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BRIEF REPORT

Progressive Ataxia due to de novo Missense Variants in the *CACNA1A* Gene

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Abstract

The *CACNA1A* gene encodes the alpha-1A subunit of P/Q type voltage-gated calcium channel $Ca_v2.1$, which is associated with a broad clinical spectrum and variable symptomatology. While few patients with progressive ataxia caused by *CACNA1A* missense variants have been reported, here we report three unrelated Chinese patients with progressive ataxia due to de novo missense variants in the *CACNA1A* gene, including a novel pathogenic variant (c.4999C > G) and a previously reported pathogenic variant (c.4037G > A). Our findings and a systematic literature review show the unique phenotype of progressive ataxia caused by missense variants and enlarge the genetic and clinical spectrum of *CACNA1A*. This suggests that in addition to routine screening for dynamic mutations, screening for *CACNA1A* variants is important for clinicians facing patients with progressive ataxia.

Keywords Progressive ataxia · *CACNA1A* · Missense variant · De novo

Introduction

Progressive ataxias are a group of complex neurological disorders that can be caused by hereditary ataxia, idiopathic cerebellar ataxia and multiple system atrophy cerebellar type [1]. The *CACNA1A* gene encodes the alpha-1A subunit of the P/Q type voltage-gated calcium channel Cav2.1, which is expressed especially abundantly in the cerebellar Purkinje and granule cells [2]. Pathogenic variants in this gene are associated with several dominantly inherited disorders: episodic ataxia type 2 (EA2, MIM#108,500), familial hemiplegic migraine (FHM1, MIM#141,500), spinocerebellar ataxia type 6 (SCA6, MIM#183,086), and developmental and epileptic encephalopathy 42 (DEE42, MIM#617,106) [3]. Initial reports suggested that FHM1 is caused by missense variants and EA2 by truncating variants (nonsense, frameshift, splice site) in *CACNA1A*, while the expanded CAG repeats cause SCA6, which is characterized by slowly progressive cerebellar ataxia with a relatively late onset [4]. However, some patients with expanded repeats presented with episodic ataxia [5], and conversely, missense variants were implicated in progressive ataxia [6]. Besides, progressive ataxia associated with missense variants differ from those caused by expanded CAG repeats in terms of early onset and distinct associated clinical characteristics [7]. The substantial phenotypic overlap among these disorders complicates the correlation between phenotypes and genotypes. To date, only a few variants associate with progressive ataxia in the *CACNA1A* gene have been identified worldwide, while no patients in the Chinese population have been reported.

We herein reported the genetic features and clinical findings of three Chinese families with progressive ataxia associated with de novo missense variants within *CACNA1A*. We subsequently summarized patients with progressive ataxia associated with *CACNA1A* missense variants so as to better understand this disorder.

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Materials and Methods

Subjects

Participants were enrolled between February 2016 and May 2023 in the Second Affiliated Hospital of Zhejiang University. Inclusion criteria were as follows: (1) progressive ataxia; (2) negative molecular genetic tests for CAG expansions in *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *PPP2R2B*, *TBP*, *ATN1* and several ARCA genes [8]; (3) no established acquired cause of ataxia. Whole exome sequencing (WES) and bioinformatics analysis were performed in the probands. The clinical evaluations and neurological examinations were performed by at least two senior neurologists. Written informed consents were obtained from all the participants or their legal guardians. This study was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine.

Genetic Analysis

Genomic DNA was extracted from each participant's peripheral blood using a commercial blood genomic extraction kit (Qiagen, Hilden, Germany) and then screened by WES. Details on library preparation, sequencing protocol, bio-informatics analysis, and filtering methods of WES were conducted as described previously [9]. Sanger sequencing was performed to further validate the filtered variants in all probands and the family members. The primers for Sanger sequencing were listed in Table S1. The parenthood of patients with de novo variants were analyzed using 21 core short tandem repeat (STR) regions. The pathogenicity of variants was classified according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines [10]. The sequence was compared with the published human gene sequence (*CACNA1A*, NM_001127221) in the National Center for Biotechnology Information Database (http://www.ncbi.nlm.nih.gov).

