



# Autosomal Recessive Cerebellar Ataxia Type 1: Phenotypic and Genetic Correlation in a Cohort of Chinese Patients with SYNE1 Variants

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## Abstract

Mutations in the synaptic nuclear envelope protein 1 (SYNE1) gene have been reported to cause autosomal recessive cerebellar ataxia (ARCA) type 1 with highly variable clinical phenotypes. The aim of this study was to describe the phenotypic-genetic spectrum of SYNE1-related ARCA1 patients in the Chinese population. We screened 158 unrelated patients with autosomal recessive or sporadic ataxia for variants in SYNE1 using next-generation sequencing. Pathogenicity assessment of SYNE1 variants was interpreted according to the American College of Medical Genetics standards and guidelines. We identified eight truncating variants and two missense variants spreading throughout the SYNE1 gene from six unrelated families, including nine novel variants and one reported variant. Of the six index patients, two patients showed the classical pure cerebellar ataxia, while four patients exhibited non-cerebellar phenotypes, including motor neuron symptoms, cognitive impairment, or mental retardation. The variants associated with motor neuron or cognition involvement tend to be located in the C-terminal region of SYNE1 protein, compared with the variants related to pure cerebellar ataxia. Our data indicating SYNE1 mutation is one of the more common causes of recessive ataxia in the Chinese population. The use of next-generation sequencing has enabled the rapid analysis of recessive ataxia and further expanded our understanding of genotype-phenotype correlation.

**Keywords** Autosomal recessive cerebellar ataxia 1 (ARCA1) · SYNE1 gene · Genotype · Phenotype · Whole-exome sequencing (WES)

## Introduction

The autosomal recessive cerebellar ataxias (ARCAs), also called spinocerebellar ataxias autosomal recessive (SCARs) are a group of complex neurodegenerative conditions with significant genetic and clinical heterogeneity [1]. They are usually characterized by early-onset ataxia with a variable range of other neurological manifestations such as pyramidal or extrapyramidal signs, cognitive deterioration, peripheral

neuropathy, epilepsy, retinopathy, and endocrine manifestations. To date, the Society for Research on the Cerebellum and Ataxias Task Force identified 59 disorders that are classified as primary ARCAs, including 15 disorders that are more prevalent and widely distributed, and 44 disorders that are less frequent and reported only in certain populations or few families [2].

In 2007, SYNE1 (OMIM 608441) was identified as a causative gene of ARCA1 or SCAR8 (OMIM 610743) in a group of 26 French-Canadian families originating from the Beauce and Bas-St-Laurent regions of Quebec [3]. SYNE1 is one of the largest genes in the human genome, with the longest isoform comprising 147 exons. It encodes the spectrin repeat containing nuclear envelope protein 1 with 8797 amino acid residues (1000 kDa) [3]. The protein contains two N-terminal actin-binding regions that comprise tandem-paired calponin-homology domains, a transmembrane domain, multiple spectrin repeats, and a C-terminal Klarsicht/ANC-1/Syne homology (KASH) domain. It is a member of the spectrin family of structural proteins and mediates the formation of

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macromolecular assemblies called LINC (linkers of the nucleoskeleton to the cytoskeleton) complexes that span the nuclear envelope and underlie nuclear migration and anchorage to the actin cytoskeleton [3]. SYNE1 is expressed in multiple tissues including the central nervous system and is particularly abundant in the cerebellum [4].

As next-generation sequencing becomes increasingly available, SYNE1-related ataxia has been widely reported from Europe to South America, North America, Oceania, Africa, and Asia [5–16], suggesting that this disease is distributed worldwide. These reported SYNE1 ataxia patients show a remarkable heterogeneity in clinical features and disease severity, ranging from pure cerebellar ataxia to a complex multisystem disorder [17].

So far, SYNE1 ataxia has been reported in only two Chinese families with variable ataxia symptoms [16]. Here, we screened SYNE1 variants in a cohort of 158 unrelated index patients with unexplained autosomal recessive or sporadic ataxia in China, by whole-exome sequencing or targeted gene panel sequencing. Our aim was to obtain a more comprehensive overview of SYNE1 ataxia in China and better understand the clinical characteristics of the patients.

