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Spinocerebellar ataxia type 27 (SCA27) is an uncommon cause of dominant ataxia among Chinese Han population

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HIGHLIGHTS

- Mutations in *FGF14* gene were screened in 67 unrelated Chinese Han probands with ADCA by DHPLC and DNA direct sequencing.
- We found a pair of siblings carried the same heterozygous variation (c.-10delC) characterized by different clinical features.
- A probable novel insertion/deletion (I/D) polymorphism (c.-10delC) was found.
- It suggests that SCA27 is a rare subtype in China.

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ABSTRACT

Autosomal dominant cerebellar ataxias (ADCAs), genetically classified into spinocerebellar ataxias (SCAs), are a highly heterogeneous group of neurodegenerative disorders. Recently, mutations in the fibroblast growth factor 14 gene (*FGF14*) have been reported to cause SCA27 subtype. To evaluate the frequency of *FGF14* mutations in mainland of China, we performed molecular genetic analysis in 67 unrelated familial ataxia cases and 500 normal controls by denaturing high-performance liquid chromatography (DHPLC) and DNA direct sequencing.Interestingly, we found a pair of siblings carried the same heterozygous variation (c.-10delC) characterized by different clinical features, which is probably a novel insertion/deletion (I/D) polymorphism in the 5′UTR region of the exon 1b. It suggests that SCA27 is a rare subtype in China.

1. Introduction

Autosomal dominant cerebellar ataxias (ADCAs), genetically classified into spinocerebellar ataxias (SCAs), are a group of high heterogeneous neurodegenerative disorders characterized by progressive cerebellar symptoms of imbalance, progressive gait and limb ataxia, and dysarthria [3,6]. Till now, 33 distinct genetic subtypes have been defined, and 19 seemingly unrelated disease genes have been identified (http://neuromuscular.wustl.edu/ataxia/domatax.html). The disease is caused by trinucleotide or polynucleotide repeat expansions within the coding region or non-coding region of the corresponding gene (SCA1, 2, 3, 6, 7, 8, 10, 12, 17, 31, 36 and dentatorubral-pallidoluysian atrophy [DRPLA]), and non-repeat mutations (SCA types 5, 11, 13, 14, 15/16/29, 23, 27, 28, 35), with the heterogeneity of the pathogenic mechanisms leading to cerebellar degeneration and ataxia [12].

Among nine SCA causative genes involved in non-repeat mutations, *FGF14* is responsible for SCA27, which encodes a member of a subclass of fibroblast growth factors (FGF), and was reported to be expressed in developing and adult central nervous system [7]. The *FGF14* gene is located at chromosome 13q34 and composed of five exons, including alternatively spliced transcript variants differing in exon1 [11]. In 2003, van Swieten described a large three-generation Dutch family with a novel form of early-onset tremor, dyskinesia and slowly progressive cerebellar ataxia (assigned as SCA27) (OMIM ID: 609307), associated with a novel mutation of the *FGF14* gene [10]. Till now, only a heterozygous mutation (F145S mutation) and a frameshift mutation (p.Asp163fsX12) in the *FGF14* gene have been reported in Dutch and Germany, while no other pathogenic DNA variations were identified worldwide [2,8,10,14].

To further define the frequency of *FGF14* mutations in Chinese mainland patients, we examined the coding region of *FGF14* in 67 unrelated probands with familial history diagnosed as ADCA by means of DHPLC and DNA direct sequencing.

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2. Materials and methods

2.1. Subjects

67 unrelated affected individuals with ADCA enrolled from the outpatient neurology clinics of Xiangya Hospital, Central South University from January 1995 to March 2011, were previously excluded for mutations on SCA1, 2, 3, 6, 7, 8, 10, 12, 17, 35 and DRPLA gene. The clinical diagnosis of SCA was made based on the criteria proposed by Harding [4]. The subjects consisted of 39 men and 28 women, for which the clinical data could be procured as follows: mean age: 39.08 ± 14.14 years (range 12–71 years); mean age at onset of the first neurological symptoms related to ataxia: 34.17 ± 13.66 years (range 12–69 years); mean course: 4.61 ± 5.54 (range 4 months–40 years). A total of 500 healthy Chinese individuals were recruited as a control group. Informed consent was obtained from all patients and controls for participation in the study.

2.2. Methods

Genomic DNA was extracted from peripheral blood leukocytes by standard extraction methods. All exons (1a, 1b, 2, 3, 4 and 5) of *FGF14* were amplified via primer and conditions published before [10]. PCR product screening was performed using a DHPLC method (WAVE DNA fragment analysis system, Transgenomic). Each PCR sample of the patients was mixed with normal control identified by direct sequencing. The mixture were denatured at 95 °C for 5 min and gradually re-annealed to 25 °C before DHPLC analysis. Two different melting temperatures were chosen by WaveMaker software for each PCR fragment in the process of DHPLC analysis (64.1 and 66.1 °C for exon 1a; 56.5 and 57.5 °C for exon 1b; 54.2 and 55.2 °C for exon 2; 54.6 and 55.6 °C for exon 3; 55.0 and 56.0 °C for exon 4; 58.4 and 59.4 °C for exon 5). Samples revealing abnormal peaks were sequenced directly.

