Clinical commentary

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Magnetoencephalogram-assisted diagnosis of familial focal epilepsy with variable foci in a Chinese family with a novel *DEPDC5* mutation*

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ABSTRACT – Familial focal epilepsy with variable foci (FFEVF) is an autosomal dominant disorder characterized by focal seizures arising from different brain lobes in different family members. Currently, the diagnosis of this syndrome mainly depends on the combination of semiology and EEG after exclusion of other types of familial focal epilepsy. Mutations in dishevelled, Egl-10, and pleckstrin domain-containing protein 5 (DEPDC5) have been recently identified as a common cause of this syndrome. We studied a Chinese four-generation FFEVF family with nine affected individuals. Targeted next-generation sequencing was performed for the proband and the suspected mutation was confirmed by Sanger sequencing. Magnetoencephalography (MEG) was applied to two MRI-negative patients with refractory epilepsy. We identified a novel splice site mutation in *DEPDC5* (c.280-1 G>A) in this family. The MEG results showed different dipole-clustered areas in these two patients. This is the first report of the use of MEG to confirm a diagnosis of FFEVF, in a Chinese family with a novel *DEPDC5* mutation. Furthermore, the MEG results also revealed the possibility of surgical resection for these two intractable patients.

Key words: *DEPDC5*, familial focal epilepsy with variable foci, refractory epilepsy, magnetoencephalogram

Familial focal epilepsy with variable foci (FFEVF) is a disorder characterized by focal seizures arising from different brain lobes in different family members, and typically each individual has only one type of seizure. Currently, the diagnosis of this syndrome mainly depends on the combination of semiology and EEG after exclusion of other types

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of familial focal epilepsy (Scheffer *et al*., 1998). Although FFEVF has generally been considered as an epilepsy syndrome without cerebral structural lesions, malformation of cortical development (MCD), especially focal cortical dysplasia (FCD), has been reported recently. Moreover, surgical resection turned out to be a favourable approach for FFEVF patients with suspected FCD (Scheffer *et al*., 2014; Baulac *et al*., 2015; Scerri *et al*., 2015). Pedigree studies have revealed an autosomal dominant inheritance pattern, and mutations in dishevelled, Egl-10, and pleckstrin domain-containing protein 5 (*DEPDC5*) have been recently identified as a common cause of this syndrome. Variation in severity and incomplete penetration are two striking features of FFEVF (Dibbens *et al*., 2013; Ishida *et al*., 2013).

DEPDC5 encodes a ubiquitous protein that plays an important role in brain development from early embryonic development. Together with nitrogen permease regulator-like-2 (NPRL2) and NPRL3, it provides GTPase-activating protein activity towards rags complex 1 (GATOR1), an inhibitor of the mammalian target of rapamycin (mTOR) complex 1 pathway.

This pathway regulates cell growth, proliferation, and apoptosis by acting on the cell cycle, transcription, and translation (Bar-Peled *et al*., 2013). Abnormal neuronal migration and disturbed neuronal excitability, which may lead to epileptogenesis, were observed in *DEPDC5* knock-out mice (Marsan *et al*., 2016; Ribierre *et al*., 2018). *DEPDC5* is not only a common gene affected in familial focal epilepsy, such as FFEVF, but variants have also been reported in other epilepsy syndromes, such as benign epilepsy of childhood with centro-temporal spikes (BECTS) (Lal *et al*., 2014), epileptic spasms (Carvill *et al*., 2015), sudden unexpected death in epilepsy (SUDEP) (Nascimento *et al*., 2015), and malformation of cortical development (Scheffer *et al*., 2014; Baulac *et al*., 2015; Scerri *et al*., 2015; Cen *et al*., 2017).

In this study, we report a four-generation FFEVF family with a novel splice site mutation in the *DEPDC5* gene. To confirm the diagnosis, we performed magnetoencephalography (MEG) in two patients with refractory epilepsy.

Case study

We studied a Chinese four-generation FFEVF family with nine affected individuals. Electroclinical information was collected from direct interview and medical records. Written informed consent was obtained from all participants and guardians of minors. This study was approved by the ethics committees of Xuanwu Hospital Capital Medical University.

