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Case Report

CASE REPORT

DEPDC5 variant in focal cortical dysplasia: a case report and review of the literature

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Abstract

Germline and 2-hit brain somatic variants in *DEPDC5* gene, a negative regulator of the mammalian target of rapamycin (mTOR) pathway, are increasingly recognized in patients with focal cortical dysplasia (FCD). Next-generation targeted sequencing identified a heterozygous germline variant in *DEPDC5* gene (c.3241A>C, p.Thr1081Pro), classified as of unknown significance, in a patient with clinical features compatible with *DEPDC5* phenotype (FCD, focal epilepsy, attention-deficit/hyperactivity disorder and borderline intellectual functioning). This missense variant has previously been reported in two other epileptic patients. Although interpretation of missense variants remains a challenge, *DEPDC5* variants in patients with FCD and epilepsy cannot be neglected. Null variants were the most frequently reported in FCD patients, but missense variants have been described as well. The recognition of *DEPDC5* phenotype and the appropriate interpretation of the detected variants are essential, since it may have important treatment implications in the near future, namely the use of mTOR inhibitors.

INTRODUCTION

The advent of next-generation sequencing enabled the detection of novel loss-of-function variants in *DEPDC5* gene associated to human brain malformations. *DEPDC5* acts as an upstream negative regulator of mammalian target of rapamycin complex 1 (mTORC1) (Fig. 1a), essential to neuronal growth and migration during embryonic corticogenesis [1–3]. Besides the association to different epilepsy phenotypes, germline and 2-hit

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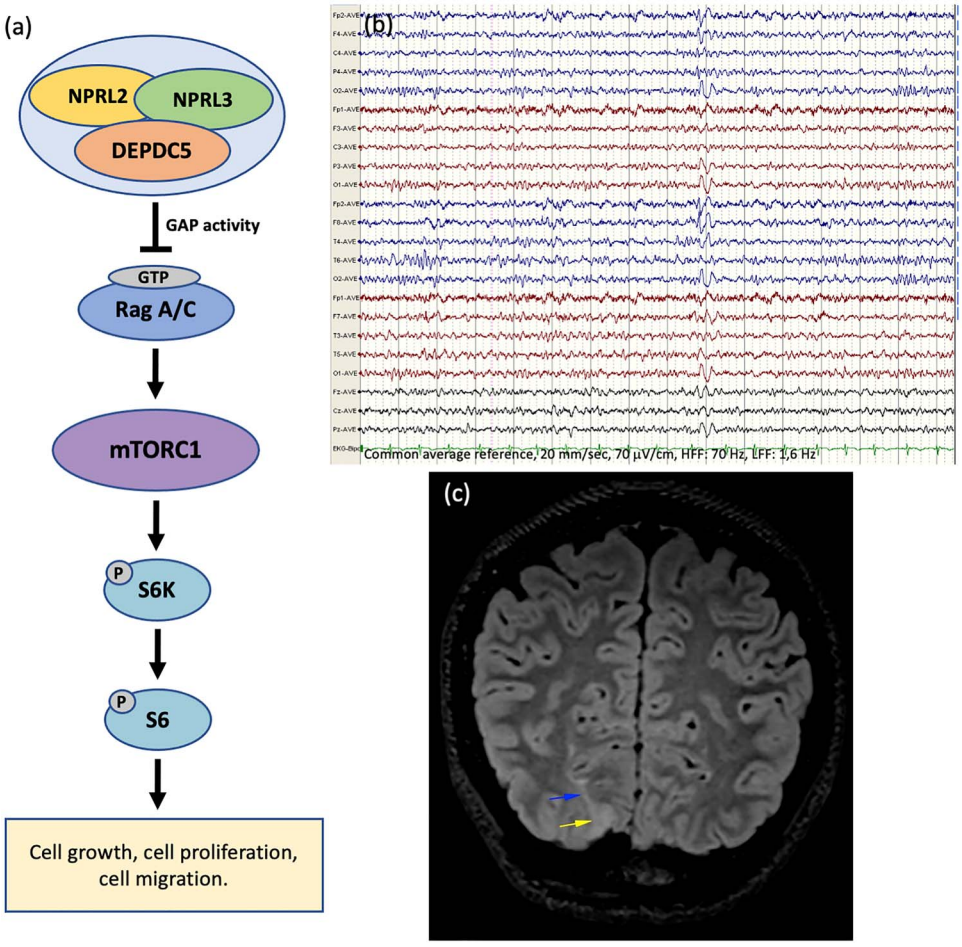

Figure 1: (**a**) Schematic representation of the GATOR–mTORC1 pathway. The GATOR1 complex, comprising the proteins DEPDC5, NPRL2 and NPRL3, inhibits mTORC1 through its GAP activity toward the GTPases Rag A/C, in amino acid deprivation conditions. (**b**) Interictal EEG (monopolar montage): Right frontal spike. (**c**) 3T Brain MRI (Coronal Flair): FCD (yellow arrow) and transmantle sign (blue arrow).

brain somatic *DEPDC5* variants are increasingly recognized as a common genetic scenario in focal cortical dysplasias (FCD), mainly type II [1, 4].

