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
DEPDC5 variant in focal cortical dysplasia

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.

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).
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)     | Germine                               | 1               | —                                                | Focal epilepsy                                                                                         |
| Baulac et al. [1]   | c.715C>T (p.Arg239∗)         | Germine, inherited (asymptomatic father) | 7               | I, Ila                                           | Borderline IF ADHA, Focal epilepsy (FFEVF; SHE) Mild ID Psychiatric disorders (depression, transitory psychosis, impulsivity) |
|                     | c.1264C>T (p.Arg422∗)        | Germine, inherited (affected father)   | +               |                                                  |                                                                                                       |
|                     | c.715C>T (p.Arg239∗)         | Germine, inherited (asymptomatic mother) | Germine          |                                                  |                                                                                                       |
|                     | c.1264C>T (p.Arg422∗)        | Germine, inherited (affected father)   | +               |                                                  |                                                                                                       |
|                     | c.484-1G>A (p.?)             | Germine                                | Germine          |                                                  |                                                                                                       |
|                     | c.1759C>T (p.Arg587∗)        | Germine, inherited (affected father)   | Germine          |                                                  |                                                                                                       |
| Carvill et al. [9]  | c.2390delA (p.Gln797Argfs∗18) | Germine, de novo                       | 2               | Ia                                               | Focal epilepsy (IS) Epileptic encephalopathy Global development delay ASD                               |
|                     | c.2390delA (p.Gln797Argfs∗18) | Germine, inherited (affected father)   | 2               | Ia                                               |                                                                                                       |
|                     | c.842A>T (p.Tyr281Phe)       | Germine, inherited (asymptomatic mother) | 1               |                                                   |                                                                                                       |
| Ricos et al. [6]    | c.3994C>T (p.Arg1332∗)       | Germine, inherited (asymptomatic father) | 1               | —                                                | Focal epilepsy (TLE)                                                                                   |
| Ribierre et al. [4] | c.856C>T (p.Arg286∗)         | Germine, inherited (affected father)   | 1               | Ia                                               | Focal epilepsy (FLE)                                                                                   |
|                     | +                             | Germine, inherited (asymptomatic mother) | +               |                                                  |                                                                                                       |
|                     | c.865C>T (p.Gln289∗)         | 2-hit brain somatic                    | 2               |                                                  |                                                                                                       |
| D’Gama et al. [10]  | c.783_786delTGAG (p.Asn261Lysfs∗11) | All germine                         | 3               | IIb                                              | Focal epilepsy                                                                                         |
| Baldassari et al. [2] | c.1310delA (p.Asn437Metfs∗21) | Germine, inherited (asymptomatic mother) | 12              | I, Ila, IIb                                      | Focal epilepsy (SHE; IS; FLE) ADHA/attention deficit Learning difficulties Mild ID Developmental delay ASD Psychiatric disorder (anxiety; ODD) |
|                     | c.1264C>T (p.Arg422∗)        | Germine, inherited (affected father)   | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.279+1G>A (p.?)             | Germine, inherited (affected mother)   | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.1400_1401insGG (p.Phe467Leufs∗51) | Germine                              | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.715C>T (p.Arg239∗)         | Germine, inherited (affected father)   | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.856C>T (p.Arg286∗)         | Germine, inherited (affected father)   | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.982C>T (p.Arg328∗)         | Germine, de novo                      | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.1165dupC (p.Arg389Profs∗2) | Germine, inherited (affected mother)   | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.1663C>T (p.Arg555∗)        | Germine, inherited (affected father)   | 12              | I, Ila, IIb                                      |                                                                                                       |
|                     | c.4674G>A (p.Thr1508Profs∗2) | Germine, inherited (affected mother)   | 12              | I, Ila, IIb                                      |                                                                                                       |
| Sim et al. [3]      | c.1114C>T (p.Gln372∗)        | Germine                               | 5               | Ila, IIb                                         |                                                                                                       |
|                     | c.3639G>A (p.Thr1213∗)       | Germine                               | 5               | IIb                                              |                                                                                                       |
|                     | c.3802C>T (p.Arg1268∗)       | Germine                               | 5               | IIb                                              |                                                                                                       |
|                     | c.3406A>T (p.Arg1136∗)       | Germine                               | 5               | IIb                                              |                                                                                                       |
|                     | c.4521_4522delAA (p.Thr1508Profs∗2) | Germine                              | 5               | IIb                                              |                                                                                                       |
| Liu et al. [8]      | c.3092C>A (p.Pro1031His)     | 2-hit brain somatic                   | 1               |                                                  | Focal epilepsy (FLE)                                                                                   |
|                     | c.4162_4169dupGTACTCTTT (p.Phe1399His) | Germine                               | 1               |                                                  |                                                                                                       |

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 imagingological 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 another 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 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 [8]. 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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