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Report

SCA8 Repeat Expansion: Large CTA/CTG Repeat Alleles Are More Common in Ataxic Patients, Including Those with SCA6

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We analyzed the *SCA8* CTA/CTG repeat in a large group of Japanese subjects. The frequency of large alleles (85–399 CTA/CTG repeats) was 1.9% in spinocerebellar ataxia (SCA), 0.4% in Parkinson disease, 0.3% in Alzheimer disease, and 0% in a healthy control group; the frequency was significantly higher in the group with SCA than in the control group. Homozygotes for large alleles were observed only in the group with SCA. In five patients with SCA from two families, a large *SCA8* CTA/CTG repeat and a large *SCA6* CAG repeat coexisted. Age at onset was correlated with *SCA8* repeats rather than *SCA6* repeats in these five patients. In one of these families, at least one patient showed only a large *SCA8* CTA/CTG repeat allele, with no large *SCA6* CAG repeat allele. We speculate that the presence of a large *SCA8* CTA/CTG repeat allele influences the function of channels such as α_{1A}-voltage–dependent calcium channel through changing or aberrant splicing, resulting in the development of cerebellar ataxia, especially in homozygous patients.

Causative genes have been identified for several types of dominantly inherited spinocerebellar ataxia (SCA), which include SCA1 (MIM 164400), SCA2 (MIM 183090), SCA3/Machado-Joseph disease (MJD [MIM 607047), SCA6 (CACNA1A [MIM 601011), SCA7 (MIM 164500), SCA8 (MIM 603680), SCA10 (MIM 603516), SCA12 (MIM 604326), and SCA17 (MIM 607136), as well as dentatorubropallidoluysian atrophy (DRPLA [MIM 125370). Most types, except for SCA8 and SCA10, are caused by an expanded CAG repeat allele. It has been reported that SCA8 is caused by untranslated CTA/CTG expansions on chromosome 13q21; patients with this type have slowly progressive cerebellar signs (Koob et al. 1999; Day et al. 2000). In morphometric studies, magnetic resonance imaging showed significant atrophy of the cerebellar vermis and hemisphere, and there was no significant difference between SCA8 and SCA6 in the morphometric studies (Hokezu et al. 2000; Ikeda et al. 2000*a*). However, the large *SCA8* CTA/CTG repeat allele has been reported in healthy control subjects and in nonataxic neurological and neuropsychiatric patients (Stevanin et al. 2000; Vincent et al. 2000*a,* 2000*b;* Worth et al. 2000). In addition, members of families with SCA8 who have large *SCA8* CTA/CTG repeat alleles are not always symptomatic (Ikeda et al. 2000*b;* Juvonen et al. 2000; Worth et al. 2000; Cellini et al. 2001). Thus, the pathogenic role of the large *SCA8* CTA/CTG repeat allele remains uncertain. To clarify the involvement of this allele in disease, we analyzed the length of the *SCA8* CTA/CTG repeat in large groups of Japanese patients with SCA, Parkinson disease (PD), and Alzheimer disease (AD), and in unaffected control subjects.

All subjects were of Japanese ancestry and came from the same geographic area, except those from Hokkaido, in Japan. They had no history of migration from other

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countries. All provided informed consent. Data were collected from 694 patients with SCA, including 128 with SCA3/MJD (118 families); 155 with SCA6 (127 families); 48 with SCA1, -2, -7, or -17 or DRPLA (45 families); 243 with sporadic SCA (sSCA); and 120 with hereditary SCA (hSCA). Patients with hSCA, from 119 families, showed inherited cerebellar ataxia not caused by CAG repeats at the SCA1, -2, -3, -6, -7, -12, or -17 or DRPLA loci. Among these patients with hSCA, 62 were autosomal dominant and 58 were probably autosomal recessive. Patients with sSCA showed degenerative cerebellar ataxia with no family history, and expanded CAG repeats were not detected. We did not examine the known recessive ataxia mutations, such as Friedreich ataxia (FRDA [MIM 606829]), because Friedreich ataxia has never been reported in northeast Asia (Tan and Ashizawa 2001). The 224 patients with PD and 158 patients with AD were diagnosed by neurologists, on the basis of clinical and neuroradiological findings. The 327 control subjects were healthy volunteers. The mean age ± SD of normal control subjects at examination was 61 ± 13 years, which was higher than that of the group with SCA (47 ± 16 years). The mean ages at onset ± SD in the AD and PD groups were 70 ± 10 years and 61 ± 9 years, respectively.