Literature Review

We reviewed the patients presenting with a progressive ataxia associated with *CACNA1A* missense variants. Primary research articles were searched in PubMed using the terms "Progressive ataxia" or "*CACNA1A*" until December 31, 2022. The literature search was restricted to published articles in Chinese or English. Only reports of genetically confirmed cases were considered.

Results

Pathogenic Variants Identified in *CACNA1A*

After genetic analysis, two variants within *CACNA1A* were identified in three unrelated patients. The c.4037G > A (p.R1346Q) was identified in patient 1 and patient 2, which was reported previously [11]. The novel missense variant, c.4999C > G (p.R1667G), was detected in patient 3, which was absent in the 1000 Genomes Project, ExAC and Gnome AD databases, and it has a CADD score of 23.7. Additionally, it was not found in our targeted next-generation sequencing (NGS) database covering *CACNA1A*, which contained 2000 unrelated Chinese individuals. According to the guidelines of ACMG, c.4999C > G (p.R1667G) was classified as pathogenic variant with PS2 (strong), PM1, PM2 and PM5 (moderate), PP3 (supporting). It is worth mentioning that both of the variants in three families were de novo. This was identified by Sanger sequencing that neither of patients' parents carried the variant, and the kinship was verified by 21 core STR regions (Table S2).

Clinical Features of Three Patients with Progressive *Ataxia* and *CACNA1A* Missense Variants

Patient 1 (Fig. 1A) carrying p.R1346Q variant is a 20-year-old male who presented with a 2-year history of slowly progressive gait disturbance, dysarthria and 3-month history of migraine episodes. Neurological examination showed wide-based gait, slurred speech, dysmetria, rotatory nystagmus, as well as positive Romberg sign. Brain MRI demonstrated cerebellar atrophy. Electromyography reveals decreased wave amplitude of sensory conduction evoked potentials in the right peroneal nerve.

Patient 2 (Fig. 1B) with the same p.R1346Q variant is a 32-year-old female with a chief complaint of a 10-year history of gait disturbance and involuntary tremor of head and hands. The tremor was paroxysmal episodes, independent of body position posture. Dysarthria appeared 2 years ago, without dysphagia. On examination, she had wide-base gait, dysmetria (worse on left side), increased tendon reflexes in both lower limbs. Partial horizontal ophthalmoparesis of both eyes and horizontal nystagmus were also noted. Brain MRI showed cerebellar atrophy while electromyography was normal. Her son carries the same variant and remains asymptomatic.

Patient 3 (Fig. 1C) carrying a novel and de novo pathogenic variant c.4999C > G (p.R1667G) is a 24-year-old male. He had a history of obstructed labor and delivery with hypoxia at birth. More than 20 years ago, family

