Author/s:
Carvill, GL;Crompton, DE;Regan, BM;McMahon, JM;Saykally, J;Zemel, M;Schneider, AL;Dibbens, L;Howell, KB;Mandelstam, S;Leventer, RJ;Harvey, AS;Mullen, SA;Berkovic, SF;Sullivan, J;Scheffer, IE;Mefford, HC

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Epileptic spasms are a feature of *DEPDC5* mTORopathy

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Gemma L. Carvill, PhD
Douglas E. Crompton, PhD, MBBS
Brigid M. Regan, BSc (Hons)
Jacinta M. McMahon, BSc (Hons)
Julia Saykally
Matthew Zemel, BS
Amy L. Schneider, MGen Couns
Leanne Dibbens, PhD
Katherine B. Howell, MBBS (Hons), BMedSc
Simone Mandelstam, MBChB
Richard J. Leventer, MBBS, PhD
A. Simon Harvey, MD
Saul A. Mullen, MBBS, PhD
Samuel F. Berkovic, MD, FRS
Joseph Sullivan, MD
Ingrid E. Scheffer, MBBS, PhD*
Heather C. Mefford, MD, PhD*

Correspondence to Dr. Mefford: hmefford@uw.edu or Dr. Scheffer: scheffer@unimelb.edu.au

Supplemental data at Neurology.org/ng

ABSTRACT

Objective: To assess the presence of *DEPDC5* mutations in a cohort of patients with epileptic spasms.

Methods: We performed *DEPDC5* resequencing in 130 patients with spasms, segregation analysis of variants of interest, and detailed clinical assessment of patients with possibly and likely pathogenic variants.

Results: We identified 3 patients with variants in *DEPDC5* in the cohort of 130 patients with spasms. We also describe 3 additional patients with *DEPDC5* alterations and epileptic spasms: 2 from a previously described family and a third ascertained by clinical testing. Overall, we describe 6 patients from 5 families with spasms and *DEPDC5* variants; 2 arose de novo and 3 were familial. Two individuals had focal cortical dysplasia. Clinical outcome was highly variable.

Conclusions: While recent molecular findings in epileptic spasms emphasize the contribution of de novo mutations, we highlight the relevance of inherited mutations in the setting of a family history of focal epilepsies. We also illustrate the utility of clinical diagnostic testing and detailed phenotypic evaluation in characterizing the constellation of phenotypes associated with *DEPDC5* alterations. We expand this phenotypic spectrum to include epileptic spasms, aligning *DEPDC5* epilepsies more with the recognized features of other mTORopathies. ***Neurol Genet* 2015;1:e17; doi: 10.1212/NXG.0000000000000016**

GLOSSARY

ExAC = Exome Aggregation Consortium; **FCD** = focal cortical dysplasia; **FFEVF** = familial focal epilepsy with variable foci; **MAF** = minor allele frequency; **mTOR** = mammalian target of rapamycin; **TSC** = tuberous sclerosis complex.

Autosomal dominant mutations in *DEPDC5* cause familial focal epilepsy with variable foci (FFEVF).[1,2] FFEVF is characterized by seizures arising from different cortical regions in different family members, and onset ranges from infancy to adulthood.[1,3–7] Clinical presentation is highly variable and reduced penetrance of ~66% is usual.[1,2] Families may show patterns that are effectively subsets of FFEVF, such as a phenotypically homogeneous pattern of autosomal dominant nocturnal frontal lobe epilepsy; individuals with rolandic epilepsy have also been described.[1,2,8–10] Recently, *DEPDC5* mutations were reported in patients with various brain malformations, challenging the long-held distinction between lesional and nonlesional epilepsies.[11–13]

DEPDC5 forms part of the GATOR1 complex, a negative regulator of the mammalian target of rapamycin (mTOR) pathway.[14] Mutations in other mTOR pathway proteins TSC1 and

*These authors contributed equally to the manuscript.