The pedigree of the four-generation family is shown in *figure 1*. The average onset age of the family was 9.3 years (three months to 20 years), but the onset age of the proband and her daughter (III-7 and IV-5) was earlier.

The proband (III-7) was a 32-year-old female who had seizure onset at three months after birth. She had recurrent impaired awareness seizures with autonomic features, such as flushing and tachycardia. Most seizure attacks were preceded by an aura of *déjà-vu*. She was diagnosed clinically with temporal epilepsy. EEG confirmed the diagnosis and showed sharp and slow wave complexes predominantly in the right temporal area (Sph-R, Fp2). She was treated with multiple antiepileptic drugs (AEDs), including oxcarbazepine (OXC), valproic acid (VPA), clonazepam (CZP), and lamotrigine (LTG). However, she still had three to five seizure attacks per week.

The proband's daughter (IV-5) was a three-year-old female who had recurrent episodes that included a "strange" smile and transient respiratory arrest from three months after birth. Her clinical presentation was hard to classify in terms of any particular type of epilepsy. Ictal and interictal EEG showed diffuse slow waves at seizure onset, and we could not locate the origin of seizures. She was also refractory to drug treatment which included OXC, VPA, LTG, phenobarbital (PB), and phenytoin (PHT), and she still had 8-10 seizure attacks per day.

The proband's father (II-6) had seizure onset at 20 years old. He had several refractory nocturnal hypermotor seizures per month, which were poorly controlled by multiple drugs (OXC, PB, and PHT). Frontal lobe epilepsy was highly suspected.

The proband's grandfather (I-2), uncles (II-5), aunt (II-8), two cousins (III-2, III-4), and niece (IV-1) all had a history of epilepsy, however, they were free of seizure attacks from middle age and the types of seizure were unclassified. The proband's aunt (II-8) and niece (IV-1) were treated with CBZ, and they stopped their treatment two years after becoming seizure-free. Other members were unable to recall the name of the drug used due to the early termination of treatment.

Neuroimaging study

Magnetic resonance imaging (MRI) was performed for two patients with refractory epilepsy (the proband and her daughter; III-7 and IV-5). However, no abnormality was observed on brain MRI. We then performed MEG in these two patients and used the single equivalent current dipole (ECD) method and Neuromag software (Elekta Neuromag) to localize the spikes. For the proband (III-7), the dipoles mainly clustered at the

