

Focal cortical dysplasia: a practical guide for neurologists

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Abstract

Focal cortical dysplasia (FCD) is a malformation of cortical development (MCD) characterised by disruption of cortical cytoarchitecture. Classification of FCDs has initially been based on correlation of the histopathology with relevant clinical, electroencephalographic, and neuroimaging features. A recently proposed classification update recommends an integrated, multi-layered, genotype–phenotype approach which integrates findings from histopathology, genetic analysis of resected tissue, and presurgical MRI. FCDs are caused by single somatic activating mutations in *MTOR* pathway genes or by double hit inactivating mutations with a constitutional and a somatic loss-of-function mutation in repressors of the signalling pathway. Mild malformation with oligodendroglial hyperplasia in epilepsy (MOGHE) is caused by somatic pathogenic *SLC35A2* mutations. FCD most often presents with drug resistant focal epilepsy or epileptic encephalopathy. Most patients respond to surgical treatment. The use of mTOR inhibitors may complement the surgical approach. Treatment approaches and outcomes have improved with advances in neuroimaging, neurophysiology and genetics, although predictors of treatment response have yet to be determined.

Key points:

- Focal cortical dysplasia is a malformation of cortical development characterised by disruption of cortical cytoarchitecture
- FCD most often presents with drug resistant focal epilepsy or epileptic encephalopathy
- Surgical treatment and/or use of mTOR inhibitors represent the most effective treatment
- Diagnostic findings should be merged into a multi-layered, genotype–phenotype classification scheme

- **What is it? Definition and classification**

Focal cortical dysplasia (FCD) is a malformation of cortical development (MCD) characterised by disruption of cortical cytoarchitecture. The term ‘focal cortical dysplasia’ was coined in 1971 when an unusual microscopic abnormality was reported in the lobectomy specimens removed surgically from the brains of ten patients with temporal lobe epilepsy. The malformation was described histologically as ‘congregations of large, bizarre neurones which were littered through all but the first cortical layer’.(1)

Classification of FCDs has initially been based on correlation of the histopathology with relevant clinical, electroencephalographic (EEG), and neuroimaging features.(2,3) The International League Against Epilepsy (ILAE) has provided a first international FCD consensus classification in 2011,(4) where abnormalities in radial or tangential cortical lamination, without evidence of any additional principal epileptogenic lesion in the brain, are deemed Type I (FCDI); the presence of dysmorphic neurons and/or balloon cells indicates Type II (FCDII) and cortical lamination abnormalities in combination with another epileptogenic lesion (e.g. hippocampal sclerosis, tumours, vascular lesions, glial scars, or inflammation) indicate Type III (FCDIII). Mild malformation of cortical development (mMCD) were introduced for lesions comprising an excess of heterotopic neurones in layer I (type I) and the white matter (type II) Recently, a new pathological entity has been described as a mild malformation with oligodendroglial hyperplasia in epilepsy (MOGHE), characterised by excess Olig2 and PDGFR α -immunoreactive oligodendroglia, heterotopic white matter neurons and patchy reduction in white matter myelination.(5) The histological features of this newly described pathology may be subtle and difficult to distinguish from other mMCD or gliosis.

Whilst FCDII is easily detected by MRI, there are ongoing challenges in both the neuroimaging and histopathological diagnosis of FCD I and FCD III subtypes. To address these issues, an *ad hoc* task force of the ILAE diagnostic methods commission recently proposed an update of FCD classification with an integrated, multi-layered, genotype– phenotype approach.(6) Such approach should include and integrate findings from histopathology (Level 1), genetic analysis of resected tissue (Level 2), and presurgical MRI (Level 3).

They also suggested the new category of “no definite FCD on histopathology”, a diagnosis which applies when the anatomic orientation and organization of the surgical specimen remains ambiguous, and an abnormality cannot be definitively evidenced by strict histopathology measures after applying also immunohistochemical staining to confirm any FCD subtype.

- **Why it develops? Developmental and molecular mechanisms**

Thanks to next-generation deep sequencing technologies and bioinformatics pipelines for somatic variants, two distinct pathomechanisms have been identified in the aetiology of FCD.