## Material and Methods

### Subjects

A cohort of 158 unrelated index patients (72 autosomal recessive, 86 sporadic) was enrolled at the Department of Neurology, Movement Disorder & Neurogenetics Research Center, China-Japan Friendship Hospital from 2005 to 2019. The patients were diagnosed with unexplained autosomal recessive or sporadic ataxia, accord with the following terms: occult onset without obvious triggers, age at onset  $\leq$  50 years; the secondary causes of infection, poisoning, metabolism, ischemia, immunity, and tumor were excluded; ataxia is accompanied by different degrees of symptoms of the nervous system and other systems; the disease is progressive; parents have no similar symptoms; some families have inbreeding; compatriots may be sick. The repeat expansion disorders including SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17, SCA31, SCA36, DRPLA, and Friedreich's ataxia have been excluded. This study was approved by the Ethics Committee of China-Japan Friendship Hospital. Written informed consent was obtained from all subjects engaged in this study.

### Genetic Analysis

Genomic DNA was extracted from EDTA-anticoagulated blood from index patients using a standard phenol-chloroform method. Samples were also taken from some

affected or unaffected relatives for co-segregation analysis. The 158 unrelated index patients were screened for causative gene mutations using next-generation sequencing (NGS) by Running Gene Inc. (Beijing, China). Target exome resequencing was performed in 86 index patients by a customized 194-gene sequencing panel and designed for the diagnosis of hereditary ataxia, hereditary spastic paraplegia, and other related neurological disorders ([Supplementary Materials](#)). Whole-exome sequencing was carried out on the other 72 index patients. Genomic DNA was fragmented into 250–300 bp by sonication, and the DNA library was constructed using the KAPA Library Preparation Kit (Illumina, KR0453, v3.13). Amplified DNA fragments were captured using the Agilent SureSelect XT2 Target Enrichment System (Agilent Technologies, Inc., USA). DNA fragments were sequenced with 150-bp paired-end reads on Illumina HiSeq X10 platform (Illumina, San Diego, USA). Raw data were filtered and aligned against the human reference genome (GRCh37/hg19) using the Burrows-Wheeler Alignment tool (BWA-0.7.12, <http://bio-bwa.sourceforge.net/>). Duplicated reads were filtered by Picard, and the single-nucleotide polymorphisms (SNPs), insertions, and deletions (indels) were then called by GATK software (Genome Analysis ToolKit) ([www.broadinstitute.org/gatk](http://www.broadinstitute.org/gatk)). Variants were annotated by ANNOVAR (version: 2016-05-1110:54:48-0700, 11 May 2016, [annovar.openbioinformatics.org/en/latest/](http://annovar.openbioinformatics.org/en/latest/)).

### Sanger Sequencing and Pathogenicity Prediction

The candidate causal variants with clinical significance identified via NGS were further confirmed by means of Sanger sequencing. Co-segregation analyses were conducted with samples from other family members. The effect of single-nucleotide variants (SNVs) was predicted by SIFT (<http://sift.jcvi.org/>), PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2/>), and Mutation Taster programs (<http://www.mutationtaster.org>). Conservation of the variants among different species was analyzed using BioEdit Sequence Alignment Editor (North Carolina Stl University, USA) to align the reference sequences in the Ensemble database (<http://useast.ensembl.org/index.html>). Pathogenicity of identified variants was assessed according to the standards and guidelines of the American College of Medical Genetics and Genomics (ACMG) [18].

### Clinical Evaluation

All patients underwent a standard neurologic examination conducted by two qualified neurologists. For individuals with putative SYNE1 pathogenic variants, detailed clinical data were obtained by age-appropriate examinations including the Scale for Assessment and Rating of Ataxia (SARA), International Cooperative Ataxia Rating Scale (ICARS),

Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Wechsler Adult Intelligence Scale (WAIS), Magnetic resonance imaging (MRI) scanning of the whole brain, electroencephalography (EEG), electromyography (EMG), nerve conduction study (NCS), and electrocardiograph (ECG) were conducted in the patients with putative SYNE1 pathogenic variants.

