Clinical Case Report

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A case of a novel *CACNA1G* mutation from a Chinese family with SCA42

A case report and literature review

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Abstract

Rationale: Spinocerebellar ataxia (SCA), a genetically inherited heterogeneous disorder, is characterized by gait ataxia, dysarthria, parkinsonism, choreic movements, dystonia, epilepsy, cognitive and psychiatric symptoms. Spinocerebellar ataxia-42 (SCA42), caused by heterozygous mutation in the calcium channel 1G (*CACNA1G*) gene, is a rare SCA subtype and the transmission pattern is autosomal dominant inheritance.

Patient concerns: We presented a novel mutation (c.4721T>A; p.Met1574Lys) in 3 patients from a Chinese family using whole-exome sequencing. All patients exhibited cerebellar ataxia and the clinical manifestations were similar to those that were previously reported in the French and Japanese families. In addition, cerebral magnetic resonance imaging (MRI) showed cerebellar atrophy, and the hot cross bun sign of brainstem was found in the proband and her sister.

Diagnoses: The clinical features and MRI findings indicated the diagnosis of SCA. Taken together, the symptoms, MRI findings, as well as whole-exome sequencing made the diagnosis of SCA42 most likely candidate.

Interventions and outcomes: The patient was treated with cobamamide (1.5 mg once daily) for nerve nutrition and further physical therapy. At the 4-month follow-up visit, the patient's condition did not improve obviously.

Lessons: Recently, a missense mutation in *CACNA1G* gene (c.5144G4A; p.Arg1715His) was identified in French and Japanese families with SCA42. However, there has been no report of SCA42 or its mutant loci in Chinese patients. Our finding showed a novel mutation in *CACNA1G* gene and provided important insights into the pathogenesis of SCA42.

Abbreviations: *CACNA1G* = calcium channel 1G, MRI = magnetic resonance imaging, SCA = spinocerebellar ataxia, SCA42 = spinocerebellar ataxia-42.

Keywords: *CACNA1G*, cerebellar atrophy, hot cross bun sign, SCA42, spinocerebellar ataxia

1. Introduction

Spinocerebellar ataxia (SCA) represents a heterogeneous group of genetically inherited neurodegenerative disorders that affect the cerebellum, brainstem, and spinal cord. Its clinical manifestations are progressive cerebellar ataxia, nystagmus, dysarthria, dementia, intention tremor, abnormal muscle tone, and peripheral neuropathy.[1] Spinocerebellar ataxia-42 (SCA42), caused by the calcium channel 1G (*CACNA1G*) gene, is thought to be an autosomal dominant SCA subtype.[2]*CACNA1G* is located on chromosome 17q21 and encodes the amino acid in the voltage sensor S4 segment of the Type channel protein Cav3.1, which is highly expressed in the molecular layer of the cerebellum.[3] A heterozygous missense mutation in the *CACNA1G* gene (c.5144G4A; p.Arg1715His) was concurrently reported in French and Japanese families with SCA42.[4,5] To date, there has been no report of SCA42 or its mutant loci in Chinese patients. In this study, we presented a novel mutation (c.4721T>A; p.Met1574Lys) in 3 patients from a Chinese family using whole-exome sequencing.

2. Case report

A 45-year-old Han Chinese female with a white-collar job (IV-3) was referred to our hospital due to aprogressive gait abnormality over the past 2 years and dysarthria for 5 months. No apparent cause was observed at the time of symptom onset. Interestingly, it was noticed that the patient's father (III-4) and sister (IV-2) also showed symptoms of gait abnormality. There was no indication of consanguineous marriage between the patient's parents. The detailed physical examination of this patient revealed that she had dysarthria, hypomyotonia, slight hyporeflexia, and ataxia

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XL, CZ, and LC contributed equally to this work.

Informed consent: XL and SF had received consent from the patient whose case is reported.

