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ORIGINAL ARTICLE

Spectrum and prevalence of autosomal dominant spinocerebellar ataxia in Hokkaido, the northern island of Japan: a study of 113 Japanese families

Rehana Basri · Ichiro Yabe · Hiroyuki Soma · Hidenao Sasaki

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Abstract Autosomal dominant cerebellar ataxia (ADCA) is a genetically heterogeneous group of neurodegenerative disorders. To shed further light on the clinical and genetic spectrum of ADCA in Japan, we conducted a study to determine the frequency of a new variety of different subtypes of SCAs among ADCA patients. This current study was carried out from April 1999 to December 2006 on the basis of patients with symptoms and signs of ADCA disorders. PCR and/or direct sequencing were evaluated in a total of 113 families. Among them, 35 families were found to have the mutation associated with SCA6, 30 with SCA3, 11 with SCA1, five with SCA2, five with DRPLA, and one with SCA14. We also detected the heterozygous –16C → T single nucleotide substitution within the purkinje-1 gene responsible for 16q22.1-linked ADCA in ten families. In this study, unusual varieties of SCA, including 27, 13, 5, 7, 8, 12, 17, and 16 were not found. Of the 113 patients, 14% had as yet unidentified ADCA mutations. The present study validates the prevalence of genetically distinct ADCA subtypes based on ethnic origin and geographical variation, and shows that 16q-linked ADCA has strong hereditary effects in patients with ADCAs in Japan.

Keywords Autosomal dominant cerebellar ataxia · SCA6 · SCA3 · 16q-linked ADCA

Rehana Basri, Ichiro Yabe, and Hiroyuki Soma contributed equally to this work.

R. Basri · I. Yabe (✉) · H. Soma · H. Sasaki
Department of Neurology, Graduate School of Medicine, Hokkaido University, N15W7. Kita-Ku, Sapporo 060-8368, Japan
e-mail: yabe@med.hokudai.ac.jp

Introduction

Autosomal dominant cerebellar ataxia (ADCA) is a genetically heterogeneous group of neurodegenerative disorders affecting the cerebellum, brainstem, spinal cord and cranial nerve nuclei, resulting in progressive cerebellar ataxia of gait and limbs and variably associated with nystagmus, dysarthria, intention tremor and ophthalmoparesis. Disease onset is usually between 30 and 50 years of age, although early onset in childhood and onset in later decades after 60 years have been reported. Spinocerebellar ataxia (SCA) is also genetically heterogeneous, and the clinical diagnosis of subtypes of SCA is complicated by the salient overlap of the phenotype variations. Harding classified ADCA into three major categories based on clinical features and dominant mode of inheritance (Harding 1993). Classification of these ADCA was modified by Duenas on the basis of neuropathology, and provides a guideline in clinical practice to prioritize genetic tests for diagnoses (Duenas et al. 2006). ADCA type I is variably associated with ataxia of the gait, ophthalmoplegia, pyramidal and extrapyramidal signs, cognitive impairment, optic atrophy or peripheral neuropathy; ADCA type II with retinopathy; and ADCA type III with late onset, pure cerebellar ataxia with genetic heterogeneity. To date, 29 different genetic loci have been reported to be responsible for ADCA (http://www.gene.ucl.ac.uk/cgi-bin/nomenclature): spinocerebellar ataxia type 1 (SCA1) on chromosome 6p22-p23 (Orr et al. 1993); SCA2 on 12q23-q24.1 (Imbert et al. 1996; Sanpei et al. 1996); Machado-Joseph disease (MJD)/SCA3 on 14q24.3-q32.1 (Kawaguchi et al. 1994); SCA4 on 16q22.1 (Flanigan et al. 1996); SCA5 on 11q13.2 (Ranum et al. 1994); SCA6 on 19p13.1 (Zhuchenko et al. 1997); SCA7 on 3p12-p13 (David et al. 1997); SCA8 on 13p (Koob et al. 1999); SCA10 on 22q13-qter. (Matsuura et al.

