Neuroendocrinology Letters Volume 42 No. 4 2021
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Paroxysmal limbs jitter accompanied by different imaging findings in a Chinese family with spinocerebellar ataxia 40: Clinical and neuroimaging studies

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Submitted: 2020-11-10 Accepted: 2021-06-10 Published online: 2021-06-10

Key words: **SCA40; Spinocerebellar ataxia; *CCDC88C* gene; Cerebellar atrophy; Case report**

Neuroendocrinol Lett 2021; **42**(4):215–221 **PMID:** 34436841 NEL420421C02

Abstract

Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group accompanied by obvious pontocerebellar limitations. This condition is complex both genetically and phenotypically, making it difficult to describe all the variants simultaneously. Herein, we report a proband from a Chinese mainland family who was admitted to our hospital with paroxysmal limbs jitter and head-shaking. She had experienced broad-based gait, dysarthria, dysmetria, and tremor for about 20 years. Similar clinical symptoms were observed in the daughter, sister and deceased father of this proband. Magnetic resonance imaging showed varying degrees of cerebellar atrophy. The results of whole-exome sequencing (WES) indicated that the three affected members carried the c.590G>A mutation in the *CCDC88C* gene. Based on the diagnosis of SCA40, this proband was treated with aggressive management. Unfortunately, the proband died of suffocation due to laryngeal oedema. Paroxysmal limbs jitter may be a rare phenotype of SCA40 and may occur as a result of involuntary motion which should be differentiated from chorea and epilepsy. In patients with SCA40, pontocerebellar atrophy occurs to varying degrees. Even in the same family, the multiple patients diagnosed did not all exhibit pontocerebellar atrophy. Furthermore, WES is indispensable for the identification of some atypical phenotypes of SCA40.

Abbreviations:

SCA	- Spinocerebellar ataxia
WES	- whole-exome sequencing
SCA40	- Spinocerebellar ataxia-40
CCDC88C	- coiled-coil domain containing the 88C
SARA	- Assessment and Rating of Ataxia
MMSE	- Mini Mental State Examination
MOCA	- Montreal Cognitive Assessment
HAMD	- Hamilton Depression Scale
MRI	- magnetic resonance imaging
EEG	- electroencephalography
HD	- Huntington's disease
JNK	- c-Jun N-terminal kinase

INTRODUCTION

Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous progressive neurodegenerative disease group that selectively targets the pons and cerebellum, characterised by ataxic gait, dysarthria, parkinsonian syndrome, and cognitive impairment (Jacobi *et al.* 2020). Common SCA types, such as SCA1 SCA2, SCA3, and SCA6, are all classified as CAG trinucleotide repeat diseases

CASE REPORT

in which the difference of clinical symptoms is mostly related to the number of CAG repeats (Lee *et al.* 2020). Spinocerebellar ataxia-40 (SCA40, OMIM #616053) is a very rare, autosomal dominant form of SCA that has thus far been reported in only six patients from two families around the world. In both of these families, missense mutations were found in the coding region of the coiled-coil domain containing the 88C (*CCDC88C*) gene (NM_001080414): the heterozygous missense mutation c.127G>A (p.Asp43Asn) was identified in a Polish family with SCA40 (Leńska-Mieciek *et al.* 2019), and the missense mutation c.G1391A (p.Arg464His) was detected in a Hong Kong SCA40 family (Tsoi *et al.* 2014). Herein, we present the first SCA 40 family from mainland China with a missense *CCDC88C* gene mutation, namely, c.590G>A (p. Arg197Gln), which enriches the phenotypic and genetic spectrum of SCA40. To our knowledge, this report describes the first confirmed SCA40 family with paroxysmal limb jitter, and the normal and atrophy cerebellums appear in the patients from the same family, which is clinically and genetically distinct from the other two reported before.