1.The first is driven by mutations in genes belonging to the mechanistic target of rapamycin (mTOR) pathway, including *AKT3*, *DEPDC5*, *NPRL2*, *NPRL3*, *PIK3CA*, *RHEB*, *MTOR*, *TSC1*, *TSC2*. Such mutations cause FCDII and other MCD characterised by brain overgrowth either global, i.e. megalencephaly, or unihemispheric, i.e. hemimegalencephaly.(7–9) At the microscopic level, the mutated cell population identified often includes dysmorphic neurons and often balloon cells, and consistently shows hyperactivation of the mTOR pathway.(9)

Two types of mutational events might explain why abnormal cells populate FCDII. The first type involves single, somatic (i.e. occurring after fertilization and confined to a

subpopulation of cells in the cerebral tissue or cells located in different body parts including the brain – systemic mosaic), activating mutations in *MTOR* or in genes encoding its upstream activators (*AKT3*, *PIK3CA*, *RHEB*), frequently encountered when deep sequencing is conducted in resected brain tissue. Patients with FCDII most often have mutations in *MTOR* itself. There is a causal direct relationship between the somatic mutation, mTOR activation, and generation of abnormal cells (i.e., dysmorphic neurons and balloon cells) as demonstrated in FCDII.(9,10)

The other possible mutational event involves double hit inactivating mutations with a constitutional (i.e., present in any cell of the body) and a somatic loss-of-function mutation in repressors of the signalling pathway (*DEPDC5*, *NPRL2*, *NPRL3*, *TSC1*, *TSC2*). But how can a constitutional mutation, resulting in a subject carrying it in all their cells, result in an FCD which is comprised of abnormal cells intermixed with normal cells, and with no effect on the rest of the body? One hypothesis is that a somatic second-hit mutational event occurs spontaneously in the wild-type allele and affects a fraction of neuroepithelial cells which would thereafter display increased mTOR activation. This hypothesis is in line with the Knudson's two-hit model of tumorigenesis.(11) A two-hit mechanism has been indeed demonstrated in several patients with FCDII or hemimegalencephaly, with somatic second-hit *DEPDC5* mutation in the dysplastic cortex, associated with a constitutional heterozygous mutation to cause biallelic inactivation of the gene.(9,10,12)The second-hit *DEPDC5* mutation is limited to dysmorphic neurons, and the somatic mutation load correlates with both dysmorphic neuron density and the epileptogenic zone.(10) In hemimegalencephaly, a slightly different two-hit mechanism has been also identified, with two independent activating somatic mutations in two different genes but both being positive regulators of the mTOR pathway.(13) One additional hypothesis is that a somatic second-hit mutation would account for the incomplete penetrance in patients who have only the constitutional mutation.(14)

2. The second pathomechanism, non-mTOR related, has been described in MOGHE in association with the *SLC35A2* gene. This gene encodes the major Golgi-localised UDP-galactose transporter required for protein and sphingolipid glycosylation. On 20 surgical MOGHE brain samples from a single-centre cohort of paediatric patients, somatic pathogenic *SLC35A2* mutations were identified in 9/20 (45%) patients, with mosaic rates ranging from 7 to 52%.(5)

Genetic testing should ideally be performed on DNA from resected brain tissue and paired blood samples to identify brain-only somatic mutations representing postzygotic mutational events. The mutation allele frequency is the percentage of alleles carrying a given mutation, i.e. the proportion of mutated cells, and is variable in patients with FCDII, ranging from less than 1% to approximately 10%. This explains why deep (i.e., high coverage) sequencing is required to identify somatic mutations in FCD, e.g at least 1000X depth is required to detect a 1% variant.(15,16) Genetic testing from surgical human brain tissue should be performed by experienced neuropathologists following specific laboratory protocols for a reliable detection of low-level brain mosaicism in FCD.(6) DNA should be extracted from lesional fresh frozen or formalin-fixed paraffin-embedded (FFPE) tissues. Hybridization capture and high-depth next generation sequencing of >1000x reading depth of FCD relevant genes (*AKT3*, *DEPDC5*, *MTOR*, *NPRL2*, *NPRL3*, *PIK3CA*, *RHEB*, *SLC35A2*, *TSC1*, *TSC2*, *SLC35A2*) should be applied.(16,17) Two proof-of-principle studies have reported that brain somatic mutations can be detected in the circulating cell-free DNA obtained from cerebrospinal fluid (CSF).(18,19) If substantiated, this finding may allow a genetic diagnosis before surgery, or when brain tissue is not available, and guide targeted treatment in the future.