## Results

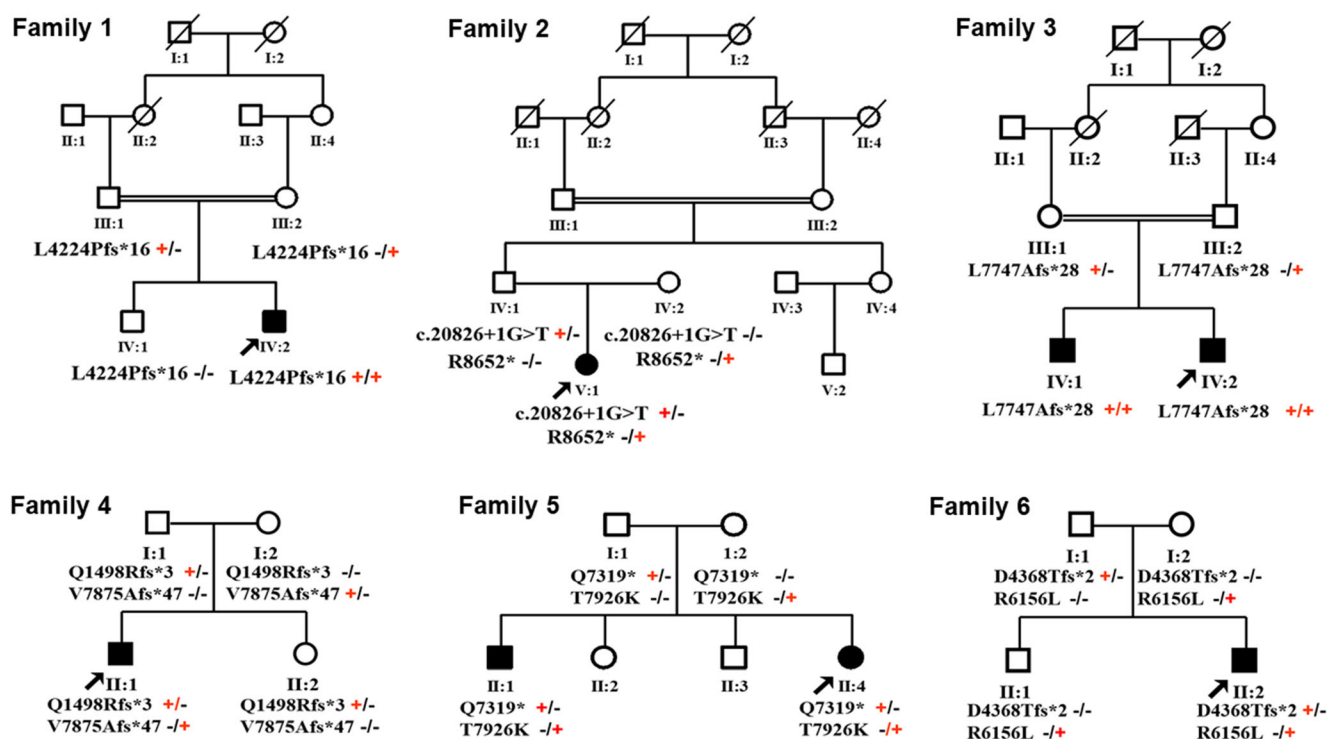
### Genetic Testing and Pathogenicity Assessment of SYNE1 Variants

We summarized the pedigree and genotypes of families with SYNE1 variants in this study in Fig. 1. Among all index patients, we identified a total of 8 truncating variants and 2 missense variants in SYNE1 (NM\_033071), including 5 frameshift (p.Q1498Rfs\*3, p.L4224Pfs\*16, p.D4368Tfs\*2, p.L7747Afs\*28, p.V7875Afs\*47), 2 nonsense (p.Q7319\*, p.R8652\*), one splicing (c.20826+1G>T), and 2 missense (p.R6156L, p.T7926K) variants. The nonsense variant c.25954C>T (p.R8652\*) has been reported previously, whereas the other 9 variants are novel. All these variants are located in the spectrin repeat domains of SYNE1 protein, the distribution of these variants along with the SYNE1 protein is in a schematic representation in Fig. 2.

