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ORIGINAL ARTICLE

Identification of genetic characteristics in pediatric epilepsy with focal cortical dysplasia type 2 using deep whole-exome sequencing

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Abstract

Background: Focal cortical dysplasia type 2 (FCD2) is a malformation of cortical development that constitutes a common cause of pediatric focal epilepsy. Germline or somatic variants in the mammalian target of rapamycin (mTOR) signaling pathway genes are the pathogenesis of FCD2.

Objective: In this study, whole-exome deep sequencing was performed on dysplastic cortex from focal epilepsy in children to explore genetic characteristics in FCD2.

Methods: Resected core lesions of FCD2 were confirmed by pathology, and peripheral blood was collected from 11 patients. Deep whole-exome sequencing (>500X) was performed on derived genomic DNA, germline, or somatic variants in brain-specific genes were analyzed and identified.

Results: In 11 patients, a heterozygous likely pathogenic germline variant of DEPDC5 was identified in one case, while somatic variants were found in four brain samples. The frequencies of the somatic variant allele were 2.52%–5.12%. Somatic variants in *AKT3*, *TSC2,* and *MTOR* (mTOR signaling pathway genes) were found in three samples. Besides, one somatic variant was detected in *MED12* which has not been reported to associate with FCD2.

Conclusion: Our study expanded the variant spectrum in the mTOR-GATOR pathway, and also detected a somatic variant in *MED12* which was potentially associated with FCD 2.

KEYWORDS

deep whole-exome sequencing, focal cortical dysplasia type 2, *MED12*, mTOR-GATOR pathway, somatic and germline variant

Rui Zhao and Min Wang contributed equally to this work.

1 | INTRODUCTION

Focal cortical dysplasia (FCD) is the most common structural cause of intractable focal epilepsy in children(Gaitanis & Donahue, 2013). According to the International League Against Epilepsy (ILAE) classification, FCDs are categorized into type 1, type 2, and type 3 at pathology level(Scheffer et al., 2017). Characteristics of FCD2 include cortical dyslamination and dysmorphic neurons (DNs) without (FCD 2A) or with balloon cells (FCD 2B)(Blumcke et al., 2011). Compared with other types of FCDs, FCD2 occurred more common in children and exhibited more severe seizures. Recent studies revealed somatic variants of FCD2 in several genes associated with mammalian target of rapamycin (mTOR [OMIM:601231]) related pathway (*PI3KCA* [OMIM:171834], *AKT3* [OMIM:611223], *MTOR*, *TSC1* [OMIM:605284], *TSC2* [OMIM:191092], *RHEB* [OMIM:601293], *DEPDC5* [OMIM:614191], and *IRS1* [OMIM:147545]) via deep targeted genes panel or whole exome sequencing (Baldassari et al., 2019; Jansen et al., 2015; Moller et al., 2016; Nakashima et al., 2015; Zhang et al., 2020; Zhao et al., 2019). Up to now, genetic exploration of FCD2 remains limited, here we aimed to uncover somatic variants in FCD 2-related genes by using deep whole exome sequencing of FCD core lesions and blood from 11 pediatric focal epilepsy.

2 | METHODS

2.1 | Clinical features

Detailed clinical features were listed in Table 1. Totally, 11 patients retrospectively analyzed who were diagnosed with focal epilepsy and had performed resective surgery from 2019 to 2021 at pediatric epilepsy center in the Children's Hospital of Fudan University. Imaging features of FCD2 including cortical thickness, signal change, gray-white blurring, and transmantle sign were collected via presurgical brain magnetic resonance imaging (MRI), subtype (FCD2A or FCD2B) was confirmed by postsurgical pathology. All FCD lesions were localized by video electroencephalography monitoring and fluorodeoxyglucose PET.

2.2 | Samples collection

The core region of FCD tissues was collected and immediately stored at −80°C at the time of surgery. Peripheral blood samples of patients were collected during hospitalization. The portion of the samples was subjected to hematoxylin–eosin (H&E) staining to confirm postsurgical pathology for FCD2. The study was approved by the Institutional Review Board (IRB) ethics committee of the Children's Hospital of Fudan University.

2.3 | Histopathology

H&E staining and light microscopy were used by neuropathologists to evaluate histopathological diagnosis of resected brain tissues.

