Chapter 12

Focal cortical dysplasia

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12.1 Introduction

Focal cortical dysplasia (FCD), first described by Taylor and colleagues in 1971, is a malformation of cortical development (MCD) characterized by a localized region of abnormal cerebral cortex (Blumcke et al., 2011; Taylor et al., 1971). Over the past several decades, the classification of FCD has evolved and the term "focal cortical dysplasia" has been used to refer to a range of MCDs. In 2011, the International League Against Epilepsy (ILAE) proposed the currently accepted three-tiered clinicopathologic classification: FCD I refers to an isolated lesion with abnormal cortical lamination, FCD II refers to an isolated lesion with abnormal cortical lamination and specific abnormal cell types, and FCD III is associated with another principal lesion (Blumcke et al., 2011). Patients with FCD usually present in childhood with focal epilepsy, with the seizure semiology dependent on the location of the lesion (Gaitanis and Donahue, 2013; Maynard et al., 2017). Magnetic resonance imaging (MRI) is the main imaging modality used for diagnosis and commonly shows localized blurring of the gray matter−white matter junction and increased cortical thickness (Palmini and Holthausen, 2013). Although patients with FCD and focal epilepsy are initially managed with antiepileptic drugs (AEDs), FCD is one of the most common causes of intractable epilepsy in children (Bast et al., 2006). Thus, patients often undergo surgical resection for attempted seizure control, and FCD is the most common cause of surgically treated intractable epilepsy in children (Bast et al., 2006; Blumcke et al., 2017). The etiology of FCD has remained a mystery for several decades, and an important advance in the past decade has been the identification of genetic causes of FCD. Multiple studies have identified mutations, mainly somatic, in genes in the mammalian target of rapamycin (mTOR) pathway in patients with FCD, mainly FCD II (Poduri et al., 2012; Scheffer et al., 2014). The mutations lead to abnormal activation of the mTOR pathway, which is critical for cell growth and proliferation. The identification of genetic causes of FCD has led to progress in understanding pathogenic mechanisms using animal models and single-cell technologies and in developing potential targeted therapies. In this chapter, we will review the classification and pathology, electroclinical presentation, imaging, etiology, and management and outcomes of FCD and discuss challenges for the future.

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12.2 Classification and pathology

FCD was first described by Taylor and colleagues in 1971, with a report on 10 patients, 8 men and 2 women, who developed focal intractable epilepsy and underwent surgical resection for attempted seizure control (Taylor et al., 1971). In all 10 patients, the cortical surface appeared normal, but the resected brain tissue contained "large, bizarre" neurons in all cortical layers except Layer I (now referred to as dysplastic neurons) and abnormal cortical lamination. In addition, in 7 of the 10 patients, the brain tissue also contained "grotesque" cells with large nuclei and excess cytoplasm in the deep cortical layers and white matter (now referred to as balloon cells).

Although Taylor and colleagues noted some similarities to cases of tuberous sclerosis complex (TSC), they argued that the clinical presentation and neuropathology of these 10 cases were distinct enough to represent a separate disease. TSC is an autosomal dominant neurocutaneous disease characterized by facial and skin lesions, renal and cardiac tumors, seizures, intellectual disability, and usually multiple cortical tubers with calcifications (Aronica and Crino, 2014). In contrast, these 10 patients had no family history of similar disease, showed no cutaneous signs or symptoms, had comparatively later onset of seizures (ranging from 2 to 35 years old), had comparatively higher IQs, and appeared to have only single cortical lesions that did not resemble typical tubers and did not contain calcifications. Thus, they suggested that these 10 cases represented a distinct form of FCD associated with focal epilepsy.

