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Letter to the Editor

Identification of 35 CAG repeats within ATXN1 as the probable shortest pathogenic allele for spinalcerebellar ataxia type 1

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Dear Editor,

Among ataxias, spinocerebellar ataxia (SCA) is a major type and is comprised of a group of autosomal dominant hereditary disorders characterized primarily by cerebellar and afferent degeneration of the cerebellum and its afferent pathways, inducing dysfunction of motor coordination [1]. Development of molecular genetics has enabled identification of the genotype of these diseases in recent years, and > 30 subtypes have been isolated, of which the most common type is the SCA3/MJD [1,2]. The pathogenesis of SCA1 is linked to the repeated glutamine-encoding sequence CAG, which leads to the prolongation of the polyglutamine chain of the encoded protein, thus resulting in abnormal protein metabolism and ultimately apoptosis [1,2]. The SCA1 gene is located on the autosomal chromosome 6q22–23, and contains nine exons, with a CAG mutation in exon 8 [5]. In completely penetrant SCA1, the amplification in CAG repeats is > 45, whereas that in the normal CAG repeats is < 35 [7]. In Chinese Han SCA1 patients, the number of CAG repeats varies from 39 to 60 [5]. SCA1 patients over the age of 20–40 years at the time of disease onset display the fllowing signs: pathological changes of the cerebellum, brain stem neuron loss, and damage to the spinocerebellar tract and posterior cable, and to a lesser degree, involvement of substantia nigra, basal ganglia, and spinal cord anterior horn cells [1]. Clinical manifestations include cerebellar ataxia, dysarthria, extraocular muscle paralysis, pyramidal tract signs, dementia, hyperopia, tendon hyperreflexia, positive pathological signs, and optic atrophy [5].

In the current study,17 subjects from a families in the West China Hospital of Sichuan University from. All patients have an autosomal dominant inheritance pattern that meets Harding's diagnostic criteria [4]. Mutation screening for sca2, sca3, sca6, sca7, sca8, sca12, and sca17 was negative for all participants. This study was carried out in accordance with the recommendations of West China hospital ethics Committee. The protocol was approved by the West China hospital ethics Committee, the approval number is 2018(77). All subjects gave written informed consent in accordance with the Declaration of Helsinki, this study strictly complies with the principle of voluntary and informed patients, and obtained the voluntary and informed right of participants or their immediate family members if patients did not have self-awareness.

The proband's parents, who have died, were cousins among the same generation of blood relatives within three generations. The incidence among the third generation of pedigrees was less than that among the second generation, and the age of disease onset showed an earlier trend with more severe clinical symptoms and rapid progress, as well as the presence of the premature inheritance phenomenon. These results are in accordance with the characteristics of SCA1 autosomal dominant inheritance. Proximal II4, age 64 with a disease onset of 41, was admitted to the hospital due to unstable walking for 20 + years, aggravated with vomiting for 5 years, but without extraocular muscle paralysis, cognitive impairment, or peripheral nerve damage. Examination of the nervous system revealed the patient was conscious and could answer the questions without significant abnormalities. in advanced neurological function. Dysarthria, no obvious abnormalities were observed in other cranial nerve examination. Limb muscle strength and muscle tone were normal, and the limbs tendon reflex symmetry was active. The left lower Babinsky a positive sign, the right lower Babinsky a negative sign, and the meningeal irritation sign was negative. There was a wide basement gait, Finger- nose tests and lower extremities knee-tibia tests results were positive. And the Rhomberg's test, with the tandem experiment can not be completed. Results from the cranial cervical MRI showed atrophy of the cerebellum and spinal cord. In family II1, II3, III1, III2 the clinical manifestations and proband were similar, all with ataxia, dysarthria, and progressive aggravation of the condition, in which II1 has been bed-bound staged, but II3, III1, III2 were still able to walk. There were 35 CAG repeats measured in II1, II4, III1, III2, III7, IV1, and IV6 of the pedigrees, and there were < 35 ATXN1 gene CAG repeats in III3, III7 and III6 (Table 1).

