# Pearls & Oy-sters: Harnessing New Diagnostic and Therapeutic Approaches to Treat a Patient With Genetic Drug-Resistant Focal Epilepsy

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## Abstract

Focal cortical dysplasia (FCD) is a congenital developmental malformation and is one of the leading causes of drug-resistant focal epilepsy (DRFE). Although focal epilepsies traditionally have been regarded as acquired disorders, increasing evidence suggests a substantial genetic contribution to the pathogenesis of focal structural epilepsies, including FCDs. Variations in the Dishevelled, Egl-10, and domain-containing protein 5 (DEPDC5) have recently emerged as a causative gene mutation in familial focal epilepsies associated with FCD type 2a, including bottom-of-sulcus dysplasia (BOSD). We present the case of a 20-year-old man with DRFE, positive for DEPDC5 c.1555C>T (p.GIn519*) heterozygous pathogenic variant. Initial 3T brain MRI was unrevealing, but subsequent 7T MRI including 7T edge-enhancing gradient echo revealed a left superior frontal sulcus BOSD concordant with the electroclinical data. The patient underwent treatment with MR-guided laser interstitial thermal ablation of the left frontal BOSD without intracranial EEG monitoring (skipped candidate), resulting in a seizure-free outcome of 9 months since the last follow-up. Our case highlights the real-world application of summative information obtained through advancements in epilepsy genetic testing, minimally invasive surgeries, and ultra-high field MRI, allowing us to provide a safe and effective treatment for a patient with a genetic DRFE.

## Pearls

- Ultra-high field 7T MRI can enhance the detection of subtle anatomical lesions for MRI-negative epilepsy, including bottom-of-sulcus dysplasia (BOSD), compared with 3T MRI.
- Increasing evidence suggests a substantial genetic contribution in the pathogenesis of focal structural epilepsies, including focal cortical dysplasias (FCDs).
- MR-guided laser interstitial thermal ablation therapy can safely and effectively treat drug-resistant focal epilepsy (DRFE) associated with a BOSD.

## Oysters

- Although genetic testing is infrequently performed in adults with lesional focal epilepsies, routine diagnostic testing is highly relevant in adults with childhood-onset nonlesional DRFE or a strong family history of epilepsy.
- Identification of BOSD using advanced imaging techniques, including 7T MRI, could potentially prevent unnecessary invasive intracranial EEG evaluation.

## Case Report

A 20-year-old left-handed student presented with drug-resistant epilepsy (DRE). He has a family history of epilepsy, with 2 maternal cousins having a seizure disorder. One cousin reportedly had absence seizures, while the other had tonic-clonic seizures. His seizures started

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## Glossary

**ASM** = antiseizure medication; **BOSD** = bottom-of-sulcus dysplasia; **DRE** = drug-resistant epilepsy; **DRFE** = drug-resistant focal epilepsy; **EDGE** = edge-enhancing gradient echo; **FCD** = focal cortical dysplasia; **MRLiTT** = MRI-guided laser interstitial thermal ablation therapy.

at 7 years of age. Initially, he had nocturnal bilateral tonic-clonic seizures, with subsequent development of daytime seizures characterized by an aura of a "fuzzy feeling in his brain" and right-sided "leg sensitivity." These would typically evolve into a focal aware motor seizure with vocalization ("no, no," "whoa"), grunting, and right-sided facial twitching. At times, these evolved into a right-sided head deviation and stiffening accompanied by loss of awareness. Infrequently, these would culminate in a focal to bilateral tonic-clonic seizure. While the focal motor seizures occurred daily, the focal to bilateral tonic-clinic seizures occurred every other month. Seizures were refractory to treatment with 4 antiseizure medications (ASMs): oxcarbazepine, lamotrigine, brivaracetam, and clobazam. He also failed treatment with levetiracetam and valproic acid.