Genomic DNA methylation analysis has been used to differentiate major FCD subtypes and there is increasing evidence of its role in an integrated clinico-pathologic and molecular classification system of FCD subtypes.(20,21)

Identification of the FCD genetic cause is also relevant for genetic counselling, i.e. pathogenic somatic mutations are not inherited and not transmissible, whilst constitutional mutations causing FCD are transmissible and possibly inherited.

- **What is the clinical and EEG presentation?**

FCD most often presents with drug resistant focal epilepsy. Seizure can start at any age, but usually clinical onset is in childhood depending also on the FCD histopathological subtype.(22,23) Febrile seizures are reported in a minority of patients.(22,24) Epilepsy types feature focal epilepsies or epileptic encephalopathies.(25) Seizure semiology depends on the location and extent of the lesion. Epileptic spasms are more frequently associated with FCDs located in the frontal lobes.(26) History of status epilepticus and epilepsy partialis continua have been reported.(22,24) Most patients do not respond to pharmacological treatment although in some patients transient complete seizure control can be achieved after initial therapy or even after longer time since epilepsy onset.(22) Patients with FCD can also exhibit behavioural disturbances, especially those with early onset epilepsy, and this may also depend on the FCD location).(4) The severity of the phenotype, which may include cognitive and behavioural impairment, has been associated with a number of factors including the extension and location of the lesion, age at seizure onset and epilepsy duration, history of epileptic spasms, seizure clusters and status epilepticus.(24,27,28)

There are no distinctive scalp EEG findings for FCDI. On the other hand, well-defined EEG signatures have been described in both FCDIIa and IIb subtypes such as focal continuous rhythmic interictal discharges and repetitive spiking that have been suggested as possible markers of the ictal-onset zone since their disappearance after surgery correlates with a good seizure outcome.(29) Invasive EEG recording studies in patients with FCDII have confirmed consistent typical EEG abnormalities, including repetitive subcontinuous spikes, spike-and-waves, polyspikes, or bursts of fast rhythms ('brushes') interspaced with relatively quiescent periods,(30) with evidence for a contribution of dysmorphic neurons to interictal spikes, fast gamma activity, and ripples (Figure 1, A-B). On the other hand, balloon cells are not considered to be the source of abnormal electrical activity.(31) Delta brushes are occasionally observed at seizure onset and are specific of FCD.(32) Patients with FCDIIb frequently have sleep-related epilepsy, which is characterised by localised brushes enhanced during non-rapid eye movement (REM) sleep and associated with well-localised, brief, low-voltage fast activity. The brief bursts of fast discharges, interrupted by activity suppression, increase during slow-wave sleep and often recur pseudo-periodically. Brushes have been associated with balloon cells in FCDIIb.(33,34)

- **Neuroimaging**

There are various factors that affect the value of MRI in the characterisation of FCDs. Such factors include the strength of the magnet, the imaging protocol, the correlation with clinical semiology and EEG findings, and the examiner's experience. Addressing these factors is crucial to obtain adequate imaging studies able to detect FCD and in turn inform the surgical approach, minimise the use of additional imaging approaches, and improve surgical outcomes.(28)

In FCDIa, there are reports of MRI showing unilateral multilobar hypoplasia and increased T2-FLAIR signals of the white matter, with posterior quadrant involvement.(35) In FCDIb MR imaging features include high T1 signal in the cortex, high T2-FLAIR signal in the cortex or subcortical white matter, increased cortical thickness, and blurring of the grey-white matter junction.(36)