CASE PRESENTATION

The proband (II-1, Figure. 1) is a 62-year-old Chinese female who presented with an episode of uncontrollable jitter of the extremities, aphasia, nausea, and vomiting, but with no loss of consciousness. These symptoms had been experienced every week for the previous 3 years, lasting approximately 10 minutes each time and could be alleviated without any special treatment. Subsequently, the jitter progressively worsened, and spread to her head. Examination of her past medical history showed that she had experienced a 20-year history of cerebellar ataxia and she first developed unsteady gait and blurred vision at the age of 42 years. Her symptoms progressed slowly, and at 4 years after disease onset, she was unable to walk unaided and suffered from a severe speech disorder. The proband stated her daughter, litter sister and dead father had similar symptoms, whereas other members of the family exhibited no neurological symptoms. She denied a family history of epilepsy. Neurological examination revealed prominent ataxia, dysdiadochokinesia, cerebellar dysarthria, hypermyotonia in the extremities, and hyperreflexia, bilateral Babinski and Chaddock signs were also elicited. Her latest Scale for the Assessment and Rating of Ataxia (SARA) score was 17/40. The patient scored 21/30 on the Mini Mental State Examination (MMSE), 23/30 on the Montreal Cognitive Assessment (MOCA), and 21 on the Hamilton Depression Scale (HAMD). Blood routine, biochemical, autoimmune, infection, and cerebrospinal fluid tests were all within the normal range.

The proband's 39-year-old daughter (III-1, Figure.1) developed tremor in both her hands at around 35 years of age. She then developed mild blurred vision, scanning speech and a wobbly walk. She has since been experiencing violent jitter in both lower limbs in the last 1 year which were similar as those of the proband, but the jitter of the lower limbs lasted for a shorter time and was not accompanied by shaking head. The jitter stopped after about 2 minutes and were sometimes accompanied by nausea. In addition, she has been losing concentration for the last six months. Neurological examination revealed ocular dysmetria, wide-based gait, dysdiadokokinesia, resting tremor, intentional tremor, hypermyotonia and normal reflexes. Her latest SARA score:6/40; MMSE:33/30; MOCA: 34/30; HAMD:16.

The proband's little sister (II-5, Figure.1) first presented ocular dysmetria at age 48 years. She developed quiescent tremor, unsteadiness when walking and slurred speech gradually within 5 years of symptom onset. She had been experiencing dizziness and nausea since the age of 48 but has not had experienced the jitter

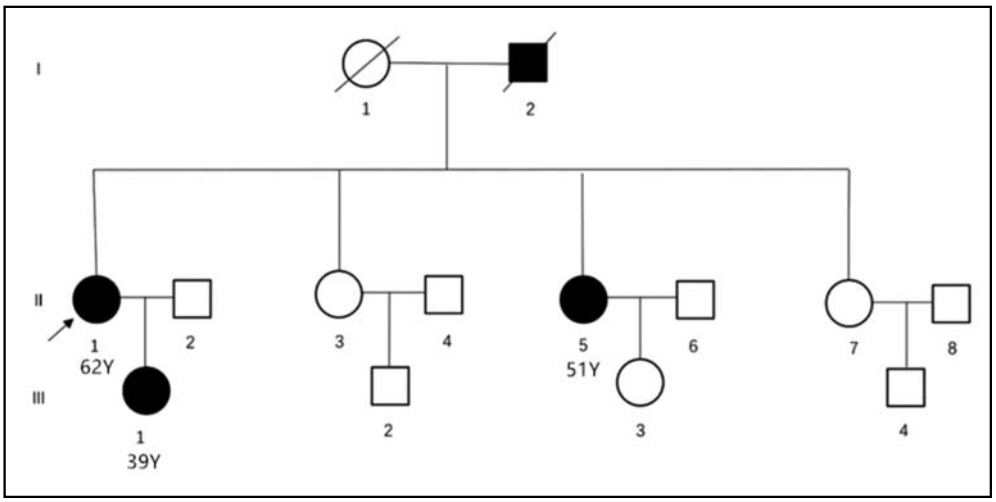

Fig. 1. Pedigree analysis of the patient's family. Black circles (females) and squares (males) indicate family members affected by the disease, while open circles and squares indicate unaffected members. The slash indicates that the patient is dead (I-1; I-2). The arrow indicates the proband.