2000); SCA11 on 15q14-q21.3 (Worth et al. 1999); SCA12 on 5q31-33 (Holmes et al. 1999); SCA13 on 19q13.3-q13.4 (Waters et al. 2006); SCA14 on 19q13.42 (Yamashita et al. 2000; Chen et al. 2003; Yabe et al. 2003); SCA15 on 3p24.2 (Gardner et al. 2005); SCA16 on 8q23-q24.1 (Miyoshi et al. 2001); SCA17 on 6q27 (Nakamura et al. 2001); SCA18 on 7q22 (Brkanac et al. 2002); SCA19 on 1p21-q21 (Verbeek et al. 2002); SCA20 on 11p11.2-q13.3 (Knight et al. 2004); SCA21 on 7p21.3-p15.1 (Vuillaume et al. 2002); SCA22 on 1p21-q23 (Chung et al. 2003); SCA23 on 20p13-p12 (Verbeek et al. 2004); SCA24 on 1p26 (Swartz et al. 2002); SCA25 on 2p21-p15 (Stevanin et al. 2004); SCA26 on 19p13.3 (Yu et al. 2005); SCA27 on 13q33.1 (Van Swieten et al. 2003); SCA28 on 18p11.22-q11.2 (Cagnoli et al. 2006); SCA 29 on 3p26 (Dudding et al. 2004) and dentatorubral pallidoluysian atrophy (DRPLA) on 12p13.31 (Koide et al. 1994; Nagafuchi et al. 1994). Among these loci, causative genes have been further identified containing trinucleotide repeats (CAG) in SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, DRPLA (Orr et al. 1993; Sanpei et al. 1996; Kawaguchi Y et al. 1994; Zhuchenko et al. 1997; David et al. 1997; Nakamura et al. 2001; Koide et al. 1994), and in the promoter region of *PPP2R2B* related to SCA12 (Holmes et al. 1999); trinucleotide repeats (CTG) within an untranslated region of the SCA8 gene (Koob et al. 1999); and a pentanucleotide (ATTCT) repeat expansion within intron 9 of the SCA10 gene (Matsuura et al. 2000). While the exact mechanism for repeat expansion is still unknown, a number of hypotheses have evolved to explain how the consequences of these expansions cause disease. A prime example is the expansion of CAG repeats in specific genes that lead to long abnormal polyglutamine (polyQ) tracts in the encoded proteins (Zoghi and Orr 2000). Polyglutamine-containing protein tends to aggregate in diseased neurons, forming characteristic nuclear and cytoplasmic inclusions (ubiquitin, proteasome, HSP70, transcription factors), which are the neuropathological hallmarks of these diseases (Ross and Poirier 2004).

On the other hand, deletion and/or point mutations were identified in the *SPTBN2*, *KCNC3*, *PRKCG*, and *FGF14* genes, recently attributed to SCA5, SCA13, SCA14, and SCA27 respectively (Ikeda et al. 2006; Waters et al. 2006; Yamashita et al. 2000; Chen et al. 2003; Yabe et al. 2003; Van Swieten et al. 2003). Point mutations may result in decreased stability of the proteins, and frameshift mutations in truncated proteins (Van Swieten et al. 2003; Dalski et al. 2005). More recently, single nucleotide substitutions have been identified in the puratrophin-1 and contactin 4 (*CNTN4*) genes, classified as 16q-linked ADCA and SCA16 respectively (Takashima et al. 2001; Li et al. 2003; Mizusawa et al. 2004; Ishikawa et al. 2005; Miura et al. 2006). These two varieties of ADCA have been seen only in Japan.

In Japan, the prevalence of spinocerebellar degeneration including multiple system atrophy (MSA) is 15.68 in 100,000 (Sasaki et al. 2003). The frequency of ADCA subtypes also varies among countries. SCA3, SCA6 and DRPLA were higher in Japanese populations than in Caucasian populations (Maruyama et al. 2002; Sasaki et al. 2003; Matsumura et al 2003), whereas SCA7, SCA8, SCA17, and SCA12 are less frequent in the Japanese population (Maruyama et al. 2002; Sasaki et al. 2000; Matsumura et al 2003; Onodera et al. 2000). SCA14 phenotype has been also reported (Yamashita et al. 2000; Yabe et al. 2003; Morita et al. 2006), but there are no reported cases of SCA27, SCA13, or SCA5. In addition, 16q22.1-linked ADCA has been identified only in the Japanese population (Wieczorek et al. 2006). Interestingly, the molecular basis of such differences in the prevalence of SCAs within and among populations is still unclear. Moreover, the causes of approximately 20–40% of dominant SCAs are still unknown (Sasaki et al. 2003).