In FCDII, MRI abnormalities feature abnormal gyration patterns indicated by a cortical dimple, cortical thickness changes, signal increase (mainly in FLAIR) both in the lesion and in the adjacent white matter, and gray-white matter blurring (Figure 1, C-D).(37) The transmante sign, a linear or triangular shaped high T2-FLAIR signal extending from the lesion toward the ventricle, indicates that FCDIb is more likely.(38) Almost one-third of patients with FCDII remain MRI-negative, some of which could be due to inadequate imaging.(37)

Bottom of sulcus FCD tend to localise in the depth of frontal lobe sulci (superior frontal sulcus, inferior frontal sulcus, and central sulcus) and less frequently in the parietal or temporal lobes. Invasive EEG recordings identify a characteristic rhythmic spiking pattern in the depth of sulcus lesion. The complete resection of the anatomic lesion achieves seizure freedom in most patients. Histopathology most often supports a diagnosis of FCDIb or less commonly FCDIIa, and mutations in mTOR pathway genes are often detected.(39)

MRI findings associated with MOGHE resemble those described in FCDIIa. Although more frequent in the frontal lobe, MOGHE can also occur in the temporal lobe or involve multiple lobes. Multilobar or extensive MRI presentation is associated with a less favourable outcome.(40)

7 T high-field MRI with postprocessing can detect subtle FCD lesions in patients with focal epilepsies and previous negative 3 T MRI.(28,41) In patients with intractable focal epilepsy undergoing surgical resection who have a 7T MRI with adequate image quality, the 'black line sign' may suggest FCDIb. Seizure freedom after surgery is more likely if the black line region is included in resection.(42,43) Machine-learning algorithm for automated detection of subtle FCD on neuroimaging are being developed.(44)

Additional functional imaging modalities, such as interictal fluorodeoxyglucose–positron emission tomography (FDG-PET) and subtraction of ictal/interictal single-photon emission computed tomography (SPECT) and its co-registration with structural MRI, may add important information in patients with subtle lesions that helps to increase the confidence of the structural MRI diagnosis.(45)

- **What is the histopathological presentation?**

FCDI is characterized by architectural disorganization of the neocortex due to compromised developmental maturation, and without evidence of any additional principal epileptogenic lesion in the brain (as confirmed by MRI or histopathology).(4)

FCDIa is histopathologically defined by an abundance of neuronal 'microcolumns' that predominate in any low-power objective microscope magnification; identification of microcolumns can be aided by neuronal nuclear antigen (NeuN). Knowledge of the Brodmann area surgically resected is paramount as some regions, for example the superior temporal gyrus or occipital lobe, a dominant columnar architecture is a normal cyto-architectonic pattern. As there are no precise quantitative criteria for FCDIa and no specific tissue immunomarker there is marked inter-observer variation in its reporting.(46) A second hallmark is the excess of heterotopic neurons in the white matter, also invading the area of U fibres, that can be visualised with microtubule associated protein 2 (MAP2) antibodies.(47) DNA methylation array analysis from routine FFPE tissue holds promise for more precise and consistent diagnosis of FCDIa in the future.(21)

FCDIb and FCDIc do not have specific clinico-pathological correlations reported so far. FCDIb is characterised by horizontal architectural dysplasia whilst in FCDIc there is a mixture of horizontal and vertical layer abnormalities.(6)

FCDII is most often localised to the frontal lobe,(48) and is characterised by the presence of dysmorphic, often cytomegalic neurons present through a region of cortex which lacks clear horizontal laminae. Dysmorphic are often intermixed with normal pyramidal cells and atypical astrocytic cells as well as reactive gliosis may be present. The additional presence of distinct balloon cell populations distinguishes FCDIIb from FCDIIa. Balloon cells are immunophenotypically immature and can express both neuronal and glial lineage markers; they often dominate in the subcortical white matter beneath the dysplastic cortex with associated dysmyelination and reduction in oligodendroglia. In FCDIIa, abnormalities in cortical thickness, cell density, myelination, and oligodendroglial cell population are often more subtle than FCD IIb (Figure 2,A-J).(49)