From the Division of Genetic Medicine (G.L.C., J. Saykally, M.Z., H.C.M.), Department of Pediatrics, University of Washington, Seattle; Epilepsy Research Centre (D.E.C., B.M.R., J.M.M., A.L.S., S.A.M., S.F.B., I.E.S.), Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Australia; Neurology Department (D.E.C.), Northern Health, Melbourne, Australia; Epilepsy Research Program (L.D.), School of Pharmacy and Medical Sciences, and Sansom Institute for Health Research (L.D.), University of South Australia, Adelaide, Australia; Department of Neurology (K.B.H., R.J.L., A.S.H., I.E.S.), Royal Children's Hospital, Melbourne, Australia; Florey Institute of Neuroscience and Mental Health (K.B.H., S.M., R.J.L., A.S.H., S.A.M., I.E.S.), Melbourne, Australia; Murdoch Childrens Research Institute (K.B.H., R.J.L., A.S.H.), Melbourne, Australia; Department of Paediatrics (S.M., R.J.L., A.S.H.) and Department of Radiology (S.M.), The University of Melbourne, Melbourne, Australia; and Epilepsy Division (J. Sullivan), Department of Neurology and Pediatrics, University of California, San Francisco.

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Table 1 Clinical and molecular features in patients with *DEPDC5* variants and epileptic spasms

Ped Ref	cDNA change (GERP)	Protein change (PolyPhen-2, SIFT, Grantham)	Age studied, sex	Epilepsy syndrome	Seizure onset	Seizure offset	Development	Seizure types (onset)	EEG/video EEG, age	MRI	Treatment	Other features
A:III:2	c.2390delA (NA)	p.Gln797Argfs*18; NA	3 y, M	IS	2 mo	Ongoing	Global DD; regression	IS, asymmetric (2 mo); FDS (9 mo)	4 mo: interictal GSW and low-voltage fast activity. In spasms: high-voltage biphasic slow waves then low-voltage fast activity.	Right temporal FCD	Improved with prednisolone. Refractory to PB, CZP, and VGB. FDS: improved with TPM and CBZ. Right anterior temporal lobectomy scheduled.	ASD
									4–24 mo: right focal slowing, right temporal interictal epileptiform discharges			Mild left leg weakness
									2 y 2 mo: as at 4–24 mo plus subclinical electrographic seizures arising from right anterior temporal region			
B:III:2	c.1555C>T (6.01)	p.Gln519*; NA	30 y, M	IS	6 wk	Ongoing	Global DD; regression; moderate-severe ID	IS (6 wk); FDS (3 y); FDS→TCS (3 y); myoclonus	28 y: generalized background slowing, multifocal interictal sharp-slow discharges, maximal centrally and posteriorly, usually bisynchronous, sometimes with background attenuation. Similar discharges with asymmetric myoclonic jerks and negative myoclonus.	ND	Refractory to CBZ, CZP, LEV, LTG, prednisolone, and VPA	Autistic features
C:III:3	c.3092C>A (5.31)	p.Pro1031His; 0.971, 0.01, 23	16 y, F	Late-onset epileptic spasms	2 y 8 mo	Ongoing	Speech and language delay; regression; mild ID	Asymmetric flexor spasms (2 y 8 mo); reflex tonic seizures precipitated by startle (10 y); atypical absences (11 y); TCS (12 y)	7 y 4 mo: interictal epileptiform spikes and sharp waves from both temporal and posterior regions in sleep. GSW, GPSW, and GPFA in slow wave sleep. Ictal EEG: (1) with spasms: polyphasic, rhythmic 2 Hz delta, maximal in midline, often with superimposed fast beta; (2) with reflex tonic seizures: generalized decrements and LVFA; and (3) with absences: GSW at 2–3 Hz.	Normal	Refractory to CBZ, CLB, ETX, KD, LCM, LTG, NZP, TPM, VGB, VPA, and ZSM	Nil
									9 y 5 mo: as above plus background slowing, interictal left central sharp-slow trains and frontotemporal delta, GSW with left temporal lead-in		10 y: left lateral temporal corticectomy, normal histopathology, no improvement	
D:II:1	c.842A>T (5.05)	Tyr281Phe; 0.997, 0.02, 22	5 y, F	IS	3 mo	Ongoing (rare)	Speech and language delay, hemispherotomy	IS; tonic seizures (27 mo)	14 mo: hypsarrhythmia with focal fast activity in left frontocentral regions. Electroclinical spasms with generalized spike/wave and pseudonormalization.	Left frontal FCD	Refractory to B6, ACTH, PB, VGB, and KD	Right HP s/p
									27 mo: (s/p left frontal lobectomy) hypsarrhythmia. Head drops, brief tonic seizures, and tonic eye deviation associated with low-amplitude fast activity.			
E:IV:2[1]	c.193+1G>A	NA	34 y, F	IS, OLE	2 mo	FDS ongoing, spasms ceased at 6 mo	Normal	IS (8 wk); FDS (11 y)	5 mo: multifocal and generalized interictal polyspike-wave discharges	Normal	Spasms: ceased with prednisolone; FDS: partial response to CBZ	Nil
									8 mo: normal			
									34 y: nonspecific episodic generalized slowing, otherwise normal			