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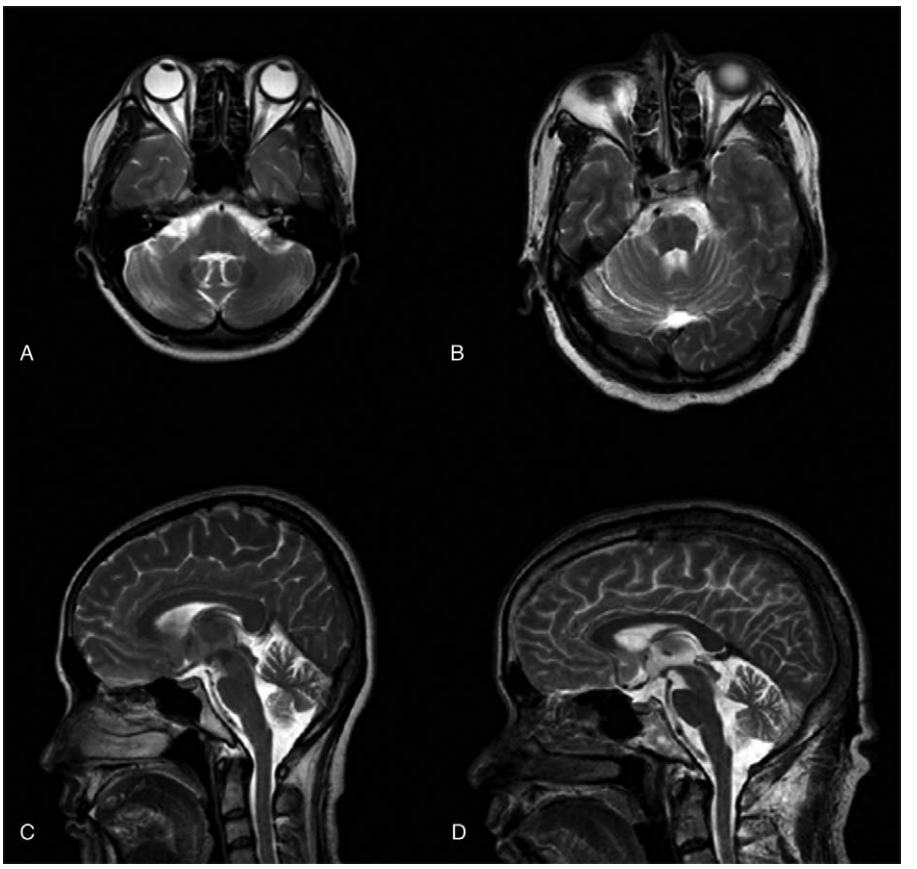

Figure 1. Magnetic resonance imaging (MRI) scans of the brain. Panels (A) and (C) show T2-weighted MRI of the patient (IV-3) brain, panel (B) shows T2-weighted MRI of the patient's sister (IV-2), while panel (D) represents the T2-weighted MRI of the patient's father (III-4).

abnormality in both of her lower limbs. She was unable to walk in a straight line, but her muscle power and sensorium of the limbs were normal. Also, no deficits in superficial or deep sensation, gaze nystagmus, or Babinski and Chaddock signs were observed. Furthermore, cerebral magnetic resonance imaging (MRI) indicated cerebellar atrophy and the hot cross bun sign in the brainstem, as shown in Figure 1. The pedigree analysis of the complete family is shown in Figure 2.

The clinical presentations, examinations of relatives, and MRI findings made the diagnosis of SCA most likely candidate.