Genomic DNA was extracted from leukocytes by a standard method. SCA8-F4 (5′-GTAAGAGATAAGCAGTATGAGGAAGTATG-3′) and SCA8-R4 (5′-GGTCCTTCATGTTAGAAAACCTGGCT-3′) were used as primer pairs for PCR analysis (Koob et al. 1999). The 5′ terminal of SCA8-F4 was labeled with polynucleotide kinase (Toyobo) and [γ-^{32}P]ATP at 37°C. Amplification was performed for 35 cycles (45 s denaturation at 94°C, 75 s annealing at 55°C, and 75 s elongation at 72°C). Genomic DNA (100 ng) was used for the PCR in 10 μl of 50 mM Tris-HCl (pH 9.2), 14 mM $(NH_4)_2SO_4$, 1.5 mM $MgCl_2$, 10% (vol/vol) DMSO, 25 μM each of dCTP, dATP, TTP, and dGTP, 4.5 μM SCA8-F4 primer, 0.5 μM [γ-^{32}P]SCA8-F4 primer, 5 μM SCA8-R4 primer, and 1 U of *Taq* and *Pwo* DNA polymerases (Boehringer Mannheim). Gel electrophoresis was performed on 5% HydroLink Long Ranger (AT Biochem) gels with 7 M urea and 48% formamide. Trinucleotide repeat length was determined by comparison with a standard M13 sequencing ladder. Samples that appeared to be homozygous underwent confirmatory Southern blot analysis, using a probe outside the *SCA8* CTA/CTG repeat region so as to reveal expansions too large to be amplified by PCR. Symptomatic patients with SCA8 have been reported to have 85–392 CTA/CTG repeats (Juvonen et al. 2000; Sobrido et al. 2001). Therefore, we tentatively divided the alleles into four classes: the small alleles (≤49 CTA/CTG repeats), intermediate-sized alleles (50–84 CTA/CTG repeats), large expanded alleles (85–400 CTA/CTG repeats), and very large expanded alleles (≥400 CTA/CTG repeats). *SCA8* CTA/CTG repeats can have either a pure uninterrupted CTG repeat tract or one or more CCG, CTA, CTC, CCA, or CTT interruptions. We sequenced three large expanded alleles and two intermediate-sized alleles, resulting in uninterrupted CTG repeat tracts. Because interruptions do not appear to influence the penetrance of large *SCA8* CTA/CTG repeat alleles (Moseley et al. 2000), we did not further account for interruptions of the CTG repeat tract. Age at onset was defined as the age when the patients first showed signs of cerebellar ataxia, such as diplopia, impaired smooth pursuit, nystagmus, dysarthria, poor coordination of trunk or limbs, or gait disturbance. Statistical analysis was performed with the χ^2 test, and results were considered significant at the .05 level. Statistical analyses were performed with JMP software (SAS Institute).

The distributions of the number of *SCA8* CTA/CTG repeats are shown in table 1. The range of *SCA8* CTA/CTG repeats was 18 to ~490 in the control group, 19–113 in the group with PD, 14–89 in the group with AD, and 14–221 in the group with SCA. In each group, 19 was the most common number of repeat units. The frequency of large alleles was significantly higher in the group with SCA than in the control group ($\chi^2 = 10.963$, $P = .0009$). There was no significant difference between the PD or AD group and the control group (PD vs. control: $\chi^2 = 0.980$, $P = .3223$; AD vs. control: $\chi^2 = 0.138$, $P = .7099$). Among the subgroups of SCA, the highest frequency of large alleles occurred in hSCA (3.8%), followed by SCA6 (2.6%) and sSCA (1.9%). Four patients (1.3%) from three families showed intermediate-sized repeat alleles. Large or intermediate-sized *SCA8* CTA/CTG repeat alleles were not observed in SCA1, -2, -3, -7, or -17 or DRPLA. Two patients with PD, one patient with AD, and three control subjects were revealed to have large or very large alleles (PD: 113 and 90 repeats; AD: 89 repeats; control: ~420, ~450, and ~490 repeats). Details of the patients with hSCA or sSCA who had large *SCA8* CTA/CTG alleles are shown in table 2; 9 of these had no family history (sporadic disease). Long *SCA8* repeats and early age at onset were not significantly correlated ($n = 15$, $r^2 = 0.098$, $P = .25$). Homozygotes for large alleles were observed only in the group with SCA, as described elsewhere (Koob et al. 1999; Stevanin et al. 2000). These 15 patients (table 2) showed cerebellar ataxia and other clinical signs. The effect of homozygosity on age at onset was not clear (patients 2, 5, and 6). All patients showed cerebellar ataxia clinically characterized by high frequencies of poor coordination of trunk and limbs, impaired pursuit movement, nystagmus, ataxic dysarthria, and wide-based gait. The other clinical signs included mental retardation, dementia, depressive state, suicidal ideation, dysphagia, hyporeflexia, hyperreflexia, pyramidal signs,

