Original article

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DEPDC5 mutation and familial focal epilepsy with variable foci: genotype and phenotype of a family*

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ABSTRACT – *Aims.* Familial focal epilepsy with variable foci is a relatively rare autosomal disease with an unclear incidence, which is characterized by focal seizures arising from different cortical regions in different family members.
Methods. We describe three members of a two-generation Argentine family with familial focal epilepsy with variable foci syndrome and a *DEPDC5* gene mutation.
Results. The mean onset age was nine years old. The father experienced episodes with occipital semiology and both siblings exhibited frontal lobe seizures. Their neurological examination and neuroimaging studies were normal. All three patients are currently seizure-free, in spite of initially experiencing frequent seizures. Complete exome sequencing revealed a new *DEPDC5* gene mutation (NM_001242896: c.4718T>C; p.L1573P).
Conclusions. This study of a family with clinical characteristics that met all the criteria for familial focal epilepsy with variable foci demonstrates the usefulness of exome sequencing as a diagnostic tool. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: familial focal epilepsy with variable foci, *DEPDC5*, semiology, occipital seizure semiology, frontal seizures

VIDEO ONLINE

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Familial focal epilepsy with variable foci (FFEVF) is included among epilepsy syndromes of genetic origin (Dibbens *et al*., 2013). It was first reported in an Australian family in 1998 by Ingrid Scheffer (Scheffer *et al*., 1998), who initially associated it with chromosome 2. Later, in 1999, it was reported in two Canadian families, suggesting linkage to chromosome 22 and showing probable genetic heterogeneity (Xiong *et al*., 1999; Klein *et al*., 2012).

FFEVF is characterized by a wide range of onset age, with an average of 13 years. Epileptic seizures may take place during daytime, night-time, or both, and they frequently originate in the frontal or temporal lobes, although they may occasionally be of occipital or parietal origin (Morales-Corraliza *et al*., 2010; Ishida *et al*., 2013).

Most patients with this syndrome have a normal neurological examination, although there have been isolated reports in which autistic spectrum disorder, psychiatric disorders, and intellectual disability were present as comorbidities (Klein *et al*., 2012).

Neuroimaging studies are also often normal and most patients show an excellent response to antiepileptic drugs (AEDs) (Morales-Corraliza *et al*., 2010).

DEPDC5 is an important gene in focal epilepsy, especially in patients with a positive family history (Tsai *et al*., 2017). Mutations in this gene have been identified in more than 8% of families with FFEVF, causing activation of the downstream mTOR pathway (Weckhuysen *et al*., 2016). Reports suggest that *DEPDC5* is not only the most common gene associated with familial focal epilepsy but also could be a significant gene involved in sporadic focal epilepsy (Tsai *et al*., 2017). *DEPDC5* mutation has also been linked to an increased risk of sudden unexpected death in epilepsy (SUDEP), as it is described in one family with *DEPDC5*-related epilepsy which included two family members with SUDEP (Nascimento *et al*., 2015). The significance of *DEPDC5* mutations in patients with sporadic focal epilepsy has yet to be characterized. Here, we describe an Argentine family meeting all the criteria for FFEVF with *DEPDC5* gene mutation.

Patients and methods

Clinical studies

We studied two generations of a non-consanguineous family. All three affected members had focal epilepsy: two had frontal epilepsy and one had occipital epilepsy.

A 32-channel video-EEG recording was carried out for the proband and an EEG for the other two affected members of the family.

Informed consent was obtained from each participant family member or, in the case of the two children, their legal guardian.

Exome sequencing and Sanger sequencing

Whole-exome sequencing (WES) was performed on purified DNA samples from the patient using the Agilent SureSelect Human All Exon V5 Kit (Agilent Technologies, Santa Clara, CA) with an Illumina sequencing system. Bioinformatic analysis was performed following procedures described by our group (Koile *et al*., 2018). The identified variant in *DEPDC5* was validated by Sanger sequencing following standard procedures. The presence of this variant was investigated in affected members of the family.

Clinical description

The proband was a 10-year-old male who experienced his first seizure at the age of eight. At first, episodes occurred more than 20 times per day, during both sleep and awake states. The episodes were characterized by eye opening, followed by ocular and cephalic deviation to the left, associated with monosyllabic vocalization. He then presented right hand automatisms associated with left upper limb flexion. During some episodes, he extended the lower limbs and flexed the upper limbs, as if he was stretching out. These events were occasionally associated with smiling (mainly while awake).