2.4 | DNA extraction, sequencing, and data analysis

Frozen tissues were lysed and homogenized using mirVana kit lysis buffer (Ambion), a micropestle, and QIAshredder columns (Qiagen). DNA was isolated using TIANamp Genomic DNA Kit (Tiangen) following the official instruction. DNA integrity was confirmed by agarose gel electrophoresis, and concentration was determined by Qubit 2.0 fluorometer (Invitrogen).

The exon region was captured from peripheral blood and tissue DNA using xGen Exome Research Panel probes (IDT, USA) following the manufacturer's recommendations, then sequenced on MGISEQ 2000 platform (paired-end 150). The average depth per sample was larger than 500 coverage. Sequence alignment was performed by a Burrows–Wheeler algorithm (BWA), and variant calling was performed by Genome Analysis Tool Kit (GATK v4) best practices (https://software.broadinstitute.org/gatk/bestpractices/) from the Broad Institute. Variants were annotated via ANNOVAR (http://www.openbioinformatics.org/annovar/). Candidate variants were picked up in exonic and splicing regions with a minor allele frequency of ≤0.005 in SNP database (ExAC_EAS, ExAC_ALL, 1000Genomes, gnomAD). Sorting Intolerant from Tolerant (SIFT) and Polymorphism Phenotyping version 2 (PolyPhen-2) were utilized to predict the deleteriousness of amino acid substitution for the protein. Pathogenic classification was evaluated following the ACMG (American College of Medical Genetics and Genomics) guidelines.

3 | RESULTS

3.1 | Clinical features of patients with FCD2

Eleven pediatric patients with FCD2 who underwent surgical resection were explored, including five cases with FCD 2A and six cases with FCD2B. Among them, six patients were males and five were females. The age at

TABLE 1 Clinical details of patients with FCD 2

Case	Sex	Age at surgery	Age at seizure onset	Seizure duration	Seizure type	FCD location	Development	Postoperative outcome: Engel classification	Subtype of FCD II
1	Male	2	1.5	0.5	FS	L.T	Normal	I	FCD 2A
2	Male	10	1	9	FS	L.F	Moderate Delay	I	FCD 2A
3	Female	7	6.25	0.75	FS	R.TPO	Mild Delay	III	FCD 2A
4	Female	1.75	1.5	0.25	FS	R.F	Mild Delay	I	FCD 2A
5	Male	14	3	11	FS	R.F	Mild Delay	I	FCD 2A
6	Male	4.75	3.5	1.25	FS	R.I	Normal	I	FCD 2B
7	Male	14	12	2	FS	R.F	Normal	I	FCD 2B
8	Male	1.75	1.5	0.25	FS, ES	L.F	Normal	I	FCD 2B
9	Female	4.25	0.75	3.5	FS	R.F	Normal	I	FCD 2B
10	Female	2.75	2.25	0.5	FS	R.F	Normal	I	FCD 2B
11	Female	3.5	1	2.5	ES	R.F	Mild Delay	I	FCD 2B

Abbreviations: F, frontal; FS, focal seizure; I, insular; L, left; O, occipital; P, parietal; R, right; T, temporal.

surgery ranged from 1.75 to 14 years old (median age 3.5–4.25), the age at seizure onset was from 0.75 to 12 years (median age 1.5) and the duration of seizures was from 0.25 to 11 years (median year 0.75–1.25). Nine patients exhibited focal seizures, one exhibited epileptic spasm, and one with focal seizure and epileptic spasm simultaneously. One lesion localized at left temporal lobe, one at right temporo-parieto-occipital lobe, one at right insular, two at left frontal lobe, and six at right frontal lobe (Table 1). MRI and histopathology of FCD2 were shown in Figures 1 and 2, respectively.

3.2 | Genetic findings

In 11 patients, a heterozygous frameshift germline variant of *DEPDC5* (NM_001242896.3: c.2875delA, p.Ile959Serfs*35) was identified in case 5 with FCD 2A and classified as likely pathogenic according to the ACMG guideline (Table 2).