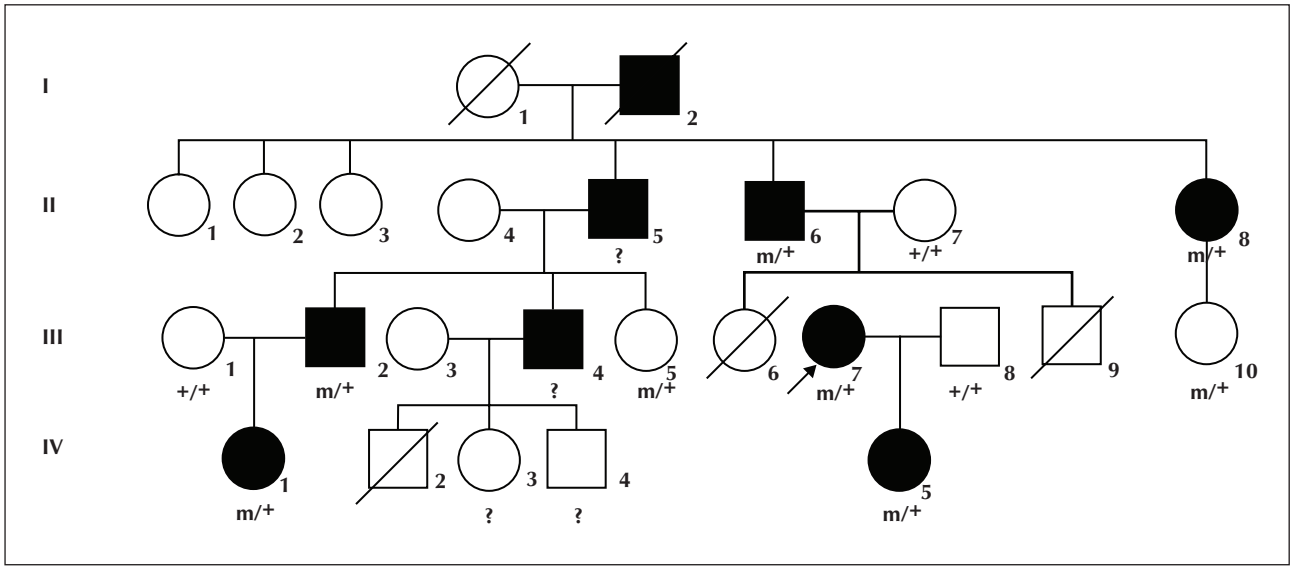

Figure 1. Pedigree of the Chinese FFEVF family. Affected individuals are indicated by black solid squares (males) or black solid circles (females). Unaffected individuals are indicated by open symbols. Deceased individuals are indicated by slashes (/). The proband is indicated by an arrow. Individuals with a mutation in *DEPDC5* are indicated by (m/+), and individuals tested for mutations and found to be negative are indicated by (+/+). Individuals whose blood samples were unavailable are indicated by (?).

bottom of the right frontal lobe (*figure 2A*). However, in her daughter (IV-5), the dipoles mainly clustered in the left parietal lobe around the angular gyrus (*figure 2C*).

Genetic study

A novel splice site mutation in *DEPDC5* (c.280-1 G>A) was identified in the proband (III-7) using a targeted next-generation sequencing epilepsy panel (*figure 3*). This mutation was verified by Sanger sequencing in available members and revealed that besides five affected individuals (II-6, II-8, III-2, IV-1, IV-5), two unaffected members (III-5, III-10) also carried this mutation. Four individuals (II-5, III-4, IV-3, IV-4) refused to participate in this study, and their blood samples were unavailable. This mutation was not found in 1000 Genomes, ExAC, or in silico prediction programs (Human Splicing Finder 3.1), and the mutation was suggested to affect splicing due to an alteration in the wild-type acceptor site.

Discussion

We report a novel splice site mutation in a Chinese FFEVF family and applied the non-invasive method of MEG to locate the epileptogenic site, which assisted us in confirming the diagnosis for this family.

In FFEVF, the origins of seizures are different among family members. Currently, the diagnosis of FFEVF is mainly based on the combination of EEG and semiology (Scheffer *et al*., 1998). However, it is difficult to localize the origins of epileptic discharges, and the clinical manifestation may be atypical. In the present study, we could not locate the origin of seizures in individual IV-5 according to her EEG. MEG is a non-invasive method which can be used to record the undamped magnetic signals generated by small electric currents in neurons. MEG has excellent spatial resolution; sources can be localized with millimetre precision. It is more accurate and less subject to distortion than EEG. The results of MEG in these two drug-resistant patients eliminated any doubt in the diagnosis of FFEVF by showing that the dipoles clustered in different lobes in each individual. Therefore, we propose that MEG can be used to accurately diagnose this disorder.

After the diagnosis of FFEVF, we performed targeted next-generation sequencing in this family and identified a heterozygous novel splice site mutation in *DEPDC5* (c.280-1G>A), which was located in exon 6 in nine affected individuals and two unaffected individuals. The incomplete penetration in this pedigree is consistent with former studies. Haploinsufficiency was speculated to be the underlying mechanism of the *DEPDC5*-related epilepsy syndrome. Based on previous studies, transcribed mRNA with nonsense mutations and a premature stop codon will be digested by the nonsense-mediated decay system (NMD) which leads to haploinsufficiency (Ishida *et al*., 2013; Picard *et al*., 2014).