Over the past several decades, "FCD" has been used to describe various types of MCDs and the classification system has evolved (Table 12.1). In 1995, Mischel and colleagues proposed one of the first classification systems based on the neuropathological characteristics of resected brain tissue from 77 patients with cortical dysplasia and intractable epilepsy (Mischel et al., 1995). This system identified nine microscopic patterns that correlated clinical severity with developmental time. In 1996, Barkovich and colleagues created the first classification system for MCDs, including FCD, based on embryology, pathology, imaging, and genetics (Barkovich et al., 1996). They divided MCDs into three main classes based on abnormalities occurring during three fundamental events of cortical development: proliferation, migration, and organization. In this system, FCD with balloon cells was placed under the first main class, malformations due to abnormal neuronal and glial proliferation, and further specified as a focal or multifocal malformation due to abnormal proliferation but nonneoplastic. FCD without balloon cells was placed in the third main class, malformations due to abnormal cortical organization, and further specified as a focal or multifocal malformation. This MCD classification system has been updated several times, but the FCD classification was not significantly updated until 2012, when the ILAE classification system, discussed below, was incorporated (Barkovich et al., 2001, 2005, 2012).

In 2002, Tassi and colleagues proposed a simpler FCD classification system of three subtypes based on the neuropathological characteristics of resected brain tissue from 52 patients with cortical dysplasia and intractable partial epilepsy (Tassi et al., 2002). The first subtype, architectural dysplasia, was defined by abnormal cortical lamination and ectopic neurons in the white matter. The second subtype, cytoarchitectural dysplasia, was defined by abnormal cortical lamination and "giant" neurons with increased neurofilament content. The third subtype, "Taylor-type" cortical dysplasia, was defined as abnormal cortical lamination with dysmorphic neurons and balloon cells. The authors noted that the imaging, electroencephalogram (EEG), and surgical outcomes might differ between the three subtypes; for example, the seizure frequency was significantly lower in architectural dysplasia compared to the other two subtypes.

In 2004, a panel of experts proposed the first system that classified FCD into Type 1 and Type II based on neuropathology, and this system has been commonly used in the published literature (Palmini et al., 2004). Importantly, the panel suggested that the term "FCD" should not be used as a general descriptive term for various MCDs, but as a specific diagnostic term for intracortical MCDs with certain neuropathological characteristics. Type I FCD was defined by abnormal cortical architecture without dysmorphic neurons and subdivided based on the absence (Type 1A) or presence (Type 1B) of giant or immature neurons. Type II FCD was defined by "Taylor-type" FCD with dysmorphic neurons and subdivided based on the absence (Type IIA) or presence (Type IIB) of balloon cells. The panel also defined a separate category of mild MCD, subdivided into Type 1, with ectopic neurons in or next to Layer I, and Type 2, with neuronal heterotopias outside Layer I. Although studies using the Palmini classification system suggested that the imaging, EEG, and surgical outcomes differed between the two types, assessment of reproducibility showed only moderate inter- and intraobserver reproducibility, with greater concordance for Type II compared to Type I FCD cases (Chamberlain et al., 2009).

Thus, in 2011, an ILAE task force proposed the currently used three-tiered classification system based on neuropathology, electroclinical presentation, imaging, and postsurgical outcomes (Blumcke and Muhlebner, 2011; Blumcke et al., 2011). FCD Type I was defined as an isolated lesion with abnormal cortical lamination, subdivided into Type Ia with abnormal radial cortical lamination, Type 1b with abnormal tangential cortical lamination, and Type Ic with abnormal radial and tangential cortical lamination (Blumcke et al., 2011). Cellular abnormalities observed in Type 1 include small immature neurons (1a, 1b, and 1c), hypertrophic pyramidal neurons outside Layer V (1a, 1b, and 1c), and neurons with

TABLE 12.1 Focal cortical dysplasia (FCD) classification systems.