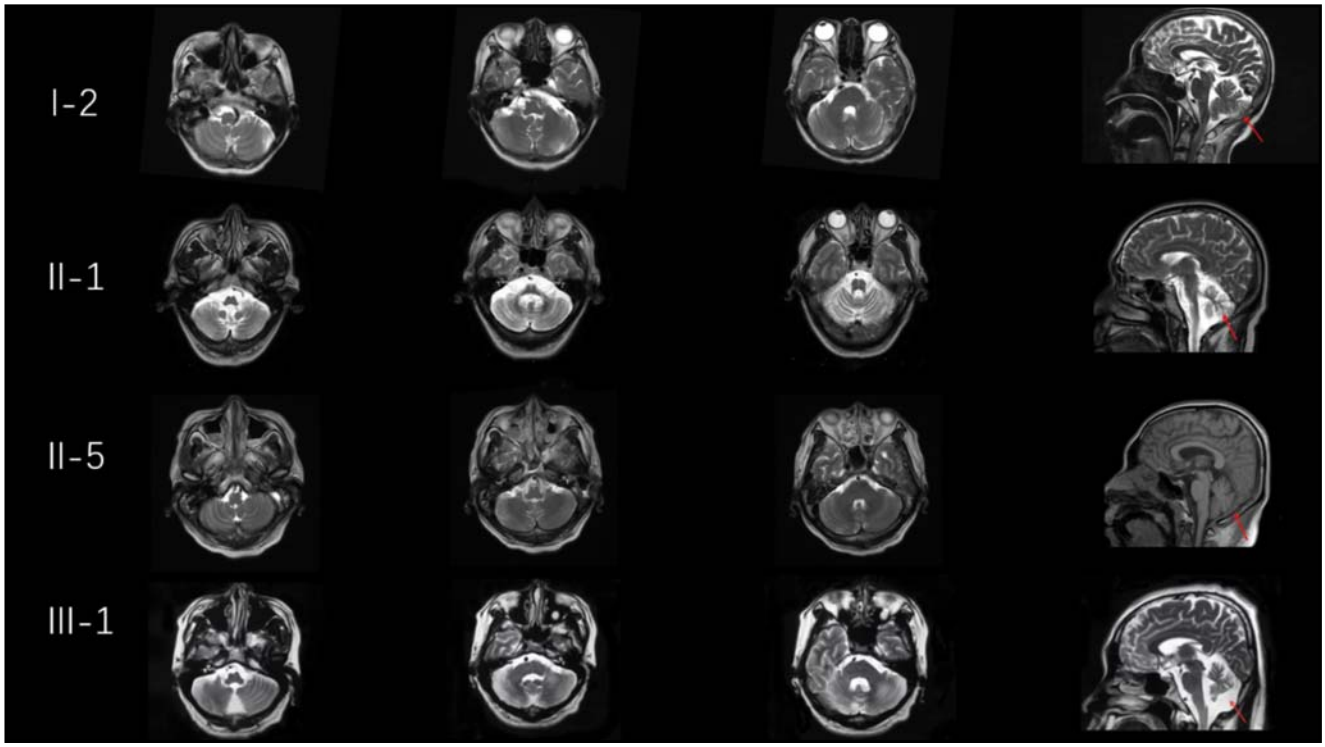

Fig. 2. T2-weighted MRI of the brain scans of the proband and her daughter showed pontocerebellar atrophy (II-1, III-1 red arrow). The overall structure of the cerebellum and pons was generally normal in the proband's sister (II-5, red arrow). The father of the proband showed age-related atrophy in the brain and cerebellum, but it was within the normal range (I-2, red arrow).

like the proband. Neurological examination showed ocular dysmetria, moderate ataxia (SARA:10/40), dystonia and hyper reflexes. MMSE:20/30; MOCA: 24/30; HAMD:23.