Autosomal dominant spinocerebellar ataxias (spinocerebellar ataxias, SCA) are a group of neurodegenerative diseases in adults, in which cerebellar ataxia is the main manifestation [6]. With the progress of molecular genetics, the concept of SCA genotyping has been introduced on the basis of Harding clinical classification [4]. SCA1 was caused by abnormal amplification of the CAG trinucleotide sequence of exon 8 of the ATXN1 gene located at 6p23 [5,7,8]. We collected information on an SCA pedigree from Sichuan, China. The main clinical manifestations were unstable walking with vague language, cranial MRI manifestations of cerebellar atrophy, and, excluding the known sca2, sca3, sca6, sca7, sca8, Sca12, and sca17 trinucleotide abnormal repeat mutations, amplification of the ATXN1 gene CAG repeat 35. According to previous studies, the number of SCA1 gene repeats can range from 39

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Table 1
Clinical manifestations and characteristics of all patients in family.

	II1	II3	II4	III1	III2
Gender	Female	Female	Male	Female	Female
Age(year)	75	72	64	52	48
Age of onset(year)	50	51	41	41	40
CAG repeat	29/35	Unclear	29/35	27/35	27/35
Dysarthria	Yes	Yes	Yes	Yes	Yes
Choking	Yes	Yes	Yes	Yes	Yes
Ataxia	Yes	Yes	Yes	Yes	Yes
Hyper-reflexia	Yes	Yes	Yes	Yes	Yes
Nystagmus	No	No	No	No	No
Exophthalmos	No	No	No	No	No
Ophthalmoplegia	No	No	No	No	No
Muscular tone	Normal	Normal	Normal	Normal	Normal

to 60 times [3], and here, the family showed typical SCA1 symptoms, and abnormal amplification of the ATXN1 gene of only 35, a finding that was closely related to the clinical manifestations of the patients, indicating the presence of a pathological mutation. Based on our research, we draw the conclusion that 35 CAG repeats of ATXN1 may be the shortest pathogenic allele of SCA1. Due to the low prevalence and the rarity of SCA1, the number of CAGs amplified in ATXN1 is only scored in a minority of cases, and the reason for the low threshold for CAG repeat of SCA1 remains to be determined. The findings of this study further confirms the low threshold of SCA1 and gene data. Therefore, this study enrolled a Chinese SCA1 pedigrees and identified 35 CAG repeats within the ATXN1 gene, which may be the shortest pathogenic allele of SCA1.

References

[1] P. Pazarci, H. Kasap, A.F. Koç, S. Altunbaşak, M.A. Erkoç, Mutation analysis of 6 spinocerebellar ataxia (SCA) types in patients from southern Turkey, Turk J Med Sci 45 (2015) 1228–1233, https://doi.org/10.3906/sag-1402-101.

[2] H. Tsoi, A.C. Yu, Z.S. Chen, et al., A novel missense mutation in CCDC88C activates the JNK pathway and causes a dominant formof spinocerebellar ataxia, J Med Genet 51 (9) (2014) 590–595, https://doi.org/10.1136/jmedgenet-2014-102333.

[3] J.L. Wang, Q. Xu, L.F. Lei, et al., Studies on the CAG repeat expansion in patients with hereditary spinocerebellar ataxia from Chinese Han, Chin J Med Genet 26 (6) (2009) 620–625.

[4] A.E. Harding, Clinical features and classification of inherited ataxias, Adv. Neurol. 61 (1993) 1e14.

[5] Q.Y. Xie, X.L. Liang, X.H. Li, Frequency of different subtype of spinocerebellar ataxia in Hans of South China, Chin J Lab Med 27 (9) (2004) 555–557, https://doi.org/10.3760/j:issn:1009-9158.

[6] H.A. Teive, R.P. Munhoz, W.O. Arruda, et al., Spinocerebellar ataxias: genotype-phenotype correlations in 104 Brazilian families, Clin- ics(Sao Paulo) 67 (2012) 443–449.

[7] W.Y. Lee, D.K. Jin, M.R. Oh, et al., Frequency analysis and clinical characterization of spinocerebellar ataxia types 1,2,3,6,and 7 in Korean patients, Arch. Neurol. 60 (2003) 858–863.

[8] M. Obayashi, G. Stevanin, M. Synofzik, et al., Spinocerebellar ataxia type 36 exists in diverse populations and can be caused by a short hexanucleotide GGCCTG repeat expansion, J Neurol Neurosurg Psychiatry 86 (9) (2015) 986–995.

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