Table 1

Distribution of the Number of *SCA8* CTA/CTG Repeats

Subjects (No. of Alleles)	No. (%) of Subjects with			
	⩽39 Repeats	40–84 Repeats	85–399 Repeats	⩾400 Repeats
Control Subjects (654)	647 (98.9)	4 (.6)	0	3 (.5)
Patients with:				
PD (448)	446 (99.6)	0	2 (.4)	0
AD (316)	315 (99.7)	0	1 (.3)	0
SCA:				
SCA3/MJD (256)	256 (100)	0	0	0
SCA6 (310)	298 (96.1)	4 (1.3)[a]	8(2.6)[b]	0
SCA1, 2, 7, 17, DRPLA (96)	96 (100)	0	0	0
sSCA (486)	477 (98.1)	0	9 (1.9)	0
hSCA (240)[c]	231 (96.2)	0	9 (3.8)[d]	0
All SCA (1,388)	1,358 (97.8)	4 (.3)	26 (1.9)	0

[a] Intermediate-sized *SCA8* CTA/CTG repeats were observed in four patients from three families.

[b] Large *SCA8* CTA/CTG repeats were observed in six patients from two families that appear to have SCA6 (fig. 1). Two patients were homozygous.

[c] Sixty-two patients were autosomal dominant, and 58 were probably autosomal recessive.

[d] Large *SCA8* CTA/CTG repeats were observed in six patients from five families. Three patients were homozygous.

parkinsonism, involuntary movement, reduced vibratory sense, and urinary disturbance. Mental retardation was common (60%) among the patients with early onset of disease (at age ⩽20 years) and large *SCA8* CTA/CTG alleles.

Patient 9 showed slowly progressive cerebellar ataxia and had no apparent family history. Her mother showed progressive dementia without cerebellar ataxia and received a diagnosis of AD on the basis of clinical and neuroradiological findings. She also had a large *SCA8* CTA/CTG repeat allele (120 repeats). Patient 10 showed a large *SCA8* CTA/CTG repeat allele and also an intermediate-sized *MJD1* CAG repeat allele (45 CAG repeats). Although his father had a very large *SCA8* repeat allele (~650 repeats), he showed no apparent neurological abnormalities and no significant atrophy in his cerebellum at 50 years of age.

In five patients from two families, at least one large *SCA8* CTA/CTG repeat allele and a large *SCA6* CAG repeat allele coexisted (figs. 1*a* and 1*b*). Early age at onset was correlated with number of *SCA8* repeats ($r^2 = 0.79$, $P = .043$) rather than number of *SCA6* re-

Table 2

Patients with hSCA or sSCA Who Had Large *SCA8* CTA/CTG Repeat Alleles

Patient	Type	Sex	Age at Onset	SCA8 Repeat Length	Cerebellar Ataxia	Other Clinical Signs
1	hSCA	M	14	221/24	+	Hyperreflexia, facial grimacing, mental retardation, euphoria
2	hSCA	M	10	172/172	+	Hyperreflexia, mental retardation, involuntary movement
3	hSCA	M	13	172/27	+	Hyperreflexia, mental retardation, involuntary movement
4	hSCA	F	10	144/27	+	Urinary disturbance
5	hSCA	F	61	126/101	+	Hyperreflexia
6	hSCA	F	40	123/112	+	Neck and truncal titubation, hyporeflexia
7	sSCA	M	56	221/19	+	Bradykinesis, tremor, rigidity, dementia, dysphagia
8	sSCA	F	34	160/19	+	Neck titubation, hyperreflexia, spastic gait
9	sSCA	F	31	140/28	+	Depressive, dementia, hyperreflexia
10	sSCA	M	17	126/29	+	Hyperreflexia, myoclonus, spasticity, equinovarus
11	sSCA	F	41	110/19	+	Bulging eye, snoring, suicidal
12	sSCA	F	63	109/30	+	Decreased vibratory sense
13	sSCA	F	53	100/82	+	Hyporeflexia
14	sSCA	F	29	100/26	+	Hyperreflexia
15	sSCA	M	36	86/28	+	Hyperreflexia, Babinski sign, decreased vibratory sense, muscle atrophy in lower limb

Note.—Patients 2 and 3 were brothers.