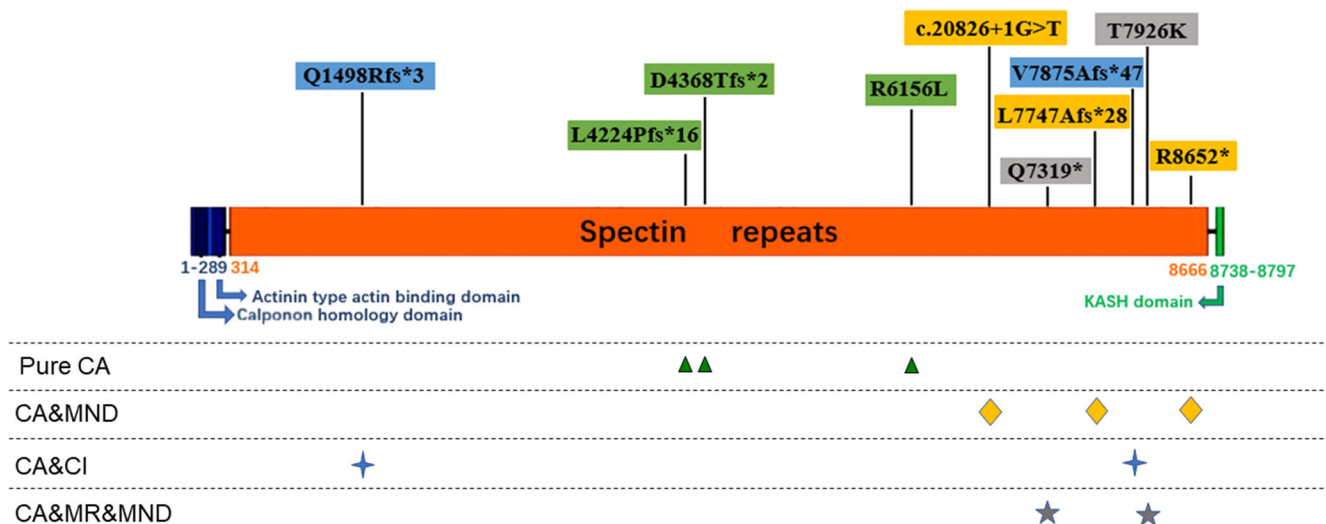
We summarized the results of in silico analysis and pathogenicity predicted of the SYNE1 variants in Table 1. Patients of pedigree 1 and pedigree 3 carry a homozygous frameshift variant. Other patients in pedigree 2, 4, 5, and 6 all carry heterozygous truncated variants. To establish the functional effects and determine the pathogenicity of these variants, we utilized the multiple bioinformatics tools (Material and Methods) and classified them according to the standards and guidelines of ACMG.

### Clinical Features

We aggregated clinical features from 8 patients from the 6 ARCA1 index families in Table 2. Ages of disease onset were variable, ranging from 10 to 27 years old (median age at disease onset 18.0 years old). Gait coordination disturbances were the most common initial symptom in 5/8 subjects; other initial symptoms include dysarthria (2/8), distal extremities atrophy and weakness (2/8), and mental retardation (1/8). At the last examination (median age 29.5 years old), patients showed a variable phenotypic spectrum of SYNE1-related ataxia: (i) pure cerebellar ataxia (2/8, patients 1-IV2, 6-II2); (ii) cerebellar ataxia plus motor neuron disease (MND) (3/8, patients 2-V1, 3-IV1, IV2); (iii) cerebellar ataxia plus cognitive impairment (2/8, patient 4-III, 5-III); (iiii) cerebellar ataxia plus motor neuron disease and mental retardation (1/8, patient 5-II4). Ataxia severity was evaluated using SARA ( $12.88 \pm 3.56$ ) and ICARS ( $33.63 \pm 6.44$ ).



**Fig. 1** Summary of the pedigree and genotypes of families with SYNE1 variants. Pedigrees of the six families with SYNE1 variants in this study. Circles: females; squares: males; shaded symbols: affected individuals; arrows: probands; "+": variant allele; "-": wild-type allele; "/": dead individuals



**Fig. 2** The location and distribution of 10 variants in a 2D schematic representation of the SYNE1 protein. Graphical overview of the variants identified in this study in relation to the SYNE1 domains. The N-terminal contains the actinin-type actin-binding domain and calponin-homology domains (in blue); the spectrin repeats domain (orange) and contains all the variants identified in this study; the C-terminal contains

the KASH domain (green). Green boxes variants: pure cerebellar ataxia (pure CA); yellow boxes variants: cerebellar ataxia plus motor neuron disease (CA&MND); blue boxes variants: cerebellar ataxia plus cognitive impairment (CA&CI); gray boxes variants: cerebellar ataxia plus mental retardation and motor neuron disease (CA&MR&MND)

## Radiological Findings

Cranial MRI of all the patients showed different degrees of cerebellar atrophy with prominent vermis and cortical hemisphere atrophy (Fig. 3a–c, e, f, h). In addition, MRI of patient 3-IV2 also showed spinal atrophy besides cerebellar atrophy (Fig. 3d). MRI of patient 5-II4 also showed frontotemporal cortical, midbrain, and dorsal pons atrophy besides cerebellar atrophy (Fig. 3f, g).