The patient was initially treated with valproic acid, then clobazam and topiramate. While receiving the latter, he experienced visual hallucinations and hyperexcitability. An increase in seizure frequency was observed when levetiracetam was added to this treatment regimen. He was then started on carbamazepine and became seizure-free.

A 24-hour video telemetry recording revealed seven events. The ictal EEG showed sharp rhythmic spikes in the right fronto-central region, followed by fast low-voltage activity and, four or five seconds later, a sharp-and-slow-wave bilateral fronto-central temporal activity (*figure 1, video sequence*). The interictal EEG showed frequent spike-and-sharp-wave discharges from the right fronto-central temporal region (*figure 2*). These observations led to the hypothesis that the episodes originated in the right fronto-temporal area. A 3-tesla MRI brain scan was performed showing no abnormalities.

The neuropsychological assessment showed normal intellectual performance with language difficulties and attention deficit.

The proband's father presented with episodes with a semiology suggesting occipital lobe involvement;

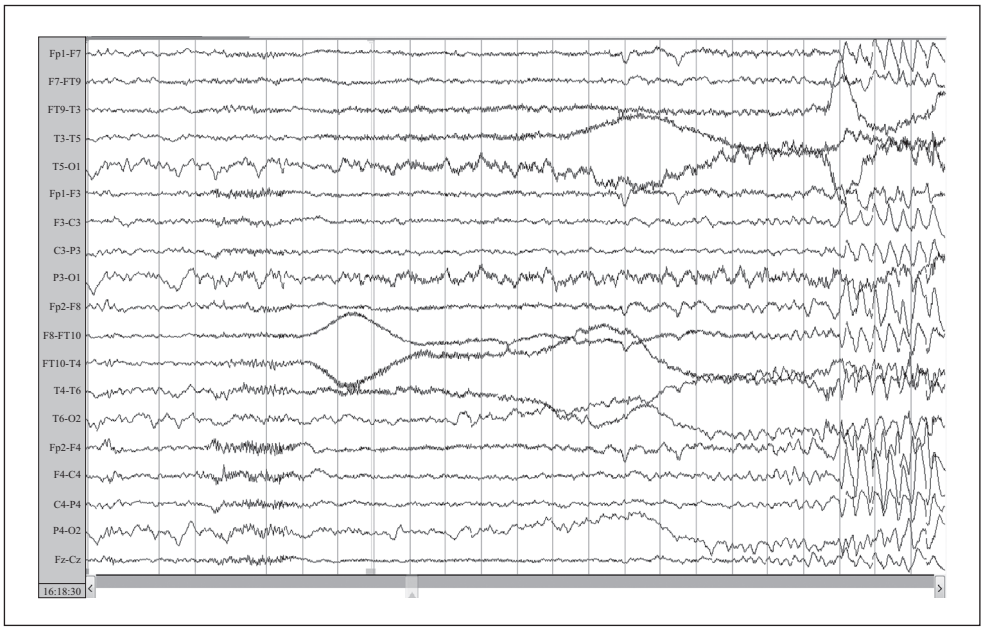

Figure 1. Ictal EEG: bilateral montage showing fronto-central fast activity (27-29-Hz) followed by a diffuse low-voltage fast activity starting three seconds before the clinical onset. Twelve seconds later, a slow fronto-temporal (4-5-Hz) rhythmic activity evolves.