3. Results

Mutations in *FGF14* were screened in 67 unrelated Chinese Han patients who were clinically diagnosed as ADCA. A deletion variation (c.-10delC) in the 5′UTR region of the exon 1b was found in one proband using DHPLC analysis and direct sequencing. The

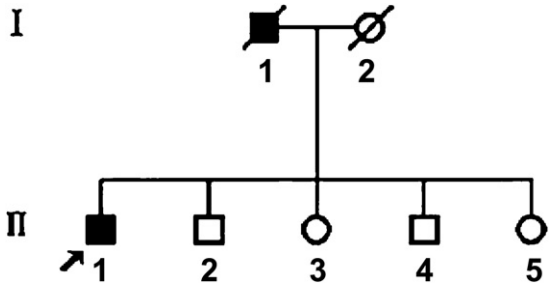

Fig. 1. Partial pedigree structure of the Chinese family M0696. Open symbols indicate unaffected family members; filled symbols represent affected subjects; the arrow indicates the proband. Deceased subjects are marked by a diagonal line.

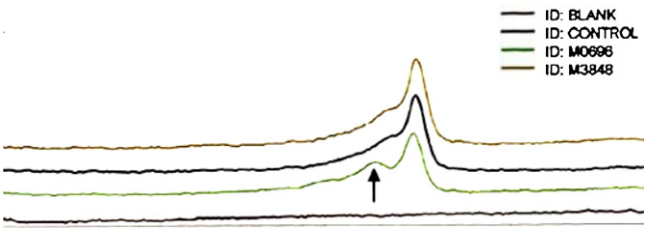

Fig. 2. The arrow indicates abnormal peak of the sample owing to the c.-10delC variation of the proband (II-1, M0696).

sample of the patient showed an abnormal elution profile, with the further evidence supported by DNA sequencing (Figs. 1–3). In the two-generations family, the proband(II-1) was a 61-year-old male suffered from progressive gait unsteadiness accompanied by increasing muscle weakness in the upper limbs since 38 years old and presented with limb paralysis 23 years later with remarkable cerebellar symptoms. Upon neurological examination at age 61, he showed severe speech disturbance, dysarthria, oculomotor disorders and mental retardation, with muscle atrophy in thenars observed. Also, tendon hyperreflexia and Babinski's sign were found. The International Ataxia Cooperative Rating Scale (ICARS), Scale for the Assessment and Rating of Ataxia (SARA) and Mini-Mental State Examination (MMSE) were 90, 39 and 18 respectively. The MRI of the brain indicated the moderate and mild atrophy in the cerebellum. Moreover, his father(I-1), 50 years old at onset,

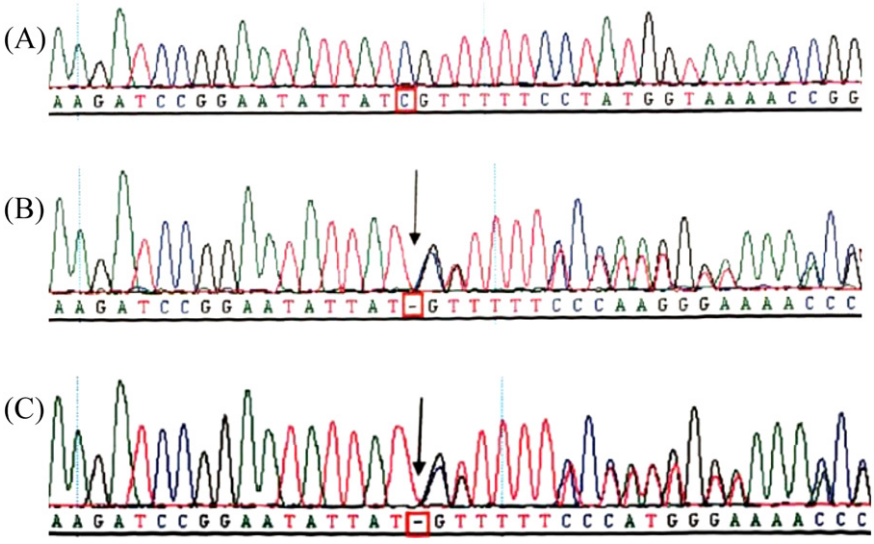

Fig. 3. Sequence chromatograms show the mutation detected in the 5′UTR region of the exton 1b of FGF14 gene. Both normal (A) and mutated (B: II-1, C: II-2) DNA sequences are shown. The arrows indicate the heterozygous c.-10delC variation in the proband(II-1) and his brother(II-2).