Continued

Table 1 Continued

Ped Ref	cDNA change (GERP)	Protein change (PolyPhen-2, SIFT, Grantham)	Age studied, sex	Epilepsy syndrome	Seizure onset	Seizure offset	Development	Seizure types (onset)	EEG/video EEG, age	MRI	Treatment	Other features
E:IV:4[1]	c.193+1G>A	NA	16 y, M	IS	6 wk	6 mo	Global DD; ID	IS (6 wk)	5 mo: background slowing, multifocal spike-wave and polyspike-wave activity, left occipital electrographic seizure	Normal	Controlled on VGB	Autistic features
									3 y 7 mo: within normal limits			Infantile esotropia

Abbreviations: ACTH = adrenocorticotropic hormone; ASD = autistic spectrum disorder; B6 = pyridoxine; CBZ = carbamazepine; CLB = clobazam; CZP = clonazepam; DD = developmental delay; ETX = ethosuxamide; FCD = focal cortical dysplasia; FDS = focal dyscognitive seizure; FDS→TCS = focal dyscognitive seizure evolving to a bilateral convulsive/tonic-clonic seizure; FSRA = focal seizure with retained awareness; GERP = Genome Evolutionary Rate Profiling; GPFA = generalized paroxysmal fast activity; GPSW = generalized polyspike-wave; GSW = generalized spike-wave; HP = hemiparesis; ID = intellectual disability; IS = infantile spasms; KD = ketogenic diet; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; LVFA = low-voltage fast activity; NA = not applicable; ND = not done; NZP = nitrazepam; OLE = occipital lobe epilepsy; PB = phenobarbitone; Ped Ref = pedigree reference; s/p = status post; TCS = tonic-clonic seizure; TPM = topiramate; VGB = vigabatrin; VNS = vagal nerve stimulator; VPA = valproate; ZSM = zonisamide.
Variant coordinates based on *DEPCD5*: NM_001242896.1 and protein NP_001229825.1.
GERP score ranges from least (−12.3) to most highly conserved (6.17) residues. Combined Annotation Dependent Depletion (http://cadd.gs.washington.edu/) phred scaled scores range from 0 to 99. All PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) scores calculated under the HumVar model for mendelian disorders, range 0–1, with 1 most likely to be damaging. SIFT (http://sift.bii.a-star.edu.sg/) range 0–1, with 0 predicted to be most damaging, Grantham scores range from 0–215, with 215 predicted to be most damaging.

TSC2 lead to tuberous sclerosis complex (TSC). Infantile spasms are common in TSC, the prototypical disorder of the mTOR pathway.

Infantile spasms are part of the clinical triad of epileptic spasms, hypsarrhythmia, and developmental arrest or regression that forms the infantile spasms syndrome or West syndrome.[15] While epileptic spasms typically begin in infancy at around 6 months, later onset may occur. The etiology of infantile spasms is an important determinant of developmental outcome but is unknown in one-third of cases.[16,17] Given that spasms are a frequent feature in TSC and we observed spasms in 1 family in our initial report of *DEPDC5* in FFEVF,[1] we systematically searched for *DEPDC5* variation in 130 patients with epileptic spasms.