The father of the proband (I-2, Figure 1) died of acute myocardial infarction at the age of 72. The proband stated her dad had marked gait instability, quiescent tremor, and Parkinson's disease while alive which persisted for over 20 years. Moreover, he was unable to walk upright by the age of 62 years. No assessment was conducted on his cognitive function and no autopsy was performed.

Brain magnetic resonance imaging (MRI) were performed in the proband, her daughter and little sister. We found severe cerebellar atrophy and mild pons atrophy in the proband (Figure 2); moderate cerebellar atrophy and mild pons atrophy in her daughter, and normal pontocerebellar structure in the proband's little sister (Figure 2). No leukoencephalopathy or abnormal posterior cranial fossa size were found in the MRI of the four patients. Additionally, the father of the proband underwent a head MRI two years before his death, which showed age-related brain and cerebellum atrophy, but within the normal range (Figure 2). Electroneurogram suggested that the conduction velocity of peripheral motor nerve of the proband slowed down, presenting demyelination changes; the tibial nerve motor and sensory nerve conduction velocity of the lower limbs in the sister of the proband slowed down and the amplitude decreased. Additionally, 24-hour electroencephalogram tests of the three patients were normal; electromyography suggests that neither of them had existing myoclonus.

Whole-exome sequencing (WES) identified a missense mutation in the *CCDC88C* gene that resulted in an amino acid change from arginine to glutamine (c.590G>A; p. Arg197Gln) in the proband, her daughter and sister (Figure 3). In addition, the presence of the variant was validated with PCR and Sanger capillary bidirectional sequencing in the proband, her sister and daughter. All patients gave written, informed consent and the study was approved by the local ethics committee.

The four patients above were diagnosed with SCA40 based on their clinical features, imaging findings, and genetic results. The proband was treated with clonazepam (1 mg/d), flupentixol (0.5 mg/d), supportive treatment such as nutrition support therapy and vitamin B and C supplements for 15 days. The proband's daughter and sister were treated with flupentixol (0.5 mg/d), mecobalamine (0.5 mg/d) to improve nerve nutrition in addition to physical therapy. Unfortunately, the proband died of suffocation due to laryngeal oedema after 14 months of follow-up, and the proband's little sister and daughter showed no significant improvement.