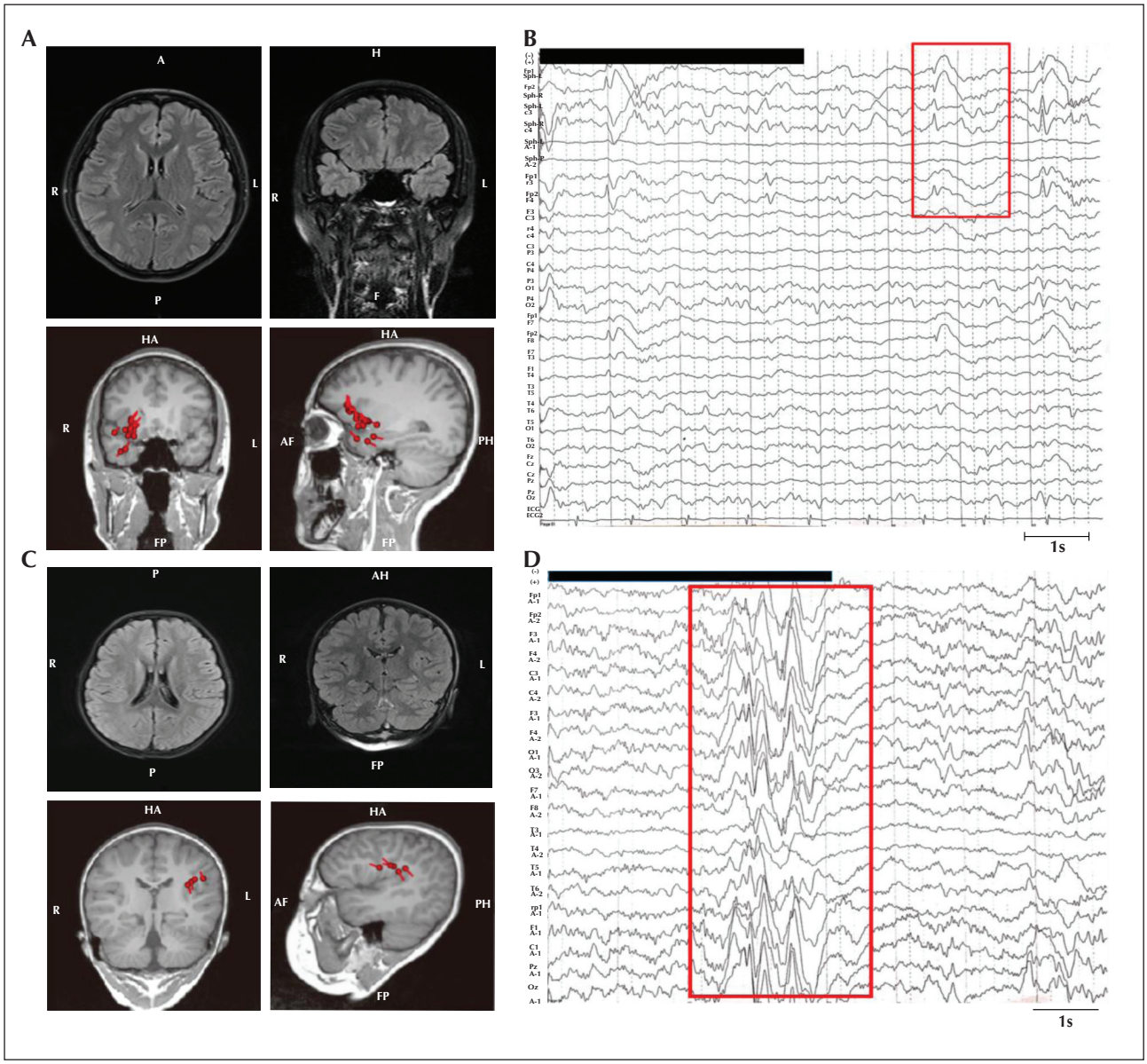

Figure 2. Neuroimaging results and interictal EEG of two drug-resistant patients. (A) MRI and MEG of proband (III-7); MRI shows no obvious lesion, however, MEG shows dipoles mainly clustered at the bottom of the right frontal lobe. (B) Interictal EEG of proband (III-7); EEG shows sharp and slow wave complexes predominantly at FP2 and bilateral sphenoid derivations. (C) MRI and MEG of individual IV-5; MRI shows no obvious lesion, however, MEG shows dipoles mainly clustered in the left parietal lobe around the angular gyrus. (D) Interictal EEG of individual IV-5; EEG shows a generalized sharp and slow wave complex.