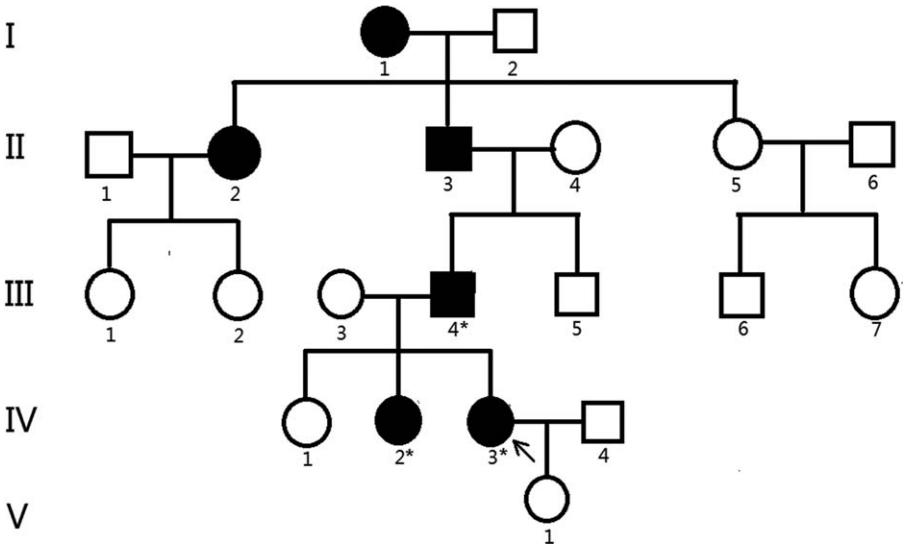

Figure 2. Pedigree analysis of the patient's family. Black circles (female) and squares (male) indicate family members affected with the disease, while open circles or squares indicate unaffected members. Asterisks indicate the patients used for exome sequencing. Arrows indicate the proband. MRI = magnetic resonance imaging.

Subsequently, we conducted exome sequencing analysis to confirm the diagnosis and clarify the subtypes of this disorder. The same heterozygous missense mutation (c.4721T>A; p. Met1574Lys) was observed in affected 3 family members, as shown in Figure 3. All 3 family members (III-4, IV-2, and IV-3) displayed progressive ataxia abnormality and mild-to moderate speaking difficulty. The detailed clinical manifestations were summarized in Table 1. Cerebral MRI showed cerebellar atrophy in the patient (IV-3), the patient's sister (IV-2) and their father (III-4), and the hot cross bun sign of brainstem was only observed in the patient (IV-3) and the patient's sister (IV-2).

Based on clinical symptoms, MRI findings, and whole-exome sequencing, the case was diagnosed with SCA42. The patient was treated with cobamamide (1.5 mg once daily) for nerve nutrition and further physical therapy. At the 4-month follow-up visit, the patient's condition did not improve obviously.

