The clinical phenotypes and genetic characteristics of seven epilepsy patients related to heterozygous *DEPDC5* variants in China

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Abstract

Objective: DEPDC5 together with NPRL2 and NPRL3 forms the GATOR1 which plays an important role in the the mechanistic target of rapamycin (mTOR) pathway. Deregulation of mTOR signalling has been associated to various neurological conditions, including epilepsy. Variants in the gene encoding GATOR1 complex, especially in *DEPDC5*, have been implicated in the pathogensis of several focal epilepsies. While there was little report on the electroencephalogram (EEG) feature of *DEPDC5* related epilepsy, we decided to investigate the specific EEG pattern and the prognosis of *DEPDC5* related epilepsy.

Methods: The records of 546 epilepsy patients with unknown causes who were admitted in Xijing Hospital and underwent whole exome sequencing (WES) from 2015 to 2019 were retrospectively reviewed. Finally, the clinical data of these 7 patients with *DEPDC5* variants were collected in this study. We analyzed their clinical manifestations, EEG and magnetic resonance imaging (MRI).

Results: Seven *DEPDC5* variants, including six novel mutations, were identified in seven individuals with focal epilepsy. Among these patients, one had family history. Four showed specific interictal EEG patterns, periodic-like sharp waves or spike waves, were found in four patients. Five out of seven patients (71.4%) were well-controlled by anti-epilepsy drugs while two patients with sleep-related hypermotor epilepsy had either drug resistance or relapse of epilepsy.

Conclusion: *DEPDC5* variants were related to focal epilepsy in patients with or without family history. The EEG abnormalities of *DEPDC5* related epilepsy were heterogeneous among different patients, while periodic-like sharp waves or spike waves might be the most characteristic interictal EEG pattern for *DEPDC5* related epilepsies. In this study the prognosis of *DEPDC5* related epilepsy was similar to other epilepsies. *DEPDC5* variants may not predict the prognosis so far.

Keywords: *DEPDC5* related epilepsy, EEG pattern, Drug resistance

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Introduction

Epilepsy, as a chronic neurological disease caused by transient brain dysfunction, has become the second most common neurological disease. According to a recently research on global burden of epilepsy, there were 45.9 million patients with all-active epilepsy in 2016 [1]. In 2017, the International League Against Epilepsy (ILAE) updated the framework for classifying seizure types and epilepsy, and suggested that genetic factors may be the most important independent epileptic factors [2]. In recent years, with the concept of precision medicine and the development of next-generation sequencing technology, many epilepsy related genes have been localized and cloned.

DEPDC5 (Dishevelled, egl-10, and pleckstrin domain–containing protein 5), NPRL2 (Nitrogen permease regulator-like-2) and NPRL3 (Nitrogen permease regulator-like-3) together form the GATOR1 (GAP activity towards rags complex 1) complex. GATOR1 complex constitutes the amino acid-sensitive part of the mechanistic target of rapamycin (mTOR) pathway [3]. When cells stay in an environment of amino acids deprivation, this complex acts as a repressor of the mechanistic target of rapamycin complex 1 (mTORC1) pathway through interfering the localization of mTORC1 to the lysosome [3]. Mutations in *DEPDC5, NPRL2* or *NPRL3* may resulted in dysfunction of these proteins, which will cause over-activation of mTORC1. The over-activation of mTOR pathway in brain tissue will lead to altered neuronal morphology, enhanced cell size, and abnormal cortical lamination, resulting in focal cortical dysplasia (FCD) [4].

