RESEARCH ARTICLE

First report of a Japanese family with spinocerebellar ataxia type 10: The second report from Asia after a report from China

Hiroyuki Naito[1☯], Tetsuya Takahashi[1☯]*, Masaki Kamada[2], Hiroyuki Morino[3], Hiroyo Yoshino[4], Nobutaka Hattori[5], Hirofumi Maruyama[1], Hideshi Kawakami[3], Masayasu Matsumoto[1,6]

1 Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan, 2 Department of Neurological Intractable Disease Research, Kagawa University School of Medicine, Kagawa, Japan, 3 Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan, 4 Research Institute for Diseases of Old Age, Juntendo University School of Medicine, Tokyo, Japan, 5 Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan, 6 Japan Community Health care Organization, Hoshigaoka Medical Center, Osaka, Japan

☯ These authors contributed equally to this work.
* tetakaha@mac.com

Abstract

Spinocerebellar ataxia type 10 (SCA10) is an autosomal-dominant cerebellar ataxia that is variably accompanied by epilepsy and other neurological disorders. It is caused by an expansion of the ATTCT pentanucleotide repeat in intron 9 of the *ATXN10* gene. Until now, SCA10 was almost exclusively found in the American continents, while no cases had been identified in Japan. Here, we report the first case of an SCA10 family from Japan. The clinical manifestations in our cases were cerebellar ataxia accompanied by epilepsy, hyperreflexia and cognitive impairment. Although the primary pathology in SCA10 in humans is reportedly the loss of Purkinje cells, brain MRI revealed frontal lobe atrophy with white matter lesions. This pathology might be associated with cognitive dysfunction, indicating that the pathological process is not limited to the cerebellum. Examination of the SNPs surrounding the SCA10 locus in the proband showed the "C-expansion-G-G-C" haplotype, which is consistent with previously reported SCA10-positive individuals. This result was consistent with the findings that the SCA10 mutation may have occurred before the migration of Amerindians from East Asia to North America and the subsequent spread of their descendants throughout North and South America.

Introduction

Spinocerebellar ataxia type 10 (SCA10; OMIM#603516) is an autosomal-dominant neurodegenerative disorder presenting with ataxia, seizure and other neurological symptoms [1]. SCA10 is caused by a large expansion of a pentanucleotide ATTCT repeat in intron 9 of the *ATXN10* gene [2]. The ATTCT repeat region in SCA10 ranges from 9 to 32 repeats in the

normal population, but it may be as large as 4,500 repeats in alleles of affected persons [2,3]. The physiological function of the 55-kd ataxin-10 protein encoded by the *ATXN10* gene remains largely unknown [4].

Recent studies have shown that RNA toxicity is an underlying mechanism in diseases with repeat expansions in non-coding sequences, including such diseases as SCA8, SCA31, SCA36, Huntington disease-like 2 [5], myotonic dystrophy types 1 and 2, fragile X-associated tremor/ataxia syndrome, Fuchs endothelial corneal dystrophy [6] and amyotrophic lateral sclerosis and frontotemporal dementia *C9ORF72* expansion [7]. Similarly, the RNA-mediated gain of toxic function, but not the loss of function of ataxin-10, is considered to be a key pathogenic mechanism in SCA10 [8].

Currently, SCA10 has mainly been found in patients from American continents, and it is the second most common form of SCA in Mexico and Brazil, after SCA2 and SCA3, respectively [4]. Clinical manifestations in Mexican SCA10 families include cerebellar ataxia accompanied by epilepsy and other extracerebellar symptoms, including cognitive impairment and sensory polyneuropathy [9], while the most common phenotype in southern Brazil is pure cerebellar ataxia [10]. Haplotype analyses suggest a common ancestral origin of SCA10 in Mexican and Brazilian SCA10 families, which is generally considered to have arisen in an ancestral Amerindian population [11]. A population-based epidemiological study in Japan showed no reports of SCA10 cases [12]. However, an SCA10 family with epilepsy was recently reported in China, suggesting the possibility that the original SCA10 mutation may have occurred before the divergence of Proto-Amerindians from ancestral Asians [13]. In this report, we present the first known case of an SCA10 family from Japan, thereby proving a new clue about the geographical distribution of this disease.

Materials and methods

Ethics statement

The written informed consent used for this study was approved by the Human Subjects Committees of Hiroshima University. Blood samples were drawn, and genomic DNA was extracted from leucocytes using conventional procedures.

Family history and clinical examination

A detailed history was taken, and a clinical examination and laboratory tests were performed.