Study	Methods	Classification	Description
Taylor et al. (1971)	10 surgical cases	FCD	Abnormal cortical lamination with large bizarre neurons in all cortical layers except Layer I (dysplastic neurons) +/− grotesque cells with large nuclei and excess cytoplasm in deep cortical layers and white matter (balloon cells)
Mischel et al. (1995)	77 surgical cases	Mild	Cortical disorganization, heterotopic white matter neurons, neurons in the cortical molecular layer, persistent remnants of the subpial granular layer, and marginal heterotopia
		Moderate	Mild plus polymicrogyria and neuronal heterotopia
		Severe	Moderate plus neuronal cytomegaly and balloon cells
Tassi et al. (2002)	52 surgical cases	Architectural dysplasia	Abnormal cortical lamination with ectopic neurons in white matter
		Cytoarchitectural dysplasia	Abnormal cortical lamination with giant neurons
		Taylor-type dysplasia	Abnormal cortical lamination with dysmorphic neurons and balloon cells
Palmini et al. (2004)	Panel of experts	mMCD Type I	Ectopic neurons in or next to Layer I
		mMCD Type II	Neuronal heterotopias outside Layer I
		Type Ia	Abnormal cortical lamination
		Type Ib	Abnormal cortical lamination with giant or immature neurons
		Type IIa	Abnormal cortical lamination with dysmorphic neurons
		Type IIb	Abnormal cortical lamination with dysmorphic neurons and balloon cells
Blumcke et al. (2011)	ILAE task force	Type Ia	Abnormal radial cortical lamination
		Type Ib	Abnormal tangential cortical lamination
		Type Ic	Abnormal radial and tangential cortical lamination
		Type IIa	Abnormal cortical lamination with dysmorphic neurons
		Type IIb	Abnormal cortical lamination with dysmorphic neurons and balloon cells
		Type IIIa	Abnormal cortical lamination associated with hippocampal sclerosis
		Type IIIb	Abnormal cortical lamination adjacent to a glial or glioneuronal tumor
		Type IIIc	Abnormal cortical lamination adjacent to a vascular malformation
		Type IIId	Abnormal cortical lamination adjacent to any other lesion acquired early in life

disoriented dendrites (1b and 1c). NeuN and MAP2 are commonly used immunohistochemistry (IHC) markers for visualizing the abnormal cortical lamination and abnormal neurons (Blumcke and Muhlebner, 2011).

FCD Type II was defined as an isolated lesion with abnormal cortical lamination and dysmorphic neurons, subdivided into Type IIa without balloon cells and Type IIb with balloon cells (Blumcke et al., 2011). Cortical layers apart from Layer I cannot be identified (IIa and IIb), the junction between gray matter and white matter is usually blurred (IIa and IIb), and myelin staining is usually reduced in the underlying white matter (mainly IIb). Dysmorphic neurons, which can be found throughout the cortex and subcortical white matter, have an increased cell diameter, increased nuclear diameter, abnormally distributed Nissl substance, and accumulated cytoplasmic neurofilament proteins. Balloon cells, which can similarly be found in cortex or white matter, have an increased cell diameter, glassy eosinophilic cytoplasm, minimal neurite

outgrowth, and accumulated intermediate filaments vimentin and nestin. Marker studies have demonstrated that dysmorphic neurons and balloon cells express proteins found in pyramidal neurons and do not express proteins found in interneurons, suggesting that they derive from progenitors in the ventricular zone and not from progenitors in the medial ganglionic eminence (Lamparello et al., 2007). In addition, balloon cells often express both neuronal and glial proteins, as well as doublecortin, a marker of immaturity, suggesting that they maintain a somewhat embryonic phenotype (Lamparello et al., 2007). Balloon cells are also identified in abnormal brain tissue from patients with hemimegalencephaly (HME) and in cortical tubers from patients with TSC (referred to as "giant cells" in TSC) (Aronica and Crino, 2014). Commonly used stains for IHC include neurofilament stains (e.g., SMI32) and H&E to identify dysmorphic neurons, intermediant filament stains (e.g., vimentin and nestin) to identify balloon cells, and Luxol fast blue staining to identify myelin abnormalities (Blumcke and Muhlebner, 2011).