The relationship between genes encoding components of GATOR1 complex and epilepsy was firstly reported in familial focal epilepsies in 2013 [5]. From then on, heterozygous germline variants in the GATOR1-encoding genes have continuously been found to be associated with focal epilepsy syndromes, such as sleep-related hypermotor epilepsy (SHE) [6, 7], familial focal epilepsy with variable foci (FFEVF) [5, 8] and familial temporal lobe epilepsy (FTLE) [8]. Mutations in *NPRL2* and *NPRL3* causing focal epilepsy were first reported in 2015 [9, 10], which is later than *DEPDC5* [5]. Recently, Baldassari *etal* reported 73 patients with GATOR1 variants including 63 patients carried mutations in *DEPEC5*, which is the largest cohort study ever reported [11]. However, in all of these studies, there was little report on the EEG feature of *DEPDC5*-related epilepsy. Hence, in this study, we investigate the clinical phenotype, genetic characteristics, the prognosis as well as the EEG features of epilepsy related to *DEPDC5* variants, which may deepen the understanding of GATOR1-related epilepsy syndrome and lay the foundation of further researches.

Methods

Patients

The records of 546 epilepsy patients with unknown causes who underwent whole exome sequencing (WES) in the Department of Neurology, Xijing Hospital of Fourth Military Medical School from 2015 to 2019 were retrospectively reviewed. The present study is a mono-center observational study, developed in accordance with the STROBE [12] guidelines for observational studies and those for epidemiological studies on epilepsy [13]. The study was approved by the local Ethical Committees. Due to the retrospective and noninterventional nature of the study, informed consent was not required.

Whole exome sequencing

Blood of the 546 epilepsy patients with unknown cause were collected and genomic DNA was extracted using the Blood Genome Column Medium Extraction Kit (Kangweishiji, China) according to the kit instructions. Liquid hybridization of the genomic DNA was performed using Roche Nimble Gen Seq EZ Exome Enrichment Kit V2.0 and Seq EZ Exome Enrichment Kit V2.0 capture probes (Roche, USA), and the target DNA fragments were enriched to construct exome library covering 19 119 genes with whole exons and partial introns. Each enriched region shared 40 Mb of targeted sequences. High-throughput sequencing was performed by Illumina NovaSeq 6 000 series sequencer (PE150), and no less than 99% of target sequences were sequenced. The sequencing process was performed by the Zhiyin Oriental Translational Medicine Research Center. The processes of bioinformatics analysis are as follows: (1) Quality control: Raw data were cleaned after adapters being removed; low-quality reads filtering and other quality control protocols. (2) Variants calling: The clean data were aligned to the NCBI human reference genome (hg18) using BWA and variants were called using GATK. Samtools and Pindel were used to call single nucleotide polymorphisms (SNPs) and indels, respectively. The clean data were than filtered, according to the quality of the sequencing, for further protocol. (3) Variants annotation and prediction: Nonsynonymous substitutions and SNPs with minor allele frequency (MAF) lower than 1% were filtered using SIFT. The function of mutated genes and their pathogenicity were then analyzed referencing to dbSNP, 1 000 Genomes Project, ExAC, ESP, OMIM, Swiss-var, HGMD, ClinVar and other disease databases. (4) The single base variants of unknown pathogenicity were analyzed by Provean, SIFT, Polyphen2-HVAR, Polyphen2-HDIV, Mutationtster and other protein structure prediction software. MaxEntScan was used to screen potential splice sites. All of these variants underwent Sanger sequencing to confirm.

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Long term video electroencephalogram (VEEG)

EEG signals were recorded with 21 scalp electrodes placed according to the 10–20 system. Data from several recording systems (Nihon Kohden, biologic, Nicolet) were reviewed in an average reference montage. In some patients, one or two bipolar electromyographic signals were recorded in parallel from major muscles activated during motor seizures. Patient behavior was captured with a simultaneous video recording. EEG signals were recorded with pairs of 9-mm diameter silver/silver chloride electrodes placed 2-cm apart over muscle bellies. We recorded deltoid and quadriceps muscles according to the site of the most common movement disorders. EEG signals were band-pass filtered at 53–120 Hz. The patients took the 24 h VEEG annually. Twelve patients took at least twice 24 h VEEG. In the nine patients left, eight patients took one 24 h VEEG while one patient took one time of 15 h VEEG.

