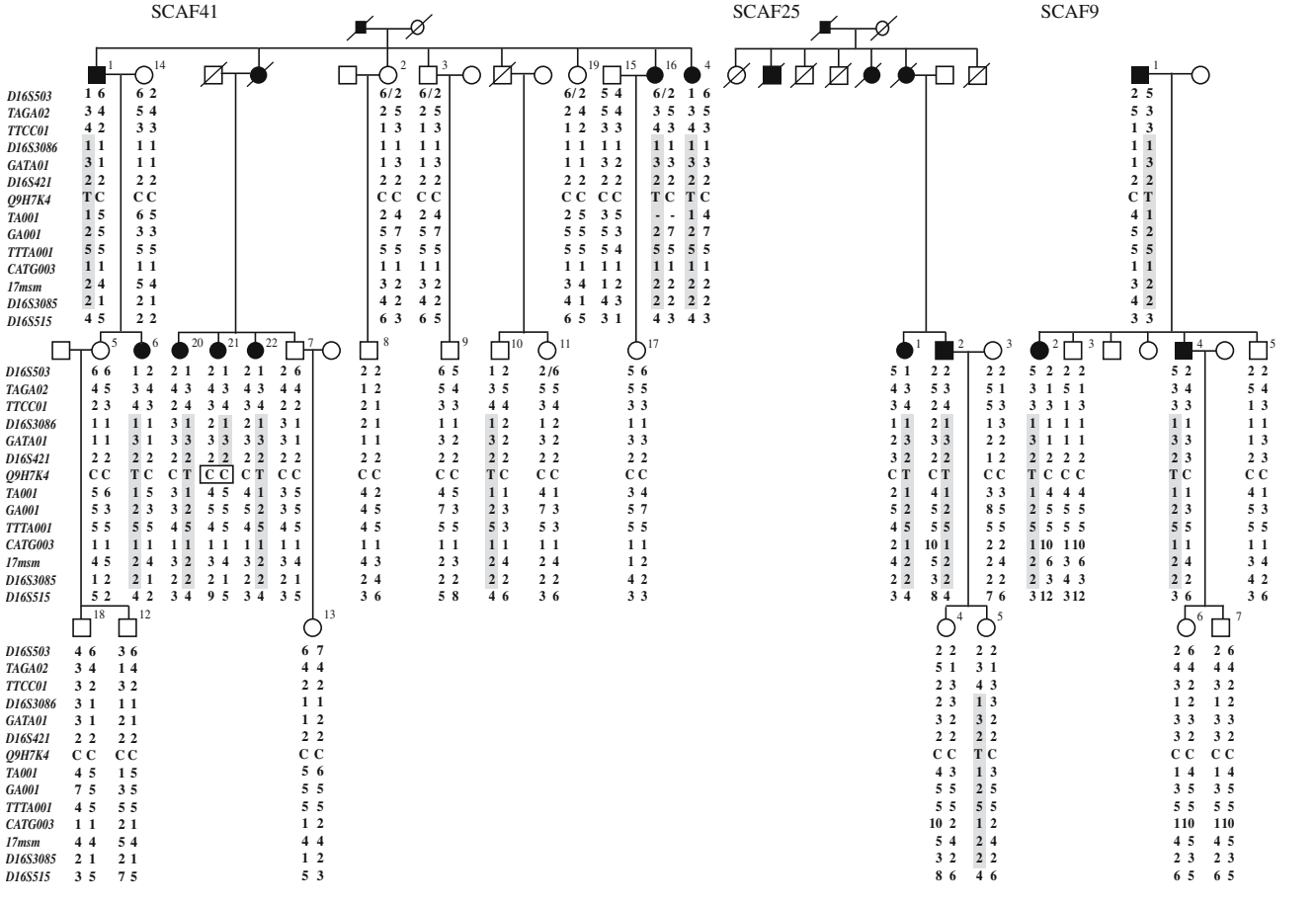

Fig. 1 Haplotype analysis in three large ADCA families, SCAF41, SCAF25, and SCAF9. Thirteen polymorphic markers mapped to 16q21–16q23 and the −16C > T substitution in *puratrophin-1 (Q9K7H4)* are shown. Twelve affected and two unaffected individuals had a common haplotype (1-3-2) at *D16S3086−GATA01−D16S421*. The −16C > T substitution was found in 11 out of 12 affected and 2 out of 22 unaffected individuals