Finally, the major change from the Palmini classification system was the introduction of Type III. FCD Type III was defined as abnormal cortical lamination (i.e., Type I) associated with another principal lesion, subdivided into FCD IIIa associated with hippocampal sclerosis, FCD IIIb adjacent to a glial or glioneuronal tumor, FCD IIIc adjacent to a vascular malformation, and FCD IIId adjacent to any other lesion acquired early in life (e.g., trauma, hypoxic-ischemic injury, encephalitis) (Barkovich et al., 2005). Of note, if Type II is observed in association with another principal lesion, the two lesions are believed to be distinct and termed double or dual pathology. NeuN and MAP2 staining is commonly used to visualize the abnormal cortical lamination and abnormal neurons in Type III, along with additional stains based on the associated lesion (Blumcke and Muhlebner, 2011).

In 2012, Barkovich and colleagues integrated the FCD ILAE classification system into the updated MCD classification system (Barkovich et al., 2012). FCD Type II was placed in the first main category, malformations secondary to abnormal neuronal and glial proliferation or apoptosis, and further specified as a focal cortical dysgenesis with abnormal cell proliferation but without neoplasia. FCD Type II was placed in the same subcategory as HME and TSC. FCD Types I and III, as well as milder MCDs, were placed in the third main category, malformations due to abnormal postmigrational development, and further specified as FCDs because of late developmental disturbances. An assessment of reproducibility for the ILAE classification system demonstrated improved reproducibility compared to the previous study assessing the Palmini classification system, with good intra- and interobserver reproducibility using a virtual slide system (Coras et al., 2012).

Recently in 2018, proposed updates and challenges for the ILAE classification system were published (Najm et al., 2018). For FCD Type I, Type Ia remains the most well-documented and accepted subtype. In terms of etiology, the microcolumns observed in Type Ia may represent a focal maturational arrest—the microcolumar architecture normal in early embryonic development is not properly reorganized at midgestation and thus becomes pathologic. Types Ib and Ic are less well-documented and remain controversial, especially given that many acquired lesions can result in abnormal tangential cortical lamination. In addition, we know very little about the underlying genetic and molecular basis of Type I lesions. Thus, the authors suggest that Types Ib and Ic could be eliminated in a future classification system. The most progress has been made for FCD Type II; as discussed below, we believe that a significant percentage of FCD Type II and HME cases are caused by abnormal activation of the mTOR pathway. However, the genetic etiology for the unsolved cases remains a mystery, and it is unclear how distinct Types IIa and IIb really are. FCD Type III was created in the original ILAE classification system to describe FCD I lesions adjacent to another principal lesion. Types IIIa, IIIb, and IIId are currently problematic in terms of pathogenesis because the FCD is believed to arise during cortical development, but the associated lesions are often acquired (e.g., hippocampal sclerosis for IIIa, postnatally acquired tumors for IIIb, and postnatally acquired ischemic injury for IIId). Type IIIc makes the most sense, as most vascular malformations are developmental. Thus, Type IIIa needs to be better understood, Type IIIb may be better classified as FCD adjacent to a developmental tumor (e.g., gangliogliomas and dysembryoplastic neuroepithelial tumors), Type IIId may be better classified as FCD adjacent to ischemic injury acquired during fetal life, and Type IIIe could be created to describe FCD adjacent to any other lesions (e.g., trauma). Alternatively, the authors suggest that Type III could be removed in a future classification system. Overall, while the field agrees on the existence of different FCD subtypes, future studies need to further investigate the genetic etiologies and molecular mechanisms underlying these subtypes to improve the usefulness of the classification system.

As mentioned above, HME, which is characterized by abnormal enlargement of much or all of a cerebral hemisphere, appears microscopically similar to FCD IIb. The abnormal brain tissue displays abnormal cortical lamination as well as dysmorphic neurons and balloon cells. Macroscopically, the abnormal brain surface is enlarged and malformed with various gyral abnormalities (Flores-Sarnat et al., 2003). Most commonly, patients present with isolated HME; however, patients may also present with total HME, which is characterized by abnormal enlargement of a cerebral hemisphere as well as the ipsilateral brainstem and cerebellum, or with syndromic HME, which is characterized by abnormal enlargement of a cerebral hemisphere as well as cutaneous and other systemic manifestations (Flores-Sarnat, 2002) (Fig. 12.1).

