Seizure Control Outcomes following Resection of Cortical Dysplasia in Patients with DEPDC5 Variants: A Systematic Review and Individual Patient Data Analysis

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Abstract

There is insufficient evidence regarding the efficacy of epilepsy surgery in patients with pharmacoresistant focal epilepsy and coexistent DEPDC5 (dishevelled EGL-10 and pleckstrin domain-containing protein 5) pathogenic (P), likely pathogenic (LP), or variance of unknown significance (VUS) variants. To conduct a systematic review on the literature regarding the use and efficacy of epilepsy surgery as an intervention for patients with DEPDC5 variants who have pharmacoresistant epilepsy. A systematic review of the current literature published regarding the outcomes of epilepsy surgery for patients with DEPDC5 variants was conducted. Demographics and individual patient data were recorded and analyzed. Subsequent statistical analysis was performed to assess significance of the findings. A total of eight articles comprising 44 DEPDC5 patients with genetic variants undergoing surgery were included in this study. The articles primarily originated in high-income countries (5/8, 62.5%). The average age of the subjects was 10.06 ± 9.41 years old at the time of study. The most common form of epilepsy surgery was focal resection (38/44, 86.4%). Thirty-seven of the 40 patients (37/40, 92.5%) with reported seizure frequency results had improvement. Twenty-nine out of 38 patients (29/38, 78.4%) undergoing focal resection achieved Engel Score I postoperatively, and two out of four patients achieved International League Against Epilepsy I (50%). Epilepsy surgery is effective in patients with pharmacoresistant focal epilepsy and coexistent DEPDC5 P, LP, or VUS variants.

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Introduction

Epilepsy is a common neurological disorder with a prevalence of 1.2% in the U.S. population.[1] Approximately 30% of these individuals have pharmacoresistant epilepsy or drug-resistant epilepsy.[2] Focal cortical dysplasia (FCD) is a congenital abnormality characterized by aberrant and chaotic growth of brain layers. FCD is the most common underlying causes of surgically treatable pharmacoresistant focal epilepsy.[3] Complete surgical resection of FCD lesions is associated with high rates of seizure freedom with approximately 62 to 72% of patients achieving seizure freedom.[4–6]

The underlying genetic basis for FCD is still an area of active research, but different genetic associations have been established. One gene of interest is dishevelled EGL-10 and pleckstrin domain-containing protein 5 (DEPDC5). DEPDC5 is a part of the GATOR-1 complex that functions as a potent inhibitor of the mammalian target of rapamycin (mTOR) pathway, specifically the mTORC1 signaling pathway. Dysregulation of DEPDC5, and consequently the mTORC1 pathway, is implicated in the pathogenesis of cortical malformations.

There is a paucity of data on outcomes following resective epilepsy surgery for patients with DEPDC5 pathogenic, likely pathogenic, or variance of unknown significance (VUS) variants and focal epilepsy related to FCD. The medical literature contains few case series that are disparately reported. Thus, the practicing clinician has limited information to make clinical decisions and provide well-informed prognostic information to patients with this diagnosis. The objective of this paper is to perform a systematic review of the outcomes of resective epilepsy surgery in patients with FCD and DEPDC5 pathogenic, likely pathogenic, or VUS variants and present an individual patient data (IPD) analysis.

Materials and Methods

Design and Search

A systematic review of DEPDC5 pathogenic, likely pathogenic, or VUS variants and outcomes of surgery was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines as well as the PRISMA-IPD guidelines.[7–10] In December 2022, we searched PubMed MEDLINE (National Library of Medicine) including the search terms "depdc5," "epilepsy," and "surgery." The full search terms are presented in ►**Supplementary Table S1** (available in the online version). There were no restrictions on date, article type, or language during the search. No protocol was prepared or registered.