At age 18 years, he underwent presurgical evaluation at an outside hospital. Inpatient video EEG monitoring revealed rare low-to-moderate amplitude spike-and-wave discharges in the bifrontal head region (left > right). Multiple electroclinical seizures were also captured. EEG onset was poorly localizing, although most were predominantly associated with rhythmic alpha discharges in the left frontal lobe. Clinically, these were accompanied by right-sided facial twitch and repetitive mouth movements, perhaps repeating words. 3T brain MRI and PET scans were unrevealing. Magnetoencephalography identified dipoles in the left superior frontal gyrus (Figure 1, A and B). Neuropsychological testing showed overall superior intelligence. Given his age at onset and a strong family history of epilepsy, genetic testing was performed using an epilepsy gene panel (Invite, San Francisco, CA). This identified DEPDC5 c.1555C>T (p.GIn519*) heterozygous pathogenic variant. His case was discussed at an epilepsy surgical conference, and recommendation was made to proceed with intracranial EEG monitoring using a stereoelectroencephalography approach.

He underwent a repeat presurgical evaluation at our institution. Inpatient video-EEG revealed repetitive sharp spikes and polyspike waves in the left frontocentral and midline head regions (Figure 1C). Ictal EEG showed sustained bursts of fast beta activity, sharp waves, and polyspikes, most prominent in the vertex and left frontocentral head regions (Figure 1D). During these conditions, he reported feelings of "right leg sensitivity" and facial twitching. He was aware and repeatedly vocalized "oh" and "no." An ultra-high field 7T brain MRI revealed a bottom-of-sulcus dysplasia (BOSD) in the left superior frontal sulcus, most evident on the 3D edge-enhancing gradient echo (EDGE) sequence (Figure 2). He was presented at our multidisciplinary epilepsy surgical conference. Recommendation was made to perform MRI-guided laser interstitial thermal ablation therapy (MRLiTT) on the left superior frontal sulcus BOSD. Given the concordant electroclinical-radiological findings, intracranial EEG monitoring was deemed unnecessary. Since the MRLiTT, he has become seizure-free for 9 months on stable doses of brivaracetam, clobazam, lamotrigine, and oxcarbazepine.