FCDIII represents abnormal architectural organization of the neocortex in the immediate vicinity of epileptogenic lesions, such as hippocampal sclerosis (FCDIIIa) (Figure 2,K-L), developmental brain tumours (FCDIIIb), vascular malformations (FCDIIIc), or any other lesion acquired during early life (FCDIIId), including typically perinatal cortical infarcts/hypoxic-ischaemic lesions or in the context of Rasmussen's encephalitis.(4) In FCDIIIa, the most consistently recognised alteration is loss of neurones in the superficial cortex (layer 2/3) with gliosis and abnormal clustering of residual neurones in patients with long-term epilepsy and hippocampal sclerosis.(50) In FCDIIIb, encompasses abnormal architectural abnormalities in the immediate proximity of developmental brain tumours but immunohistochemical assessment is required to exclude tumour infiltration/extension.(51) In FCDIIIc, various patterns of abnormal cortical layering have been described, both horizontally and vertically, adjacent to vascular malformations, for example Sturge-Weber syndrome.(52) In FCDIIId there is marked variability in the patterns of dyslamination reported, which may be limited to patchy loss of layer 4, as seen in children with perinatal hypoxic-ischemic brain injury of the occipital lobe.(53)

Mild malformation of cortical development (or mMCD) is defined by an increase of heterotopic neurones in the white matter above 30 neurones per mm², without being associated with any other principal lesion.(4)

MOGHE is a distinct mMCD subtype, microscopically primarily recognized histologically by an excess of heterotopic neurones in the white matter and oligodendroglial cell densities above 2200 Olig2-immunoreactive cells per mm².(40,54)

According to the updated histopathology-based classification scheme, 'no definite FCD on histopathology' should include cases when the anatomic orientation and organization of the surgical specimen remains ambiguous, and an abnormality cannot be evidenced by strict histopathology measures. Immunohistochemistry staining (i.e. NeuN, Neurofilaments, Vimentin and MAP2) is mandatory to confirm the absence of any FCD.(6)

- **How to treat it?**

Most patients with FCD have drug-resistant epilepsy. The choice of antiseizure medication (ASM) relies on the type of seizures (focal seizures vs spasms) and the age at seizure onset in the individual patient. Less than 20% of patients have a transient response to pharmacotherapy.(22) As one of the pathophysiological mechanisms for FCD is hyperactivation of the mTOR pathway, sirolimus or rapamycin, which act as mTOR inhibitors, suppress cytomegalic neurones and epileptic

seizures in mice.(55)In patients with focal seizures symptomatic of Tuberous Sclerosis Complex (TSC), which is caused by overaction of the mTOR pathway, another mTOR inhibitor, everolimus, used as an add-on to ASM, significantly reduced seizure frequency with a tolerable safety profile compared with placebo.(56) A first single-arm, open-label, multicentre clinical trial recently assessed the efficacy and safety of sirolimus for the treatment of epileptic seizures in patients with FCDII (FCDS-01), and found a response rate of 33%, with a tolerable safety profile.(57)

There is also some evidence that the ketogenic diet can be effective for treatment of drug-resistant epilepsy caused by FCD.(58) The mechanism of action of the ketogenic diet is still not fully understood, but one potential mechanism is the inhibition of the mTOR pathway.(59)

FCD is the most common structural brain lesion in children with drug-resistant focal epilepsies who are considered for surgical treatment. Surgical resection strategies in FCD should be tailored for each patient within a multidisciplinary team, including expertise in neurology, neurophysiology, neuroradiology, neuropsychology and neuropsychiatry.(60) The choice of surgical procedures will vary depending on the size of the dysplastic lesion and seizure onset zone and includes focal, lobar, multilobar and hemispheric resections or disconnections.(25) Surgery can be performed from the first months of life. Laser Interstitial Thermal Therapy, a minimally-invasive surgical procedure for the ablation of epileptogenic foci, is increasingly used for treatment of drug-resistant structural epilepsy due to the advantages of a decreased length of procedure time, shorter hospital stay, and lower rates of complications when compared to open surgery.(61) There is also increasing clinical and experimental evidence for selectively considering epilepsy surgery prior to drug resistance in children, especially in non-eloquent brain areas, leading to better seizure, developmental, and cognitive outcomes.(62,63)