Screening

After the search terms were established and accumulation of articles was conducted, all search results were consolidated and incorporated in Rayyan.ai.[11] The detect duplicates feature was utilized to identify and remove duplicates. Independent screening was performed by two reviewers (C.M., K.H.) to sort through the remaining articles by title and abstract for relevance. Articles included to the next phase of the study were again screened independently by two reviewers (C.M., K.H.) to assess the full text based on prespecified inclusion and exclusion criteria. Inclusion criteria were created based on a modified population, intervention, comparator, outcome framework, without a comparator term (►**Fig. 1**). Inclusion criteria for articles comprised the following: peer-reviewed full-text articles, providing primary data, written in English, population of patients with a DEPDC5 variant, surgical intervention, and describing efficacy of outcomes. Studies examining multiple epilepsy types were included if demographics and outcomes for the surgical intervention could be determined. Exclusion criteria for articles included: nonhuman studies, conference abstracts, existing reviews/meta-analyses, not focused on people with DEPDC5 variants, not utilizing surgery as an intervention, or not providing IPD on safety or efficacy outcomes. At both stages, disagreements between reviewers were resolved via consensus.

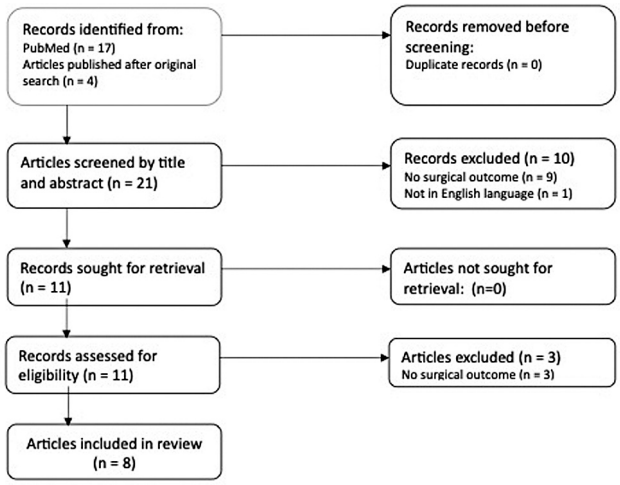

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart diagram. This figure provides visual representation of the use of the PRISMA flow model for inclusion and exclusion of articles for this review.

Data Extraction

After the set of included articles was finalized, relevant data regarding demographics, treatments, and key findings were extracted. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to determine the quality of all included studies.[12] The Risk of Bias of Non-randomized Studies—of Interventions (ROBINS-I) tool was used to determine the risk of bias of each included study.[13] Classification of epilepsies was based off the International League Against Epilepsy (ILAE) Classification and Terminology criteria.[14] The surgical outcome for patients was classified in ordinance with Engel Score. The overall risk of bias for this study was determined by considering the risk of bias of all included studies in aggregate. Once study-level data extraction was completed, IPD were collected from all studies providing demographic, clinical, and surgical outcome data for people with DEPDC5 variants who underwent any form of surgical intervention. Demographic data of patients included sex, age at study, age at onset of seizures, and comorbidities. Clinical data included

seizure types, symptoms, magnetic resonance imaging (MRI) results and findings, electroencephalography (EEG) findings, stereoelectroencephalography (SEEG) findings, other presurgical studies and respective findings, laterality, ILAE classification, history of previous surgery, type of surgical intervention used, and resection site. Outcome data included improvement in seizure frequency, Engel score, and other significant findings from the studies. All data were stored in Excel 2010 (Microsoft Inc., Redmond, Washington, United States).

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics viewer and Microsoft Excel descriptive, univariate, bivariate, and multivariate analysis options. A statistical significance of 0.05 ($\alpha = 0.05$) was used to assess statistical significance for findings with scores lower than this deemed statistically significant. Concurrent confidence interval and *t*-scores were used to further corroborate findings.

Results

Included Studies

Of the 18 articles retrieved in the original literature search, five studies were included in the systematic review, with three additional studies included external to the original literature search (►**Fig. 1**).[15–22] Three studies were case reports (37.5%), three were cohort studies (37.5%), one was a review article (12.5%), and one was a case series (12.5%). Only one article included in this study focused solely on DEPDC5 patients. Five studies originated from high-income countries (62.5%), two were from upper-middle-income countries (25%), and one was from a low-income country (12.5%). Six studies originated from Australia, the United States, France, Canada, and China (75%). The quality of included studies was most often low per use of the GRADE criteria. The risk of bias was most often high, predisposing this study to a high risk of bias overall. ►**Table 1** highlights pertinent information on all included studies.