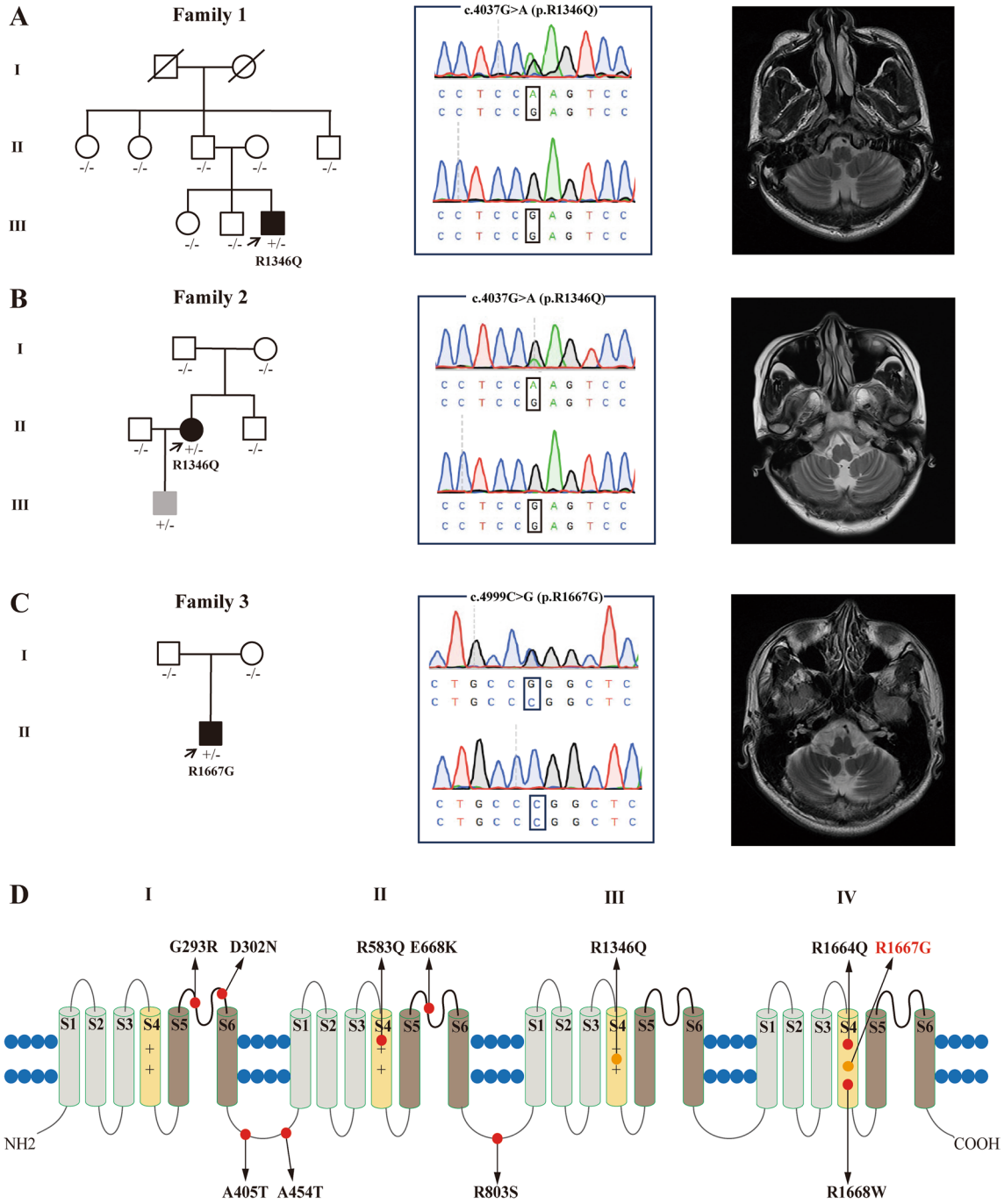

Fig. 1 Pedigree patterns of three families with progressive ataxia and localization of *CACNA1A* missense variants associated with progressive ataxia. **A**, **B**, **C**. Family pedigree, chromatogram of the *CACNA1A* variants identified, and MRI images showing cerebellar atrophy in the probands. The arrow points to the proband. Black symbols represent patients while gray symbols represent preclinical individuals. T2 weighted coronal MRI showing atrophy of both cerebellar hemispheres. **D**. Localization of *CACNA1A* missense variants on the secondary structure of Cav2.1. Voltage-sensing segment S4 is shown in yellow and Ca2+-selective pore-forming segments S5-S6 are shown in brown. Red dots indicate previously known variants, orange dots highlight variants identified in this study, and the dot featuring a yellow pentagram inside denotes the novel pathogenic variant

members noticed that his gait was worse than that of children with similar age, subsequently, his unsteadiness of walking gradually worsened. Six years ago, he began experiencing daily involuntary head tremors lasting 10 min each without unconsciousness or involuntary movement of limbs during attacks. Fine movements could trigger the attacks, which were more frequent when the temperature was low. Neurologic examinations revealed slurred speech, dysmetria, rotatory nystagmus, as well as positive Romberg sign. Brain MRI also showed cerebellar atrophy while electromyography was normal.