We aimed to contribute to unravel the genetic basis of FCD and its association to *DEPDC5* gene. We also performed a literature research for an updated overview of *DEPDC5* variants in patients with FCD.

CASE REPORT

An 18-year-old, right-handed, Caucasian male, son of healthy and non-consanguineous parents, at the age of 12 started with frequent brief nocturnal episodes of stereotyped movements in the upper and lower limbs, noticed by his mother. Regarding clinical background, there were no risk factors for epilepsy and no relevant family history. Neurological examination was normal. EEG background activity was normal. Interictal electroencephalogram (EEG) showed an intermittent slow in the right occipital region and rare right frontal epileptiform discharges (Fig. 1b). The video-EEG recorded a paroxysmal arousal followed by a brief asymmetric tonic seizure during non-rapid eye movement (NREM) sleep associated to a focal ictal EEG onset in the right frontal region, confirming a diagnosis of focal epilepsy.

Brain magnetic resonance imaging (MRI) (3.0 Tesla) showed a right paramedian inferior occipital non-enhancing lesion, characterized by cortical thickening, gray–white matter blurring and an increased T2 signal of the subcortical white matter with transmantle sign, probably corresponding to FCD type II (Fig. 1c). There were no imaging signs of mesial temporal sclerosis.

The patient had also learning difficulties and a disinhibited and impulsive behavior. He was diagnosed with attention-deficit/hyperactivity disorder (ADHD). At the age of 13, the wechsler intelligence scale for children - third edition (WISC-III) [5] revealed a borderline intellectual functioning (IF) [Full Scale IQ: 77 (inferior); Verbal IQ: 75 (inferior); Performance IQ: 87 (under average); Verbal Comprehension Index: 71 (inferior); Perceptual Organization Index: 94 (average); Processing Speed Index: 86 (under average)].

Next-generation sequencing of 343 epilepsy-related genes, with a mean depth of coverage of 147 reads and 98.3% of the targeted bases covered by at least 20 reads, identified a germline, heterozygous, missense variant in *DEPDC5* (c.3241A>C, p.Thr1081Pro), classified as a variant of unknown significance (VUS). The parents were not available to segregation studies, but the results of this analysis would not allow to change the classification of the variant.

Table 1: *DEPDC5* variants reported in patients with FCD

References	cDNA variant (protein change)	Variant information	No. of subjects	Neuropathological subtypes of FCD (if applicable)	Other features
Present study	c.3241A>C (p.Thr1081Pro)	Germline	1	—	Focal epilepsy Borderline IF ADHA
Baulac *et al.* [1]	c.715C>T (p.Arg239*) + c.1264C>T (p.Arg422*) c.715C>T (p.Arg239*) c.715C>T (p.Arg239*) c.1264C>T (p.Arg422*) c.484-1G>A (p.?) c.1759C>T (p.Arg587*) c.1759C>T (p.Arg587*)	Germline, inherited (asymptomatic father) + Brain somatic Germline, inherited (affected father) Germline, inherited (asymptomatic mother) Germline Germline, inherited (asymptomatic father) Germline Germline	7	I, IIa	Focal epilepsy (FFEVF; SHE) Mild ID Psychiatric disorders (depression, transitory psychosis, impulsivity)
Carvill *et al.* [9]	c.2390delA (p.Gln797Argfs*18) c.842A>T (p.Tyr281Phe)	Germline, *de novo* Germline, inherited (affected father)	2	IIa	Focal epilepsy (IS) Epileptic encephalopathy Global development delay ASD
Ricos *et al.* [6]	c.3994C>T (p.Arg1332*)	Germline, inherited (asymptomatic father)	1	—	Focal epilepsy (TLE)
Ribierre *et al.* [4]	c.856C>T (p.Arg286*) + c.865C>T (p.Gln289*)	Germline, inherited (asymptomatic mother) + 2-hit brain somatic	1	IIa	Focal epilepsy (FLE)
D'Gama *et al.* [10]	c.783_786delTGAG (p.Asn261Lysfs*11) c.624+1G>A (p.?) c.1218-18_1218-15delTGTT (p.?) c.1355C>T (p.Ala452Val)	All germline	3	IIb	Focal epilepsy
Baldassari *et al.* [2]	c.1310delA (p.Asn437Metfs*21) c.279+1G>A (p.?) c.1264C>T (p.Arg422*) c.1400_1401insGG (p.Phe467Leufs*51) c.542T>A (p.Met181Lys) c.715C>T (p.Arg239*) c.856C>T (p.Arg286*) c.982C>T (p.Arg328*) c.1165dupC (p.Arg389Profs*2) c.1663C>T (p.Arg555*) c.4031T>A (p.Leu1344*) c.4674G>A (p.Trp1558*)	Germline, inherited (asymptomatic mother) Germline, inherited (affected mother) Germline, inherited (asymptomatic father) Germline, inherited (asymptomatic father) Germline, inherited Germline, inherited (asymptomatic father) Germline, inherited (asymptomatic mother) Germline, *de novo* Germline Germline, inherited (asymptomatic father) Germline, inherited (asymptomatic father) Germline	12	I, IIa, IIb	Focal epilepsy (SHE; IS; FLE) ADHA /attention deficit Learning difficulties Mild ID Developmental delay ASD Psychiatric disorder (anxiety; ODD)
Sim *et al.* [3]	c.1114C>T (p.Gln372*) c.3639G>A (p.Trp1213*) c.3802C>T (p.Arg1268*) c.3406A>T (p.Arg1136*) c.4521_4522delAA (p.Thr1508fs) + c.4162_4169dupGTACTCTT (p.Phe1399fs)	Germline Germline Germline Germline Germline + 2-hit brain somatic	5	IIa, IIb	Focal epilepsy (IS) Early infantile epileptic encephalopathy
Liu *et al.* [8]	c.3092C>A (p.Pro1031His)	Germline, homozygous-inherited (asymptomatic mother) + *de novo*	1	—	Focal epilepsy (FLE)