METHODS

Standard protocol approvals, registrations, and patient consents. Patients were recruited from the epilepsy clinic at Austin Health, from the practices of investigators, and by referral for epilepsy genetics research from around Australia and internationally. Electroclinical phenotyping was performed as previously outlined. In patients with *DEPDC5* variants, brain MRI was systematically reviewed by a pediatric neuroradiologist. Informed consent was obtained from the patient or his or her parent or legal guardian. The study was approved by the Institutional Review Boards of Austin Health and The University of Washington.

Targeted resequencing of *DEPDC5*. We used molecular inversion probes to capture all exons and 5 base pairs of flanking intronic *DEPDC5* sequence; next-generation sequencing and data analysis were performed as described previously in 130 patients with epileptic spasms of unknown etiology.[15,18] Known epileptic encephalopathy genes had been excluded in many cases (unpublished data, Carvill et al., January 2015).[18]

We considered only nonsynonymous, splice site, or frameshift variants that were present at an allele frequency <1% in ~61,000 exomes of the Exome Aggregation Consortium (ExAC) data set (to exclude single nucleotide polymorphisms) (http://exac.broadinstitute.org/) for further analysis and performed segregation analysis for these rare variants in available family members. We considered truncating variants to be pathogenic and missense variants that were either inherited from an affected parent or arose de novo to be possibly pathogenic. Maternity/paternity was confirmed using the PowerPlex S5 system (Promega, Madison, WI). We included an additional novel *DEPDC5* case, identified through commercial genetic testing (D:II:1), and additional phenotypic data on cousins from our earlier report (family E).[1]

Accession numbers. *DEPDC5*: mRNA NM_001242896.1 and protein NP_001229825.1.

RESULTS

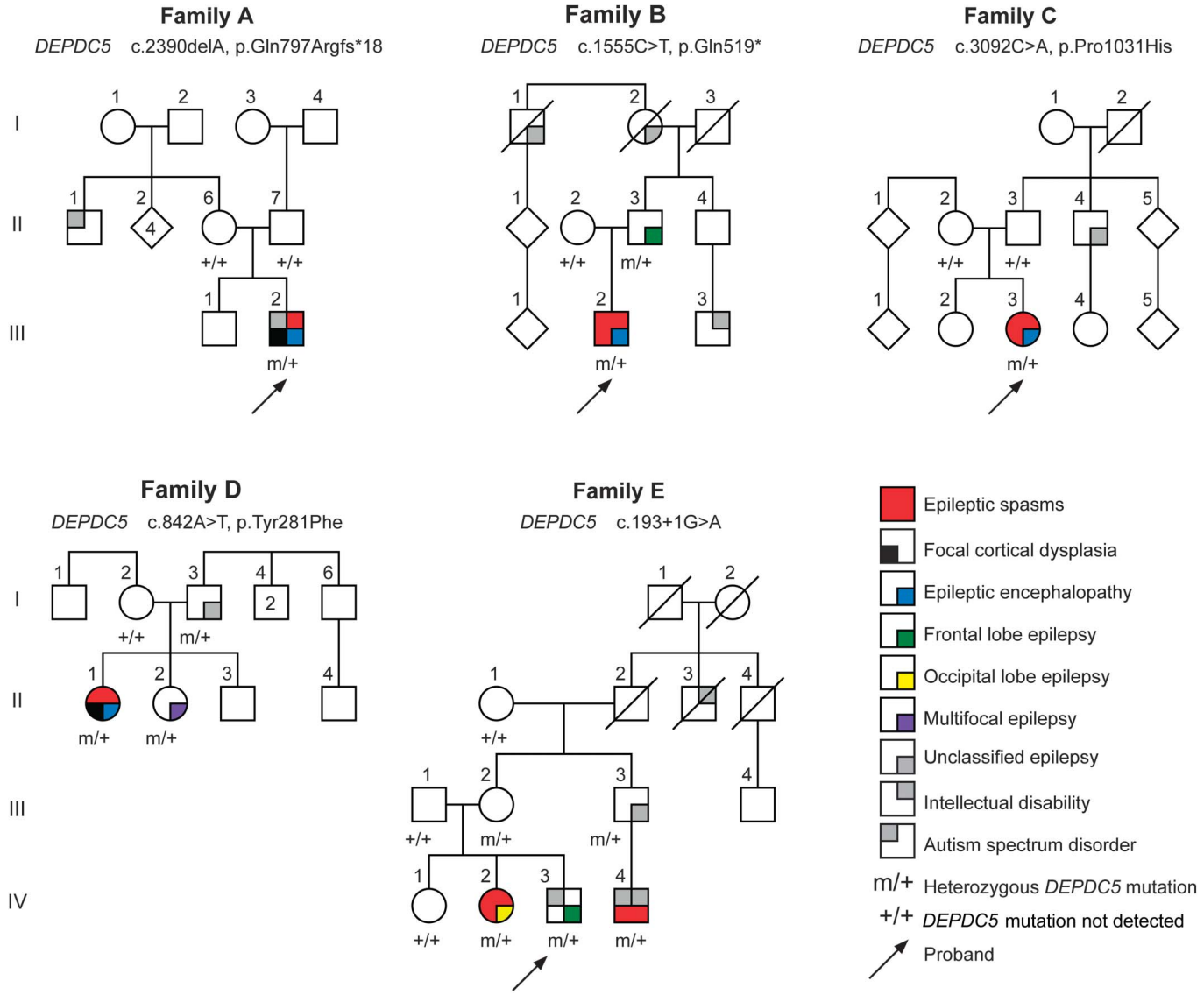
Molecular analysis. We sequenced all *DEPDC5* target base pairs to a depth of 50× at a median of 90% across all samples. We identified likely pathogenic variants in 3 of 130 (2.3%) patients with epileptic spasms of unknown etiology (table 1,