Classification of the prognosis

The response to treatment was classified into four categories: seizure freedom (defined as no seizures for at least 1 year), effectiveness (seizure reduction 50–99%), no beneficial effect, or increase of seizure frequency. Treatment success was defined as achieving ≥ 50% reduction in seizure frequency or seizure freedom after receiving treatment. Relapse was defined as the reappearance of epilepsy after stopping taking drug for at least three years. Refractory epilepsy is defined as epilepsy in which seizures persist and seizure freedom is very unlikely to be attained with further manipulation of anti-epileptic drugs (AEDs) therapy [14].

Results

Genetic findings

In total, there were seven different *DEPDC5* variants, which were considered pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics guideline [15], detected in seven patients, including four truncation variants, two splicing site variants and one frame-shift variant (Table 1). All these variants were validated by Sanger sequencing. In all these

seven variants, six of them were novel variants and none of them can be located in the databases we chose. Splicing site variants, frame-shift variants and truncation variants were predicted by MutationTaster, MaxEntScan (data not shown). In the patients conducting WES-trios, there are no de novo mutations. All of these 7 variants were heterozygous variants. In addition, these variants spread across DEPDC5 protein and four of them located at the structural axis for binding arrangement (SABA) domain. The other three variants located at steric hindrance for enhancement of nucleotidase activity (SHEN) domain, C-terminal domain (CTD) and the Lasso B part between SHEN domain and Dishevelled, Egl-10 and Pleckstrin (DEP) domain (Fig. 1) [16].

Clinical findings

In this study, 7 patients with *DEPDC5* pathogenic or likely pathogenic variants (disease duration, median 10 years, range 1–19 years) were selected from 546 patients who had underwent WES. The clinical data, including seizure type, EEG, neuroimaging characteristics, treatment and prognosis are listed in detail in Table 2 and Table 3. In these patients, only one patient was adult onset. The seizure onset age of the other six patients ranged from 1 to 12 (median 6.5) years, two thirds of them in childhood (4/6, 66.7%).

Seizure type

In these seven patients, all of them were diagnosed as focal epilepsy (Table 2). Among the seven patients, three of them only had this kind of seizure while the other four patients had different attack models. In patient 1 and 5, sleep-related focal hypermotor seizures were the most common type. Mostly, the epilepsy in patient 2 and 4 were presented as behavior arrest with impaired awareness. All of these patients mentioned above had focal seizures evolving into bilateral tonic-clonic seizures. In patient 3, only focal to bilateral tonic-clonic seizures were observed. In total, focal to bilateral tonic-clonic seizures were reported in six patients (6/7, 85.7%). Besides, focal clonic seizures without impaired awareness were observed in patient 6.

Table 1 Variants found in seven patients

No	Gene	Nucleotide change	Amino acid change	Mutation type	ACMG score	ACMG
1	*DEPDC5*	c.504delG	p.S168Sfs*10	frame-shift variants	PVS1 + PM2	Pathogenic
2	*DEPDC5*	c.715C > T	p.R239X,1365	truncation variants	PVS1 + PS1 + PM2 + PP3	Pathogenic
3	*DEPDC5*	c.823A > T	p.K275X,1329	truncation variants	PVS1 + PM2 + PP3 + PP1	Pathogenic
4	*DEPDC5*	c.947–2(IVS14)A > G		splicing site variants	PVS1 + PM2 + PP3	Likely pathogenic
5	*DEPDC5*	c.2935G > T	p.E979X,625	truncation variants	PVS1 + PM2 + PM	Pathogenic
6	*DEPDC5*	c.3214G > T	p.E1072X,532	truncation variants	PVS1 + PM2 + PP3	Pathogenic
7	*DEPDC5*	c.4437–2(IVS41)_c.4437–1(IVS41)insG		splicing site variants	PVS1 + PM2	Likely pathogenic
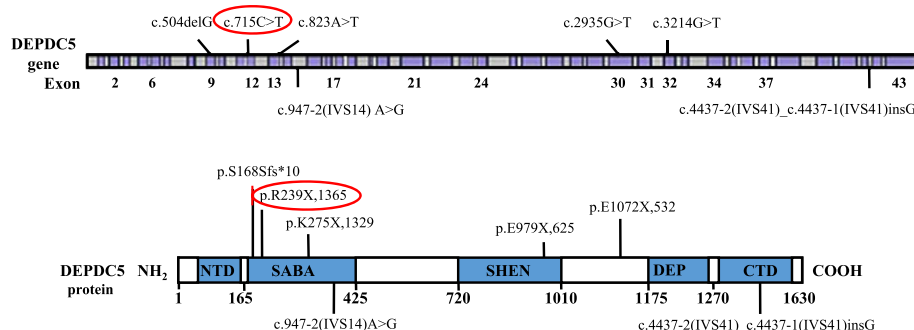
Fig. 1 Seven variants we found in the study. The variants in the red cycle indicates that it has been reported