SCA10 expansion screening

DNA samples that had been digested by *Eco*RI were separated on a 0.8% agarose gel, transferred to a nitrocellulose membrane, and subsequently analyzed using Southern blotting to assess the sizes of SCA10 expansions [2]. The number of ATTCT repeats in intron 9 of the *ATXN10* gene was analyzed using polymerase chain reaction (PCR) amplification, using the primers forward (5'-GATGGCAGAATGATAAACTCAATCATGT-3') and reverse (5'-CCTGGGCAACATAGAGAGACTTCATC-3'). PCR was carried out as follows: 40ng of genomic DNA, 2.5µM of each primer, 2.5mM dNTPs, 1M BETAIN, 10X Ex Taq Burffer and Ex Taq Hot Start Version. The PCR conditions consisted of an initial denaturing at 98˚C for 2 min, 30 PCR cycles (98˚C for 10 s, 60˚C for 1 min), and additional extension at 72˚C for 7 min. Repeat-primed PCR was also conducted to verify the abnormal repeat expansion, using a forward primer (5'-GATGGCAGAATGATAAACTCAATCATGT-3'), a first reverse primer (5'-TACGCATCCCAGTTTGAGACGAGAATAGAATAGAATAGAATAGAATAGAATAGAATAGAATA GAAT-3'), and a second reverse primer (5'-TACGCATCCCAGTTTGAGACG-3'). Each PCR

product was analyzed by 3130xl Genetic Analyzer (Life Technologies, Carlsbad, CA, USA) and the repeat number was calculated using following equation: Repeat number = ((size-118)/5) x 0.998–1.5271. Southern blotting, PCR and repeat-primed PCR were performed at BML, Inc. (Saitama, Japan).

SCA10 haplotype analysis

SCA10 haplotype analysis of the proband and her mother was performed using PCR primers for single-nucleotide polymorphisms (SNPs). The PCR primers and conditions for these SNPs have been described previously [14]. The SNPs that flank the SCA10 expansion were examined in a previous study [14] and define the C (rs5764850)-expansion-G (rs72556348)-G (rs72556349)-C (rs72556350) haplotype. The PCR primers, amplification conditions and restriction fragment length polymorphisms were used as previously described [15].

Genetic-associated frontotemporal lobar degeneration analysis

For direct sequence analysis, each exon was amplified by PCR using primers for *MAPT* and *PGRN*. These PCR products were analyzed by DNA sequence as previously described [16]. We performed repeat-primed PCR as previously described to assess an expansion of the noncoding GGGGCC hexanucleotide repeat in the *C9orf72* gene [17].

Results

History and clinical examination

The family in this report originated from Shikoku Island, one of the four main islands of Japan, which is located south of Honshu and east of the island of Kyushu. All of the family members were of Japanese origin. The pedigree chart is depicted in Fig 1.

A 34-year-old Japanese woman (IV-1) presented to our hospital with progressive unsteadiness of gait. She had no significant medical history and was not taking any medications. Upon examination, she displayed horizontal nystagmus, ataxic dysarthria, mild left limb ataxia and a wide-based gait. Motor and sensory nerve functions were preserved, except for brisk tendon reflexes, and muscle tonus was normal. Blood tests, including a blood cell count, a general chemistry panel and thyroid function tests, were normal. She was initially diagnosed with hereditary cerebellar SCA because her mother also had a history of cerebellar ataxia. However, genetic testing for SCA1, SCA2, SCA3, SCA6 and DRPLA revealed no repeat expansions. Five years after her first visit, she experienced two episodes of complex partial seizures with alert mental status and automatism; they were effectively treated with levetiracetam. Brain MRI showed cerebellar atrophy (Fig 2A), and EEG showed bilateral epileptiform discharges over the frontal-parietal lobes. Seven years after the first visit, her score on the Scale for Assessment and Rating of Ataxia was 9. Additionally, neuropsychological tests (Montreal Cognitive Assessment score 28/30) showed normal cognitive function, and she had no difficulty working as a pharmacist.

The 65-year-old mother of the proband (III-3) first noticed tremor of both hands at 35 years of age, which was accompanied by gait imbalance and dysarthria. She began to have seizures accompanied by loss of consciousness at the age of 55 years. The frequency of her seizures spontaneously decreased after she reached 60 years of age. She also suffered from dysphagia, disorientation and cognitive impairment, for which she was prescribed donepezil. She is currently bedridden with an indwelling urinary catheter and has undergone gastrostomy. Her neurological examination revealed ataxic dysarthria and cognitive impairment with a preserved ability to follow simple instructions. Her physical examination revealed slow
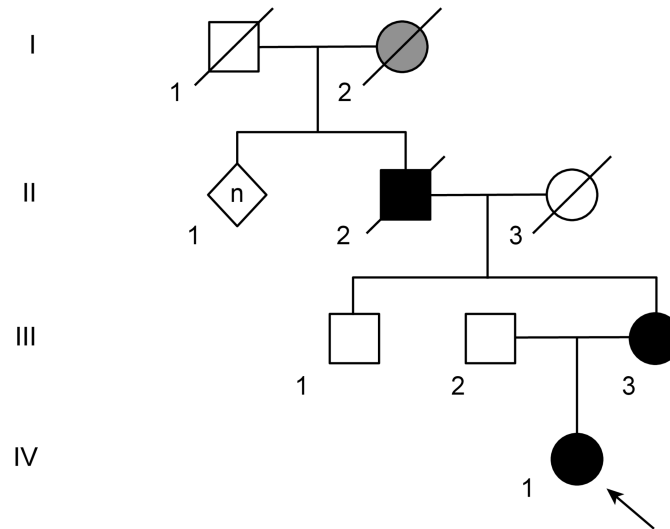
Fig 1. Pedigree chart of the Japanese spinocerebellar ataxia type 10 (SCA10) family. The proband (IV-1) and her mother (III-3) were genotyped and found to carry an expanded ATTCT region (approximately 1,500 repeats) in the SCA10 gene. Squares, males; circles, females; diamond, unknown gender; black fill, affected; gray fill, suspicious case; white fill, unaffected.

