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Observation of a Possible Successful Treatment of *DEPDC5*-Related Epilepsy with mTOR Inhibitor

Kinga Hadzsiev[1] Márta Hegyi[2] András Fogarasi[2] Tímea Bodó-Baltavári[2] Anna Zsigmond[1] Anita Maász[1] András Szabó[1] Ágnes Till[1]

[1] Department of Medical Genetics, Medical School, Clinical Center, University of Pécs, Pécs, Hungary
[2] Bethesda Children's Hospital, Epilepsy Center, Budapest, Hungary

Address for correspondence Kinga Hadzsiev MD, PhD, 7623 Pécs, József A. Street 7, Hungary (e-mail: kinga.hadzsiev@pte.hu).

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Abstract

The mechanistic target of the rapamycin signaling pathway serves as a central regulator of cell metabolism, growth, proliferation, and survival. In its regulation, the GTPase-activating protein activity toward Rags1 complex has an inhibitory effect. Mutations in genes encoding this complex protein are among the most common abnormalities in focal epilepsies. Within these mutations, the mutations affecting the *DEPDC5* gene have been associated with different autosomal dominantly inherited epilepsy types. Due to the limited data available on mTOR inhibitor therapy in nontuberous sclerosis complex epileptic patients, here we present the clinical management of a patient with intractable epilepsy, skin hypopigmentation, and a *DEPDC5* variant. The patient's phenotype is compatible with a nonlesional *DEPDC5*-related epileptic encephalopathy. We initiated compassionate, off-label everolimus treatment as the patient's condition continuously deteriorated. Due to bilateral pneumonia occurring at the beginning of the treatment, it was temporarily discontinued, and resumed in half the dose. Follow-up examination after 18 months showed a 90% reduction in seizure frequency with moderate improvement in attention function and nutritional status. Our case report emphasizes the importance of early genetic testing in patients with epileptic encephalopathy. Clinical consequences of mammalian target of rapamycin complex 1 (mTORC1) upregulation may be amenable to tailored treatment with mTOR inhibitors. A clinical trial on an international scale would be needed to draw conclusions.

Keywords
- epilepsy
- GATOR complex
- *DEPDC5* gene
- everolimus
- hypopigmentation

Introduction

The mammalian target of rapamycin (mTOR) signaling pathway serves as a central regulator of cell metabolism, growth, proliferation, and survival. Its regulation is quite complex; in addition to the tuberous sclerosis complex (TSC), the GTPase-activating protein activity toward Rags1 (GATOR) complex also has an inhibitory effect.[1] Although TSC is the classic example of mTORopathies, in recent years the GATORopathies, as a functional subclass, have drawn attention. Mutations in genes encoding GATOR complex protein are among the most common abnormalities in focal epilepsies. Within these mutations, the mutations affecting the DEP domain containing 5 (*DEPDC5*) gene have been associated with different autosomal dominantly inherited epilepsy types. Hyperactivation of the mTOR pathway has been implicated in TSC and other mTORopathies.[2,3] Recently published clinical trials of mTOR inhibitors in TSC have shown that these drugs are effective at decreasing seizure frequency.[4] Rapamycin and structural analogs, like everolimus, directly inhibit mTOR.[5] The clinicoradiological

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phenotypes associated with *DEPDC5* mutations share features with TSC, raising the possibility of therapies targeting this pathway. Due to the limited data available on mTOR inhibitor therapy in non-TSC epileptic patients,[6,7] we present the clinical management of a patient with intractable epilepsy with skin hypopigmentation and a *DEPDC5* variant.

Patient and Methods

The patient is an 18-year-old female, who was born from the first, by in vitro fertilization conceived, dizygotic twin pregnancy of the mother as the second newborn. Her sister is healthy with normal intelligence and there is no data of epilepsy or other neurological diseases in the family (►**Fig. 1**). Her postnatal adaptation and early psychomotor development were normal, so she started the elementary school. The first epileptic seizure occurred at the age of 7 and since then a clinical picture of developmental and epileptic encephalopathy has developed with therapy resistance and a continuous regression. She lost her ability to walk and speak and developed urinary and fecal incontinence. Apart from the spastic tetraparesis, the severe scoliosis with thorax deformity, an extended linear and whorled pattern hypopigmentation along Blaschko's lines with a left dominance could be observed by physical examination. She was extremely malnourished, her weight was 30 kg (<<3 percentile), her height was 156 cm (3–10 percentile), and her head circumference was 51 cm (<3 percentile), and she had no dysmorphic signs. She experienced several tonic seizures during the day, while at night hypermotor seizures were more characteristic. Generalized tonic–clonic seizures were rarely seen, as well. Interictal electroencephalography (EEG) corresponds to epileptic encephalopathy and electrical status epilepticus, with continuous bilateral synchronic irregular spike-wave pattern. The seizures always originated from the left frontocentral area. The serial brain magnetic resonance imaging showed no brain malformation. None of the antiepileptic drugs alone or in combination were able to control, even partially, the seizures. The etiology of her epilepsy has not been clarified with extensive clinical examinations. Therefore, whole-exome sequencing with copy number variants analysis (WES Plus) was performed.