The breadth of the clinical spectrum of ADCA has been reported previously, but the relative frequencies of new varieties of different subtypes of ADCA have not been considered. To shed light on this problem, we performed a study of patients with clinically and genetically confirmed ADCA. We investigated the relative prevalences of different subtypes of repeat expansions and of the other new varieties of 16q22.1-linked ADCA, SCA13, SCA5, SCA27, and SCA16 in Japanese patients on Hokkaido, the northernmost island of Japan.

Subjects and methods

The Department of Neurology at Hokkaido University Graduate School of Medicine is located in Sapporo, the capital of Hokkaido. Patients with SCA were referred by physicians to the Department for DNA diagnoses. The laboratory serves as the major molecular genetic center for neurological diseases throughout Hokkaido. Thus, patients visiting our clinic can be regarded as reflecting the relative prevalence of hereditary SCA in Hokkaido.

Subjects with ADCA

Genetic analyses of 113 unrelated Japanese families with ADCA from different areas of Hokkaido Island were carried out in our laboratory between April 1999 and the end of December 2006. Although we have previously published similar work, the study was done for those patients who were diagnosed by genetic analysis until March 1999

(Sasaki et al. 2000). Therefore, there is no overlap of the subjects between this study and the previous study. In all cases, progressive cerebellar ataxia was the cardinal clinical manifestation. Nearly all patients presented with an adult onset phenotype. In addition to neurological examination, brain MRIs showed cerebellar atrophy or pontocerebellar atrophy. All procedures of the study were approved by the Hokkaido University Ethics Committee, and informed consent was obtained from all participants.

Genetic analyses

Genomic DNA was extracted from blood lymphocytes by standard methods (Sambrook et al. 1989, Cold Spring Harbor, NY, USA). Expanded triplet repeats in the genes causing SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17, and DRPLA were amplified using the primer pairs Rep-1/ Rep-2 (Orr et al. 1993), F-1/F-2 (Sanpei et al. 1996), MJD25/ MJD52 (Kawaguchi et al. 1994), S-5-F1/ S-5-R1 (Zhunchenko et al. 1997), 4U1024/4U716 (David et al. 1997), SCA8-F3/SCA8-R4 (Koob et al. 1999), PPP2R2B-A/PPP2R2B-B (Holmes et al. 1999), TBP-F/TBP-R (Nakamura et al. 2001) and CTG-B37(699)/(840) (Koide et al. 1994) respectively. We did not test for the SCA10 mutation, because its clinical manifestation is ataxia with seizure, which was not observed in our ADCA families. Conditions for polymerase chain reaction (PCR) amplification were based on the respective original reports. All the PCR products containing triplet repeats were separated in 4% polyacrylamide/6M urea gels at 1680 V in 1·(TBE buffer for 2 h. Genotypes were determined using Gene Scan Analysis Ver. 2.0 computer software (Perkin Elmer), as described previously (Yabe et al. 1998). For the new varieties of ADCA subtypes, we also performed PCR and sequence analyses in undiagnosed ADCA families to detect mutations in all exons of the following genes: fibrous growth factor14 (*FGF14*) for SCA27, spectrin (*SPTBN2*) for SCA5, protein kinase C γ (*PRKCG*) for SCA14, and voltage-gated potassium channel (*KCNC3*) for SCA13. In puratrophin-1 (*PRTPHN1/PLEKHG4*) for 16q-linked ADCA phenotype and contactin 4 (*CNTN4*) for SCA16, each published specific single nucleotide polymorphism was analyzed. The PCR mixtures and fragment analyses were basically the same as those reported previously (Ishikawa et al. 2005; van Swieten et al. 2003; Ikeda et al. 2006; Miura et al. 2006; Yabe et al. 2003; Waters et al. 2006).

Results

A total of 113 ADCA families were examined for 15 different mutations, and 97 families (86%) were positive for various subtypes of SCA. The SCA6 mutation was found in 35 of the 113 families (31%), SCA3 was detected in 30 families (27%), SCA1 in 11 families (10%), SCA2 in five families (4%), DRPLA in five families (4%), and SCA14 in one family (1%). The screen for point mutations in the puratrophin-1, *FGF14*, *SPTBN2*, *CNTN4* and *KCNC3* genes, revealed only the –16C → T mutation in the puratrophin-1 gene in ten families (9%). The remaining 16 ADCA families (14%) were genetically unidentified. The frequency of known SCA mutations in the consecutive series of 113 families is shown in Fig. 1. Table 1 summarizes the clinical features of the ten 16q-linked ADCA families and the remaining 16 unidentified ADCA families. The two groups of patients with 16q-linked ADCA and unidentified ADCA differed in their mean age at onset, with a higher onset in the 16qADCA patients (mean ± SD age: 58 ± 8 years) than in those with unidentified ADCA (mean ± SD age: 32 ± 13 years).