Study-Level Data

This literature search identified 44 patients with DEPDC5 variants who underwent surgery. The mean age at time of study for patients was 10.06 ± 9.41 years with a range of 4 months to 49 years. Seven of the studies (87.5%) reported follow-up period. All studies included seizure type, but only one did not report the seizure semiology. The reference sequence for reporting gene-specific or protein-specific variants was reported in all articles.

Descriptive analysis was first used to examine general findings, such as frequencies of variables. A total of 40 unique gene variants were identified in this study. Of the 40 unique variants, 26 were pathogenic (26/40, 45.6%), 13 were likely pathogenic (13/40, 22.8%), and 5 were VUS (5/40, 8.8%). Most patients (40/44, 90.9%) had variants solely associated with the DEPDC5 gene. The remaining patients (4/40, 9.1%) had variants in the DEPDC5 gene with one or two additional genes, including PI3KCA, AHNAK, STX1B, DEPTOR, or NF1. Almost half (45.5%) of patients presented with FCD IIa ILAE Classification.

Patients most often had positive MRI findings (31/44, 70.5%). Pearson R test analysis of MRI-positive or negative findings and Engel Score was assessed and found to be not significant ($p = 0.079$), indicating that MRI findings were not associated with surgical outcome in this study. However, it should be noted that 84.6% of MRI-negative cases (11/13) achieved Engel Score I.

Single-factor analysis of variance (ANOVA) was then used to assess statistical significance of Engel Score versus surgery type and Engel Score versus seizure type. These results also produced nonsignificant results ($p = 0.28$, 0.58 respectively), signifying that the surgery used nor the seizure type correlated with Engel Score and surgical outcome. However, when assessing patients with reported time to seizure freedom and designated surgical type, there was a statistical significance between groups ($p = 0.017$), with focal resection achieving a shorter average in time to seizure freedom (average time to seizure freedom = 1.925 years) compared with other surgical types. The average length of time for patients who experienced improvement in seizure frequency or seizure freedom was 2.93 ± 2.78 years.

One article used ILAE outcomes to report surgical results[21] and was analyzed similarly to those that used Engel Score.[15–20,22] Single-factor ANOVA results for ILAE outcome versus seizure type and ILAE outcome versus surgical intervention were similar to Engel Score outcome in that they produced insignificant results.

Individual Patient Data

A total of eight studies with 159 patients provided IPD. Of the 159 patients, 44 were DEPDC5 patients who underwent surgery. Results regarding demographic information were included in ►**Table 2**. Results encompassing IPD were assembled into ►**Supplemental Tables S2–S4** (available in the online version). Nonsurgical data were compiled into ►**Supplemental Table S2** (available in the online version). Preimaging studies and reports for each patient were recorded in ►**Supplemental Table S3** (available in the online version). Surgical information for each patient was recorded in ►**Supplemental Table S4** (available in the online version). Lastly, overviews of each table can be seen in ►**Supplemental Tables S5–S9** (available in the online version).

The average age of these individuals was 10.06 ± 9.41 years old at the time of study. Seven out of the eight articles included patient sex. Of the articles that included sex, 28 out of 44 (65.1%) were males, and the remainder were females (34.9%). The mean age at epilepsy onset was 1.65 ± 2.50 years, with a range of 1 to 11 years old. Twenty-seven out of 44 (61.4%) patients had at least one comorbidity. Of patients with comorbidities, the most common were psychological manifestations including, mild intellectual disabilities, cognitive delays, aggression/autoaggression, attention-deficit hyperactive disorder, anxiety, and autism spectrum disorders. Cognitive delays were the most reported psychological comorbidity (28.9%). There were also physical comorbidities, including cleft palate,