Four somatic variants of brain-specific genes were detected in 4 brain samples (36.4%), and allele ranged from 2.52% to 5.12%. The somatic variants located in three mTOR signaling pathway genes (*AKT3*, *TSC2*, and *MTOR*) and *MED12*. A pathogenic somatic variant in *TSC2* (NM_000548.5: c.2713C>T, p.R905W) was found in case 8 with FCD 2B which has been reported previously in TSC. A likely pathogenic somatic variant in *AKT3* (NM_005465.7: c.232C>A, p.Q78K) was identified in case 4 with FCD 2A (Table 2).

Two variants of uncertain significance (NM_004958.4: c.7275_7276insCCC, p. Pro2425_Leu2426insPro in *MTOR*; NM_005120.3: c.298_299delinsAT, p.D100I in *MED12*) were detected in two other patients with FCD2A, respectively (Table 2).

4 | DISCUSSION

To date, several studies suggest that FCDs are malformations of cortical development caused by germline or somatic variants in genes regulating proliferation, differentiation, ion channel, and cell signaling pathways(Iffland & Crino, 2017). In particular, FCD 2 is associated with genetic variants in the crucial mTOR- GATOR pathway. Due to the limitations of most studies using conventional WES, deep targeted gene sequencing (>500×) (Baldassari et al., 2019; Jansen et al., 2015; Kumari et al., 2020; Moller et al., 2016; Sim et al., 2019; Zhang et al., 2020), or deep WES for few FCD 2 patients (Bennett et al., 2022; Jha et al., 2022; Nakashima et al., 2015; Zhao et al., 2019), the associated causative genes for FCD 2 may not be fully discovered. In this study, for 11 FCD patients with core

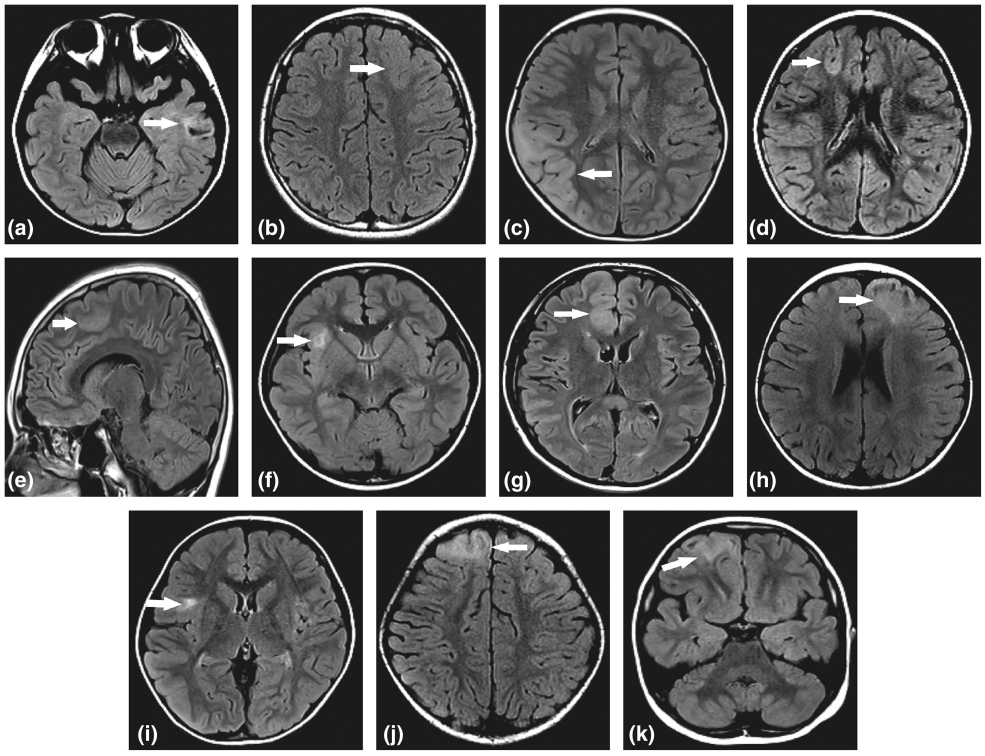

FIGURE 1 (a–k) MRI scan (T2 FLAIR sequences in axial or sagittal view) of 11 patients with FCD 2 (the order of English alphabetical corresponds to the number of case). Arrows indicate the location of FCD2 lesions.