figures 1 and 2). A total of 92 of 130 patients had West syndrome, while 38 had epileptic spasms in association with other epileptic encephalopathies. In 2 cases (families A and C), the *DEPDC5* variants occurred de novo. Patient A:III:2 had a truncating mutation not present in controls. Patient B:III:2 inherited a truncating mutation not seen in controls from a father with frontal lobe epilepsy. Patient C:III:3, who was of Chinese descent, had a de novo missense variant that disrupted a highly conserved nucleotide, which was predicted to be damaging by 2 of 3 in silico tools (table 1). This variant occurred in 71 individuals in ExAC, including 66 of 8,732 individuals of East Asian descent (minor allele frequency [MAF] 0.7%).

We describe 2 additional families with inherited *DEPDC5* variants in whom 1 or more affected family members presented with spasms (table 1, figure 1). Family D, ascertained through commercial testing, had a Tyr281Phe variant, which is highly conserved and predicted to be damaging by 2 of 3 tools (table 1). This variant was present in 5 of 67,552 (MAF 0.0007%) individuals of non-Finnish European descent. Family E carries a splice site mutation, and we describe 2 patients with infantile spasms from this previously reported family.[1]

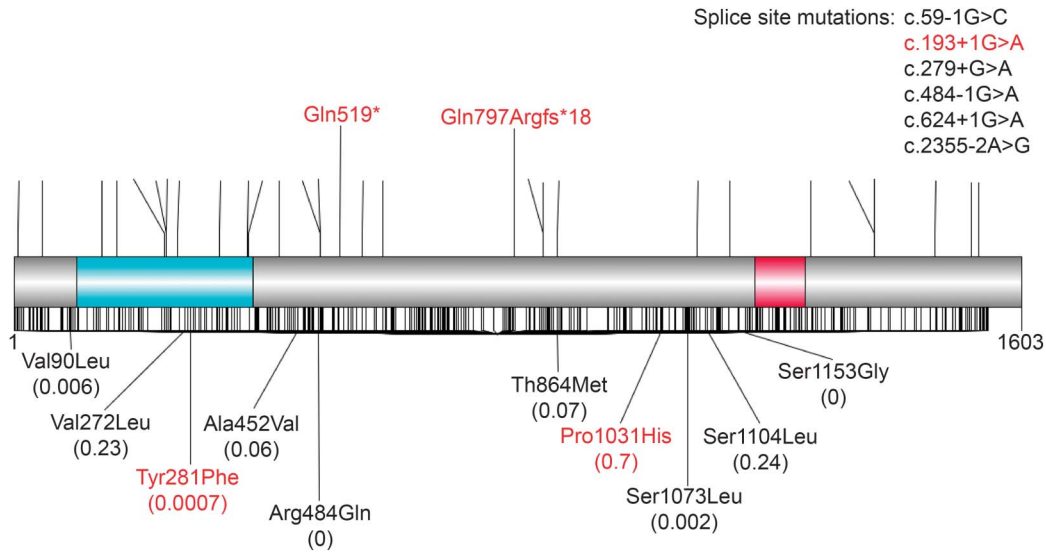
Clinical characterization. Spasms were the presenting seizure type in each case, with onset at 6–12 weeks in 5 cases and late onset at 2 years, 8 months in 1. Two had easily controlled spasms, both with offset at 6 months. In 4 cases, spasms had focal electroclinical features. EEG features included multifocal epileptiform abnormalities, generalized paroxysmal fast activity,