A: Patients with -16C>T substitution

patient ID	1	2	5	7	8	9	10	12	15	16	17	18	21	22	24	25	26	29	31	32	33	35	36	37	38	39	40	41	43	44	45	47	48	49	50	51	55	56	57	59	60	61	63	64	67	68	69	70	71	72	73	74	75
family ID	11	13	18	20	21	22	24	33	38	40	42	46	49	50	57	58	59	61	64	65	67	69	70	71	73	74	75	76	79	80	81	82	84	85	86	87	83	91	92	94	95	96	99	100	29	29	105	106	100	15	15	15	15
D16S3086	1	1/2	1	1	1	1	1	1/3	1	1/3	1	1	1/5	1/2	1	1/2	1/3	1	1	1/2	1	1/3	1/3	1	1/2	1/2	1/3	1	1/2	1	1/2	1	1	1	1	1	1	1	1/2	1/2	1	1	1	1/2	1/2	1	1	1	1	1/2	1/2	1/4	1/4	1
GATA01	3/2	2	2	2	2/5	2/1	3/1	3/2	3	3/2	3/1	2	2/1	2/1	2	3/2	2	3	2	3/1	3	3/2	3	3/2	3	3/1	3/2	3/2	3/1	3	3/2	3/1	3	2/1	2	2	2/1	2/5	2/1	2/1	2	3	3/1	3	3/1	3	2/1	2/1	3	3/1	3	3	3/1
D16D421	2	2/3	2	2	2	2/6	2/4	2	2	2	2/4	2/3	2	2	2/1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2/4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2/3	2	2	2	2	2	2
Q9H7K4	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c	t/c
TA001	1	1/8	1/6	1/5	1	1/5	1/4	1/3	1/9	1/4	1/4	1/10	1/12	1/12	1/2	1/3	1/6	1	1	1/3	1/13	1/4	1/4	1	1/3	1/2	1/4	1/4	1/3	1/4	6/14	1/5	1/5	1/5	1/5	1/5	1/4	1/3	1/4	1/4	1/3	1/13	1/13	6/14	1/5	1/2	1/4	1/4	6/14	1/7	1/4	1/4	1/2
GA001	2/3	2/5	2/1	2/3	2/3	2/3	2/6	2/3	2/1	2/6	2/6	2/5	2/6	2/5	2/5	2/4	2/1	2/3	2/3	2/5	2/5	2/7	2/6	2/3	2/3	2/6	2/7	2/5	2/5	2/9	2/6	2/5	2/5	2/5	2/3	2/3	2/5	2/1	2/5	2/5	2/4	2/5	2/5	2/5	2/5	2/3	2/5	2/5	2/5	2/6	2/6	2/6
TTTA001	5	5	5/4	5	5/4	5/4	5/4	5/4	5/4	5/4	5/4	5	5/4	5/4	5	5	5	5	5	5/4	5	5	5/4	5	5/4	5	5	5	5/4	5/6	5/2	5	5	5	5/4	5	5	5/4	5	5	5	5	5/4	5	5	5	5	5	5	5/6	5/6	5/4
CATG003	1/3	1/2	1	1/2	1	1	1/10	1/2	1/7	1	1/10	1	1	1/10	1/2	1	1	1	1	1/6	1	1	1	1	1	1/10	1	1/2	1/6	1	1	1	1	1/2	1	1	1/2	1	1/5	1/5	1	1	1/6	1/2	1	1/2	1	1	1/2	1	1	1	1/10
17msm	2/4	2/6	2/6	2/3	2/5	2	2/5	2/3	2/5	2/4	2/5	2/4	2/5	2/5	2/3	2/4	2/5	2/4	2/5	2/6	2/1	2/4	2/4	2/5	2/3	2/4	2/4	2/4	2/6	2	2/9	2/5	2/4	2	2/3	2/3	2/5	2/7	2/4	2/4	2/4	2/4	2/7	2	2/4	2/3	2/5	2/3	2	2/4	2/4	2/4	2/4
D16S3085	2	2	2	2	2	2	2/3	2	2	2	2/3	2	2	2/3	2	2	2	2	2	2/3	2	2	2	2	2	2/3	2	2	2/3	2	2/3	2	2/1	2	2	2	2/3	2	2	2	2	2	2/3	2	2	2	2/4	2	2	2/1	2	2	2/3
age of onset	61	62	46	45	66	76	N	N	57	N	N	62	57	62	61	50	69	58	54	58	50	75	53	61	54	60	59	77	78	60	73	75	77	70	N	72	68	56	50	50	61	56	69	74	56	54	68	48	70	44	50	45	N

B: Patients without -16C>T substitution

patient ID	3	4	6	11	13	19	20	28	34	42	46	52	53	54	58	62	65	66
family ID	14	16	19	19	34	47	48	60	68	78	19	88	89	90	93	98	102	103
D16S3086	2	1	1	1	1	1	1/3	1/3	1/2	1	1/2	1/3	1/2	1	1/2	1/3	1/3	1
GATA01	2/1	2	3	2/3	2/3	2	1	2/3	2/6	1/6	2/3	2/3	2/3	3	2	3	3	2/3
D16D421	2/5	2	2	2/3	2/3	2	2	2/3	2	2	2/3	2	2/4	2	2/3	2	2	2
Q9H7K4	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c	c/c
TA001	2/5	4/6	1	1/2	2	4/116	2/5	3/5	3/5	1/13	4	5	1/4	4	1/4	2/4	8/13	
GA001	5/6	3	3	3/5	5	3	5	1/6	3/5	5	3/5	5	5	3/9	5	3/6	5/6	4/5
TTTA001	5/2	5/4	5	5	5	5	5	5/4	5/4	5	5	5	5/2	5/4	5	5/4	5/4	5/2
CATG003	3/4	1	1/3	1/3	1/2	1/2	4	1	1/6	1	1/3	1/10	2/4	1	1/3	1	1/2	1
17msm	2/4	1/5	4/5	2/5	3	4	4	4/8	3/4	5	4/5	5	4/10	2/5	3/5	4/5	2/4	4/11
D16S3085	2/1	2	2	2	2	2	2	2	2/4	2/4	2	2/3	2	2	2/3	2	2	2
age of onset	22	22	20	N	46	58	N	68	71	52	5	24	17	57	N	N	48	44