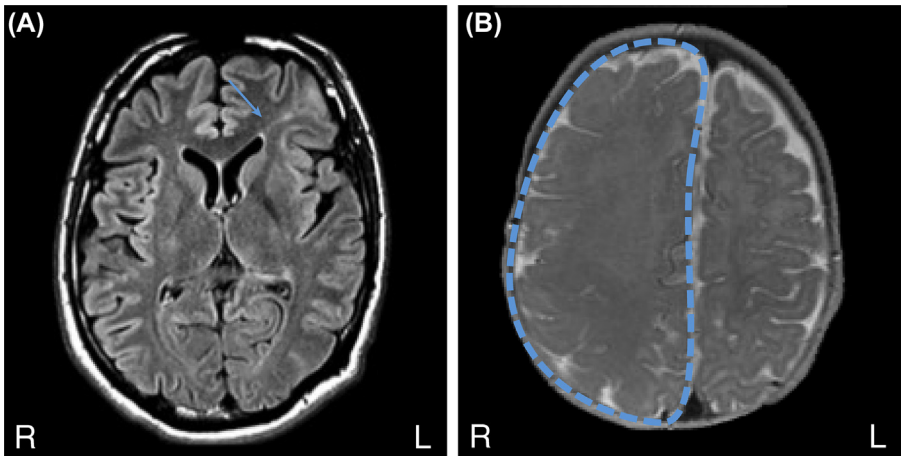

FIGURE 12.1 Brain magnetic resonance imaging (MRI) of (A) a patient with FCD-IIb and (B) a patient with HME. *FCD*, focal cortical dysplasia; *HME*, hemimegalencephaly.

12.3 Electroclinical presentation

FCD accounts for approximately 5%−10% of patients with focal epilepsy, is one of the most common causes of intractable epilepsy in children, and is the most common cause of surgically treated intractable epilepsy in children (Bast et al., 2006; Blumcke et al., 2017). In a recent study of over 9500 patients with intractable epilepsy who underwent surgery, FCD was the most common diagnosis in children based on neuropathology findings (Blumcke et al., 2017). FCD II accounted for 17% of the pediatric patients and was the most common specific diagnosis in children, FCD I accounted for 6.4%, and FCD not otherwise specified accounted for 3.4% (Blumcke et al., 2017). However, the true prevalence of FCD in the human population is unclear as current estimates are based on limited imaging and surgical findings. Some individuals with FCD may be asymptomatic and never clinically present with seizures or other neurological symptoms. These healthy individuals are unlikely to have a brain MRI, especially the high-resolution brain MRI often needed to detect FCDs. In addition, some patients with epilepsy and FCD may clinically present, most commonly with seizures, but may not undergo high-resolution MRI if their seizures are adequately controlled with AEDs or they are not considered surgical candidates or they may undergo such imaging but the FCD still may not be detected, so-called "cryptogenic" epilepsies (Bast et al., 2006). Indeed, some patients with intractable focal epilepsy who undergo surgery are diagnosed with FCD based on neuropathology, but the FCD was not detected on presurgical imaging. Thus, a negative MRI does not rule out a diagnosis of FCD and the prevalence of FCD is likely underestimated.