Clinical Phenotypes of Patients with Progressive *Ataxia* and *CACNA1A* Missense Variants Worldwide

We reviewed all of the previously reported patients with progressive ataxia associated with *CACNA1A* missense variants. In addition to the three patients reported here (Table 1), we found 18 affected individuals from 14 families, published in 9 articles. Their detailed characteristics are summarized in Table 2 and the variants distribution in the CaV2.1 channel are illustrated in Fig. 1D.

Combined with our study and previous studies, individuals with progressive ataxia associated with *CACNA1A* missense variants all have typical manifestations of cerebellar ataxia and cerebellar oculomotor disturbances. Basal ganglia sign (44.4%) and headache (28.6%) are also common. The mean age onset was 26.2 years, and more than 50% of patients had their onset before the age of 26 years, which increases to 80% while extending the onset to 32 years.

Discussion

In our study, we reported three Chinese families with *CACNA1A* missense variants, including a novel pathogenic variant (c.4999C > G) and a previously reported pathogenic variant (c.4037G > A). They all had a clinical characteristic of progressive ataxia which is typically seen in spinocerebellar ataxia. The literature review revealed progressive ataxia associated with *CACNA1A* missense variants differ from those caused by expanded CAG repeats, the individuals manifested basal ganglia signs and headache more often and did not exhibit any pyramid signs. Moreover, the onset of progressive ataxia was also earlier similar to the prior study [7]. These missense variants seem to result in a heterogeneous ataxia disorder with clinical phenotypes between SCA6, FHM1 and EA2.

The *CACNA1A* gene encodes the alpha-1A subunit of the P/Q type voltage-gated calcium channel Cav2.1, which consists of four homologous regions, each containing six transmembrane segments [2]. Pathogenic variants in this gene cause various alterations in calcium channel kinetics and loss or gain of P/Q-type channel function and have been associated with EA2 and FMH1, respectively. Expanded CAG repeats found in SCA6 do not directly affect the P/Q-type channel but may be mediated by a transcription factor, the C-terminus of the alpha-1A subunit, which is expressed

Table 1 Clinical features of the three patients carrying *CACNA1A* missense variants

Variable	Patient 1	Patient 2	Patient 3
CACNA1A variant	R1346Q	R1346Q	R1667G
Gender	Male	Female	Male
Familial history	Sporadic	Sporadic	Sporadic
Age of onset	18	22	4
Age of diagnosis	20	32	24
SARA score	9	4	9
Dysarthria	Y	Y	N
Dysphagia	N	N	N
Nystagmus	Rotatory	horizontal	Horizontal
Cognitive dysfunction	N	Y	N
UL/LL Tendon reflexes	++/++	++/+++	++/++
Babinski sign	N	N	N
Tremor	N	Y	Y
Sensory deficits	N	N	N
Bladder dysfunction	N	N	N
MRI found	Cerebellar atrophy	Cerebellar atrophy	Cerebellar atrophy
Additional symptoms	Migraine	involuntary tremor of head and hands, partial horizontal ophthalmoparesis of both eyes	Parpxysmal head tremor

Y present, *N* absent, *UL* upper limb, *LL* lower limb

Table 2 Clinical features of patients with progressive ataxia carrying *CACNA1A* missense variants in different populations