Fig. 2 Genotype of 71 patients from the other 64 families. The −16C > T substitutions in *puratrophin-1 (Q9K7H4)* was observed in 53 patients from 48 families (**A**), but not in 18 patients from 16 families (**B**). A haplotype, 2-1-2-5-1-2-2 of seven markers (*D16S421 −TA001−GA001−TTTA001−CATG003−17msm−D16S3085*) was shared by 50 patients with the −16C > T change and another haplotype, 2-6/14-2-5-1-2-2 for the same markers was shared by three patients (patient IDs, 45, 64, and 71). *N* unknown

trophin-1 gene. Additionally, four negative controls, SCA6 patients, also did not have the −16C > T change (data not shown). Among the 51 families with the −16C > T change, 49 of them shared a common haplotype around the *puratrophin-1* gene, 2-1-2-5-1-2-2 for seven markers (*D16S421 −TA001 −GA001 −TTTA001 −CATG003 −17msm −D16S3085*), and two families showed a slightly different haplotype, 2-6/14-2-5-1-2-2.

Discussion

The −16C > T change in the 5′ UTR of *puratrophin-1* was found in 51 out of 67 ADCA families (76%) from the Nagano prefecture, in which SCA1, 2, 3/MJD, 6, 7, 12, 17, and DRPLA had been previously ruled out. Among 106 ADCA families genetically analyzed to date (unpublished observation), the frequency of 16q22-linked ADCA (51 out of 106, 48%) is much higher than that of either SCA6 (18 out of 106, 17%) or DRPLA (9 out of 106, 8%). Thus, an accumulation of 16q22-linked ADCA families leads to a high prevalence of SCD in Nagano. Almost all patients shared the haplotype 2-1-2-5-1-2-2 for markers *D16S421 −TA001 −GA001 −TTTA001 −CATG003 −17msm −D16S3085*. For five of these markers, *D16S421 −TA001 −GA001 −TTTA001 −CATG003*, our haplotype 2-1-2-5-1 was identical to the haplotype 3-1-4-4-4 reported by Ishikawa et al. (2005), based on the data of four patients from two families that were analyzed independently by both groups. Sixty-four patients from 51 families with the −16C > T substitution showed pure cerebellar ataxia with middle-aged or later onset (Harding's ADCAIII; Harding 1993), while most of the patients without the substitution showed clinical phenotypes characterized by juvenile-onset cerebellar ataxia, additional extracerebellar neurological symptoms, and/or genetic anticipation. Previously, we could not confirm the common haplotype of 16q22-linked ataxia reported by Li et al. (2003; Shimizu et al. 2004), being inconsistent with the current data. This is partly explained by the fact that the focused region presented here was much narrower than the previously haplotyped region.

The −16C > T substitution in the 5′ UTR of *puratrophin-1*, a region of the gene presumed to be regulatory, is unique as a disease-causing change for ADCA. To date, pathological single nucleotide substitutions have been found only in SCA14 or SCA27 (Chen et al. 2003; van Swieten et al. 2003), both of which are missense mutations. It has been speculated that the −16C > T change might decrease mRNA expression of *puratrophin-1*, and cause aggregation of puratrophin-1 protein in Purkinje cells in affected cerebellum (Ishikawa et al. 2005).

Ishikawa et al. (2005) found the −16C > T substitution in the *puratrophin-1* gene in all affected individuals from 52 unrelated Japanese families. However, in this study there was one exceptional patient without this substitu-

tion in a family in which all other affected individuals carried the change, a finding confirmed by two independent examiners. This patient showed clinical features that did not differ significantly from the other affected members in her family. At present, it is unclear whether she may be a phenocopy or whether the real pathogenic mutation may exist in other regions within the shared haplotype between *TTCC01* and *Q9H7K4*. Careful observation of her clinical course and more comprehensive genetic analyses of her family are needed. The pathological consequence of the −16C > T substitution in the *puratrophin-1* gene should be further investigated.

In conclusion, we have found that the −16C > T substitution in the 5′ UTR of *puratrophin-1* was very prevalent in ADCA families in Nagano, where the frequency of 16q22-linked ADCA is much higher than that of SCA6, DRPLA, and SCA3/MJD, the most common subtypes in Japan. An accumulation of 16q22-linked ADCA families may be the main reason for the high incidence of SCD in Nagano. Further studies are needed to elucidate the clinical details and molecular pathogenesis of 16q22-linked ADCA.

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