- **What to expect? Prognostic aspects**

Up to 70% of patients with FCD and drug-resistant epilepsy, including children with severe epileptic encephalopathies, achieve a favourable seizure outcome after surgery.(25,64)A recent a retrospective multicentre cohort study of >9000 patients who underwent epilepsy surgery between 2000-2012 described the following findings: seizure outcomes were worst for FCDI and mMCD, possibly due to more diffuse structural abnormalities and a difficult-to-delineate epileptogenic zone, leading to incomplete resection; children had a similar prognosis regarding seizure outcome to adults, but more children discontinued medication; temporal lobe surgeries had the best seizure outcomes, and a longer duration of epilepsy was associated with reduced chances of favourable seizure outcomes and drug freedom.(23) A systematic review and meta-analysis of the literature determined the following predictors of favourable seizure outcome after surgery for MRI-detected FCD: complete resection of the lesion and location of the FCD lesion in the temporal lobe; whilst lesion extent, intracranial EEG use, or FCD histologic type were not associated with post-surgical outcome.(64) Correlation between the underlying genetic aetiology and post-surgical outcome remains to be determined.(9)

- **Clinical vignette**

We describe the clinical history of a young boy, currently 13 years-old, born from fifth pregnancy after four miscarriages. Pregnancy and childbirth were uneventful. Early development was normal as was his neurological examination.

At 2 years and 3 months, he started to exhibit focal seizures characterised by staring with impaired awareness, grimacing, pallor, and eye deviation to the right, sometimes followed by tonic extension of the left limbs.

Ictal EEG showed rapid low-amplitude activity with apparently simultaneous onset on the centro-parietal leads of both hemispheres

After carbamazepine was started 2-year seizure freedom occurred, after which seizures recurred, characterised by paraesthesia and sensation of 'weakness' affecting the left arm, sometimes associated with brief loss of awareness or headache. Clobazam, zonisamide and lacosamide were added with no improvement in seizure control.

Neuropsychology showed a normal cognitive level with no deterioration over time.

3T brain MRI revealed a non-enhancing focal cortico-subcortical area of altered T2 and FLAIR signal in the right parietal lobe, immediately posterior to the central sulcus. No spectroscopy alterations were observed.

Functional MRI under sedation showed localised responses in both hemispheres according to the representation of the cortical sensorimotor hand area, with a close relationship between functional responses and the anterior border of the lesion.

A lesionectomy was performed using intraoperative functional mapping. The patient has been seizure free since the operation, with no motor deficit. Histopathology revealed FCDIIb (Figure 3).

- **Perspectives**

FCD is one of the main causes of drug-resistant epilepsy, especially in children, with frequent cognitive and behavioural comorbidity. Advances in neuroimaging, neurophysiology and genetics have improved FCD characterisation and diagnostic definition, and in turn treatment approaches and outcomes.

Although not every centre will have access to advanced neuropathological, neuroimaging, or genetic analyses techniques for a fully integrated diagnostic approach to FCD, it is crucial to aim to obtain multi-layer information including neuropathological tissue workup, genetic findings from resected tissue, and presurgical MRI data. When there are no resources to cover one or more of these different layers, patients should be referred to centres with adequate expertise.

Brain MRI is the first non-invasive window to the identification of focal FCD lesions and, in some instances, point to their neuropathology (e.g., FCDIIb or MOGHE), inform surgical planning/type of intervention (e.g., intracranial EEG in FCDI vs intraoperative mapping in bottom of sulcus dysplasia and some FCDII), and outcome (e.g., excellent outcomes in bottom of sulcus dysplasia). Adding the level of genetic information is very relevant for the diagnosis of FCD subtype and for understanding the underlying pathophysiology which will pave the road for targeted treatments.