Table 1 Summary of article findings

Article	Country	Study design	Quality grade	Risk of bias	Number of DEPDC5 patients undergoing surgery	Total number of patients	Follow-up period	Key findings
Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations	France	Case report	Low	Moderate	7	7	4–13 y	Three patients were seizure-free postsurgically and one had a worthwhile improvement. Study also indicates that epilepsy surgery is a valuable alternative in the treatment of drug-resistant DEPDC5-positive focal epilepsies, even if the MRI is unremarkable
A comprehensive clinico-pathological and genetic evaluation of bottom-of-sulcus focal cortical dysplasia in patients with difficult-to-localize focal epilepsy	USA (Ohio)	Case report	Low	High	1	10	2 mo–11 y (mean 6 y)	Complete resection was achieved by lesionectomy or focal corticectomy in nine patients. Histopathologically, six patients had FCD type IIb & three had FCD type IIa
mTOR pathway somatic variants and the molecular pathogenesis of hemimegalencephaly	Brazil	Case report	Low	High	1	5	6 mo, 1 y	Stated they believe that the refractory epilepsy should be treated with surgery even in the presence of a clear genetic etiology
GATOR1-related focal cortical dysplasia in epilepsy surgery patients and their families: A possible gradient in severity?	Czech Republic	Review article	Moderate	High	2	4	1–13 y	Although patients with GATOR1-associated FCD are considered good surgical candidates, postsurgical seizure outcome was poor in our familial cases
The landscape of epilepsy-related GATOR1 variants	France	Cohort study	High	Low	9	73	8 mo–58 y	The majority of the DEPDC5 patients who underwent surgical intervention had improvement in seizure frequency resulting in Engle I
Familial cortical dysplasia type IIA caused by a germline mutation in DEPDC5	Australia	Cohort study	Low	Moderate	2	2	NA	NA
Epilepsy surgery outcomes in patients with GATOR1 gene complex variants: Report of new cases and review of literature	Canada	Case series	High	High	4	8	1–7 y	Engel Class I outcome observed in 3 patients at a mean follow-up of 2.3 y
Seizure features and outcomes in 50 children with GATOR1 variants: A retrospective study, more favorable for epilepsy surgery	China	Cohort study	High	Moderate	18	50	12, 24, 36, 60 mo	Epilepsy surgery provided favorable outcomes in patients with “GATOR-1 phenotypes” (DEPDC5, NPRL2, NPRL3)

Abbreviations: NA, not available; NPRL2, nitrogen permease regulator like 2; NPRL3, nitrogen permease regulator like 3.

Table 2 Demographic findings

Article	Patient	Sex (M/F)	Age at study (y)	Age at onset of seizures	Comorbidities to be noted
Baulac et al. 2015	1	M	33	2 y	NA
	2	M	6	8 mo	NA
	3	F	25	3 d	Mild ID
	4	F	23	18 mo	NA
	5	M	15	2 y	NA
	6	M	49	4 mo	NA
	7	M	10	4 y	NA
Ying et al. 2018	8	NA	13	18 mo	All patients were noted to have no neurological deficits at clinical examination
Garcia et al. 2020	9	M	5	3 mo	NA
Benova et al. 2021	10	M	NA	2 mo	NA
	11	M	NA	3 d	Aggression and autoagression
Baldassarri et al. 2019	12	M	16	6 y	Cleft palate
	13	M	7	2 y	Mild ID, ADHD, anxiety
	14	M	8	5 mo	Psychomotor (language) impairment after seizure onset
	15	M	9	2 mo	Mild ID, ASD
	16	F	3	5 mo	Intermittent strabismus, mild ataxia
	17	F	17	8 y	NA
	18	F	2	2 d	Axial hypotonia, L hemiparesia, and L hemianopsia
	19	M	14	11 y	Mild ID, autistic features
	20	F	15	5 y	NA
Scerri et al. 2015	21	M	16	1 d	NA
	22	M	10	2 wk	NA
Sahly et al. 2023	23	F	16	2.5 y	Weaknesses in processing speed, language-based skills, and aspects of executive functioning
	24	F	14	8 mo	Moderate ID
	25	M	8	6 mo	Autism, ID, anxiety, aggression
	26	M	2.5	2.5 mo	Autism
Wang et al. 2023	27	11 M: 7 F	2	3 mo	Cognitive delay
	28		2.75	2 mo	Cognitive delay
	29		8	2 mo	NA
	30		8	11 mo	NA
	31		3	4 mo	Cognitive delay
	32		4	8 mo	Cognitive delay
	33		12	72 mo	Cognitive delay
	34		0.75	0.5 mo	Cognitive delay
	35		0.33	0.1 mo	Cognitive delay
	36		6.5	2 mo	Cognitive delay
	37		7	8 mo	Cognitive delay
	38		1.42	4 mo	Cognitive delay
	39		0.25	0.67 mo	Cognitive delay
	40		3	0.23 mo	Cognitive delay
	41		8	62 mo	NA
	42		1.83	1 mo	NA
	43		8	35 mo	Cognitive delay
	44		9	66 mo	NA

Abbreviations: ADHD, attention-deficit hyperactive disorder; ASD, autism spectrum disorder; F, female; ID, intellectual disability; M, male; NA, not available.

intermittent strabismus, mild ataxia, axial hypotonia, and left hemiparesis/hemianopsia. Although neuropsychological screening was used in several articles, specific details regarding the type of screening and results were not recorded.