Family individual	Gender	Variant	Domain	Familial history	Age of onset	Age of diagnosis	Gait ataxia	Dysarthria	Dysphagia	Diplopia	Nystagmus	Headache/migraine	Hemiplegia
F1-1	Male	R1346Q	IIIS4	Sporadic	18	20	Y	Y	N	N	Y	Y	N
F2-1	Female			Sporadic	22	32	Y	Y	N	N	Y	N	N
F3-1	Female			AD	-	32	Y	-	-	-	-	Y	Y
F4-1	Male	R1667G	IVS4	Sporadic	4	24	Y	N	N	N	Y	N	N
F5-1	Male	R803S	II-III loop	AD	29	32	Y	Y	N	Y	N	N	N
F6-1	Female	G293R	IS5-S6	AD	15	54	Y	Y	N	N	Y	N	N
F7-1	Female	E668K	IIS5-S6	AD	61	78	Y	Y	Y	N	Y	N	N
F7-2	Female			AD	63	72	Y	Y	N	N	Y	N	N
F7-3	Male			AD	39	48	Y	Y	N	N	Y	N	N
F7-4	Male			AD	31	58	Y	Y	N	N	Y	N	N
F7-5	Male			AD	30	42	Y	Y	N	N	Y	N	N
F7-6	Male			AD	32	54	Y	Y	N	N	Y	N	N
F8-1	Male	R583Q	IIS4	AD	25	86	Y	Y	N	N	-	Y	N
F8-2	Female			AD	20	68	Y	Y	N	N	-	N	N
F8-3	Male			AD	19	57	Y	Y	N	N	N	Y	N
F9-1	Female			AD	16	52	Y	Y	N	N	Y	Y	Y
F10-1	Female	D302N	IS5-S6	AD	15	63	Y	Y	N	N	Y	N	N
F11-1	Female	R1668W	IVS4	AD	48	73	Y	Y	N	N	Y	N	N
F12-1	Female	A405T	I-II loop	AD	6	12	Y	Y	N	N	N	Y	N
F13-1	Female	A454T	I-II loop	AD	30	47	Y	Y	N	N	Y	N	N
F14-1	Male	R1664Q	IVS4	Sporadic	1	1	Y	N	N	N	Y	N	N

Family-individual	Cognitive dysfunction	UL/LL Tendon reflexes	Babinski sign	Tremor/basal ganglia sign	Sensory defects	MRI found	Additional symptoms	References
F1-1	N	++/++	N	N	N	cerebellar atrophy	-	this study
F2-1	Y	++/+++	N	Y	N	cerebellar atrophy	involuntary tremor of head and hands, partial horizontal ophthalmoparesis of both eyes	this study
F3-1	N	++/++	-	-	-	cerebellar atrophy	coma after a car accident without head trauma	Alonso et al. 2004 [11]
F4-1	N	++/++	N	Y	N	cerebellar atrophy	paroxysmal head tremor	this study
F5-1	N	++/++	N	N	N	cerebellar atrophy		Balck et al. 2017 [13]
F6-1	N	++/++	N	Y	N	cerebellar atrophy with diffuse cortical atrophy	wheelchair, horizontal gaze-evoked nystagmus, rebound nystagmus, dysmetria	Yue et al. 1997 [6]

Table 2 (continued)

Family individual	Gender	Variant	Domain	Familial history		Age of onset	Age of diagnosis	Gait ataxia	Dysarthria	Dysphagia	Diplopia	Nystagmus	Headache/ migraine	Hemiplegia
F7-1	Y	+ +/+	Y	N	Y		-			-			Bürk et al. 2014 [14]	
F7-2	N	+ +/+ +	N	Y	Y		-			-			Bürk et al. 2014 [14]	
F7-3	Y	+/+	N	N	N		-			hip dysplasia diabetes			Bürk et al. 2014 [14]	
F7-4	Y	+ +/+ +	N	N	N		-			hearing loss			Bürk et al. 2014 [14]	
F7-5	N	+ +/+ +	N	N	N		-			N			Bürk et al. 2014 [14]	
F7-6	N	+ +/+ +	N	N	N		-			N			Bürk et al. 2014 [14]	
F8-1	N	+ +/+ +	-	-	-		-			N			Bürk et al. 2014 [14]	
F8-2	N	+ +/+ +	-	-	-		-			Psychosis			Bürk et al. 2014 [14]	
F8-3	N	+ +/+ +	N	Y	N		-			migraine with infrequent attacks, few aura episodes with scotoma, aphasia or hemi-hypesthesia			Bürk et al. 2014 [14]	
F9-1	N	+ +/+ + +	N	N	N		cerebellar atrophy			N			Duque et al. 2020 [15]	
F10-1	Y	+/+	N	Y	N		-			vertigo			Bürk et al. 2014 [14]	
F11-1	N	+ +/+ +	Y	N	N		cerebellar atrophy			N			Marti et al. 2008 [16]	
F12-1	N	+ + +/+ + +	Y	Y	N		-			dysmetria, epileptic seizure, hypotonus			Romaniello et al. 2010 [17]	
F13-1	N	+ + +/+ + +	N	Y	N		cerebellar atrophy			N			Cricchi et al. 2014 [18]	
F14-1	N	+ +/+ +	N	N	N		-			N			Tonelli et al. 2006 [19]	