https://doi.org/10.1371/journal.pone.0177955.g001

saccades with bilateral gaze-evoked nystagmus, dysphagia and prominent limb ataxia without pyramidal or extrapyramidal signs. She was unable to sit, stand or walk even with support. In addition to cerebellar atrophy, brain MRI showed atrophy of corpus callosum and of the bilateral frontal lobes with white matter lesions (Fig 2B–2D).
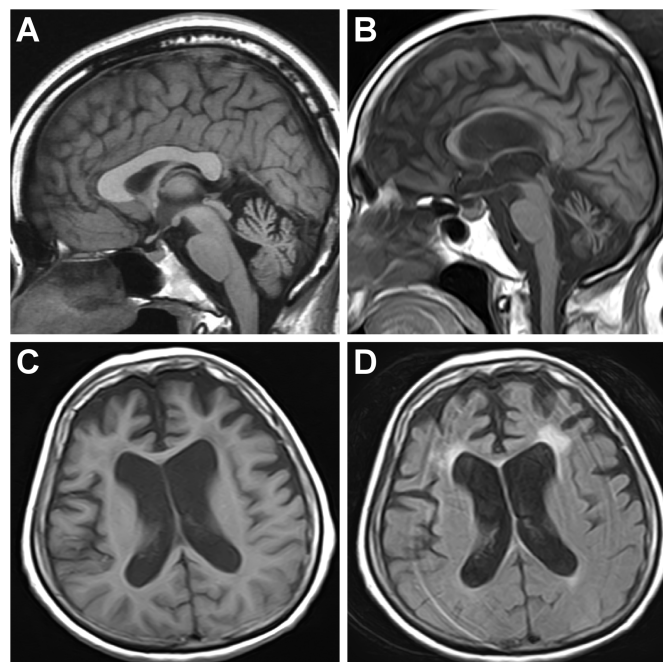
Fig 2. Brain MRI of the proband (IV-1) and her mother (III-3). T1WI sagittal brain MRI image showings cerebellar atrophy in the proband (IV-1, 39 years old) and her mother (III-3, 65 years old) (A, B). Additionally, T1WI and FLAIR axial images show frontal atrophy with white matter lesions in the mother (III-3) (C, D).

https://doi.org/10.1371/journal.pone.0177955.g002
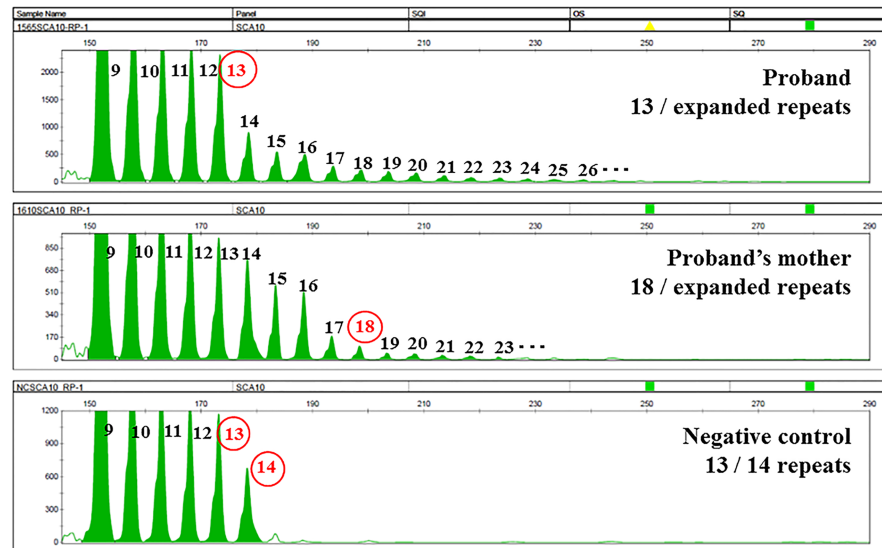
Fig 3. Fluorescent repeat-primed PCR analysis in SCA10. Fluorescent repeat-primed PCR analysis of the *ATXN10* gene revealed an expanded ATTCT pentanucleotide repeat in the proband (IV-1) and in her mother (III-3).