The compilation of the various layers of diagnostic findings into a multi-layered, genotype–phenotype classification scheme of FCD should be addressed by the treating physician (e.g., neurologist, epileptologist, neurosurgeon) and preferably with an interdisciplinary effort at a postsurgical patient management conference.(6)

There remain several challenges in the diagnosis and treatment of FCD. Histopathological diagnosis might not always be sensitive or accurate, sometimes also due to neurosurgical sampling errors. Neuroimaging data might be misinterpreted, for example temporopolar atrophy with signal hyperintensity and grey-white matter blurring in the context of hippocampal sclerosis where white matter lesions have been demonstrated to be secondary to reduction in axonal density.(65) Surgical treatment should always be considered, but the role of genetic findings on the pre-surgical work-up

remains to be fully elucidated. Equally the use of mTOR inhibitors may complement the surgical approach but whether they should be used prior of after surgery is yet to be defined.

Prospective large studies and clinical trials are needed to shed further light on treatment options, and predictors of surgical outcome.

Competing interests

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SB drafted the manuscript. CB and MT generated the figures and critically reviewed the manuscript. RG critically reviewed the manuscript.

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Figure legend

Figure 1. 7-yr-old boy with epileptic spasms, focal seizures and FCDIIa. A. Scalp ictal EEG showing a right frontal discharge spreading to the vertex (see arrows). B. Stereo-EEG exploring fronto-parietal areas and showing an ictal right frontal anterior discharge. C. 3T MRI, FLAIR sequence: Mild right fronto-mesial blurring. D) 3T MRI T1 sequence: right fronto-mesial cortical dimple.

Figure 2. A. The 'bottom of sulcus dysplasia' (FCDII) with dyslamination in this region, appreciated on NeuN immunostaining at lower power with an overall reduction in neuronal density. B. This same case is shown in higher magnification with scattered enlarged dysmorphic cells seen (arrow) between normal appearing neurones. C. Neurofilament immunohistochemistry also highlights the dysplastic neuronal populations in the FCD regions with their abnormal neuronal morphology and laminar positioning (SMI32 antibody). D. H&E appearances of typical hypertrophic and dysmorphic neurones in FCDII with enlarged cell bodies, abnormal pyramidal shape and orientation in the cortex and abundant Nissl substance. E. p62 immunohistochemistry as evidence of mTOR pathway activation in the dysmorphic neurones of FCD. F. A manifestation of mTOR pathway activation can be altered autophagy flux and in some cases accumulation of lipofuscin like material is accelerated in the dysmorphic neurones (Periodic acid Schiff stain shown in the inset) with marginalization of the neurofilaments to the periphery of the cell. In some cases, this has been linked to DEPDC5 mutation. G The balloon cells that characterize FCDIIb appear as enlarged cells with peripheral nuclei and abundant glassy pink cytoplasm on H&E stain; (Inset top) they can also be visualized with vimentin or GFAP immunohistochemistry (bottom inset). H. Balloon cells are often prominent in the immediate subcortical region, shown with vimentin stain and, as shown in I., this may be associated with a reduction in myelination, highlighted with myelin basic protein immunostaining (SMI94). J. FCDIIIa is one of

the better characterized cortical laminar abnormalities in the FCDIII group and associated with hippocampal sclerosis. In the H&E section the lamination may be perceived as indistinct in the upper layers (I to III) but K. In the NeuN staining cluster of neurones in the outer part of layer II is noted with neuronal loss in the deeper parts of layer II and involving layer III and accompanied by superficial cortical gliosis, as shown in L on GFAP immunostaining.

The bar shown in A is equivalent to approximately 1.5 mm, 250 microns in B, C, J, K and L and 70 microns in other figures.

Figure 3. A.Structural 3T MRI: Right parietal FLAIR hyperintensity area. B.Functional 3T MRI: functional activation (yellow) posterior to the lesion area during active motor task of the left hand. C.Interictal EEG during sleep showing spikes intermingled with K complexes (see arrows)

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