Although *DEPDC5*-associated FFEVF has been regarded as a non-lesional epilepsy syndrome, a growing number of studies have revealed that this mTOR repressor plays a role in MCD, especially FCD. Histopathological studies of resected brain tissue have revealed FCD IIa in some patients, as well as activation of the mTOR pathway in *DEPDC5*-related FCD patients (Scerri *et al.*, 2015). The "second-hit" theory was introduced based on secondary effects from genetic and environmental factors in order to explain the formation of FCD and the variation between patients (Scheffer *et al.*, 2014; Baulac *et al.*, 2015). Further research has strengthened this theory based on the discovery of a second brain somatic *DEPDC5* mutation with a higher rate of mosaicism in the seizure onset zone (SOZ) than in the surrounding epileptogenic zone (EZ) (Ribierre *et al.*, 2018). Taken together, we propose that for drug-resistant patients carrying a *DEPDC5* mutation, MCD should be suspected.

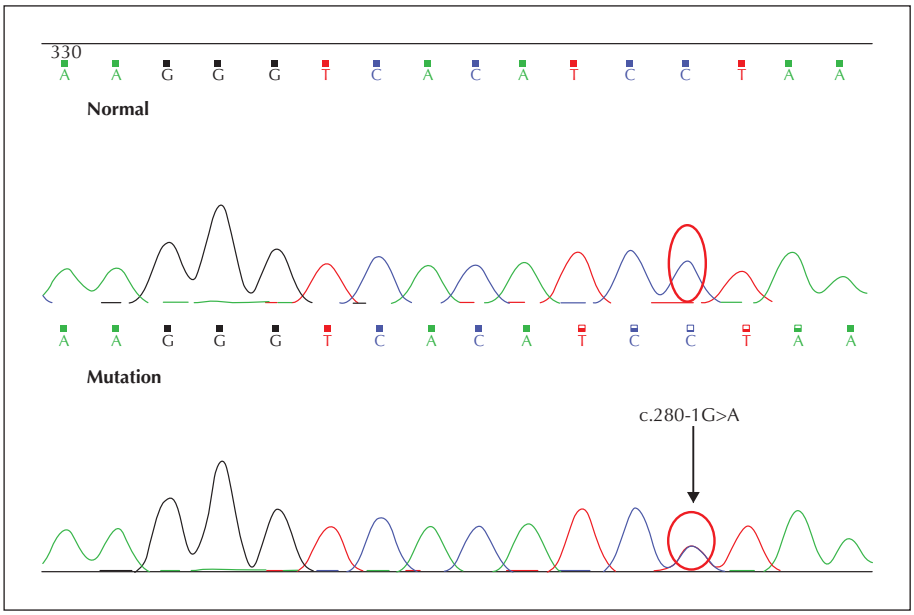

Figure 3. *DEPDC5* mutation in the FFEVF family; DNA sequence chromatograms show the mutation in *DEPDC5* identified in the family studied.

For drug-resistant patients carrying *DEPDC5* mutations, surgery proved to be a good approach with favourable outcome. In a previous study, five patients carrying *DEPDC5* mutations underwent surgical resection, and all these patients had electroclinical phenotypes highly suggestive of FCD II; three patients became seizure-free and significant improvement was achieved in another (Baulac *et al*., 2015). Generally, we rely on MRI to identify MCD, however, MRI may be negative in nearly 29% patients. MEG has previously been applied for presurgical localization of epilepsy, and may be particularly important for those with no lesion visible on MRI (RamachandranNair *et al*., 2007). Consistent with the family reported here, both the proband and her daughter had negative brain MRI. The findings of dipole-clustered areas in these patients not only helped us make the diagnosis, but also revealed the possibility of surgical resection.

To conclude, we identify a novel splice site *DEPDC5* mutation in a Chinese FFEVF family. Furthermore, we applied MEG for the first time to confirm the diagnosis of FFEVF by locating the epileptogenic site in two refractory patients with negative MRI, which also provided guidance for possible surgical resection in the future. □

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TEST YOURSELF

(1) What disorder should be suspected in refractory patients with *DEPDC5* mutation?

(2) Why can affected members in the same FFEVF family with *DEPDC5* mutation have different clinical severity?

(3) What is the advantage of MEG compared to EEG?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".