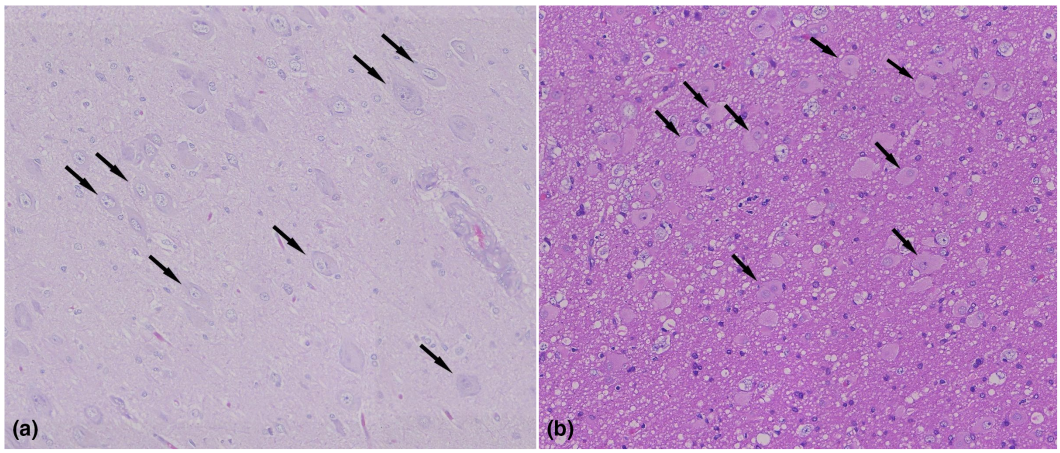

FIGURE 2 Hematoxylin–eosin (H&E) staining of brain tissues. Arrows indicated dysmorphic neurons (a) and balloon cells (b).

lesion and peripheral blood, we identified the *DEPDC5* germline variant in a patient with FCD 2A; *ATK3*, *MTOR*, and *MED12* somatic variants in three FCD 2A patients and *TSC2* somatic variant in an FCD 2B patient through deep whole-exome sequencing.

Recent studies have demonstrated that the somatic variants of genes within the PI3K-AKT–mTOR/TSC signaling pathway were the most important pathogenesis of FCD 2, such as *PIK3CA*, *AKT3*, *MTOR*, *TSC1/2*, and *RHEB*. Therefore, more than 60 cases with FCD 2 have been reported to have pathogenic or potentially deleterious somatic variants in the above genes, and the *MTOR* and *TSC1/2* somatic variants were the most common, accounting for about 75%. The variant allele frequencies (VAFs) in FCD 2 ranged from 0.25% to 15.6%, and more than 15% were *TSC1/2* somatic variants, VAFs ranged from 1.4% to 50.1% (Baldassari et al., 2019; Bennett et al., 2022; Blumcke et al., 2021; Jansen et al., 2015; Jha et al., 2022; Kumari et al., 2020; Lee et al., 2020; Moller et al., 2016; Nakashima et al., 2015; Sim et al., 2019; Zhang et al., 2020; Zhao et al., 2019). In our study, we found that cases 2 and 4 with FCD 2A had somatic variants in *AKT3*

TABLE 2 Genetic variants detected in patients with FCD 2

Case	Subtype of FCD II	Gene	Variants	Type	VAFs (%) in brain/blood	Class
2	FCD 2A	*AKT3*	exon4: c.232C>A (p.Q78K) (NM_005465.7)	Somatic	5.12%/0.4	LP
4	FCD 2A	*MTOR*	exon53: c.7275_7276insCCC (p.Pro2425_Leu2426insPro) (NM_004958.4)	Somatic	3.66%/0.1	VUS
8	FCD 2B	*TSC2*	exon24: c.2713C>T (p.R905W) (NM_000548.5)	Somatic	2.52%/0.1	P
1	FCD 2A	*MED12*	exon3: c.298_299delinsAT (p.D100I) (NM_005120.3)	Somatic	2.55%/0.3	VUS
5	FCD 2A	*DEPDC5*	exon30:c.2875delA (p.Ile959Serfs*35) (NM_001242896.3)	Germline	48.73%/57.64%	LP

Abbreviations: LP, likely pathogenic; P, pathogenic; VAFs, variant allele frequencies; VUS, variants of uncertain significance.

and *MTOR* genes, case 8 with FCD 2B had somatic variants in *TSC2* gene, and the VAFs were 5.12%, 3.66%, and 2.52%, respectively.