Neuroimaging and video electroencephalogram

Brain magnetic resonance imaging (MRI) were available in all of these seven patients. Among them, four patients had normal MRI while the other three had different abnormalities. In patient 3, left hippocampus sclerosis was discovered. Bilateral paraventricular white matter demyelination was spotted. And in patient 6, FCD was found in the left paraventricular area. As for patient 1, besides MRI, she underwent positron emission tomography-computed tomography (PET-CT). On her PET-CT, a locus with lower metabolism was located in gyrus temporalis medius of left temporal lobe. All of these seven patients underwent long-term VEEG annually. At the last check, seizures were captured in two patients (patient 4 and 5). In patient 4, three seizures were recorded in his VEEG and concentrate in light sleep period. All of these seizures rise from the left temporal leads and spread to all leads and the patient started to develop tonic seizure lasting for 30 s with tachycardia. In patient 5, ten seizures were recorded in his VEEG. The moment paroxysmal rapid waves appeared in his right frontal leads, he started to developed hypermotor seizures which presented as pedaling, screaming and unconsciousness. As for the interictal EEG, four patients, including patient 1, 3, 4 and 7, had the same EEG pattern. Their interictal EEG were presented as periodic spike waves and sharp waves in their frontal leads. Three of them were diagnosed as frontal lobe epilepsy (FLE) while the other was diagnosed as temporal lobe epilepsy (TLE). As for patient 6, she underwent several EEGs. However, all of them showed normal EEG. Considering her clinical symptoms and the FCD on her MRI, she was diagnosed as unspecified focal epilepsy. All of the meaningful EEG pictures were

Table 2 Clinical data of the seven patients

No	Sex	Age of onset	Duration of epilepsy	Seizure type	Diagnose	EEG	MRI	Treatment	Prognosis
1	F	4	10	Focal onset, impaired awareness, hyperkinetic automatism, focal to bilateral tonic-clonic seizure	FLE	Lt ea	Normal	TPM, CZP, CBZ, LEV, LCM	refractory epilepsy
2	M	1	19	Focal onset, impaired awareness, behavior arrest, focal to bilateral tonic-clonic seizure	F-TLE	Bt ea	Normal	LTG, LEV	seizure freedom
3	M	8	18	Focal onset, focal to bilateral tonic-clonic seizure	TLE	Lt ea	Left HS	CBZ	seizure freedom
4	M	20	1	Focal onset, impaired awareness, behavior arrest, focal to bilateral tonic-clonic seizure	FLE	Lt ea	Normal	OXC, LEV	seizure freedom
5	M	2	9	Focal onset, impaired awareness, hyperkinetic automatism, focal to bilateral tonic-clonic seizure	FLE	Rt ea	Bilateral paraventricular white matter demyelination	OXC	relapse
6	F	12	12	Focal onset, without impaired awareness, clonic seizure	unspecified focal epilepsy	Normal	left paraventricular focal cortical dysplasia	LEV, OXC	effectiveness
7	F	10	11	Focal onset, focal to bilateral tonic-clonic seizure	FLE	Bt ea	Normal	LTG, LEV	effectiveness