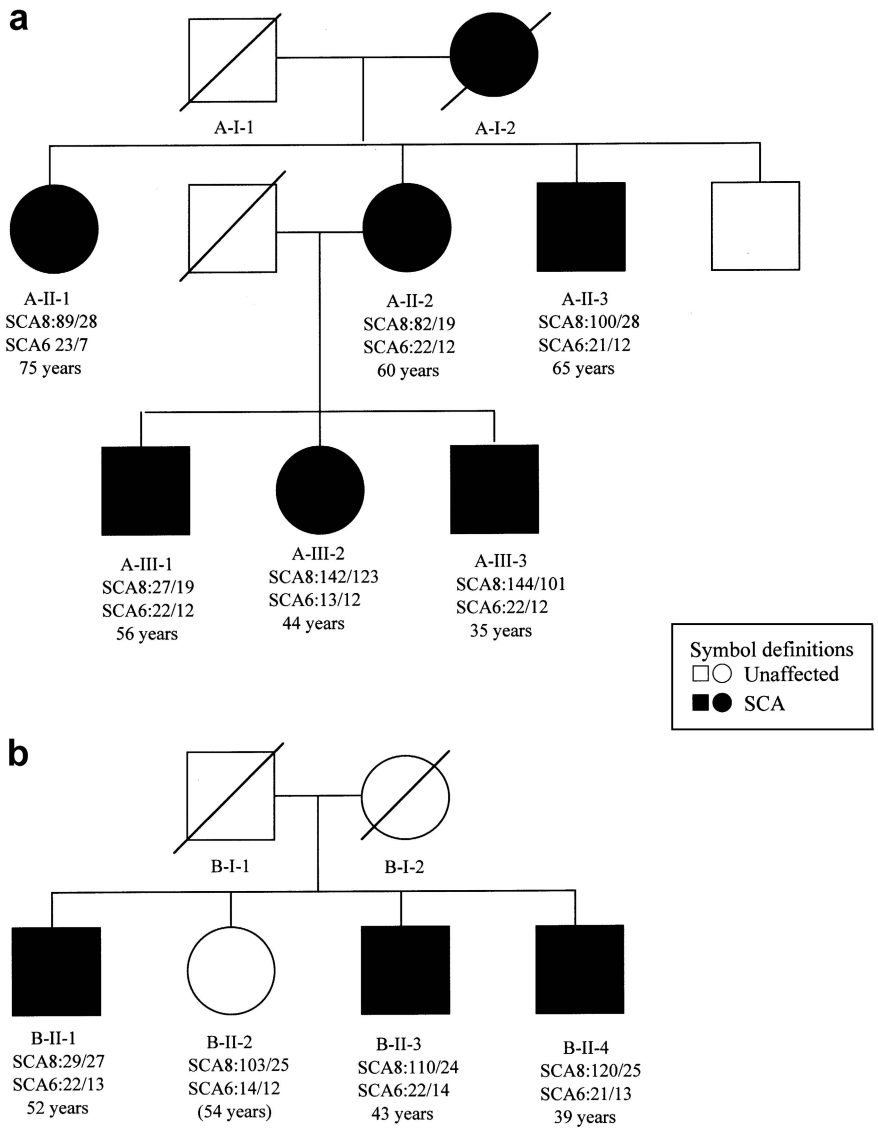

Figure 1 Pedigrees of two families with SCA. The age at onset is shown below the repeat size. *a*, Family A. *b*, Family B.

peats ($r^2 = 0.15$, $P = .527$) in these five patients. In family A, patient A-III-2 showed only a large *SCA8* repeat allele, and patient A-III-1 showed only a large *SCA6* repeat allele; the remaining patients in this family showed large repeat expansions at both loci (patient A-II-2 showed an intermediate-sized *SCA8* CTA/CTG repeat expansion). In family B, subjects with large repeats at both loci or only at *SCA6* were symptomatic, whereas the subject with a large repeat only at *SCA8* was asymptomatic. All symptomatic patients from family A showed clinically pure cerebellar ataxia. On the other hand, pyramidal signs and neck tremor, as well as cerebellar ataxia, were observed in family B. Clinical symptoms in families A and B tended to be severe in patients with large alleles at both loci. The mean age at onset of patients with large repeats at both loci (50.2 years) was lower than that of patients with only one locus (53.0 years).