Genetic testing

DNA was extracted from peripheral blood leukocytes, and tests for SCA1, SCA2, SCA3, SCA6 and DRPLA were performed; all of the tests produced normal results. PCR showed a single band corresponding to 13 repeats in the proband and 18 repeats in her mother; the single bands implied that these repeat regions were either homozygous or hemizygous. Additionally, repeat-primed PCR analysis showed characteristic ladder products that were longer than 13 repeats in the proband and longer than 18 repeats in her mother (Fig 3). Southern blot analysis revealed an ATTCT repeat expansion of approximately 1,500 repeats in both cases and the expansion in the proband was only slightly larger than that of the proband's mother (Fig 4). The haplotype of the proband (IV-1) is homozygous for the C (rs5764850)-expansion-G (rs72556348)-G (rs72556349)-C (rs72556350) haplotype, which is identical to a previously described genotype [11,13,14] (Table 1). One of the haplotype of the proband's mother was also a common haplotype among SCA10 patients. The proband and her mother did not have *MAPT* and *PGRN* gene mutations, and repeat-primed PCR revealed no expanded hexanucleotide repeats in the *C9orf72* gene (S1 Fig).

Discussion

We report here the first Japanese family affected by SCA10, which is one of the increasing number of autosomal-dominant cerebellar ataxias [18]. The prevalence of different types of SCA differs substantially across the world. Machado-Joseph disease/SCA3, SCA6, SCA31 and DRPLA are reportedly common among autosomal- dominant SCA in Japan [12,19,20]. However, the relative regional frequencies of SCA also differ within Japan [20–22], likely reflecting the origin of individuals of differing ethnicities. Previous reports have indicated that approximately 10–30% of patients have an undetermined diagnosis among the relative frequencies of autosomal-dominant SCA in the Japanese population [18,19]. In nationwide investigations of
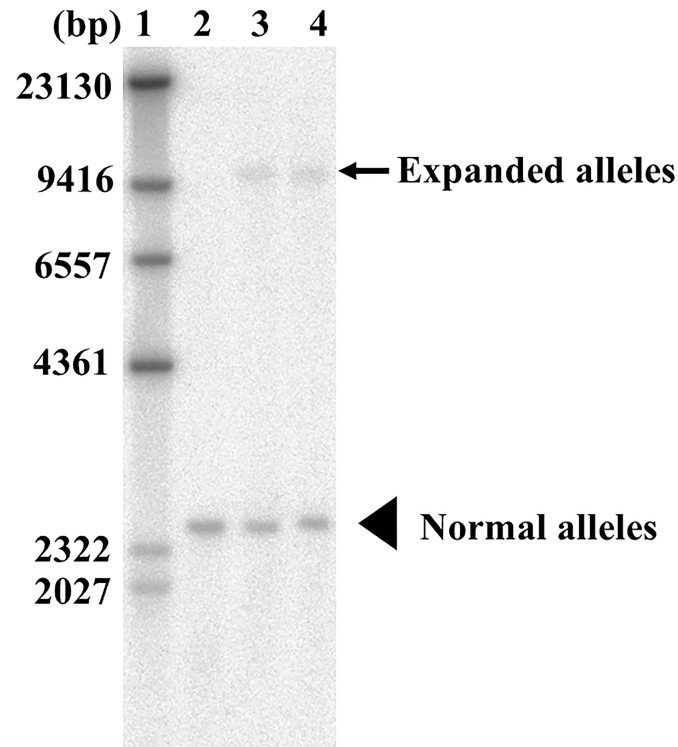
Fig 4. Southern blot analysis in SCA10. Lane 1 is a size marker, lane 2 is a negative control (13/14 repeats), and lanes 3 and 4 are DNA samples from the proband and her mother, respectively. Southern blot analysis shows an SCA10 repeat expansion of approximately 1,500 repeats in the proband (IV-1) and in her mother (III-3). The arrow shows expanded alleles and arrow head shows normal alleles.

https://doi.org/10.1371/journal.pone.0177955.g004

autosomal-dominant SCA, no cases of SCA10 were identified in France, Italy, Portugal, China, Thailand or Japan [12,23–27].

SCA10 was first identified in families originating from Mexico [2,28] and was subsequently reported in families of Brazilian origin [10]. Until recently, SCA10 has been reported primary in North and South America, but cases of SCA10 reported outside the American continents

Table 1. Haplotype analysis of single-nucleotide polymorphisms (SNPs) surrounding the SCA10 locus in the proband.