The type of seizures diagnosed included focal epilepsy, general tonic–clonic seizures, ictal spasms, status epilepticus, sleep-related hypermotor epilepsy, or frontal lobe epilepsy. The most prominent type of seizure upon presentation was focal epilepsy (32/44, 72.7%). For literature reporting of symptoms of seizures, there was a wide variability in the vocabulary used (►**Supplementary Table S2**, available in the online version). Three out of seven articles did not report antiepileptic drug (AED) usage prior to or after the study. Only one study reported specific pharmaceutical drug resistance. Patients were reported to have been treated with a mean of 5 AEDs prior to surgery.

All studies reported usage and findings of MRI screening. Thirty-one out of 44 (70.5%) patients had MRI-positive findings, the most frequent of which were descriptions with inclinations of hypertrophic abnormalities such as cortical dysplasia, broadening or thickening of gyri or sulci, or cerebral or cerebellar volume increases. Three out of eight studies (37.5%) did not report any usage of EEG as a presurgical investigative tool. Of the studies that reported EEG, only one patient (1/24, 5.8%) had an EEG that could not localize seizure onset. There was inconsistent documentation of the number of electrodes used in SEEG testing. Only one article reported specific parameters of use[21] (►**Supplementary Table S3**, available in the online version). The frontal lobe was the most common area for lesion localization, which occurred in 10 out of 21 patients (10/21, 47.6%). Most lesions were unilateral.

As for surgical pathology findings, 3 out of 40 patients had inconclusive results (3/40, 7.5%), 3 had FCD I (7.5%), 1 had FCD Ia (2.5%), 1 had FCD Ib (2.5%), 1 had FCD Ic (2.5%). Twenty had FCD IIa (50.0%), 5 had FCD IIb (12.5%), and 1 had a normal result (2.5%). No patients had previous surgical intervention reported.

Surgical intervention type was most often focal resective surgery (38/44, 86.4%). Examples of resective surgeries include hemispherectomies, corticectomies, lobectomies, and biopsies. Six out of eight studies reported the site of surgical resection. Six out of the 16 patients (6/16, 37.5%) with reports of surgical site were left-sided, while 9 out of 16 were right-sided (9/16, 56.3%). Thirty-seven out of 40 patients (93.2%) reported improvement in seizure frequency to varying degrees. Twenty-nine out of the 37 patients with improvement in seizure frequency (29/37, 78.4%) became seizure free after surgery. Twenty-seven of the 37 patients had documented time to seizure freedom. Mean time to seizure freedom was 2.93 ± 2.78 years, with a median of 2.00 years. No articles reported complications from surgery. Twenty-nine out of 44 patients (65.9%) had reported an Engel Score of I, 24 of which had an Engel Score of I, four had an Engel Score of IA, and one had an Engel Score of IB. Two patients were reported to have an Engel Score of II (II, IIb). One patient had an Engel Score of III (IIIa). Finally, five patients were reported to have Engel Score IV (IV, IVb).

Discussion

In this article, we present a systematic review and analysis of IPD of surgical outcomes in patients with pharmacoresistant epilepsy and coexistent DEPDC5 variants. As it currently stands, surgical outcomes of epilepsy patients with DEPDC5 and other focal lesions with pathogenic, likely pathogenic, or variants of unknown significance remain unclear. Although the argument exists that surgical outcomes vary by pathogenic variant type that results in FCD, it has been primarily germline pathogenic variants in genes encoding ion channels and synaptic proteins that achieved significantly less seizure freedom. Meanwhile, patients with variants in the mTOR pathway, like DEPDC5, achieved significantly greater seizure freedom outcomes.[23]