FLE Frontal lobe epilepsy, *F-TLE* Frontotemporal lobe epilepsy, *TLE* Temporal lobe epilepsy, *Lt* Left, *Rt* Right, *Bt* Bilateral, *TPM* Topiramate, *CZP* Clonazepam, *CBZ* Carbamazepine, *LCM* Lacosamide, *LEV* Levetiracetam, *LTG* Lamotrigine, *OXC* Oxcarbazepine

Table 3 Sum-up of clinical data of the patients

Variate	DEPDC5
Probands	7
Gender (male:female)	4:3
Age at SZ onset median(range)	10.5(1,20)
Epilepsy phenotype	
Focal onset	7
TLE	2/7(28.6%)
FLE	4/7(57.1%)
F-TLE	1/7(14.3%)
unspecified focal epilepsy	1/7(14.3%)
EEG(interictal)	
Lt ea	3/7(42.9%)
Rt ea	1/7(14.3%)
Bt ea	2/7(28.6%)
Normal	1/7(14.3%)
Neuroimaging	
Normal	4/7(57.1%)
Hippocampus sclerosis	1/7(14.3%)
Demyelinating leision	1/7(14.3%)
FCD	1/7(14.3%)
AEDs	
Monotherapy	2/7(28.6%)
2 AEDs	4/7(57.1%)
≥ 3 AEDs	1/7(14.3%)
Prognosis	
Effectiveness	2/7(28.6%)
Seizure freedom	3/7(42.9%)
Relapse	1/7(14.3%)
Refractory epilepsy	1/7(14.3%)

FLE Frontal lobe epilepsy, *F-TLE* Frontotemporal lobe epilepsy, *TLE* Temporal lobe epilepsy, *Lt* Left, *Rt* Right, *Bt* Bilateral

presented in Fig. 3, while all of their EEG can be seen in the supplementary materials.

Familiy history
In these seven patients, one patient had certain family history. The genealogic tree for this patient was presented in Fig. 2. In Family a (proband: patient 3), the other affected individual (II-1) had the similar clinical characteristic with the proband and got seizure free after receiving AEDs. II-1 also carries the same variants found in the proband. Besides, the proband's mother also carries the variant but doesn't have any clinical symptoms.

Treatment and prognosis
In these seven patients, five patients responded well to AEDs, especially the therapeutic regimen based on

levetiracetam. Three patients got seizure free after receiving AEDs (patient 2, 3 and 4). The seizure frequency of the other two patients also decreased for more than 90%. However, there was one refractory case (patient 1) who had already received five AEDs but still had seizure attacks for about 10 times per month. As for patient 5, he had been well controlled with sodium valproate and withdrawn all his medication at 2015. However, in 2018, his epilepsy relapsed. Until last follow-up, he still had seizures for about seven times per night, mainly as hypermotor seizures.

Discussion
The mTORC1 pathway is a central regulator of cell growth [17]. Nutrients, such as amino acids, signal to mTORC1 through the Rag GTPase heterodimer (RAGA or RAGB bound to RAGC or RAGD) [18]. DEPDC5 together with NPRL2 and NPRL3 forms GATOR1 complex regulating the activity of Rag GTPase heterodimer by acting as GTPase acticvating protein (GAP). In the situation of amino acid deprivation, GATOR1 complex will interfere the localization of mTOR complex 1 to the lysosomal surface, which prevents the activation of mTOR pathway [3]. According to the structure model presented by Shen et al. these three subunits, together with the Rag GTPase heterodimer, have complex interactions between each other and the intactness of GATOR1 is needed for its GAP function [16]. When there are mutations in any of these three subunits, the interactions are interfered and the intactness of GATOR1 is affected. The loss-of-function (LoF) of GATOR1 results in the over-activation of mTOR pathway. In brain, this over-activation may lead to FCD and epilepsy [4].