Discussion

Among the 113 families with ADCA examined in our department in Hokkaido from April 1999 to the end of December 2006, SCA6 (31%) was the most prevalent subtype, followed by SCA3/MJD (27%), SCA1 (10%), 16q-ADCA (9%), SCA2 (4%), and DRPLA (4%). This is in good agreement with a previous study which also reported that SCA6 (29%) and SCA3 (23%) were the most prevalent in the Hokkaido region (Sasaki et al. 2000). Earlier reports from other districts also demonstrated that the frequencies of SCA6 and SCA3 were the most prevalent in Japan (Sasaki et al. 2003; Matsumura et al. 2003; Maruyama et al. 2002), presumably due to the founder effect. SCA3 is quite frequent in many countries with different ethnic backgrounds, such as Portugal (80%), Germany (40%), Japan (40%), and France (30%) (Storey

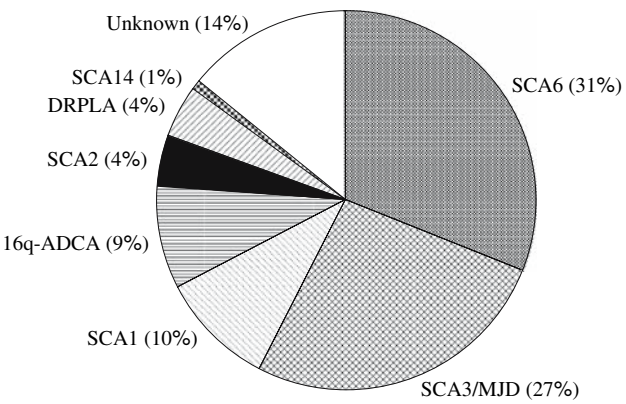

Fig. 1 The frequency of different subtypes of ADCA in 113 families from April 1999 to December 2006

Table 1 Clinical features of patients with 16q-ADCA and other unknown ADCAs

	16q-ADCA	Unknown ADCA
Number of families	10 (M = 4, F = 6)	16 (M = 9, F = 7)
Family history	AD	AD
Mean age at examination (range)	66.9 (52–76)	53.0 (30–80)
Mean age at onset (range)	58.0 (45–66)	32.4 (3–55)
Disease duration (years)	9.1 (2–19)	20.2 (7–60)
Neurological findings		
Dysarthria	100%	100%
Gaze nystagmus	100%	38%
Limb ataxia	100%	100%
Truncal ataxia	100%	100%
Hyporeflexia	10%	26%
Hyperreflexia	0%	43%
Spasticity	0%	38%
Babinski/Chaddock reflexes	0%	43%
Hearing impairment	20%	0%
Decrease vibration sence	20%	43%
Dystonia	0%	17%
Dementia	0%	13%

ADCA Autosomal dominant cerebellar ataxia

et al. 2000). In the Nagano district of Japan, DRPLA was reported to be the second most frequent of the ADCA subtypes (10%) (Shimizu et al. 2004). There have also been a few reports of DRPLA from Korea (Jin et al. 1999), USA (Brunetti-Pierri et al. 2006) and Canada (Espay et al. 2006). The expanded repeat ranges and the clinical features of the SCA6, SCA3, SCA1, SCA2, and DRPLA families were similar to those reported previously (data not shown) (Zhuchenko et al. 1997; Kawaguchi Y et al. 1994; Orr et al. 1993; Sanpei et al. 1996; Koide et al. 1994).

That we did not find any cases of SCA17, SCA12, SCA7, and SCA8 is in agreement with previous reports showing that the frequencies of these subtypes were not common in most of the districts of Japan (Maruyama et al. 2002; Sasaki et al. 2000; Matsumura et al 2003; Onodera et al. 2000). The SCA10 expansion appears to be restricted to a few families of Mexican (Matsuura et al. 2000) and Brazilian (Teive et al. 2004) origin. The SCA12 mutation has been identified only in a large pedigree of German descent and in an Indian family (Holmes et al. 1999; Bahl et al. 2005). These data clearly indicate that ethnic origin and geographical variation play important roles in the prevalence of SCA types.