## Discussion

The field of ARCA or SCARs has developed rapidly in recent years, with the discovery of a growing number of causal genes and an expanding phenotypic spectrum. SYNE1-related ARCA1 was first described in 2007 as adult onset, relatively pure cerebellar ataxia in families originating from the Beauce region of Quebec, Canada [3]. Recent studies on SYNE1 ataxia have changed the definition of ARCA1 from a geographically limited pure cerebellar recessive ataxia to a complex multisystem syndrome that is relatively common on a global scale. Previous studies showed the prevalence of SYNE1 ataxia from 1.6 to 6.0% in 7 independent research cohorts of recessive and sporadic ataxia patients in Table 3. In this study, we identified 6 unrelated index patients carrying two truncating SYNE1 variants or one truncating plus one missense variant, with a prevalence of 3.8% (6/158) in this Chinese cohort of recessive and sporadic ataxia patients. To date, this is the largest number of causal variants of SYNE1 ataxia reported by one single study in China.

In previous studies, SYNE1-related ARCA was described as pure cerebellar ataxia characterized by gait ataxia, dysarthria, dysmetria, mild oculomotor system abnormalities, and diffuse cerebellar atrophy on brain imaging [3, 13]. It is now believed that pure cerebellar ataxia only accounts for 20% of SYNE1 ataxia cases, while the other 80% of patients show complex ataxia phenotypes with a wide range of extra-cerebellar neurologic and non-neurologic dysfunctions [7–9, 14]. The most common extra-cerebellar neurologic dysfunctions included MND, mental retardation or cognitive impairment, and brainstem dysfunction. Other reported extra-cerebellar neurologic and non-neurologic dysfunctions included musculoskeletal abnormalities (pes cavus, scoliosis, Achilles tendon contractures), elevated serum creatine kinase level, urinary urge incontinence, reduced vibration sense, respiratory distress, ophthalmoparesis, and strabismus [7, 16]. These findings support a new and more comprehensive recognition of SYNE1-related ataxia as a multisystemic spectrum disease.

Our study provided new evidence supporting this notion. Patients 1-IV2 and 6-II2 showed an adult onset of pure cerebellar ataxia with normal neurophysiological findings. The cerebral MRI showed prominent cerebellar atrophy with sparing of vermis and cortical hemisphere. In contrast, other patients showed complex neurodegenerative symptoms in addition to cerebellar ataxia. Patient 2-V1 exhibited marked signs of upper MND, with lower limb pyramidal signs, hyperreflexia, and hypertonia. Patients 3-IV1 and IV4 presented with upper and lower motor neuron involvement several years before he developed cerebellar ataxia, which mimicked juvenile-onset amyotrophic lateral sclerosis (ALS).