DEPDC5 (DEP domain containing 5) combines with *NPRL2* and *NPRL3* to form the GATOR1 complex, which is a critical repressor of the mTOR pathway. Recently, several studies have identified germline and somatic variants in the *DEPDC5* gene in FCD 2 patients (Baldassari et al., 2019; Blumcke et al., 2021; Gaitanis & Donahue, 2013; Lee et al., 2020; Ribierre et al., 2018; Sim et al., 2019). In our study, a likely pathogenic germline *DEPDC5* variant (c.2875delA, frameshift) was found in case 5 with FCD 2A. It is unclear how germline variants in the *DEPDC5* gene cause FCD, while possible mechanism of a second-hit somatic variant has revealed the development of DNs (Lee et al., 2019; Ribierre et al., 2018). However, the second hit of the *DEPDC5* somatic variant is unable to be detected in our case, similar to the results of some studies using deep targeted sequencing (Blumcke et al., 2021; Lee et al., 2020). Therefore, the exact correlation between FCD and *DEPDC5* second-hit somatic variant requires to be explored by new research methods, such as single-cell sequencing for DNs.

MED12 is a subunit of the mediator complex which regulates cell growth, development, and differentiation, plays a crucial role in neural development. Hemizygous pathogenic missense variants in *MED12* located on chromosome Xq13.1 cause three different but overlapping X-linked neurodevelopmental syndrome, such as FG syndrome, Lujan–Fryns syndrome, and Ohdo syndrome. The common phenotypes of the nervous system in these three syndromes were characterized by mental retardation, relative macrocephaly, and seizures (Polla et al., 2021; Srivastava & Kulshreshtha, 2021).

As part of the Mediator kinase module, *MED12* is involved in multiple signaling pathways leading to transcriptional repression or activation, such as Wnt, mTOR pathway, etc. (Srivastava & Kulshreshtha, 2021). Several studies have demonstrated the Wnt pathway is critical for cellular determination during embryogenesis, and that downregulation of *MED12* results in inactivation of the Wnt signaling in embryos, while inhibition of glycogen synthase kinase 3 (GSK3) in the Wnt pathway can phosphorylate *TSC1* and *TSC2* activate mTOR (Hermida et al., 2017; Inoki et al., 2006; Kim et al., 2006). Meanwhile, recent studies have shown that *MED12* variants increase *AKT* expression in cell, resulting in simultaneous inhibition of GSK3β and activation of the mTOR pathway which might be associated with autophagy abrogation and cell proliferation (El Andaloussi et al., 2020). We identified a somatic missense variant of the *MED12* gene in a male FCD 2A individual. Based on the above results, it is reasonable to speculate that *MED12* is potentially pathogenic gene for FCD, and further research is necessary to confirm the relationship between *MED12* and FCD.

In summary, we found four somatic and one germline variants including *ATK3*, *MTOR*, *TSC2*, *MED12*, and *DEPDC5* in 5 of 11 FCD 2 pediatric individuals with epilepsy. Similar to previous studies of cortical malformations, we further demonstrated FCD 2 was associated with genetic variants in the crucial mTOR- GATOR pathway. *MED12* leading to neurodevelopmental syndrome and being an upstream regulator of the mTOR pathway, however, somatic variant in *MED12* has not been reported in FCD 2 patient before. Our findings suggest that the somatic variant in *MED12* was potentially associated with FCD 2 and then further functional experiments are required to determine the role of *MED12* in FCD 2 formation.

AUTHOR CONTRIBUTIONS

YX, RZH, and WM were the first author and co-first authors who performed data analysis and interpretation,

and drafted the manuscript., XHW and YYM performed interpretation of clinical data. HL and YW conceived the idea for the study and supervised the study. BBW and YFZH is the corresponding author and conceived the idea for the study, designed the experiments, responsible for the analysis and interpretation of sequencing data and drafted and revised the manuscript content. All authors participated in the proofreading. The authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS APPROVAL

The local ethics committee of Children's Hospital of Fudan University approved the study protocol.

CONSENT TO PARTICIPATE

Parents gave written informed consent for study participation.

CONSENT FOR PUBLICATION

Written informed consent for publication for identifying images or other personal or clinical details was obtained from both the patient's parents.

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