In our study, the age at epilepsy onset ranged from 1 to 20 years (median 10.5 years), mostly in their childhood (5/7, 71.4%), which was later than the group reported by Baldassari et al. recently [11]. We found seven different variants in *DEPDC5*. Four variants, including two truncation variants, one frame-shift variants and one splicing site variants, affects the SABA domain. This domain is in charge of the interaction between DEPDC5 and NPRL2 [16]. One truncation variant, c.2935G > T, affects SHEN domain. This domain plays an important role in the interaction between DEPDC5 and RAGA [16]. In the two variants left, one truncation variant (c.3214G > T) affects Lasso B part between SHEN and DEP domain while the other splicing site variant (c.4437−2(IVS41)_c.4437−1(IVS41)insG) affects CTD domain. These two variants may affect the intactness of DEPDC5, which also brings negative affect on the function of GATOR1. All in all, all these variants were thought to be related to patients' symptoms.

In our study, there was one patient with family history. In this family, there was a patient (II-1) with the same variant and similar symptoms compared with the proband. However, mother of the proband who carried the
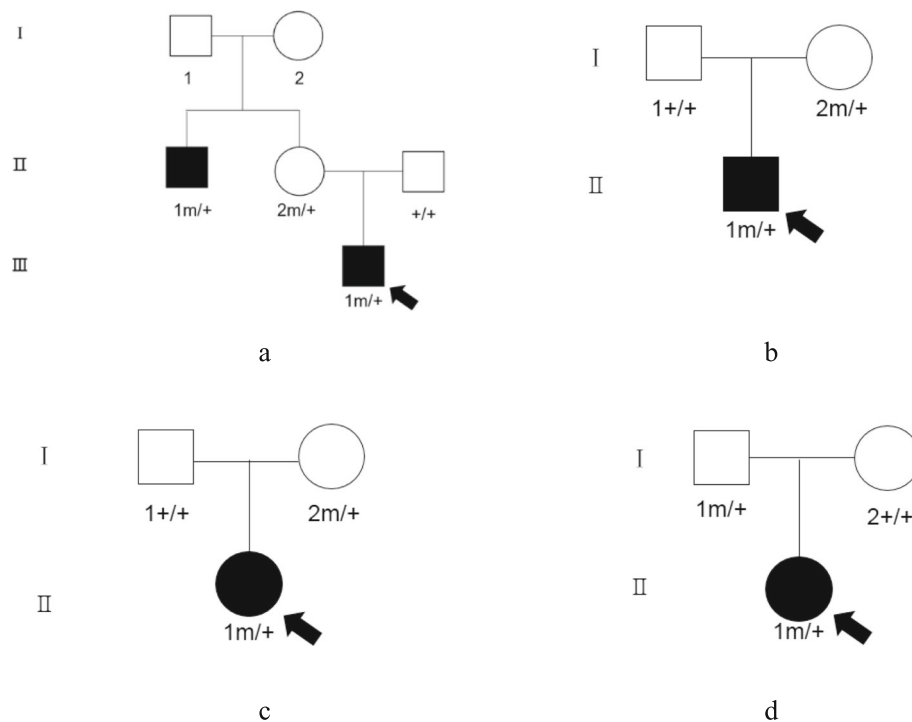
Fig. 2 a-d Genealogic tree of patient 3, 5, 6 and 7. The solid squares indicate patients with epilepsy while the hollow ones indicate healthy people. The letter "m" indicates the carrier of variants while "+" indicates wild type

same variant didn't have any symptoms, which indicates incomplete penetrance of *DEPDC5* variant. According to Baldassari et al. variants inherited from asymptomatic parents in 64% of the cases [11]. So, there is still a great need for future basic research to definitively settle on their pathogenicity.