This is the first report, to our knowledge, that several patients with SCA showed coexistence of large *SCA8* CTA/CTG repeat alleles and large *SCA6* CAG repeat alleles. The coexistence is specific to SCA6 and is not seen in other SCAs or DRPLA, among the ataxias with CAG repeat expansions. Although only 1.6% (2/127) of the SCA6 families were found to have large SCA8 alleles, 12.5% (2/16) of the SCA8 families were found to have large SCA6 alleles. When patients with intermediate alleles of SCA8 were included, 22.2% (4/18) of

SCA8 families were found to have large SCA6 alleles. Therefore, the *SCA6* locus/product should be included in a pathway of appearance of SCA8 phenotype. SCA6 is caused by small CAG expansions in the α_{1A}-voltage–dependent calcium channel gene (*CACNA1A*) (Zhuchenko et al. 1997). The small expansion (usually 21–34 repeats) is believed to change the channel function and to lead to neuronal cell death. In other SCA subtypes and DRPLA, the elongated polyglutamine (at least 30 repeats) is excluded from the gene products. The excluded polyglutamine fragments aggregate and lead to neuronal cell toxicity. The mechanisms of the development of diseases are thought to be different in SCA6 and other subtypes, even those with the same CAG repeat expansions. We speculate that the presence of a large *SCA8* CTA/CTG repeat transcript influence the products of the *CACNA1A* gene, resulting in an increase in aberrant transcripts, or the mRNA of CAG repeats in the coding region among many alternative splicing products of the gene. The changed transcripts will produce loss of calcium channel protein in the membrane or an increase in calcium channel protein with polyglutamine repeats (Matsuyama et al. 1999). The result may be a development of cerebellar ataxia in patients without SCA6, especially in patients who are homozygous for large *SCA8* repeats.

A similar mechanism has recently become evident in dystrophia myotonica (DM [MIM 160900]). DM is also caused by the expansion of CTG repeats in the 3′ noncoding region of *DMPK*. In DM, RNA with expanded CUG repeats increases CUG-binding protein (CUG-BP). CUG-BP regulates alternative splicing of specific preMRNAs, and the increased CUG-BP causes aberrant splicing of cardiac troponin T, insulin receptor, and the muscle-specific chloride channel (ClC-1). Aberrant splicing of ClC-1 results in loss of ClC-1 protein and in myotonic myopathy (Charlet-B et al. 2002; Mankodi et al. 2002).

As described elsewhere (Juvonen et al. 2000; Silveira et al. 2000), cognitive impairment is frequently observed in patients with SCA who have large *SCA8* repeat alleles; however, the major pedigree described in SCA8 has basically only a slowly progressive cerebellar ataxia without cognitive impairment (Koob et al. 1999; Day et al. 2000). Mental retardation is observed in most patients with congenital DM, whereas cognitive impairment is not always observed in adult-onset DM. CpGs in the region of the CTG repeat are aberrantly methylated in congenital DM, whereas this region is not methylated in adult-onset DM (Steinbach et al. 1998). Similarly, patients with SCA8 may be divided into two types—congenital (showing mental retardation) and adult-onset—by some genetic mechanisms.

Patient 10 had a cerebellar ataxia with a large *SCA8* CTA/CTG repeat allele (126 repeats). His father had a very large *SCA8* repeat allele (~650 repeats) but appeared asymptomatic. Very large CTA/CTG alleles were observed only in the control group (table 1). As described elsewhere (Juvonen et al. 2000; Vincent et al. 2000*a*), normal subjects sometimes have very large expanded alleles. In SCA8, very large CTA/CTG repeat alleles (i.e., ⩾400 repeats) might be transcriptionally silent, as in the full mutation (>200 CGG) of fragile X mental retardation syndrome (FMR1 [MIM 309550]) (O'Donnell and Warren 2002).

We have discussed the possibility that SCA8 works through SCA6 gene products. There may be other types of interaction of SCA6 and SCA8. Further evidence from the clinical, pathological, and biochemical analysis of SCA8 and from studies using cellular and animal models is needed to understand the mechanisms of development of the disease.

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Electronic-Database Information

Accession numbers and the URL for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SCA1 [MIM 164400], SCA2 [MIM 183090], MJD [MIM 607047], CACNA1A [MIM 601011]), SCA7 [MIM 164500], SCA8 [MIM 603680], SCA10 [MIM 603516], SCA12 [MIM 604326], SCA17 [MIM 607136], DRPLA [MIM 125370], FRDA [MIM 606829], DM [MIM 160900], and FMR1 [MIM 309550]

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