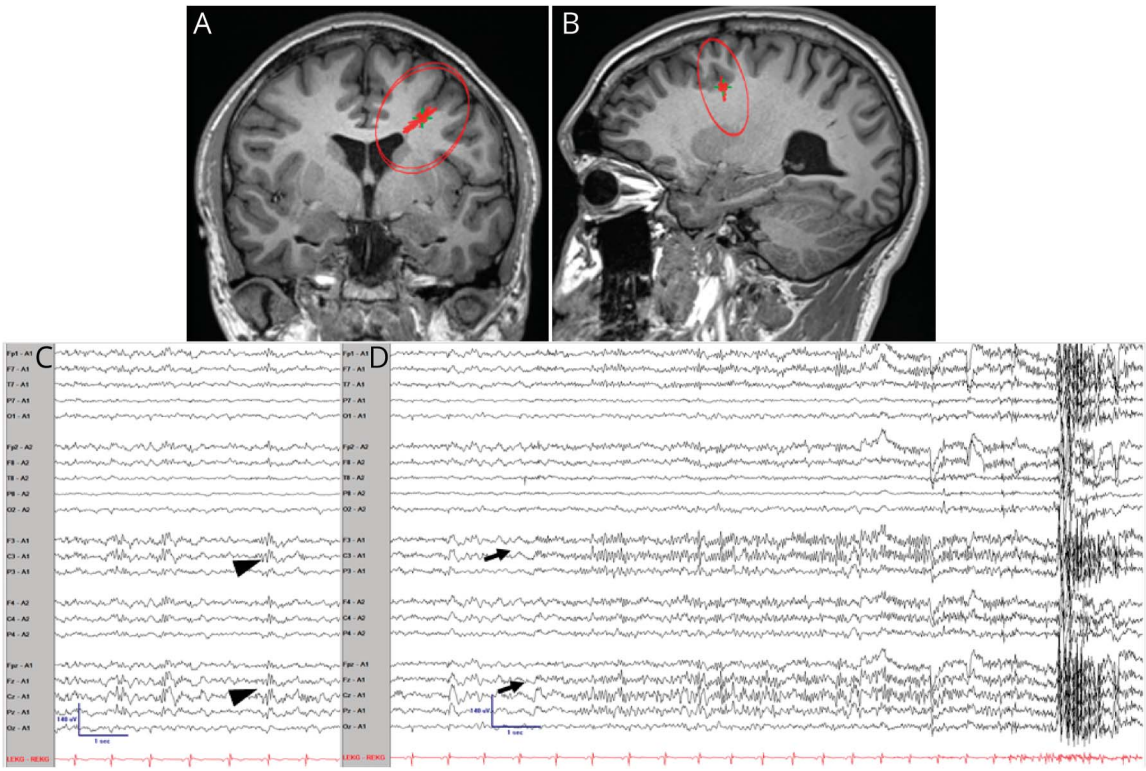
## Discussion

We present the case of a young man with DRFE on whom a genetic test was performed, given his age at onset and a strong family history of epilepsy. Identifying a DEPDC5 heterozygous pathologic variant prompted the pursuit of ultra-high field 7T-MRI that revealed a left superior frontal sulcus BOSD. The concordant electroclinical-radiological findings obviated the need for invasive intracranial EEG monitoring. MRLiTT of the presumed BOSD led to seizure freedom, albeit he is yet to attain the ideal 2-year seizure freedom cutoff.

Focal cortical dysplasias (FCDs) are localized regions of the malformed cerebral cortex and are frequently associated with epilepsy. Seizures associated with FCD are often resistant to ASMs.[1] In 2011, the ILAE Commissioned Task Force proposed a 3-tiered classification system for FCDs. In brief, FCD type I refers to isolated lesions with dyslamination of the neocortex, type II consists of isolated lesions characterized by cortical dyslamination and dysmorphic neurons, either without balloon cells (type IIa) or with balloon cells (type IIb), and type III lesions are defined by their association with another principal lesion (e.g., mesial temporal lobe sclerosis).[2] BOSD is a highly localized form of FCD type II in which the electrophysiologic, MRI, and pathologic abnormalities are confined to a single sulcus, maximal at the bottom-of-the sulcus.[3]

Cortical thickening, subcortical hyperintensity, blurring in the gray-white matter interface, and transmantle sign are considered major findings in the MRI diagnosis of FCD. However, many of these features are more common in the more conspicuous type IIb FCD.[4] Other signs include elongation and straightening of the dysplastic sulcus and depression or unusual sulcation of the overlying cerebral surface.[4] Recently, Tang et al. reported a "black line" sign on the 7T-weighted gradient echo sequence in 20 patients with DRFE with pathologically confirmed FCD, but exclusively seen in type IIb FCD.[5] FCD type I and IIa are often far more subtle and frequently undetectable with conventional MRI. Besides, BOSDs, which can

**Figure 1** MEG Images and EEG Tracings Show a Left Frontal Seizure Focus

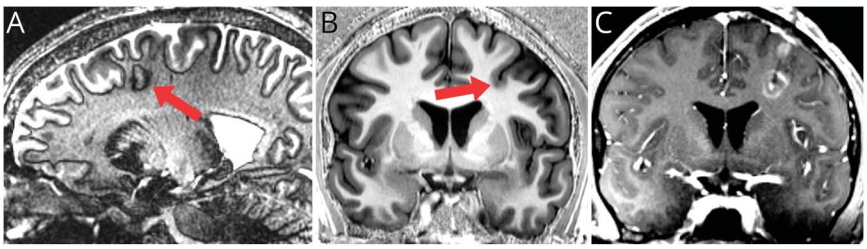



Magnetoencephalography source localization with the equivalent current model, coronal (A) and sagittal views (B), show dipoles in the left superior frontal gyrus and insula (not shown). Interictal (C) and ictal (D) EEG tracings in a referential montage show left frontocentral and midline spikes and fast activity (arrowheads) and low-amplitude fast seizure discharge arising from the same region (arrows-onset), respectively.