SNP ID	North American SCA10 [14]	Brazilian/Mexican SCA10 [14]	Japanese SCA10 (proband)	Japanese SCA10 (proband's mother)
rs136002	A/G	A	A	A
rs5765626	G	G	G	G
rs5764850	C/A	C	C	C/A
SCA10				
rs72556348	G	G	G	G/A
rs72556349	G	G	G	G/A
rs72556350	C	C	C	C
rs136005	C/T	C	C	C
rs9614518	A	A	A	A
rs6006808	G	G	G	G
rs11912672	A	A	A	A
rs9614781	C	C	C	C

https://doi.org/10.1371/journal.pone.0177955.t001

have occurred in Europe in an immigrant from Peru [29] and in China [13]. To date, nearly all cases of SCA10 from Latin America have been identified in individuals having Amerindian ancestry [1,9–11,14]. Mexican and Brazilian families with SCA10 originating from Latin America shared the same intragenic haplotype, suggesting that SCA10 in Latin America has a common origin from an Amerindian population [11]. The report of a patient of Sioux Indian descent from North America indicates that the SCA10 mutation may have occurred early, when the Americas were first being populated [14]. Additionally, population and genomic data suggest that Amerindians and Native American ancestors migrated from East Asia across the Bering Strait land bridge to North America and that their descendants spread throughout North and South America [30,31]. Interestingly, Wang, et al. recently reported the presence of SCA10 in China of Han descents, and the haplotype was shared by persons from North America, Mexico, and Brazil, in agreement with this hypothesis [13]. The haplotype in our case was also identical to that in previous reports [11,13,14], further supporting the hypothesis. However, we cannot exclude the possibility that the backflow of human migration from America to East Asia through the Bering Strait [32] affected SCA10. In addition, each SNPs surrounding the SCA10 locus in our patients are relatively frequent among Japanese [33]. Therefore, there is another possibility that the shared haplotype in our case might also be frequent, as previously suggested by Wang, et al [13].

Our cases have several features in common with previous reports. First, extracerebellar signs, including epileptic seizures, mild pyramidal signs and cognitive dysfunction, were present in our case family. The extracerebellar signs associated with SCA10 are epileptic seizures, pyramidal signs, polyneuropathy and cognitive and neuropsychiatric impairment [9]. As SCA10 cases in Mexican families are often associated with extracerebellar signs; the clinical presentation in our case closely resembles that of Mexican patients with SCA10. Second, anticipation in our case family was not remarkable. Southern blotting showed that the repeat size in the proband was only slightly larger than that of her mother, suggesting that repeat size is relatively stable in case of maternal transmission [34]. Third, the difference in the age of onset of epileptic seizure between the two patients in our family was approximately 20 years, though the repeat sizes were slightly different between them.

Cognitive disability is more common in SCA10 with epilepsy than in that without epilepsy [13,35,36]. Whereas overt progressive dementia is not observed, some individuals with SCA10 exhibit mild cognitive dysfunction (IQ~70) and suffer from mood disorders, including depression and aggressive behavior [9]. However, neuroradiological and pathological examinations have not revealed the causative lesions of such cognitive and neuropsychiatric impairments, at least in humans. Thus, our case is the first to show an association between an abnormality on brain MRI and cognitive dysfunction, such as the frontal lobe atrophy with white matter lesions that might be associated with cognitive dysfunction in the proband's mother. Whereas the primary pathology of SCA10 in humans is reportedly Purkinje cell loss [37], transgenic mice containing SCA10 pentanucleotide repeats showed neuronal loss in the cerebral cortex, hippocampus and pontine nuclei [38]. In addition to its expression in the brain, human ataxin-10 mRNA is expressed in a wide variety of tissues, including skeletal muscle, heart, liver and kidney [2,39]. Therefore, the changes in our case suggest that the pathological process is associated not only with the cerebellum but also with widespread regions of the brain, consistent with the presence of extracerebellar symptoms. It is possible that the cognitive impairment of the mother is due to the coincidental occurrence of dementia, as the proband did not show cognitive impairment. However, frontal lobe atrophy with white matter lesions associated with cognitive dysfunction may be a part of SCA10 pathology at a late stage of the disease. Certainly, frontal lobe atrophy with white matter lesions in our case was not reported previously in cases with SCA10. Although detailed neuropsychological examinations had not been conducted, the

age of onset and the remarkable frontal lobe atrophy indicate the possibility of comorbidity, such as frontotemporal lobar degeneration (FTLD). While two mutations in one patient are rare, such cases have been reported [40, 41]. Thus, we investigated genes associated with FTLD. As a result, repeat-primed PCR revealed no expanded hexanucleotide repeats in the *C9orf72* gene in the proband or her mother. Likewise, we disclosed that they did not have *MAPT* and *PGRN* gene mutations. However, in Asia, the prevalence of patients with sporadic FTLD is more frequent than that with familial FTLD [42]; therefore, the possibility of comorbidity with FTLD cannot be excluded.