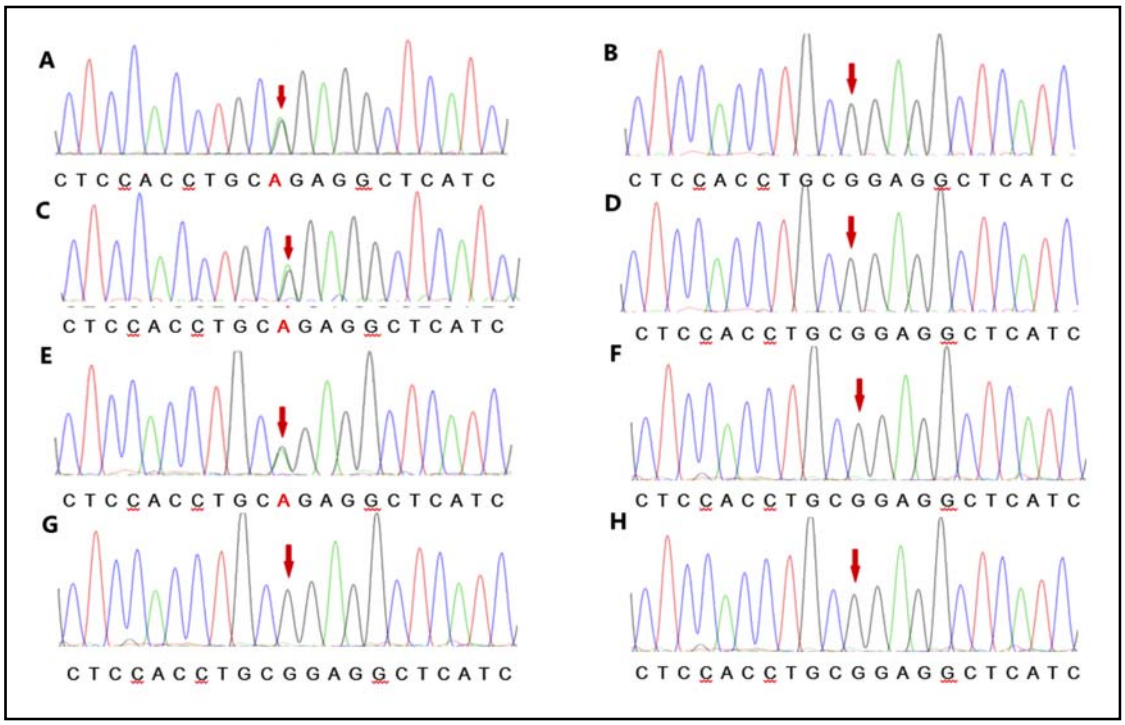

Fig. 3. Sequencing analysis of the CCDC88C gene locus in the SCA40 family. Genetic profiles of the proband (A, II-1), the proband's daughter (C, III-1), and the proband's sister (E, II-5) (D) carried the c.590G>A (p. Arg197Gln) mutation in the CCDC88C gene. Five unaffected relatives did not contain the same mutation. (B: II-3; D: II-7; F: III-2; G: III-3; H: III-4).

DISCUSSION

We report here the first Chinese mainland family with SCA40, in which all affected members examined carried a heterozygous variant of the coiled-coil domain containing *CCDC88C* gene. The proband and her daughter had a rare clinical feature of chorea-like paroxysmal limbs jitter, with pontocerebellar atrophy in MRI findings. The proband's sister and deceased father exhibited progressive ataxia without limbs jitter or abnormalities in the cerebellum. We reviewed and summarized the clinical symptoms and imaging findings for these four patients as well as previously reported families with this condition in Hong Kong and Poland (Table 1). The age of onset in the affected patients ranged from 35 to 49 years and the average disease duration was over 15 years. Similar with patients with other SCAs, all patients with SCA40 reportedly presented with varying degrees of progressive pure cerebellar ataxia, including gait ataxia, slurred speech dystonia, and tremor. Compared to the Hong Kong family, the Polish family had mild ataxia, good functional mobility, and significant features of Parkinson's disease and cognitive impairment. Neuropsychological assessment showed impaired mood disorders such as moderate depression in the Chinese mainland family, which is markedly different from the findings in previously reported SCA40 families. In addition, the proband's daughter reported frequent but non-obvious inattention, which suggests that clinicians should be alert for non-motor symptoms of cerebellar dysfunction in SCA40 patients, such as cognitive impairment and mood disorders.

Chronic, recurrent chorea-like jitter is a characteristic clinical manifestation of SCA40, which appeared in the proband and her daughter and attracted the attention of neurologists. Although none of the other family members experienced jitter, we do not believe the manifestation in both the proband and her daughter is a coincidence. Paroxysmal limbs jitter should be considered one of the clinical phenotypes of SCA40, especially in patients with pontine and cerebellar atrophy. This special type of limbs jitter is obviously different from tremors, and its shaking range is larger and more intense. We suspect this jitter falls under the category of involuntary movement accompanied by autonomic nervous dysfunction which has been described in previous case reports in patient with SCA2 (Li 2019), while the paroxysm is rare. Additionally, negative electroencephalography (EEG) and electromyography findings like those observed for our patients are indicative of dystonic episodes or other movement disorders rather than true epileptic seizures or myoclonus. No epilepsy or myoclonus has been reported in patients with SCA40, but EEG and changes in patient consciousness must be considered in the differential diagnosis of progressive ataxia, as epilepsy is one of the symptoms of SCAs and has been reported in multiple SCA subgroups (Hashem *et al.* 2020). Myoclonus is another key characteristic that originates mostly in the cortex and is strongly activated by motor and sensory stimuli, resulting in disabling convulsions, which have

Tab. 1.