FFEVF: familial focal epilepsy with variable foci; SHE: sleep-related hypermotor epilepsy; FLE: frontal lobe epilepsy; IS: infantile spasms; TLE: temporal lobe epilepsy; ODD: oppositional defiant disorder; ASD: autistic spectrum disorder; ID: intellectual disability.

The patient was treated with valproic acid (1000 mg/day) and clobazam (10 mg/day), with resolution of the nocturnal seizures for a follow-up period of 4 years. Methylphenidate (20 mg/day) and risperidone (3 mg/day) were also prescribed, with good tolerability and stabilization of the neuropsychiatric symptoms.

DISCUSSION

In this case report, we describe a patient with a clinical presentation compatible with *DEPDC5* phenotype (FCD with imagological features of type II, focal epilepsy, ADHD and borderline IF), in which was identified the germline variant c.3241A>C, p.Thr1081Pro in *DEPDC5* gene. This missense variant, located at 22q12.3 in a coding region of exon 32, has previously been reported in two other heterozygous patients: a patient with epileptic encephalopathy with continuous spike and wave in slow-wave sleep and intellectual disability, which was maternally inherited from an unaffected heterozygous carrier [6], and other patient with drug-resistant focal epilepsy in infancy that developed a West Syndrome [7]. *DEPDC5* variants are inherited in an autosomal dominant manner, but asymptomatic carriers are common in *DEPDC5*-related families (Table 1), illustrating its incomplete penetrance (~60%) [2, 8]. There is also a high expression variability, including for the presence of cortical abnormalities, with 50% of the patients presenting FCD in neuroimaging [2]. The same variant in *DEPDC5* has been described in both lesional and non-lesional phenotypes [1, 2, 8]. Epilepsy onset usually ranged from childhood to adolescence [2, 6]. Intellectual disability and neuropsychiatric features, although rare, have been described as well (Table 1) [1, 2, 6, 9].

FCD may be the result of both a germline and a somatic mutation in a subset of brain cells affecting *DEPDC5* (Table 1), suggesting a biallelic 2-hit mutational mechanism [1, 4]. Null variants (nonsense and frameshift) were the most frequently reported in FCD patients [1–3], but missense variants have also been described (Table 1) [2, 8–10]. Since loss-of-function variants in *DEPDC5* lead to hyperactivation of mTORC1, as evidenced by the increase in phosphorylated S6 immunostaining in resected FCD tissue (Fig. 1a) [4], mTORC1 inhibitors, like rapamycin, may be a potential targeted treatment [4].

Missense variants are common in *DEPDC5*-related focal epilepsies [1, 2]. This type of variants still poses an important problem for pathogenicity assessment [2], especially in isolated patients where segregation data cannot be supportive. Ricos *et al.* [6] considered the variant c.3241A>C, p.Thr1081Pro as pathogenic based on its very low allele frequency (minor allele frequency (MAF): 0.0078%) in the Exome Variant Server database. The classification of this protein coding-altering variant was not consensual according to different *in silico* prediction tools [6]. Despite a compatible clinical phenotype, due to lack of both functional assay and supportive genetic evidence (strong segregation support, incomplete penetrance, absence of recurrent missense variants), this variant is classified as VUS, according to the American college of medical genetics and genomics (ACMG) guidelines (https://www.acmg.net). Although a new classification framework adapted specifically to GATOR1 variants [2] has proven valuable to increase the accuracy of the clinical classification, interpretation of missense variants remains a challenge and the future implementation of *in vitro* functional experiments to prove deleterious effect on protein function may therefore be useful [9]. In patients with malformations of cortical development, heterozygous missense variants clustered in structural axis for binding arrangement domain, close to the binding sites to NPRL2/NPRL3 complex [8].

In conclusion, the case reported can provide further evidence that *DEPDC5* variants in patients with FCD and epilepsy cannot be neglected. Predicting the clinical consequences of missense variants is a laborious task, and functional studies are important. The recognition of the clinical phenotype and the appropriate interpretation of the detected variants may have relevant treatment implications in the near future. Thus, a review of the variants described in *DEPDC5* in association with FCD is useful.

CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

Procedures were approved by the local ethics committee.

CONSENT

Subject has given his written informed consent to publish this case report.

GUARANTOR

Joana B. Melo

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