Conclusions

Our cases represent the first report of SCA10 observed in a Japanese family. Similar to Mexican and Chinese SCA10 cases, our SCA10 patients presented with cerebellar ataxia and extra-cerebellar signs that included epilepsy and cognitive dysfunction. The presence of SCA10 in Japan is very significant with respect to the migration of the human race and suggests that we should perceive SCA10 as a differential diagnosis of autosomal dominant cerebellar ataxia in Japan, especially in cases with epilepsy.

Supporting information

S1 Fig. Fluorescent repeat-primed PCR analysis to assess *C9orf72* mutation in an SCA10 family. Fluorescent repeat-primed PCR analysis of the *C9orf72* gene revealed the presence of repeat expansion in the positive control but not in the proband (IV-1) or in her mother (III-3). (TIF)

Acknowledgments

Author Contributions

Conceptualization: TT HN.

Data curation: TT HN.

Investigation: MK H. Morino HY H. Maruyama HK.

Project administration: TT.

Supervision: TT NH.

Validation: H. Maruyama MM.

Visualization: HN.

Writing – original draft: HN.

Writing – review & editing: TT.

References

1. Ashizawa T. Spinocerebellar ataxia type 10. Handb Clin Neurol. 2012; 103: 507–519. https://doi.org/10.1016/B978-0-444-51892-7.00032-2 PMID: 21827910

2. Matsuura T, Yamagata T, Burgess DL, Rasmussen A, Grewal RP, Watase K, et al. Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nat Genet. 2000; 26: 191–194. https://doi.org/10.1038/79911 PMID: 11017075

3. Wang JL, Wu YQ, Lei LF, Shen L, Jiang H, Zhou YF, et al. [Polynucleotide repeat expansion of nine spinocerebellar ataxia subtypes and dentatorubral-pallidoluysian atrophy in healthy Chinese Han population]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2010; 27: 501–505. https://doi.org/10.3760/cma.j.issn.1003-9406.2010.05.006 PMID: 20931525

4. Lin X, Ashizawa T. Recent progress in spinocerebellar ataxia type-10 (SCA10). Cerebellum. 2005; 4: 37–42. https://doi.org/10.1080/14734220510007897 PMID: 15895557

5. Kobayashi H, Abe K, Matsuura T, Ikeda Y, Hitomi T, Akechi Y, et al. Expansion of intronic GGCCTG hexanucleotide repeat in NOP56 causes SCA36, a type of spinocerebellar ataxia accompanied by motor neuron involvement. Am J Hum Genet. 2011; 89: 121–130. https://doi.org/10.1016/j.ajhg.2011.05.015 PMID: 21683323

6. Du J, Aleff RA, Soragni E, Kalari K, Nie J, Tang X, et al. RNA toxicity and missplicing in the common eye disease Fuchs endothelial corneal dystrophy. J Biol Chem. 2015; 290: 5979–5990. https://doi.org/10.1074/jbc.M114.621607 PMID: 25593321

7. Donnelly CJ, Zhang PW, Pham JT, Haeusler AR, Heusler AR, Mistry NA, et al. RNA toxicity from the ALS/FTD C9ORF72 expansion is mitigated by antisense intervention. Neuron. 2013; 80: 415–428. https://doi.org/10.1016/j.neuron.2013.10.015 PMID: 24139042

8. White MC, Gao R, Xu W, Mandal SM, Lim JG, Hazra TK, et al. Inactivation of hnRNP K by expanded intronic AUUCU repeat induces apoptosis via translocation of PKCdelta to mitochondria in spinocerebellar ataxia 10. PLoS Genet. 2010; 6: e1000984: e10000984. https://doi.org/10.1371/journal.pgen.1000984 PMID: 20548952

9. Rasmussen A, Matsuura T, Ruano L, Yescas P, Ochoa A, Ashizawa T, et al. Clinical and genetic analysis of four Mexican families with spinocerebellar ataxia type 10. Ann Neurol. 2001; 50: 234–239. https://doi.org/10.1002/ana.1081 PMID: 11506407

10. Teive HA, Roa BB, Raskin S, Fang P, Arruda WO, Neto YC, et al. Clinical phenotype of Brazilian families with spinocerebellar ataxia 10. Neurology. 2004; 63: 1509–1512. https://doi.org/10.1212/01.WNL.0000142109.62056.57 PMID: 15505178

11. Almeida T, Alonso I, Martins S, Ramos EM, Azevedo L, Ohno K, et al. Ancestral origin of the ATTCT repeat expansion in spinocerebellar ataxia type 10 (SCA10). PLoS One. 2009; 4: e4553. https://doi.org/10.1371/journal.pone.0004553 PMID: 19234597