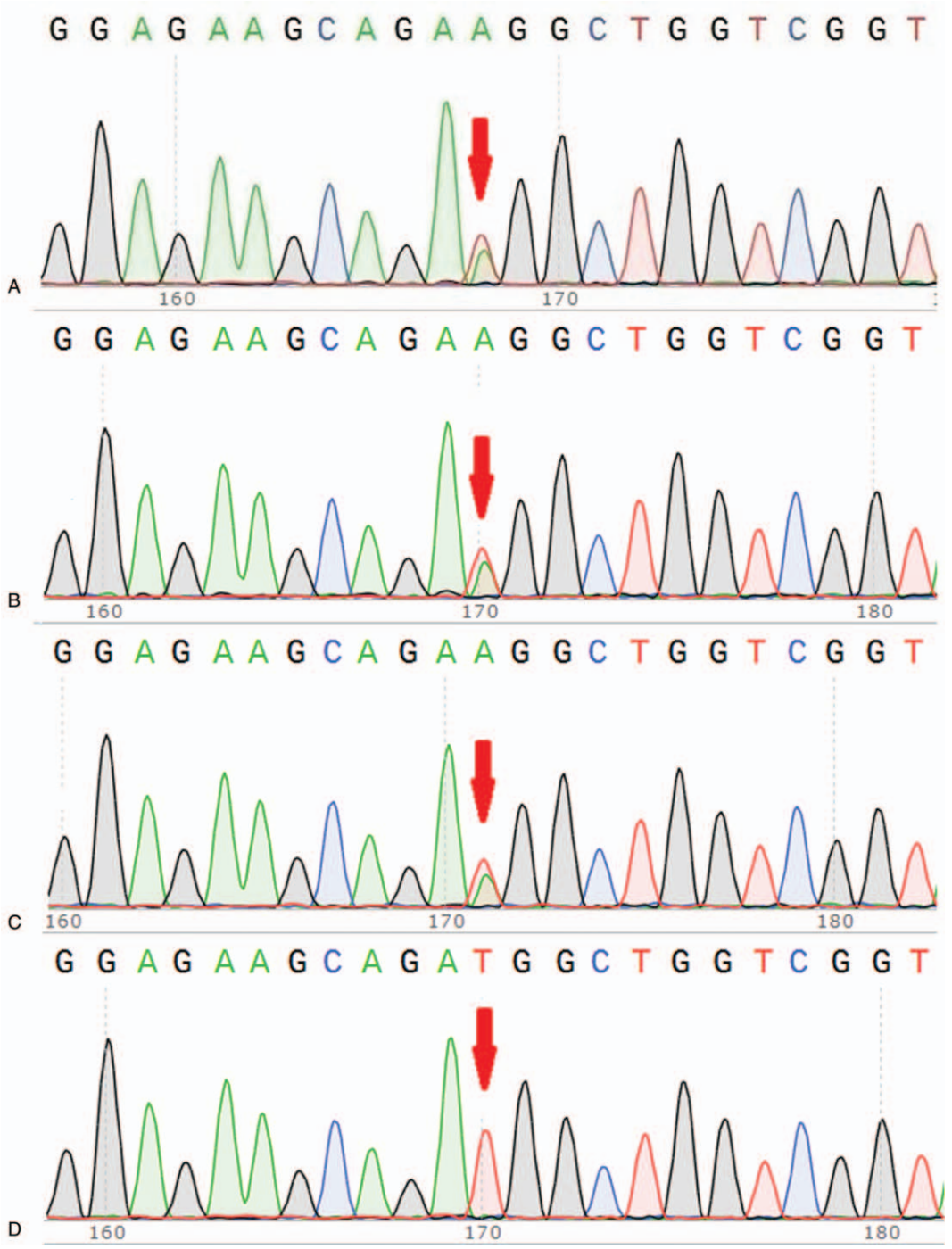

Figure 3. Sequencing analysis of the *CACNA1G* gene locus. Panel (A) shows the genetic profile of the patient (IV-3). Panel (B) represents the genetic profile of the patient's father (III-4), while panel (C) corresponds to the genetic profile of the patient's sister (IV-2). Panel (D) depicts the genetic profile of a family member not affected with the disease (IV-1).

Table 1

Clinical characteristics of the patient and the affected family members.

Clinical characteristics	III-4	IV-2	IV-3
Age at examination, years	70	48	45
Age at onset, years	60	46	43
Disease duration	18	2	2
Gait instability	+	+	++
Nystagmus	–	–	–
Dysarthria	+	+	++
Ataxia of upper limb	–	+	–
Ataxia of lower limb	+	+	++
Reflexes of upper limb	Normal	Hyporeflexia	Hyperreflexia
Reflexes of lower limb	Normal	Hyporeflexia	Hyperreflexia
Muscle tone	Normal	Normal	Normal
Resting tremor	–	–	–
Cognitive impairment	–	–	–
Epilepsy	–	–	–
Cerebral MRI	Cerebellar atrophy	Cerebellar atrophy and hot cross bun sign	Cerebellar atrophy and hot cross bun sign
Other signs	None	None	None

MRI = magnetic resonance imaging.