Figure 1 **Pedigrees of families with *DEPDC5* variants and epileptic spasms**



We describe 6 patients in 5 families with *DEPDC5* variants and spasms. Variants arose de novo in 2 cases (families A and C) and were inherited in 3 (families B, D, and E).

Figure 2 Distribution of *DEPDC5* variants in patients and controls



Upper panel of the schematic shows all previously reported truncating mutations (black)[1,2,8–13] and those described in this study (red). Lower panel shows all missense mutations in previous studies (black) and those described in this study (red), numbers in parentheses show the highest population MAF from the ExAC data set, and black lines show the missense variants present in ExAC and variable frequencies. Many of the missense mutations described in patients are present at appreciable frequencies in controls, and there are many missense variants across the gene. It will be vital to perform functional experiments to test the functional effect of these variants, to understand whether and how they cause disease, and to understand the incomplete penetrance that is a common feature of this disorder. ExAC = Exome Aggregation Consortium; MAF = minor allele frequency.

and slow spike waves (figure e-1 at Neurology.org/ng). Hypsarrhythmia was seen in 1 patient. Three cases had later focal seizures with impaired awareness and onset from 9 months to 13 years; all were refractory. Atypical absence seizures beginning at age 11 occurred in C:III:3.

One patient, E:IV:2, had normal intellect and no developmental regression with spasm onset; at 34 years, she was a professional. Three patients showed regression with seizure onset and 1 was never normal. Patient C:III:3 showed an additional later decline at age 15 years. Three had autistic features.

Brain MRI revealed temporal focal cortical dysplasia (FCD) in A:III:2 and frontal FCD in D:II:1 (figure e-2). MRI was normal in 3 cases and not performed in 1. Epilepsy surgery was performed in 2 cases. D:II:1 had a histologically confirmed left frontal FCD type IIA (figure e-3). After anatomic left frontal lobectomy, the patient was seizure-free for 6 months and then had return of head drops and tonic seizures. Repeat surgery with a functional left hemispherectomy resulted in seizure freedom for 2.5 years. She now has monthly staring spells. Left lateral temporal corticectomy in C:III:3 was unsuccessful; pathology was normal.

DISCUSSION We first identified *DEPDC5* in familial focal epilepsy, and here we show its relevance to epileptic spasms, illustrating the convergence of phenotypes in genetic mutations of the mTOR pathway. Our findings suggest that greater significance should be attributed to a family history of focal seizures in patients with epileptic spasms. Affected family members had focal epilepsies emanating from different cortical regions, consistent with the pattern of FFEVF.

Infantile spasms have an identifiable etiology in ~60% cases and may include hypoxic-ischemic or metabolic encephalopathies, malformations, infection, and chromosomal anomalies.[16] A family history of spasms is rare but has been described in conditions such as TSC and specific genetic diseases such as *ARX*.[19] The importance of de novo mutations has recently been emphasized, with a pathogenic mutation attributed to a single gene identified in 5%–16% of cases (n = 268 from 3 studies using next-generation sequencing technologies) (table e-1). The most frequently mutated genes were *STXBP1* (n = 6), *CDKL5* (n = 2), *KCNQ2* (n = 2), and *ALG13* (n = 2).[18,20,21] Our finding of a *DEPDC5* variant in up to 2.3% of patients in our cohort suggests that this gene may be one of the more frequent genes associated with epileptic spasms, taking into account that this cohort had been previously screened for many of the known genes. As only 1 patient showed classic hypsarrhythmia, the cohort may have some fundamental differences from other studies of infantile spasms in which hypsarrhythmia is essential for inclusion.