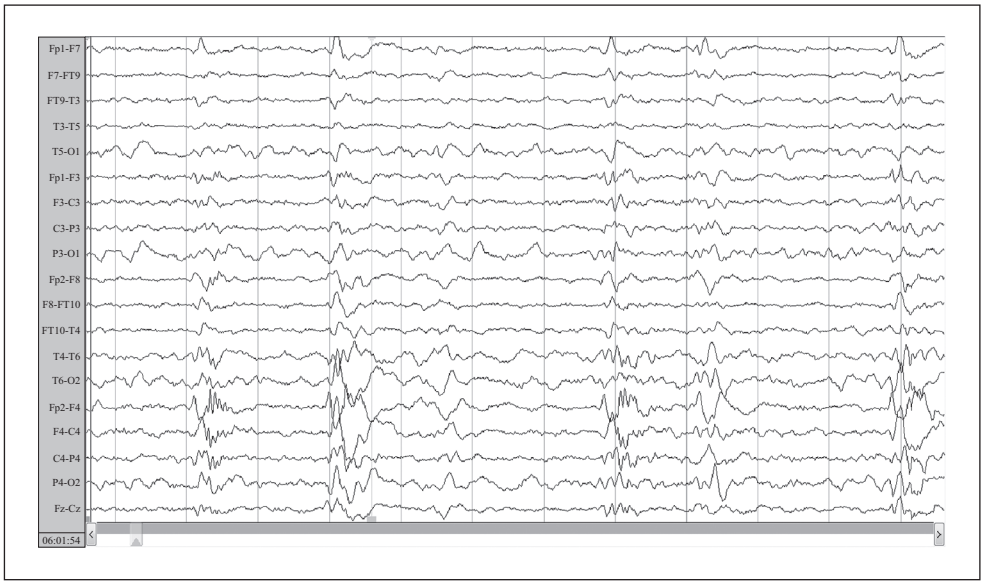

Figure 2. Interictal EEG showing frequent right fronto-temporal polyspikes and sharp waves.

he described elementary hallucinations characterized by flashes of lights. He has been seizure-free for five years, receiving valproic acid. His EEG and MRI showed no abnormalities.

The proband's sister had seizures that exhibited a frontal lobe semiology, characterized by daytime asymmetric tonic posturing of her extremities, evolving into a generalized tonic-clonic seizure. She had a good response to carbamazepine and has been seizure-free for the last three years. Her MRI was normal and EEG showed bilateral anterior sharp waves.

The diagnostic hypothesis was FFEVF due to the epileptic family history.

Genetic investigation: exome sequencing

WES, performed on purified DNA samples from the patient using the Agilent SureSelect Human All Exon

V5 Kit (Agilent Technologies, Santa Clara, CA) with an Illumina sequencing system, led to identification of a likely pathogenic novel mutation in the *DEPDC5* gene (NM_001242896: c.4718T>C; p.L1573P). Segregation analysis by Sanger sequencing confirmed the presence of this variant in the proband and in the other affected relatives.

Discussion

The main familial focal epilepsies of known genetic origin with specific age-related and electroclinical characteristics include: autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial mesial temporal lobe epilepsy (FMTLE), familial lateral temporal lobe epilepsy TLE (FLTLE) or autosomal dominant partial epilepsy with auditory features (ADPEAF), and FFEVF. These familial syndromes show phenotypic overlap and small families may be initially labelled with ADNFLE or FLTLE/ADPEAF, and later recognized to have FFEVF when new affected members are identified (Dibbens *et al*., 2013).

FFEVF is a relatively rare autosomal dominant disease with an unclear incidence, characterized by focal seizures arising from different cortical regions in different family members (Klein *et al*., 2012). Reports of FFEVF describe a mean age at onset of 13 years with a large range extending from one month to 52 years. In our study, the proband had his first seizure at the age of eight, the father at ten, and the sibling at age nine.

Patients with FFEVF usually have normal neurological examination and normal neuroimaging (Klein *et al*., 2012). However, based on studies published in 2015, patients with FFEVF and focal neurological deficit (hemiparesis) were reported, together with neuroimaging findings of focal cortical dysplasia. The response to AEDs is variable. While some individuals respond well to first-line AEDs, others are more refractory to treatment. All members of the study family had a normal neurological examination and became seizure-free on AEDs.

ADNFLE (involving *CHRNA4*, *CHRNA2*, *CHRNB2*, and *KCNT1* gene mutations) is characterized by short nocturnal episodes, usually presenting as a cluster with hypermotor seizures, which are also commonly observed in FFEVF (Callenbach *et al*., 2003; Dibbens *et al*., 2013; Ishida *et al*., 2013). As a consequence, the latter is often misdiagnosed as the former, although episodes during daytime are rare in this epilepsy type. The patient we studied presented with focal episodes with and without loss of conscience, which took place during the day and the night, initially with multiple daily seizures. Therefore, video telemetry monitoring was performed, allowing us to hypothesize a frontotemporal epileptogenic origin.

In contrast to other FFEVF families which include individuals with nocturnal frontal lobe epilepsy (NFLE), our family could easily be distinguished from NFLE due to the predominant diurnal seizures and a posterior epilepsy in the other member of the family.