3. Discussion

SCA42, a rare autosomal dominantly inherited SCA subtype,[6] was caused by mutation in *CACNA1G* on chromosome 17q21, which encoded the T-type calcium channel Cav3.1. Cav3.1 is classified as a low-threshold voltage-dependent calcium channel protein and is widely expressed in the brain, especially the molecular layer of the cerebellum and inferior olive nucleus.[7] Cav3.1 plays a predominant role in the regulation of membrane potential and in the modulation of calcium signaling pathways. The mutation in the *CACNA1G* gene induced the amino acid change in the voltage sensor S4 segment of domain IV in Cav3.1 and thus affected the activation and inactivation of Cav3.1. Then, the mutant Cav3.1 resulted in decreased neuronal excitability in deep cerebellar nuclei neurons. Taken together, *CACNA1G* is regarded as a causative gene.

To our best knowledge, the mutation in *CACNA1G* gene was first identified from 3 unrelated French families in Coutelier et al's[5] study and the patients with SCA harbored the missense mutation (c.5144G>A; p.Arg1715His). Subsequently, Morino et al[4] presented the same mutation in *CACNA1G* gene from 2 unrelated Japanese families with slowly progressive SCA. We summarized the main characteristics of the French and Japanese families (Table 2). The age at symptom onset was highly variable and the most common manifestation was gait instability. It should be noted that the symptoms caused by the same mutation were somewhat different between the families. It may be explained by the fact that *CACNA1G* gene was independently

Table 2

Clinical characteristics of Japanese and French families with SCA42.

	Japanese		French		
Clinical characteristics	Family 1	Family 2	AAD-SAL-233 AAD-SAL-454		AAD-GRE-319
Total members	29	7	44	11	8
Examined members	11	7	6	3	1
Age at onset, years	20–70	18–57	9–78	9–78	9–78
Gait instability	NA	NA	9*		
Transient diplopia	NA	NA	7*		
Nystagmus	NA	NA	NA		
Cognitive impairment	—	—	2*		
Epilepsy	—	—	NA		
Muscle atrophy	—	—	NA		
Involuntary movement	—	—	NA		
Resting tremor	—	2	N A		
Cerebral MRI	—	(III-1) Cerebellar atrophy	Vermian atrophy Vermian atrophy and white matter hypersignals cerebellar and brainstem hypoplasia and atrophy		
Pyramidal signs	NA	NA	5*		
Depression	NA	NA	3*		
Babinski sign	NA	NA	1*		

MRI = magnetic resonance imaging, NA = not applicable, SCA42 = spinocerebellar ataxia-42.

— negative.

* Number of the total members that received examination.

identified in the different races. Further studies are warranted to clarify the clinical characteristics of the *CACNA1G*-dependent SCA42 in more detail.

To date, c.5144G>A was the only reported missense mutation of *CACNA1G* using whole-exome sequencing. To identify other causative mutations in *CACNA1G*, we searched OMIM and HGMD databases, and the results indicated that SCA42 was possible to present in other mutant loci. We identified a novel mutation (c.4721T>A; p.Met1574Lys) in 3 patients with SCA from a Chinese family using whole-exome sequencing.

In the current study, the age at onset ranged from 43 to 60 years and all patients exhibited the pure form of cerebellar ataxia including gait abnormality and dysarthria. However, nystagmus was not observed. In neuroimaging, in addition to cerebellar atrophy, the hot cross bun sign of brainstem was observed in the proband and her sister, which was of particular interest to us. It was reported that the hot cross bun sign was observed in SCA1,[8] 2, 3, 7, 8,[9,10] 23,[11] and 34.[12] However, further epidemiological studies are needed to determine the prevalence of this sign in SCA42.

Currently, there are not effective therapies for SCA patients. Since the progression of the disorder is relatively slow, symptomatic treatment may contribute some to delaying further progression and improving the overall quality of life in patients. However, development of novel therapeutic approaches must be seriously considered.

In conclusion, our finding showed a novel mutation in *CACNA1G* gene and provided important insights into the pathogenesis of SCA42. However, further electrophysiologic studies are warranted to be conducted to support the mutant site.

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Author contributions

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Visualization: Chunkui Zhou, Chenglin Wang.
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