12. Tsuji S, Onodera O, Goto J, Nishizawa M, Study Group on Ataxic Diseases. Sporadic ataxias in Japan—a population-based epidemiological study. Cerebellum. 2008; 7: 189–197. https://doi.org/10.1007/s12311-008-0028-x PMID: 18418674

13. Wang K, McFarland KN, Liu J, Zeng D, Landrian I, Xia G, et al. Spinocerebellar ataxia type 10 in Chinese Han. Neurol Genet. 2015; 1: e26. https://doi.org/10.1212/NXG.0000000000000026 PMID: 27066563

14. Bushara K, Bower M, Liu J, McFarland KN, Landrian I, Hutter D, et al. Expansion of the spinocerebellar ataxia type 10 (SCA10) repeat in a patient with Sioux Native American ancestry. PLoS One. 2013; 8: e81342. https://doi.org/10.1371/journal.pone.0081342 PMID: 24278426

15. McFarland KN, Liu J, Landrian I, Zeng D, Raskin S, Moscovich M, et al. Repeat interruptions in spinocerebellar ataxia type 10 expansions are strongly associated with epileptic seizures. Neurogenetics. 2014; 15: 59–64. https://doi.org/10.1007/s10048-013-0385-6 PMID: 24318420

16. Ogaki K, Li Y, Takanashi M, Ishikawa K, Kobayashi T, Nonaka T, et al. Analyses of the MAPT, PGRN, and C9orf72 mutations in Japanese patients with FTLD, PSP, and CBS. Parkinsonism Relat Disord. 2013; 19:15–20. https://doi.org/10.1016/j.parkreldis.2012.06.019 PMID: 22818528

17. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011; 72: 245–256. https://doi.org/10.1016/j.neuron.2011.09.011 PMID: 21944778

18. Depondt C, Donatello S, Rai M, Wang FC, Manto M, Simonis N, et al. MME mutation in dominant spinocerebellar ataxia with neuropathy (SCA43). Neurol Genet. 2016; 2: e94. https://doi.org/10.1212/NXG.0000000000000094 PMID: 27583304

19. Nozaki H, Ikeuchi T, Kawakami A, Kimura A, Koide R, Tsuchiya M, et al. Clinical and genetic characterizations of 16q-linked autosomal dominant spinocerebellar ataxia (AD-SCA) and frequency analysis of

AD-SCA in the Japanese population. Mov Disord. 2007; 22: 857–862. https://doi.org/10.1002/mds.21443 PMID: 17357132

20. Sugihara K, Maruyama H, Morino H, Miyamoto R, Ueno H, Matsumoto M, et al. The clinical characteristics of spinocerebellar ataxia 36: a study of 2121 Japanese ataxia patients. Mov Disord. 2012; 27: 1158–1163. https://doi.org/10.1002/mds.25092 PMID: 22753339

21. Matsumura R, Futamura N, Ando N, Ueno S. Frequency of spinocerebellar ataxia mutations in the Kinki District of Japan. Acta Neurol Scand. 2003; 107: 38–41. https://doi.org/10.1034/j.1600-0404.2003.01347.x PMID: 12542511

22. Basri R, Yabe I, Soma H, Sasaki H. Spectrum and prevalence of autosomal dominant spinocerebellar ataxia in Hokkaido, the northern island of Japan: a study of 113 Japanese families. J Hum Genet. 2007; 52: 848–855. https://doi.org/10.1007/s10038-007-0182-x PMID: 17805477

23. Fujigasaki H, Tardieu S, Camuzat A, Stevanin G, LeGuern E, Matsuura T, et al. Spinocerebellar ataxia type 10 in the French population. Ann Neurol. 2002; 51: 408–409. https://doi.org/10.1002/ana.10126 PMID: 11891842

24. Brusco A, Gellera C, Cagnoli C, Saluto A, Castucci A, Michielotto C, et al. Molecular genetics of hereditary spinocerebellar ataxia: mutation analysis of spinocerebellar ataxia genes and CAG/CTG repeat expansion detection in 225 Italian families. Arch Neurol. 2004; 61: 727–733. https://doi.org/10.1001/archneur.61.5.727 PMID: 15148151

25. Vale J, Bugalho P, Silveira I, Sequeiros J, Guimarães J, Coutinho P. Autosomal dominant cerebellar ataxia: frequency analysis and clinical characterization of 45 families from Portugal. Eur J Neurol. 2010; 17: 124–128. https://doi.org/10.1111/j.1468-1331.2009.02757.x PMID: 19659750