Recently, a novel form of cerebellar ataxia linked to the 16q22.1 locus was reported (Takashima et al. 2001; Li et al. 2003; Mizusawa et al. 2004; Ishikawa et al. 2005). Several of these Japanese ADCA families also mapped within the SCA4 candidate region, and the disease was reported as "16q-linked ADCA type III" (Nagaoka et al. 2000; Li et al. 2003). 16q-linked ADCA is the third most prevalent subtype of ADCA in Japan, after SCA6 and SCA3, and is distributed nation-wide (Mizusawa et al 2004). In our study, the –16C → T change in the 5′UTR of the puratrophin-1 gene causing 16q22-linked ADCA diseases was found in ten families from the Hokkaido island. Ishikawa also previously reported on the existence of 16q22-linked ADCA families from this island (Ishikawa et al. 2005). Thus, an accumulation of 16q-linked ADCA families leads to a moderately high prevalence of SCD in Hokkaido. 16q-linked ADCA was also very prevalent in ADCA families in the Nagano districts of Japan (Ohata et al. 2006). Table 2 summarizes the high prevalence of 16q-linked ADCA in various localities throughout Japan.

Clinically, 16q-ADCA shows a slowly progressive pure cerebellar ataxia of late-onset (onset > 50 years old), increased deep tendon reflexes, hearing impairment, and normal sensation and behavior. 16q22-linked ADCA demonstrates a strong founder effect in Japan (Hirano et al. 2004;

Table 2 Frequencies of 16q-linked ADCA type III in Japan

Location	Number of SCA families	16q-linked ADCA type III	References
Kagoshima and southern Miyazaki, the Southern Kyushu	30 families	20 cases/4 families	Hirano et al. (2004)
Throughout Japan	52 families	109 cases/52 families	Ishikawa et al. (2005)
Tokyo	1 family	12 cases/1 family	Owada et al. (2005)
Tohoku, Northernmost part of Honshu Island	218 families plus 128 sporadic case	31 cases, 7 case/26 families	Onodera et al. (2006)
Nagano	67 families	63 cases/51 families	Ohata et al. (2006)
Tochigi, a northern region of Kanto Plane	24 families	20 cases/9 families, plus 2 sporadic cases	Ouyang et al. (2006)
Honshu Island	686 families	65 cases/57 families	Nozaki et al. (2007)
Hokkaido	113 families	10 cases/10 families	Present study

Ishikawa et al. 2005). The spectrum of these 16q-linked ADCA symptoms appears more commonly in the Japanese population, but was not detected in 537 European patients with unknown ADCA (Wieczorek et al. 2006). However, the Japanese 16q22.1-linked ADCA ataxia and the European SCA4 have the same locus, but the European SCA4 gene has not yet been identified. In addition to the clinical phenotypes of the Japanese patients, 16q-linked ADCA is clearly distinguishable from the SCA4 disorder. The neuropathology of 16q-linked ADCA type III was characterized by abnormal Purkinje cells in the cerebellum, including shrunken cell bodies, abnormal dendrites, somatic sprouts, and amorphous materials surrounding the cells, all indicative of degeneration processes (Owada et al. 2005).

The more recently discovered SCA14, SCA27, SCA13, SCA16, and SCA5 are distinguished by alterations in amino acid compositions and/or frameshift mutations within the *PRKCG* (protein kinase C gamma), *FGF14*, *KCNC3*, *CNTN4* and *SPTBN2* genes respectively. We detected one family of SCA14 displaying axial myoclonus followed by ataxia at early onset; this family has already been described (Yabe et al. 2003), and other Japanese patients with SCA14 displayed slowly progressive cerebellar syndromes with late onset that included gait and limb ataxia, dysarthria, and saccadic pursuit. Brain MRI of these patients revealed atrophy of the cerebellum (Hiramoto et al. 2006; Morita et al. 2006). More recently, a Dutch family with SCA14 patients was also described with early onset, mildly generalized myoclonus (Vlak et al. 2006; Verbeek et al. 2005). SCA14 is present in various different ethnic populations (Japan, German, Dutch, Portuguese and French) and displays a heterogeneous mutation spectrum (Yabe et al. 2003; Dalski et al. 2006; Verbeek et al. 2005; Alonso et al.2005; Klebe et al. 2005).

Several pathways might be interrupted to cause neurodegenerations and neuronal function loss, which remains unclear. In addition, we detected 16 families (14%) with unidentifiable types of ADCA. Thus, further studies are needed to improve genetic diagnoses, and epidemiological surveys and genetic counseling are needed for awareness and prevention of ADCA disease progress.

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