Clinical characteristics	Family 1 (Chinese mainland)				Family 2 (Hong Kong)		Family 3 (Poland)			
	I-2	II-1	II-5	III-1	II-4	II-5	III-1	IV-1	IV-2	IV-3
Sex	M	F	F	F	F	M	M	F	M	M
Age	72	62	50	39	65	62	84	63	59	53
Age of image (years)	68	62	50	39	61	64	NA	NA	NA	NA
Age at onset of disease (years)	48	42	40	35	43	42	NA	45	49	33
Disease duration (years)	24	20	10	4	20	20	NA	18	10	20
Time from disease onset to wheelchair use (years)	14	9	NA	NA	18	17	NA	NA	NA	NA
Gait ataxia	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
ocular dysmetria	NA	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
spastic paraparesis	NA	(–)	(–)	(–)	(–)	(+)	(–)	(–)	(–)	(–)
Resting tremor	(+)	(+)	(+)	(+)	(–)	(–)	(+)	(+)	(+)	(+)
Action tremor	NA	(–)	(–)	(–)	(–)	(+)	(–)	(–)	(–)	(–)
Intentional tremor	NA	(+)	(–)	(–)	(+)	(–)	(–)	(+)	(+)	(–)
Dystonia	NA	(+)	(+)	(+)	NA	(+)	(+)	(+)	(+)	(+)
Slurred speech	(+)	(+)	(+)	(+)	(+)	(+)	NA	NA	NA	NA
Parkinsonism	(+)	(+)	(–)	(–)	(–)	(–)	(–)	(+)	(+)	(+)
Paroxysmal jitter	(–)	(+)	(–)	(+)	NA	NA	NA	NA	NA	NA
Cognitive impairment	(–)	(+)	(+)	(–)	(–)	(–)	(+)	(+)	(+)	(+)
Hyper reflexes	NA	(+)	(+)	(–)	(+)	(–)	(–)	(–)	(+)	(–)
SARA score	NA	17/30	10/30	6/30	24/40	22/40	NA	5/40	10/40	3/40
MMSE score	NA	21/30	20/30	33/30	NA	NA	NA	NA	NA	NA
MOCA score	NA	23/30	24/30	34/30	NA	NA	NA	NA	NA	NA
HAMD score	NA	21	23	16	NA	NA	NA	NA	NA	NA
Vermis and Cerebellar atrophy	Mild	Severe	Normal	Moderate	Mild	Mild to moderate	NA	Normal	Normal	Normal
Posterior cranial fossa size	Normal	Normal	Normal	Normal	Normal	Normal	NA	NA	NA	NA
Pons atrophy	Mild	Normal	Mild	Normal	Mild	Mild	NA	Normal	Normal	Normal
Amino acid change	c.590G>A; (p.Arg197Gln)				c.G1391A (p.Arg464His)		c.127G>A;(p.Asp43Asn)			

NA=not available; MMSE= Mini Mental State Examination; MOCA= Montreal Cognitive Assessment; HAMD= Hamilton Depression.

been reported in SCA13 and SCA14 patients (Montaut *et al.* 2017; Chelban *et al.* 2018). However, whether the paroxysmal jitter in this patient are related to the occurrence of cerebellar atrophy is unclear and needs to be further explored.