**Table 1** Molecular features and predicted pathogenicity of SYNE1 variants identified in this study

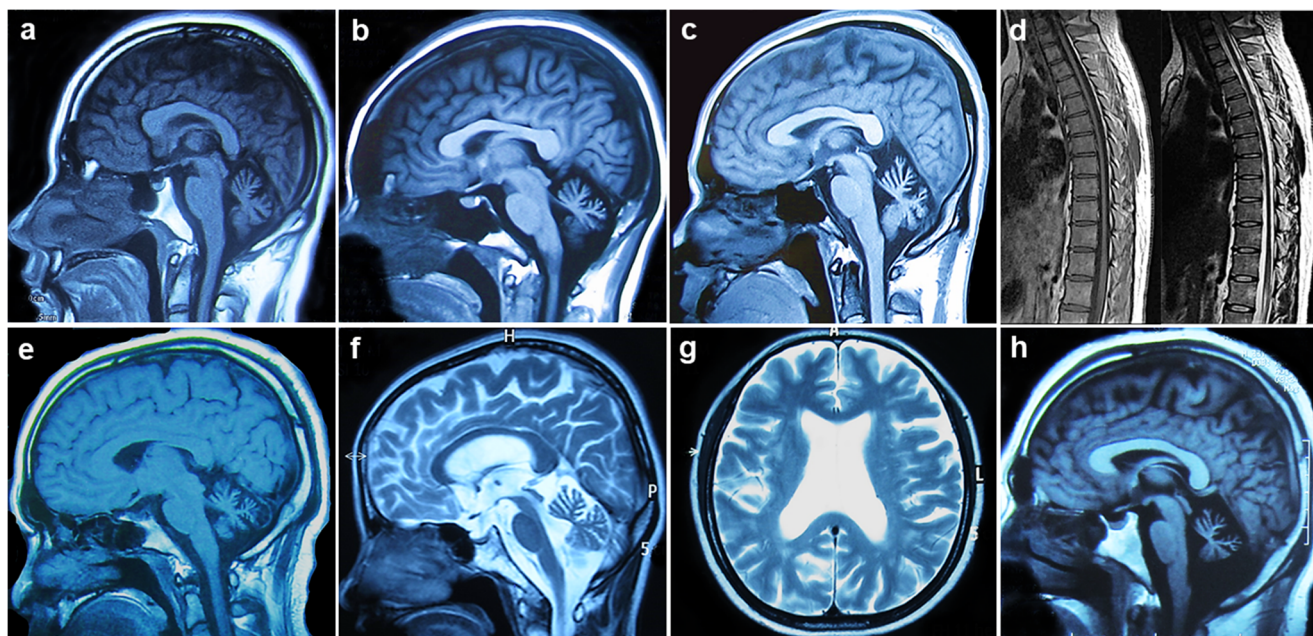
Family number	Inheritance	Mutation	Nucleotide	Amino acid	Bioinformatics prediction		ACMG	Database	HGMD Report								
					Changes	Changes				Mutation taster	Polyphen-2	SIFT	Evidence	Classification	EXAC	1000G	gnomAD
1 - IV2	AR		c.12670dupC		p.L4224Pfs*16	-	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Unreported	
	CM																
2 - V1	AR		c.20826+1G>T		Splicing	Damaging (1)	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Unreported	
	CM		c.25954C>T		p.R8652*	Damaging (1)	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Reported	
3 - IV1	AR		c.23237_23238insA		p.L7747Afs*28	-	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Unreported	
3 - IV2	CM																
4 - III	AR		c.4491delT		p.Q1498Rfs*3	-	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Unreported	
	CM		c.23624delT		p.V7875Afs*47	-	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Unreported	
5 - III	AR		c.21955C>T		p.Q7319*	Damaging (1)	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Unreported	
5 - II4	AR		c.23777C>A		p.T7926K	Damaging (1)	Probably damaging (1)	Damaging (0.001)	PM1+PM2+PM3+PP3			Likely Pathogenic	NF	NF	NF	Unreported	
6 - II2	AR		c.13102delG		p.D4368Tfs*2	-	-	-	-	-	PVS1+PM2+PM3	Pathogenic	NF	NF	NF	Unreported	
	CM		c.18467G>T		p.R6156L	Tolerated (0.924)	Benign (0.132)	Damaging (0.007)	PM2+PM3			VUS	NF	NF	NF	Unreported	

AR, autosomal recessive; CM, consanguineous mating; Hom, homozygous mutations; Het, heterozygous mutation; SIFT, sorting intolerant from tolerant; ACMG, American College of Medical Genetics and Genomics; -, unable to predict using this software; VUS, variation of uncertain significance; EXAC, exome aggregation consortium (<http://exac.broadinstitute.org/>); 1000G, 1000 genome project (<http://www.1000genomes.org/>); gnomAD, Genome Aggregation Database; NF, variant was not found in this database