FCDs can be located in any cortical area and vary in size. FCD I is commonly located in the temporal lobe, and FCD II is commonly located extratemporally, especially in the frontal lobe, fronto-central area, peri-rolandic area, or posterior quadrants (Palmini et al., 2004). The most common clinical presentation is epilepsy, especially intractable epilepsy. A recent study found that 71% of children with FCD based on brain imaging developed epilepsy and 33% developed intractable epilepsy; thus, 46% of the patients with FCD and epilepsy developed intractable epilepsy (Maynard et al., 2017). Patients with epilepsy were significantly more likely to have FCDs located in the temporal or frontal lobes (Maynard et al., 2017). Although the exact semiology depends on the location of the FCD, the seizures are generally simple or complex partial seizures that sometimes secondarily generalize, and status epilepticus is not uncommon (Gaitanis and Donahue, 2013). For example, patients with FCD located in the temporal lobe often present with complex partial seizures and patients with FCD located in the peri-rolandic or premotor areas often present with partial motor or sensorimotor seizures (Palmini and Holthausen, 2013). Seizures can begin at any age from in utero to adulthood, but usually begin in childhood. Of the patients with FCD, 60% develop epilepsy before 5 years old and 90% before 16 years old; only 10% develop epilepsy in adulthood (Maynard et al., 2017). In a recent study of patients with FCD and intractable epilepsy, the average age of onset for epilepsy was 6.3 years old (Fauser et al., 2015). Patients with drug-resistant epilepsy have a significantly earlier age of seizure onset than patients with drug-responsive epilepsy, and one study found that each additional year in terms of age of seizure onset increased the odds of drug-responsive epilepsy by approximately 22% (Maynard et al., 2017).

Compared to patients with FCD I, patients with FCD II are usually younger at seizure onset, have a higher seizure frequency, and are younger at time of epilepsy surgery (Palmini and Holthausen, 2013). In the 2002 study where Tassi and colleagues proposed their FCD classification scheme, they found that patients with architectural dysplasia had lower

seizure frequency compared to patients with cytoarchitectural and Taylor-type dysplasia (Tassi et al., 2002). Fauser and colleagues, in a 2006 study, found that patients without cytoarchitectural abnormalities had significantly later seizure onset compared to patients with such abnormalities (Fauser et al., 2006). Recently, Isler and colleagues similarly found that patients with FCD II were younger at epilepsy onset and at time of epilepsy surgery compared to patients with FCD I (Isler et al., 2017).

Scalp EEGs in FCD patients commonly show focal rhythmic epileptiform discharges (REDs) (Gambardella et al., 1996). REDs are defined as repetitive rhythmic sharp waves or spikes that last longer than 1 second (Gambardella et al., 1996). REDs are seen in approximately 50% of FCD patients and are spatially correlated with the lesion in 80% of FCD patients (Gambardella et al., 1996). Intracranial recordings in FCD patients commonly show continuous epileptiform discharges (CEDs) in three patterns that last longer than 10 seconds: rhythmic spikes that progressively increase to a frequency of 12−16 Hz and then decrease, bursts of spikes at 10−20 Hz, or rhythmic spikes or sharp waves at 1−8 Hz (Gambardella et al., 1996). REDs on scalp EEG are strongly correlated with CEDs on intracranial recording, and CEDs are similarly spatially colocalized with the MRI lesion in over 80% of surgical patients (Gambardella et al., 1996). Neurophysiology studies have suggested that the abnormal brain tissue, especially for FCD II, is intrinsically epileptogenic (Chassoux et al., 2000; Palmini et al., 1995), and IHC studies have shown an increase in excitatory neurotransmission and a decrease in inhibition within and around the lesions (Ferrer et al., 1992; Spreafico et al., 1998).