Results

A heterozygous missense c.2763A > T (p.Leu921Phe) variant in the *DEPDC5* gene (NM_001242896.1) was detected by WES Plus, which was classified as a variant of uncertain significance (VUS) by the laboratory. The patient's phenotype was compatible with a non-lesional *DEPDC5*-related epileptic encephalopathy. Considering the limited therapeutic alternatives, we hypothesized that everolimus could be a therapeutic option as observed in studies of TSC patients with intractable seizures.[4] We initiated compassionate, off-label 10 mg/day everolimus (Votubia, Novartis Europharm Ltd, Dublin, Ireland) treatment. The therapy was well tolerated, a definite reduction in seizure frequency could be observed. In the 12th week of administration, severe pneumonia with hydrothorax occurred. A combined antibiotic treatment and thoracic drainage were done, and the patient recovered in a relatively short period. Everolimus therapy was temporarily discontinued, and resumed at 5 mg/day doses after 4 weeks. During the therapeutic break, the patient's epileptic seizures became more frequent, and her general condition also deteriorated. Receiving the lower dose, the blood level of rapamycin was almost always in the therapeutic range (4.3–9.5 µg/L), as previously reported in TSC patients.[4] Follow-up examination after 18 months showed a 90% reduction of seizure frequency with moderate improvement in attention function and nutritional status. According to parental opinion, a significant improvement in quality of life was observed. Unfortunately, there was no significant improvement on the encephalopathic EEG. The targeted genetic examination of the healthy mother and sister were carried out in our laboratory and both of them proved to be carriers regarding the *DEPDC5* variant.

Discussion

Although the variant has been classified as VUS and is also carried by the healthy mother and sister, this variant could

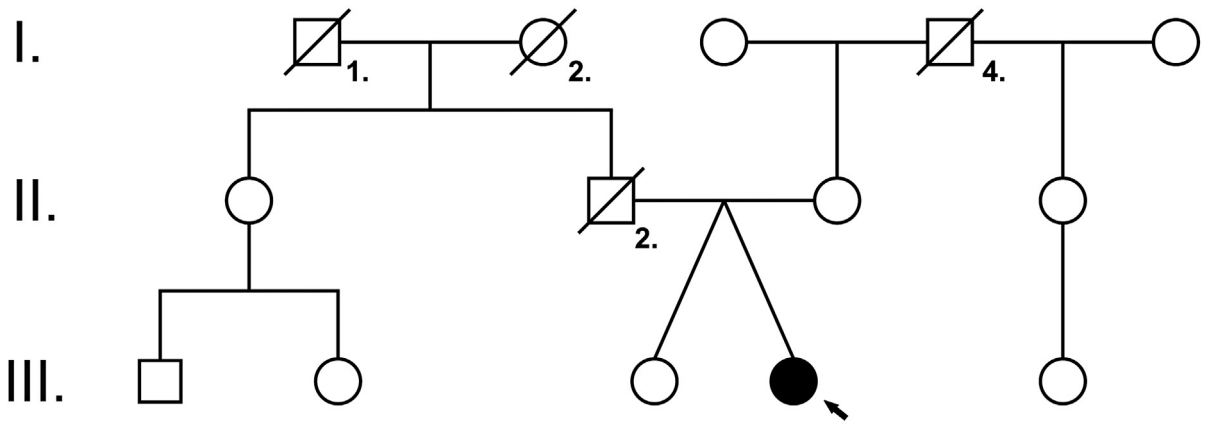

Fig. 1 The pedigree of the family. The arrow indicates the patient. II./2 member of the family died in a car accident at a younger age. I./1., I./2., and I./4 members of the family died at an advanced age due to unknown causes.

be responsible for the patient's phenotype. The *DEPDC5* gene-associated disorders are known to be inherited in an autosomal dominant manner. Penetrance of the disease is incomplete and may be as low as 60%; asymptomatic heterozygotes are common in families with *DEPDC5*-related epilepsy.[8] Several authors hypothesize that a possible somatic mutation in the brain serves as a second-hit and it may play an important role in the development of focal cortical dysplasias and related-epilepsies.[9,10] Furthermore, the role of a second mosaic mutation in the ectodermal cell-line is also supported by the patient's phenotypic overlap with the mTOR-related hypomelanosis of Ito. It is a recognizable neurocutaneous phenotype of patterned dyspigmentation, epilepsy, intellectual deficiency, and brain overgrowth. In a recently published study, Carmignac et al detected pathogenic mosaic *MTOR* variants in the DNA samples from hypopigmented skin only, absent from blood-derived DNA in half of their cohort. Their findings are also consistent with upregulation of mTORC1, resulting in hypopigmentation due to partial suppression of melanogenesis, similar to hypochromic patches in TSC.[11] The clinical history of our patient supports this second-hit hypothesis. It is also confirmed by the significant reduction in the frequency of epileptic seizures as a result of the applied mTOR inhibitor therapy. The limitation of our study is not to prove the existence of the second somatic mutation. We are planning to do a skin biopsy from the hypopigmented area of the patient and do an in-depth exome sequencing on it. This case also supports the theory that both assisted reproduction technology and twin pregnancies and the complications associated with them, have an increased risk of neurological disease and epilepsy ("Early Neuroimpaired Twin Entity"). Even in case of monozygotic twins, it is known that the clinical manifestation of genetic epilepsy resulting from a de novo gene mutation may differ significantly between twins. This can be in part explained by the variable level of postzygotic somatic mosaicism in the cerebral cortex, in part by other genetic factors, like variable imprinting effects.[12] To the best of our knowledge, our case is the first one receiving everolimus treatment based on a putative germline *DEPDC5* variant in the background of intractable epilepsy. Our case report emphasizes the importance of early genetic testing in patients with developmental and epileptic encephalopathy. This can provide an opportunity for early detection and effective decision-making for the most appropriate therapy. Clinical consequences of mTORC1 upregulation may be amenable to tailored treatment with mTOR inhibitors, although data on efficacy are inconclusive so far.[13] A clinical trial on an international scale would be needed to draw conclusions.

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Conflict of Interest
None declared.

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