There have been reports of EEG studies with interictal focal discharges, such as in our patients and one report from a French-Canadian family who presented with normal interictal EEG (Xiong *et al*., 1999), as in the father.

The penetrance of *DEPDC5* mutation associated with FFEVF was estimated at 66%, and obligate gene carriers without a history of seizures can often be identified within a family (Dibbens *et al*., 2013). In this study, genetic testing (PCR followed by LOD scores) was only performed in the three symptomatic members of the family. In all of them, FFEVF was associated with chromosome 22q12. We could not perform genetic testing in other family members. In 2012, 16 families with autosomal dominant focal epilepsy were reassessed and exome sequencing was carried out in all cases. Two patients with FFEVF presented with the same *DEPDC5* gene mutation (deletion), which was also detected in asymptomatic relatives. This strengthens the theory of incomplete penetrance and expression variability within a family, suggesting that the phenotype is modulated by other genes or environmental and epigenetic factors (Ishida *et al*., 2013).

The mutation described here would introduce a premature stop, causing loss of *DEPDC5* gene function and the subsequent epilepsy phenotype. Neither the *DEPDC5* nor the *LGI1* gene (associated with autosomal dominant lateral temporal lobe epilepsy) encode a transmembrane receptor subunit or ion channel (Ishida *et al*., 2013). In another study, the exomes of an Australian family and a Dutch family were sequenced, leading to the detection of a nonsense mutation of the *DEPDC5* gene. Thus, different *DEPDC5* gene mutations are associated with FFEVF (Dibbens *et al*., 2013).

Recently, in 2014, Ingrid Scheffer confirmed the variability of phenotypes associated with *DEPDC5* gene mutations. She identified a nonsense variant of the *DEPDC5* gene in two siblings with focal cortical dysplasia type IIA by exome sequencing, which had previously been associated only with normal neuroimaging studies. The father and paternal uncle in her study had the same mutation, but had normal neuroimaging studies and good response to carbamazepine (Scerri *et al*., 2015). A missense variant of the *NF1* and *DEPTOR* genes was also found, but only in both siblings with focal cortical dysplasia. In our study, we did not find other gene mutations in any of the three patients. The three genes, *DEPDC5*, *DEPTOR*, and *NF1*, encode components of the mTOR pathway, which could contribute to the phenotype variability associated with the *DEPDC5* gene (which inhibits mTORC1),

causing both lesional and non-lesional epilepsy. The association between *DEPDC5* and the mTOR pathway genes and the presence of cortical malformations in these patients is still unclear.

Recently, with regards to FFEVF, advances in exome sequencing have revealed an association between DEPDC5 gene mutation and other genes such as *DEPTOR* and *NF1*, which could be linked to severe epilepsy with focal cortical malformations (cortical dysplasia type IIA and focal heterotopia) (Scerri *et al*., 2015; Baulac *et al*., 2015; Tsai *et al*., 2017). No clear genotype-phenotype correlations have been described, although, to date, missense variants have been reported mostly in small families including individuals with apparently non-lesional epilepsies. The family presented here had a missense mutation with normal MRI. Moreover, all individuals with reported brain malformations (focal cortical dysplasia or hemimegalencephaly) had nonsense or frameshift variants leading to a premature stop codon (Scheffer *et al*., 2014; Scerri *et al*., 2015; Ricos *et al*., 2016; Weckhuysen *et al*., 2016).

Conclusion

FFEVF is a genetic epilepsy syndrome with autosomal dominant inheritance, incomplete penetrance, and large phenotypic variability. We emphasize the importance of the patient's family medical history as a basis for selecting relevant diagnostic testing which leads to accurate diagnosis and subsequent management. □

Legend for video sequence

A typical seizure of the patient. The seizure semiology starts three seconds from the first change in EEG with eye opening, followed by ocular and left versive cephalic deviation, associated with vocalization. The patient then presents with right hand automatisms associated with left lower limb flexion, followed by bilateral manual automatisms.

Key words for video research on www.epilepticdisorders.com

Phenomenology: focal seizure
Localisation: variable foci
Syndrome: familial focal epilepsy with variable foci
Aetiology: DEPDC5 mutation

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) In what other epileptic syndromes can *DEPDC5* mutations be found?

(2) Can patients with *DEPDC5* mutations have brain malformations?

(3) What genetic counselling would you give to a patient with *DEPDC5*-related epilepsy?

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".