In addition to epilepsy, patients with FCD may present with additional neurological symptoms including developmental delay, intellectual disability, and various focal neurologic deficits. The location, size, and subtype of the FCD are thought to play roles in the extent of neurological symptoms (Bast et al., 2006). For example, if the FCD is large, patients may present with severe symptoms more similar to HME; patients with HME commonly present with global developmental delay and contralateral hemiparesis and hemianopia (Flores-Sarnat, 2002; Palmini and Holthausen, 2013). Several studies have reported on cognitive deficits in FCD patients, although the results are not clear-cut. Chassoux and colleagues reported that earlier seizure onset was associated with intellectual disability (Chassoux et al., 2000). Tassi and colleagues reported intellectual disability in 9% of patients with architectural dysplasia, 66% with cytoarchitectural dysplasia, and 33% with Taylor-type dysplasia (Tassi et al., 2002); Widdess-Walsh and colleagues reported below average IQ in 38% of patients with FCD 1a, 57% with FCD Ib, 67% with FCD IIa, and 68% with FCD IIb (Widdess-Walsh et al., 2005); and Krsek and colleagues reported below average IQ in 96% of patients with FCD I and 67% with FCD II (Krsek et al., 2009). However, an earlier study by Krsek and colleagues found no differences in neuropsychological testing between FCD subtypes (Krsek et al., 2008). Differences in the clinical characteristics of the patients, for example, in age at seizure onset and FCD size, likely contribute to differences between these studies.

12.4 Imaging

Brain imaging is important for the detection and diagnosis of FCD in patients presenting with epilepsy and for presurgical planning in patients who develop intractable epilepsy. Brain computed tomography is usually unable to detect FCDs, and brain MRI remains the main imaging modality used (Spreafico and Tassi, 2012). Common MRI findings include blurring of the gray matter−white matter junction, which is the most common abnormality detected, increased cortical thickness, abnormalities of the gyri and sulci, focal brain hypoplasia, and cortico-subcortical signal abnormalities (Palmini and Holthausen, 2013).

Some imaging abnormalities are more likely to be detected in specific subtypes, but the imaging findings for FCD I and FCD II often overlap (Kim et al., 2012). For FCD I, blurring of the gray matter−white matter junction, increased cortical thickness, and abnormalities of the gyri and sulci are often subtle. Imaging findings more likely to be detected in FCD I include increased white matter signal on T2 weighted and FLAIR images and focal white matter volume loss leading to focal brain hypoplasia (Shaker et al., 2016; Krsek et al., 2009). Blurring of the gray matter−white matter junction, increased cortical thickness, and abnormalities of the gyri and sulci are more commonly detected in FCD II. In addition, increased cortico-subcortical signal on T2 weighted and FLAIR images, the transmantle sign, and "bottom of the sulcus" dysplasia (BOSD) are more specific imaging findings in FCD II (Gaitanis and Donahue, 2013; Krsek et al., 2009). The transmantle sign, associated with FCD IIb, refers to a funnel-shaped signal on T2 weighted and FLAIR images that extend from the pia to the surface of the lateral ventricle (Barkovich et al., 1997). BOSD, similarly associated with FCD IIb, refers to a funnel-shaped signal on T2 weighted and FLAIR images that extends from the bottom of the sulcus to the surface of the lateral ventricle (Harvey et al., 2015). Finally, MRI findings in FCD III are usually those associated with the adjacent principal lesion, and blurring of the gray matter−white matter junction and increased cortical thickness are less likely to be detected in FCD III compared to isolated FCD (FCD I and FCD II) (Lee and Kim, 2013; Najm et al., 2018).

Although brain MRI is an important method for noninvasively detecting FCD, the MRI is normal in a significant percentage of patients. In fact, FCD is the most common neuropathologic diagnosis (approximately 50%) among patients with intractable focal epilepsy and normal MRI who undergo surgery (Bast et al., 2006). Many patients with FCD I have a negative MRI (37%); specifically, the diagnostic sensitivity is 30% for FCD Ia and 60.7% for FCD Ib (Lee and Kim, 2013). Although the majority of patients with FCD II have an abnormal MRI—the diagnostic sensitivity is 75% for FCD IIa and 81% for FCD IIb—15% of FCD II patients also have a negative MRI (Lee and Kim, 2013). Thus, from a clinical perspective, a negative routine MRI does not necessarily rule out a diagnosis of FCD in a patient presenting with epilepsy or other neurological symptoms that raise suspicion for FCD. Of note, the MRI field strength plays an important role in the diagnostic sensitivity. For example, 3 Tesla (T) MRI can detect lesions in 20% of patients with FCD II and negative 1.5 T MRI, and a recent study using 7 T MRI detected lesions in over 20% of patients with focal epilepsy and negative lower field MRI (mainly 3 T) (Mellerio et al., 2014; Veersema et al., 2017). MRI postprocessing, such as voxel-based analysis, can also improve detection of imaging abnormalities (Najm et al., 2018).