Extensive analyses displaying the success of epilepsy surgery in patients with FCD have long been described, with seizure freedom being reported from a range of 62 to 72% of patient populations.[4,5] Even as of recency, despite the increasing numbers of genes identified to be involved with cortical dysplasia resulting in pharmacoresistant epilepsy, surgery can be a successful alternative for treatment. For example, two recent cohort studies conducted by Kang et al and Barba et al have shown that patients with focal dysplastic lesions because of SLC35A2, a membrane transport protein, pathogenic variants have benefitted as a result of epilepsy surgery. In these two studies, all, if not most, patients achieved improvement in seizure frequency or seizure freedom.[24,25]

As stated previously, genes involved with the mTOR pathway have been consistently reported to have success from surgical intervention. However, there has been some hesitation on whether to proceed with surgery due to varying reports of success. From our review, we exhibit and validate the findings of success postoperatively. In the studies accumulated, 92.5% of patients achieved improvement in seizure frequency, with 65.9% of this subset of patients achieving Engel Score I. Patients achieved seizure freedom at a mean of 2.93 ± 2.78 years and a median of 2.00 years. This finding is unsurprising as over half (25/40, 62.5%) were diagnosed with FCD II (FCD IIa and FCD IIb). Patients with FCD II have been shown to have success through surgical treatment.

It must be noted that complications nor risks of surgery are explored or demonstrated throughout these articles, leading to potential bias of underestimating the risk of surgery. One such complication that can be considered is the risk of SEEG. Since its induction into the United States in 2013, it has quickly displaced the complication-ridden technique of subdural electrodes, which included an extremely high complication rate of 5 to 17%.[26–30] The complication rate with SEEG usage has most recently been reported as $<1\%$ from a meta-analysis conducted by Cardinale et al, but reports of complication rates fluctuating between 1.2 and 2.6% in other studies.[31,32]

Another consideration for complications is, inherently, the surgical procedure itself. As expressed through the data, focal resection was the most common procedure performed in this

population of patients. Although complications were not reported in these articles, a previous systematic review conducted by Hader et al demonstrated that patients undergoing epileptic surgery, either focal resection or invasive EEG monitoring, has produced a minor complication rate of 7.7%. Major complications were only reported in 0.6% of patients, with the most common complication being cerebrospinal fluid leak.[33] From this same systematic review, it was concluded that mortality as a result of epilepsy surgery was present, albeit rare.[33] Another large-scale retrospective study ($n = 251$; last follow-up = 9 years) was conducted by Hsieh et al, in which epilepsy surgery was analyzed for effectiveness in pharmacoresistant epilepsy patients. There were several vital results: (1) if seizures persisted postoperatively, most patients with pharmacoresistant epilepsy still benefitted from a substantial reduction in seizure frequency; (2) greater than 70% of patients who underwent resection had seizure-freedom at long-term last follow-up (median = 11.9 years); and (3) over 90% of patients experienced periods of >1 year of seizure freedom.[34]

Lastly, a common factor that provided apprehension for surgical use was the lack of a defined epileptic zone from MRI. This could potentially be ameliorated through the combinatory approach of positron emission tomography (PET)-MRI, which was shown to further enhance difficult-to-localize lesions in FCD type II and better identify MRI-negative candidates for surgery.[35] Nevertheless, this systematic review and other studies have demonstrated that MRI-negative findings do not preclude patients from achieving significant or complete seizure reduction. In this study, 11 of 13 patients with MRI-negative results achieved either improvement in seizure frequency or seizure freedom (11/13, 84.6%). Almost half of this subset of patients did not undergo PET monitoring (5/11, 45.5%). Also, two previous studies conducted by Harvey et al. and Capraz et al., comprising 49 patients with MRI-negative findings, demonstrated postoperative success, with approximately 79 to 88% of patients achieving seizure improvement or freedom.[36,37] Thus, a lack of a defined epileptic zone should not prohibit one from considering surgical intervention as a therapeutic possibility in these instances.

Conclusion

Despite the dearth of significant findings and high bias included from these studies, we have demonstrated that the use of surgical intervention on DEPDC5 patients with coexistent pharmacoresistant epilepsy has produced favorable results in the patients included in the study. Additionally, we have described the minimal risk associated with the procedure. Data on DEPDC5 surgical outcomes are limited. Future studies are necessary to develop treatment algorithms or guidelines to further enhance the efficacy of surgical intervention on DEPDC5 patients.

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Conflict of Interest
None declared.

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