**Table 2** Summarize the clinical features of the 8 patients

Phenotype	Patients ID							
	1-IV2	2-V1	3-IV1	3-IV2	4-III	5-III	5-II4	6-II2
Sex/gender	M	F	M	M	M	M	F	M
Origin/ethnicity	Guizhou/Han	Hebei/Han	Hubei/Han	Hubei/Han	Hebei/Han	Xinjiang/Uyghur	Xinjiang/Uyghur	Hebei/Han
Age (year) at examination onset	27	22	30	23	29	42	35	33
Age (year) at onset	23	18	12	10	24	18	15	27
Initial symptoms	Gait ataxia	Spastic gait	Distal muscle atrophy and weakness	Distal muscle atrophy and weakness	Gait ataxia Dysarthria	Gait ataxia	Mental retardation	Gait ataxia Dysarthria Limbs ataxia
Additional clinical features	Limbs ataxia	Limbs ataxia	Gait and limbs ataxia	Gait and limbs ataxia	Abnormal pursuit	Limbs ataxia	Gait and limbs ataxia	Limbs ataxia Nystagmus Slow saccades
Phenotype category	Dysarthria Slow saccades	Hyperreflexia in LL Hypertonia in LL	Hypertonia in LL Brisk reflexes	Hypertonia in LL Brisk reflexes	Hypertonia Mild cognitive decline	Dysarthria Slow saccades	Dysarthria Nystagmus	Nystagmus Slow saccades Hypotonia
	Abnormal pursuit Hypotonia	Pathologic reflex	Pathologic reflex	Pathologic reflex	Pathologic reflex	Abnormal pursuit	Slow saccades	
	Pure cerebellar ataxia	Cerebellar ataxia and upper motor neuron disease	Cerebellar ataxia and juvenile-onset amyotrophic lateral sclerosis	Cerebellar ataxia and juvenile-onset amyotrophic lateral sclerosis	Cerebellar ataxia & Cognitive impairment	Cerebellar ataxia & Cognitive impairment	Cerebellar ataxia and upper motor neuron disease and mental retardation	Pure cerebellar ataxia
SARA score	12	16	9	8	11	16	18	13
ICARS Score	32	41	27	26	30	40	42	31
MR imaging	Cerebellar atrophy	Cerebellar atrophy	n.d.	Cerebellar atrophy & Spinal atrophy	Cerebellar atrophy	n.d.	Cerebellar atrophy and slight frontotemporal atrophy	Cerebellar atrophy
EMG	n.d.	Chronic neurogenic	n.d.	Extensive neurogenic	Normal	n.d.	Chronic neurogenic	n.d.
EEG	n.d.	Normal	n.d.	Normal	Normal	n.d.	Frontotemporal slow waves	n.d.
MMSE	29	28	28	28	26	23	24	27
MoCA	27	26	27	28	22	21	20	26
WAIS								
FIQ	n.d.	n.d.	91	92	72	70	62	n.d.
PIQ	n.d.	n.d.	87	88	69	65	56	n.d.
VIQ	n.d.	n.d.	95	96	78	75	69	n.d.

FIQ, Full Scale Intelligence Quotient; EEG, electroencephalograph; EMG, electromyography; ICARS, International Cooperative Ataxia Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; n.d., not done; PIQ, Performance Intelligence Quotient; WAIS, Wechsler Adult Intelligence Scale (age > 16); SARA, Scale for Assessment and Rating of Ataxia



**Fig. 3** Cerebral MRI features of 6 probands with SYNE1 variants. T1 sagittal view of moderate cerebellar atrophy in patients 1-IV2 (a), 2-V1 (b), and 3-IV2 (c); T1 and T2 sagittal view of thoracic spinal atrophy in patient 3-IV2(d); T1 sagittal view of marked cerebellar atrophy in patients

4-III (e) and 6-II2 (h); T2 sagittal view of moderate cerebellar atrophy, midbrain, and dorsal pons atrophy in patient 5-II4 (f); T2 axial view of mild frontotemporal cortical atrophy in patient 5-II4 (g)

Patient 5-II4 presented with mental retardation and behavioral disorder as initial symptoms, followed by cerebellar ataxia and upper MND. Patients 4-III1 and 5-III1 also showed cognitive impairment.

Several research centers reported that motor neuron dysfunction was the most frequent complication of SYNE1 ataxia patients [7, 9, 19]. Gama et al. analyzed both supra- and infratentorial white matter structures in patients with SYNE1 ataxia associated with MND through tract-based spatial statistics (TBSS) which consists of a voxel-wise analysis of diffusion tensor imaging (DTI) [20]. They observed degeneration and disruption in

the corticospinal tracts including the motor cortex, internal capsule, and cerebral peduncle, which somewhat resembles the changes described in motor neuron diseases such as ALS. In our imaging analysis, cranial MRI of patient 5-II4 provided similar evidence of atrophy from frontotemporal cortical, midbrain to dorsal pons besides cerebellar. Previous studies were unable to detect significant spinal cord impairment due to the small sample size of patients. Thoracic MRI of patient 3-IV2 showed spinal atrophy, which exactly as complementary evidence, although larger sample size is still needed to confirm this observation.

**Table 3** A comprehensive table of prevalence and relevant publication for independent research cohorts

Country/region	Ethnicity	Prevalence	Relevant publication
England, Turkey, Sri Lanka/Europe	Diverse	2.0% (4/196)	Wiethoff et al. [8]
Diverse countries/Europe, Middle East, Mediterranean	Diverse	6.0% (7/116)	Mademan et al. [9]
36 countries/Europe	Diverse	5.3% (23/434)	Synofzik et al. [7]
Diverse countries/Europe	Diverse	1.8% (6/319)	Coutelier et al. [14]
Japan/Asia	No mentioned	2.5% (3/120)	Izumi et al. [19]
China/Asia	Han	1.6% (2/126)	Peng et al. [16]
Korea/Asia	No mentioned	3.2% (2/63)	Kim et al. [15]
China/Asia	Han, Uyghur	3.8% (6/158)	This study