We identified 3 truncating mutations: 1 occurred de novo and the remaining 2 were inherited. This is

in keeping with previous reports in which the overwhelming majority of pathogenic *DEPDC5* mutations resulted in premature truncation of the protein (figure 2), suggesting that *DEPDC5* mutations cause disease by haploinsufficiency of the protein. This is further supported by the presence of only 15 truncating variants in the ~61,000 exomes in ExAC. However, we report 2 missense variants, Pro1031His (MAF 0.7%) and Tyr281Phe (MAF 0.007%), and there are more than 400 missense variants in ExAC. Tyr281Phe is exceedingly rare, and incomplete penetrance of *DEPDC5* mutations may explain the presence of these variants in the population. However, the 0.7% MAF of Pro1031His (arose de novo in family C) seems too high in this population to be explained solely by incomplete penetrance, and this result needs to be interpreted with caution. This may also be true for several reported missense mutations also present in controls at low frequencies (figure 2).[1,8] It will be important to develop robust functional experiments to assess the pathogenicity of these missense variants in the future.

We have combined a targeted resequencing approach in 130 patients and results from clinical diagnostics and extended phenotyping in a known mutation-positive family to determine several notable features that highlight the variability of onset and outcome of *DEPDC5*-associated spasms. Our findings expand the *DEPDC5* phenotypic spectrum to include more severe epilepsies presenting with spasms. First, the outcome may be excellent with normal intellect, although most of our patients had intellectual disability with or without autistic features. Second, seizures were controlled with monotherapy in 2 patients. Third, 1 patient had later onset of spasms in the third year with further cognitive decline in adolescence. Fourth, 2 patients had malformations with FCD; in 1, surgery resulted in seizure improvement. Our findings show that *DEPDC5* variants are associated with FCD type IIA. Surprisingly, only 1 patient showed hypsarrhythmia on EEG; however, all had highly abnormal EEGs with abundant epileptiform activity, which can be associated with epileptic spasms. The absence of classic hypsarrhythmia means that these patients differ from those with West syndrome, which has been the focus of many recent genomic studies.

Of note, spasms were present in patients with FCD (2 patients) and those without FCD (3 patients) after careful scrutiny of the MRI. Because many patients with focal epilepsies and *DEPDC5* mutations have normal MRI,[1,11,12] the presence of detectable lesions is not necessary for the development of seizures. Rather, loss-of-function mutations in *DEPDC5*, an inhibitor of the mTOR pathway, presumably lead to excessive signaling of this pathway, which has many functions that could conceivably contribute to hyperexcitability. Moreover, exactly how *DEPDC5* mutations lead to a cortical malformation is not known. It has been hypothesized that the presence of a "second hit" is required for the development of these lesions.[11] This scenario would be analogous to TSC, in which a second mutation in the mTOR regulators *TSC1* and *TSC2* is reported in some tumors of patients with TSC.[22] In patients with *DEPDC5* mutations, this "second hit" could occur either on the other allele or on another gene involved in the mTOR pathway. Alternatively, an acquired cause, such as a human papillomavirus, has been conjectured to be a "second hit" in FCD.[23] In the future, deep targeted or even whole-exome sequencing should be performed on resected tissue to explore this hypothesis.