be type IIa or IIb, typically found in the frontal and parietal lobes, are most likely to be overlooked.[6]

Advanced 7T MRI sequences have been shown to offer a superior contrast-to-noise ratio in detecting previously unseen subtle lesions of FCDs. In a recent study, 67 patients with DRFE and nonlesional 3T MRI reported that an unaided visual review of 7T detected previously unappreciated subtle lesions in 22%; when aided by MRI postprocessing, the yield increased to 43%.[7] However, morphometric analysis techniques have shown peak performance in detecting type IIb FCD with poor detection of the more subtle type I FCD. We show the value of 3D-EDGE at 7T in detecting subtle FCD. In most, the lesion location identified by 7T was identical or contained within the invasive EEG ictal onset zone. A complete resection of the 7T identified lesion resulted in a seizure-free outcome, with histopathology consisted mainly of FCD. In another study, 7T MRI detected new lesions in more than a third of 3T MRI nonlesional patients, confirmed and better characterized a 3T suspected lesion in one-third of patients, and helped exclude a 3T suspected lesion in the remainder.[8] Our case illustrates that the inherently low signal-to-noise ratio 3D-EDGE sequence greatly benefits from the added signal obtained at ultra-high field MRI, such as 7T, and may be one of the more valuable sequences in detecting both type I and type II FCD.[9] In centers where ultra-high field 7T MRI is unavailable, 3D-EDGE and other techniques, including a 3-dimensional fluid-attenuated inversion

**Figure 2** Ultra-High Field 7T Brain MRI Shows a Bottom-of-Sulcus Dysplasia in the Left Superior Frontal Sulcus




Sagittal 3-dimensional edge-enhancing gradient echo (3D-EDGE) acquired at 7T shows thickening and blurring of the normal junctional line at the gray matter-white matter interface (arrow) consistent with focal cortical dysplasia (A). Coronal 7T MP2RAGE T1-weighted uniform (UNI) image shows the blurring of the gray-white boundary (arrow) (B). Postoperative coronal T1-weighted postcontrast image showing the enhancing ablation zone covering the area of FCD (C).

recovery and proton density MRI can be used to improve the detection of subtle FCDs.[10]

Increasing evidence suggests a strong genetic contribution to the pathogenesis of focal structural epilepsies, including FCDs.[11] For example, mutations in the Dishevelled, Egl-10, and domain-containing protein 5, a GTPase-activating protein, have recently emerged as a significant gene mutated in familial focal epilepsies associated with FCD IIa. Although genetic testing among children with epilepsy has become a part of routine testing, few studies have focused on genetic testing in adults.[12] A European study found a diagnostic yield of 23% with genetic testing in a cohort of adult patients with DRE.[4] By contrast, a more recent study from the United States found only 10.9% of diagnostics with genetic testing.[13] Nevertheless, genetic testing of adults with focal epilepsies can help guide clinical management decisions. The diagnostic finding could have clinical implications beyond epilepsy care, including counseling for family planning. That said, the cost of testing, delays in receiving results, and problems interpreting results are barriers to its routine use in adults with focal epilepsy. Therefore, selecting the appropriate patient population that requires diagnostic genetic testing is crucial. The yield is higher among patients with epileptic encephalopathies, childhood onset and a strong family history of epilepsy, and nonlesional cases.

Identifying structural lesions on high-resolution MRI can obviate the need for an invasive intracranial EEG monitoring, as in our patient. Ideal "skip candidates" for a 1-stage surgery typically have concordant clinical data, including semiology, EEG, and a characteristic epileptogenic lesion on MRI. Traditionally, open resection surgery has been the principal therapeutic option for treating FCD-associated DRFE. Newer minimally invasive therapies such as MRLiTT have also been reported in patients with FCDs.[14] Similar to our case, previous studies had undergone 1-stage MRLiTT when the BOSD was distant from the eloquent cortex.[15] This case sums up the cumulative impact of advancements in epilepsy-genetics, ultra-high field 7T MRI, and minimally invasive surgeries in allowing us to provide a safe and effective treatment for a patient with a genetic DRFE.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