In the most recent article on epilepsy-related GATOR1 variants, Baldassari et al. reported 63 patients with *DEPDC5* variants in 73 patients. In their research, focal seizures were described in most of these patients (60/63, 95.2%), including SHE, FLE, TLE and unspecified focal seizure and the most common phenotype is SHE (22/63, 34.9%) [11]. Drug resistance in the series of Baldassari et al. was observed in half of the probands, and up to 65% in probands with SHE, supporting previous studies based on smaller cohorts of families with SHE (7/9 drug-resistant individuals) [7]. In our study, two patients were diagnosed as SHE (patient 1 and 5, 2/7, 28.6%) and one of them was diagnosed as refractory epilepsy while the other patient was experiencing relapse of his epilepsy. These findings are in concordance with the conclusion made by Baldassari et al. [11]. As for the other seizure types, things were different. All of these patients responded well to the AEDs (71.4%) and three of them had already been seizure free for at least a year. So, the drug resistance is much smaller than Baldassari et al. had reported (54% for GATOR1 variants,

52.4% for *DEPDC5* variants) [11]. This difference in drug resistance may related to the rather small sample size but it can also suggest that GATOR1 related epilepsy may be not as refractory as it was reported [11]. In these five patients with positive respond, four of them were given therapy based on LEV, which may indicate LEV as a preferential choice for patients with *DEPDC5* variants. Considering the fact that the loss-of-function variants in *DEPDC5* will lead to over-activation of the mTOR pathway, the mTOR inhibitor, such as sirolimus or everolimus, may be a complementary treatment for *DEDPC5* related epilepsy. However, this assumption needs further confirmation.

In the previous studies, there was little information on the EEG characteristics of epilepsy induced by *DEPDC5* variants. In 2018, Hu et al. created an animal model with a focal region with somatic *DEPDC5* deletion [19]. Via this model, the authors found that the EEG features were highly clinically relevant to FCD IIA, which included low-voltage fast activity (LVFA) and and bursts of rhythmic spikes [20, 21]. In our study, the periodic spike waves or sharp waves were found in four patients (Patient 1, 3, 4 and 7), which may indicate that bursts of rhythmic spikes might be a specific EEG pattern for patients with DEPDC5 related epilepsy. Interestingly, the MRI of these patients were all normal. While patient 6,
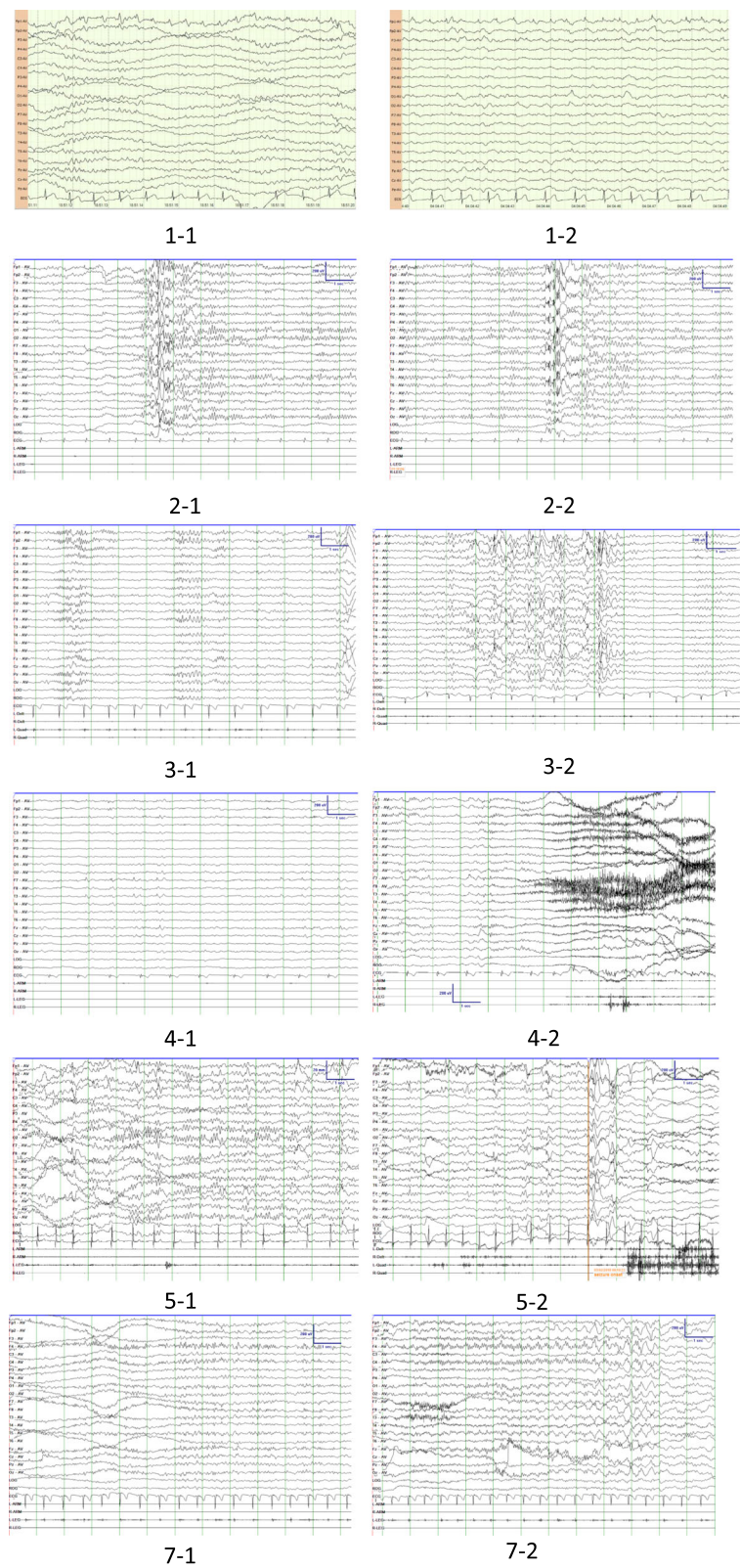
Fig. 3 EEG pictures for all patients. The first number represents the code of patient. While EEG of patient 6 was normal, it was not shown