Previous electrophysiological studies on SYNE1 ataxia associated with MND were very limited [7, 9]. Peng et al. first discussed the EMG characteristics in 3 patients with SYNE1 ataxia plus MND from two Chinese families, which differ from those in juvenile ALS [16]. Needle EMG in juvenile ALS typically shows signs of apparent denervation (positive sharp waves and fibrillation potentials) and fasciculation potentials, in combination with signs of re-innervation (large amplitude, long duration motor unit potentials, and reduced recruitment) in multiple regions [21]. In contrast, Peng et al. reported distinct signs of re-innervation due to a slower pathological process in motor neurons in SYNE1 ataxia, whereas spontaneous activities (fibrillation, positive sharp wave, and fasciculation potentials) were very rare or absent. In our study, EMG of patients 2-V1 and 5-II4 showed a similar re-innervation caused by chronic neurogenic changes. However, EMG in patient 3-IV2 showed signs of denervation with frequent spontaneous activity, which, in combination with elevated creatine kinase level, suggests that acute neurogenic damage was happening during the disease duration and progression [9].

Schmahmann and Sherman described a condition called cerebellar cognitive affective syndrome (CCAS), which is characterized by deficits in executive function, linguistic processing, spatial cognition, and affect regulation [22, 23]. The role of the cerebellum in cognition and affect in patients with ARCA1 was first explored by Laforce et al. in 2010 [24]. Among the 21 patients who showed significant deficits in attention, verbal working memory, and visuospatial skills. Since then, other studies have described mental retardation or cognitive impairment as the non-motor manifestations in the ARCA1 patients [7–9, 16, 25]. Schmahmann et al. developed the CCAS/Schmahmann Scale that was expected to be more sensitive than MMSE or MoCA in detecting impairments in the cerebellar patients [26]. Gama et al. detected reduced cortical thickness in fronto-parieto-temporal areas which are known to be associated with attention and executive functions in ARCA1 patients by DTI-TBSS analysis [20]. In this study, Neuropsychological evaluation (WAIS, MoCA) revealed significant cognitive impairment in patient 4-II1 and patients 5-II1 and II4. Patient 5-II4 showed frontotemporal cortical atrophy in MRI and slowed waves in the frontal and temporal region in EEG. The present study is limited in these aspects, although we expect future studies with larger numbers of patients will combine functional neuroimaging techniques with CCAS/Schmahmann Scale assessment, and better elucidate the mechanism of CCAS in SYNE1 ataxia.

The correlation between genotype and phenotype is being explored in SYNE1-related diseases. In this study, all variants in SYNE1 ataxia patients are distributed throughout the spectrin repeats domain, except for the N-terminal actin-binding domain and C-terminal KASH domain, and without

obvious mutational hot spot regions. Recent reports revealed that variants associated with MND tend to be located in the C-terminal region, in contrast to the variants associated with pure cerebellar ataxia [27, 28]. A similar distribution was observed in our patients: the variants related to MND (yellow boxes), cognitive impairment (blue boxes), and MND and mental retardation (gray boxes) are located in the C-terminal region (Fig. 2), which supports a genotype-phenotype correlation. In complex SYNE1 ataxia, C-terminal truncating variants may result in mixed phenotypes by generating short KASHLESS isoforms that are prevalently expressed in skeletal muscle, cerebral cortex, and other tissues, or by acting synergistically with variant forms of other key proteins [4, 27].

In conclusion, we have characterized the clinical features and genetic spectrum of a group of Chinese ARCA1 patients carrying SYNE1 variants. The frequency of SYNE1 variants in our cohort is higher than previously reported in another study conducted in China. Our study has revealed a genotype-phenotype correlation in SYNE1 ataxia. Further studies will elucidate the mechanism underlying the diversity of SYNE1-related diseases.

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**Authors' Contribution Statement** Conceived and designed the project: W.H.G. and X.H.D. Performed the experiments: X.H.D., Y.H., C.Z., and X.Z. Analyzed the data: X.H.D., Y.H., and J.Z. Contributed to the writing of the manuscript: All authors have made a significant contribution and have approved the final version of this manuscript.

## Compliance with Ethical Standards

This study was approved by the Ethics Committee of China-Japan Friendship Hospital. The methods in this study were performed in accordance with the approved guidelines. Written informed consent was obtained from all the patients.

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

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