26. Wang J, Shen L, Lei L, Xu Q, Zhou J, Liu Y, et al. Spinocerebellar ataxias in mainland China: an updated genetic analysis among a large cohort of familial and sporadic cases. Zhong NAN DA Xue Xue Bao Yi Xue Ban. 2011; 36: 482–489. PMID: 21743138

27. Choubtum L, Witoonpanich P, Hanchaiphiboolkul S, Bhidayasiri R, Jitkritsadakul O, Pongpakdee S, et al. Analysis of SCA8, SCA10, SCA12, SCA17 and SCA19 in patients with unknown spinocerebellar ataxia: a Thai multicentre study. BMC Neurol. 2015; 15: 166. https://doi.org/10.1186/s12883-015-0425-y PMID: 26374734

28. Matsuura T, Achari M, Khajavi M, Bachinski LL, Zoghbi HY, Ashizawa T. Mapping of the gene for a novel spinocerebellar ataxia with pure cerebellar signs and epilepsy. Ann Neurol. 1999; 45: 407–411. https://doi.org/10.1002/1531-8249(199903)45:3<407::AID-ANA21>3.0.CO;2-D PMID: 10072060

29. Leonardi L, Marcotulli C, McFarland KN, Tessa A, DiFabio R, Santorelli FM, et al. Spinocerebellar ataxia type 10 in Peru: the missing link in the Amerindian origin of the disease. J Neurol. 2014; 261: 1691–1694. https://doi.org/10.1007/s00415-014-7394-8 PMID: 24935856

30. Kitchen A, Miyamoto MM, Mulligan CJ. A three-stage colonization model for the peopling of the Americas. PLoS One. 2008; 3: e1596. https://doi.org/10.1371/journal.pone.0001596 PMID: 18270583

31. Reich D, Patterson N, Campbell D, Tandon A, Mazieres S, Ray N, et al. Reconstructing Native American population history. Nature. 2012; 488: 370–374. https://doi.org/10.1038/nature11258 PMID: 22801491

32. Mulligan CJ, Kitchen A, Miyamoto MM. Updated three-stage model for the peopling of the Americas. PLoS One. 2008; 3: e3199. https://doi.org/10.1371/journal.pone.0003199 PMID: 18797500

33. Ensemble Genome Broweser. http://grch37.ensembl.org/index.html

34. McFarland KN, Liu J, Landrian I, Gao R, Sarkar PS, Raskin S, et al. Paradoxical effects of repeat interruptions on spinocerebellar ataxia type 10 expansions and repeat instability. Eur J Hum Genet. 2013; 21: 1272–1276. https://doi.org/10.1038/ejhg.2013.32 PMID: 23443018

35. Grewal RP, Achari M, Matsuura T, Durazo A, Tayag E, Zu L, et al. Clinical features and ATTCT repeat expansion in spinocerebellar ataxia type 10. Arch Neurol. 2002; 59: 1285–1290. https://doi.org/10.1001/archneur.59.8.1285 PMID: 12164725

36. Teive HA, Munhoz RP, Arruda WO, Lopes-Cendes I, Raskin S, Werneck LC, et al. Spinocerebellar ataxias: genotype-phenotype correlations in 104 Brazilian families. Clinics (Sao Paulo). 2012; 67: 443–449. PMID: 22666787

37. Xia G, McFarland KN, Wang K, Sarkar PS, Yachnis AT, Ashizawa T. Purkinje cell loss is the major brain pathology of spinocerebellar ataxia type 10. J Neurol Neurosurg Psychiatry. 2013; 84: 1409–1411. https://doi.org/10.1136/jnnp-2013-305080 PMID: 23813740

38. White M, Xia G, Gao R, Wakamiya M, Sarkar PS, McFarland K, et al. Transgenic mice with SCA10 pentanucleotide repeats show motor phenotype and susceptibility to seizure: a toxic RNA gain-of-function model. J Neurosci Res. 2012; 90: 706–714. https://doi.org/10.1002/jnr.22786 PMID: 22065565

39. The human protein atlas. http://www.proteinatlas.org/ENSG00000130638-ATXN10/tissue.

40. Kapur SS, Goldman JG. Two in one: report of a patient with spinocerebellar ataxia types 2 and 10. Arch Neurol. 2012; 69: 1200–1203. https://doi.org/10.1001/archneurol.2011.3044 PMID: 22964913

41. Roxburgh RH, Smith CO, Lim JG, Bachman DF, Byrd E, Bird TD. The unique co-occurrence of spinocerebellar ataxia type 10 (SCA10) and Huntington disease. J Neurol Sci. 2013; 324: 176–178. https://doi.org/10.1016/j.jns.2012.09.030 PMID: 23083689

42. Ng AS. Genetics of frontotemporal dementia in Asia: Advancing knowledge through collaboration. Neurology. 2015; 85:2060–2062. https://doi.org/10.1212/WNL.0000000000002045 PMID: 26432849