Cerebellar and pons atrophy was reported in members of the family with SCA40 in Hong Kong, China, whereas members of the Polish family were normal, demonstrating that the occurrence of cerebellar atrophy in SCA40 is not consistent. The Chinese

mainland pedigree reported herein proves that there are differences in pontocerebellar atrophy within the same pedigree and that the degree of pontocerebellar atrophy differs in SCA40 patients. In contrast, MRI in patients with symptomatic Huntington's disease (HD) reveal marked striatal atrophy, regional or whole-brain gray and white matter changes (Tabrizi *et al.* 2013). These imaging variations could help to differentiate between a diagnosis of early SCA40 or early HD. We hypothesize that clinical heterogeneity in patients with SCA40 is closely related to the site of genetic mutation, onset of clinical symptoms, age at onset of symptoms, and environmental factors. Most notably, complex phenotype and genotype variations are typically observed in patients with SCA 40, with some symptoms may being intermittent. The correlation between clinical radiology and symptoms helps to accelerate diagnosis and treatment, minimize morbidity, and promote rehabilitation.

Genetic testing was performed on three living patients with clinical symptoms and five unaffected relatives. The results showed that all three living patients with clinical symptoms carried a rare heterozygous substitution, c.590G>A (p. Arg197Gln), in the *CCDC88C* gene, and the fiver unaffected relatives did not possess the mutation. Analysis of Arg197Gln using the SIFT and Polyphen-2 database software suggested severe alterations of protein function. The rare heterozygous substitution has been classified as pathogenic according to the American College of Medical Genetics guidelines which had been also recorded in the Clivar database, but no related pedigree was reported. Interestingly, *CCDC88C* mutations have also been reported in several families with recessive forms of congenital hydrocephalus (Wallis *et al.* 2018). Recessive *CCDC88C* mutations in congenital hydrocephalus were first identified in a large family in 2010 (Ekici *et al.* 2010); since then, three additional families with these types of mutations have been identified (Drielsma *et al.* 2012; Shaheen *et al.* 2017). Most of the affected children in these families had congenital hydrocephalus, seizures, and varying degrees of intellectual and/or motor delays. However, a report by Tsoi and colleagues described the involvement of the *CCDC88C* gene in the autosomal-dominant form of SCA40 (Tsoi *et al.* 2014). The data suggest that these two conditions may be *CCDC88C*-related allelic disorders. These mutations cause a loss of protein function through the truncation of binding motifs vital to the non-canonical Wnt pathway (Ekici *et al.* 2010; Kobayash *et al.* 2005). The *CCDC88C* gene modulates the phosphorylation status of the c-Jun N-terminal kinase (JNK) pathway (Matilla-Dueñas *et al.* 2014). A mutation in the HOOK domain of the *CCDC88C* gene was found to alter the attributes of cells by activating the JNK pathway, thereby inducing caspase-3 cleavage and triggering apoptosis (Mei *et al.* 2008; Harris 2002). This mutation also affected cellular functions such as protein trafficking and cilium formation. Genetic counseling of the family is useful to predict the incidence of the disease in the next generation because of the complexity of its inheritance and clinical variety. It should be noted that the symptoms caused by the same mutation were somewhat different between the families. Therefore, if SCA40 is suspected to exist, genetic testing is essential even if there are differences in the clinical manifestations within the same family. Furthermore, epigenetic factors and possible modifier genes require further study to explore the heterogeneity of the disease.

In conclusion, this Chinese family is the third family in the world and the first mainland Chinese family with the rare paroxysmal limbs jitter attributed to a missense mutation of the *CCDC88C* gene in SCA40. The findings in this study further confirm the role of the *CCDC88C* gene in the determination of the disease and complete the primary clinical phenotype for SCA40. Although there is currently no effective treatment for SCA40, we hope that early diagnosis by WES will improve patients' quality of life through measures such as rehabilitation training, physical therapy, and assisted walking. In addition, a long-term observational study on patients with SCA40 and their family members will be important to complete the clinical spectrum of SCA40 and clarify the contributions of genetic factors.

ACKNOWLEDGMENTS

Not applicable. We thank the patient and her family members for their cooperation.

DECLARATIONS

Reporting Checklist: The authors have completed the CARE reporting checklist.
Conflict of interest: All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.
Ethics Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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