Y present, *N* absent, *UL* upper limb, *LL* lower limb

through the internal ribosomal entry site (IRES) located in *CACNA1A* [12]. Three variants identified from patients with progressive ataxia were located in the S5-S6 connecting section of domain I (p.G293R, p.D302N) and domain II (p.E668K). The S5-S6 connecting section forms a channel hole, which selectively allows the passage of ions. And three variants were located in the loop between I-II (p.A405T, p.A454T) and II- III (p.R803S). The previous report presumed that these variants might affect the interaction between the loop and the β subunit leading to dysregulation of the inactivation kinetics [18]. The two pathogenic variants reported in this study, combined with four previously reported variants, were located in the S4 transmembrane segments of domain II (p.R583Q), domain III (p.R1346Q), and domain IV (p.R1664Q, p.R1667G, p.R1668W). The S4 segment is attached to a positive amino acid, forming the S4 transmembrane alpha-helix, which acts as a "voltage sensor". These variants replace a polar positively charged highly conserved arginine by neutral amino acid (glutamine) or non-polar amino acids (tryptophane and glycine), which may cause an excess of intracellular calcium and thus death of neurons. However, no correlation seems to exist between specific variants and phenotypic presentations, even the same variant can present diverse clinical phenotypes. The p.R1346Q missense variant has also been described in association with EA2 and FHM1 [11]. Furthermore, a different amino acid exchange at the codon 1667 (p.R1667P) has been identified in a patient with fatal brain edema [20].

When clinicians facing patients presenting with progressive ataxia always focus on searching for CAG expansions and fails to identify missense variants in *CACNA1A*. We establish here that screening for *CACNA1A* missense variants is of interest to clinicians facing patients presenting with progressive ataxia, especially when combined with headache as well as basal ganglia signs. Additionally, the variants identified here were de novo, indicating that *CACNA1A* missense variant warrant attention in sporadic cases with undiagnosed progressive ataxia.

Conclusion

In summary, we reported three Chinese patients with progressive ataxia associated with de novo missense variants within *CACNA1A*. The variants including a novel pathogenic variant (c.4999C > G) and a previously reported pathogenic variant (c.4037G > A). These cases and the pertinent literature review also suggest that in addition to routine screening for dynamic CAG variants, screening for *CACNA1A* missense mutations is of importance to clinicians facing patients presenting with progressive ataxia, especially when combined with basal ganglia signs as well as headache.

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Author's Contribution Chen-Hao Zhu: data collection, analysis and interpretation, draft of manuscript. Jin-Yang Yu: data collection, analysis and interpretation. Yin Ma: technical support. Yi Dong: analysis and interpretation. Zhi-Ying Wu: study concept and design, critical revision of the manuscript. All authors read and approved the final manuscript.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics Approval This study was approved by the ethics committee of Second Affiliated Hospital of Zhejiang University (Hangzhou).

Consent to Participate Written informed consent was obtained from each participant.

Consent to Publish Not applicable.

Conflict of Interest The authors declare that they have no conflict of interest.

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