Given the incomplete penetrance of *DEPDC5* mutations and the discovery of both inherited and de novo mutations, molecular approaches for epileptic spasms should interrogate both inheritance patterns. The detection of inherited mutations has important reproductive counseling implications for families of children with spasms, which needs to incorporate increased risk for comorbidities such as intellectual disability and autism spectrum disorders. The recognition of spasms in *DEPDC5* epilepsies parallels other mTORopathies such as TSC and STE20-related kinase adaptor alpha syndrome.[24] Although many *DEPDC5* epilepsies are milder, the convergence of the phenotypic spectrum and molecular pathways suggests that targeted mTOR therapies may benefit patients with the more severe *DEPDC5* disorders.[24]

AUTHOR CONTRIBUTIONS

G.L.C.: drafted/revised the manuscript, study design, acquisition of data, and data analysis. D.E.C.: drafted/revised the manuscript, acquisition of data, and data analysis. B.M.R.: data analysis and drafted/revised the manuscript. J.M.M.: data analysis. J. Saykally and M.Z.: acquisition of data and data analysis. A.L.S.: data analysis. L.D.: acquisition of data and revised the manuscript. K.B.H.: data analysis and drafted/revised the manuscript. S.M.: data analysis. R.J.L., A.S.H., S.A.M., S.F.B., and J. Sullivan: acquisition of data and data analysis. I.E.S. and H.C.M.: drafted/revised the manuscript, study design, acquisition of data, and data analysis.

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DISCLOSURE

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Dr. Berkovic has served on the scientific advisory board of UCB Pharma; has served on the editorial boards of *Brain*, *Epileptic Disorders*, and *Lancet Neurology*; has received research support from the National Health and Medical Research Council of Australia; has received honoraria from UCB; has a patent for *PCDH19* testing planned and is one of the inventors listed on a patent held by Bionomics Inc. on diagnostic testing of using the SCN1A gene; has received payment for development of educational presentations from UCB Pharma, Novartis Pharmaceuticals, Sanofi-Aventis, and Janssen-Cilag; and has been a consultant to Bionomics and Athena Diagnostics. Dr. Sullivan has been the chair of SAB for nonprofit entity PCDH19 Alliance; has received honoraria from Zogenix; and has received research support from Marinus Pharmaceuticals. Dr. Scheffer has served on scientific advisory boards for UCB and Janssen-Cilag EMEA; has served on the editorial boards of the *Annals of Neurology*, *Neurology*, *Epilepsy Currents*, *Progress in Epileptic Disorders* series, *Virtual Neuro Centre*, and *Epileptic Disorders*; holds patents for methods of treatment and diagnosis of epilepsy by detecting mutations in the SCN1A gene, a diagnostic method for epilepsy, mutations in ion channels, diagnostic and treatment methods relating to autosomal dominant nocturnal frontal lobe epilepsy (pending), gene and mutations thereof associated with seizure disorders, a gene and mutations thereof associated with seizure and movement disorders, and diagnostic and therapeutic methods for EFMR; may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has received speaker honoraria from GlaxoSmithKline, Athena Diagnostics, UCB, Biocodex, and Janssen-Cilag EMEA; has received funding for travel from Athena Diagnostics, UCB, Biocodex, GlaxoSmithKline, Janssen-Cilag EMEA, AOCCN Taiwan, Weizmann Institute, the American Academy of Neurology, IRCCS Oasi Maria SS, Sanofi China, QBI University of Queensland, International League Against Epilepsy, Australian Academy of Science, Commonwealth Department of Industry, Westmead Hospital, Perpetual, University of California, Matthew's Friends, SBS, PTS for NFLE conference, Turkish Child Neurology Association, European Congress on Epileptology, International Child Neurology Association, UCB, Movement Disorder Society, International Epilepsy Congress, University of Auckland, World Congress of Neurology, Epileptic Disorders, Eisai, AOCCN, Sanofi, and Transgenomic; and has received research support from the National Health and Medical Research Council of Australia, NIH, Australian Research Council, Health Research Council of New Zealand, CURE, American Epilepsy Society, US Department of Defense Autism Spectrum Disorder Research Program, the Jack Brockhoff Foundation, the Shepherd Foundation, Perpetual Charitable Trustees, The University of Melbourne, the Epilepsy Association of Tasmania, Melbourne Neurosciences Institute, Weizmann Institute, CURE SUDEP Award, and Perpetual Philanthropic Services. 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ONLINE RESOURCES

ExAC: http://exac.broadinstitute.org/
PolyPhen-2: http://genetics.bwh.harvard.edu/pph2/
SIFT: http://sift.bii.a-star.edu.sg/
CADD: http://cadd.gs.washington.edu/

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