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who had an abnormal MRI with deep-in FCD, had a normal EEG. As all of these patients underwent scalp-EEG and 1.5 T MRI, this situation may be related to the limited accuracy of the instrument.

Conclusion

In summary, here we reported seven patients with pathogenic or likely pathogenic *DEPDC5* variants. Among these patients, only one patient had family history, which may indicate incomplete penetrance. The drug resistant epilepsy is mainly concentrated in patients with SHE, but the rate of drug resistance of DEPDC5 related epilepsy may not as high as we expected. However, considering the rather small sample size and the lack of basic research on the pathogenic molecular mechanism of the variants we found, there are still much to do in order to get a further understanding of the pathogenesis of DEPDC5 related epilepsy.

Abbreviations
CTD: C-terminal domain; DEPDC5: Dishevelled, egl-10, and pleckstrin domain–containing protein 5; FCD: Focal cortical dysplasia; FFEVF: Familial focal epilepsy with variable foci; FLE: Frontal lobe epilepsy; FTLE: Familial temporal lobe epilepsy; GATOR1: GAP activity towards rags complex 1; ILAE: The International League Against Epilepsy; MRI: Magnetic resonance imaging; mTOR: The mechanistic target of rapamycin; mTORC1: The mechanistic target of rapamycin complex 1; NPRL2: Nitrogen permease regulator-like-2; NPRL3: Nitrogen permease regulator-like-3; PET-CT: Positron emission tomography-computed tomography; SABA: Structural axis for binding arrangement; SHE: Sleep-related hypermotor epilepsy; TLE: Temporal lobe epilepsy; AEDs: Anti-epileptic drugs; VEEG: Video electroencephalogram; WES: Whole exome sequencing

Ethics approval and consent to participate
Due to the retrospective and noninterventional nature of the study, informed consent was not required. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this article is consistent with those guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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