In addition to MRI, other imaging techniques can help detect FCD and are especially useful for patients with negative MRI and patients undergoing presurgical planning. 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) are more sensitive than MRI to detect FCD, with a diagnostic sensitivity of approximately 80% for FDG-PET and 90% for SPECT Marusic 2002 (Chassoux et al., 2010; Kim et al., 2011). For example, a study of 23 patients with Taylor-type FCD and negative 1.5 T MRI found that FDG-PET detected focal hypometabolism in 78% of the patients (Chassoux et al., 2010). Co-registration of FDG-PET and MRI further increases the diagnostic sensitivity up to 98% (Salamon et al., 2008).

12.5 Etiology

Until recently, the etiology of FCD remained a mystery. Given the focal nature of FCD, it has long been hypothesized that FCD is caused by somatic mutations. Traditionally studied germline mutations are present in all of the cells of an affected individual and thus can be identified in any tissue, including clinically accessibly tissues like blood. These include inherited mutations, which are present in a parent and passed on to the affected child, and de novo mutations, which occur during gametogenesis in a parent and are similarly present in the zygote and thus all cells of the affected child. In contrast, somatic mutations occur post-zygotically and are present in only a subset of cells of the affected child, specifically only in daughter cells of the originally mutated cell. If a somatic mutation occurs relatively early in development, it may be present in both brain and nonbrain tissue and identifiable from clinically accessible tissues. On the other hand, a somatic mutation that occurs relatively late in development may only be present in a subset of cells in brain tissue and require direct assaying of brain tissue to identify the mutation. Thus, somatic mosaicism could result in a focal area of abnormal cortex surrounded by normal cortex, but identifying such somatic mutations might require direct study of surgically resected brain tissue from FCD patients.

As mentioned above, some subtypes of FCD share pathological features with HME and TSC, such as the balloon cells observed in FCD IIb and HME and the giant cells observed in TSC cortical tubers (Aronica and Crino, 2014). TSC is an "mTORopathy" caused by mutations in *TSC1* and *TSC2*, whose protein products form a complex that negatively regulates the serine/threonine kinase mTOR (Laplante and Sabatini, 2012). Thus, the loss-of-function mutations identified in *TSC1* and *TSC2* in TSC patients lead to abnormal activation of the mTOR pathway. This pathway is critical for sensing environmental cues, including amino acids, growth factors, stress, oxygen, and energy status, and regulating major cellular processes, including protein synthesis, cell growth, and metabolism (Laplante and Sabatini, 2012). IHC studies looking at phosphorylation of downstream targets of the mTOR pathway, such as S6 kinase and ribosomal protein S6, have demonstrated increased phosphorylation in cortical tubers from patients with TSC. In 2004, two studies demonstrated increased phosphorylation in surgically resected brain tissue samples from FCD patients (Baybis et al., 2004; Miyata et al., 2004). Further studies then showed increased phosphorylation in dysmorphic neurons in FCD IIa and balloon cells in FCD IIb, as well as in surgically resected brain tissue samples from HME patients (Aronica and Crino, 2014; Ljungberg et al., 2006). These similarities suggested that increased activation of the mTOR pathway might be a common mechanism underlying FCD, HME, and TSC.

Over the past few years, advances in next-generation sequencing (NGS) have helped us understand that FCD II and HME are also "mTORopathies" caused by germline and somatic mutations that abnormally activate the mTOR pathway. Briefly, NGS refers to massively parallel sequencing experiments, and the depth of coverage for an experiment refers to the average number of sequencing reads covering each genomic location in the target region. A germline heterozygous mutation is expected to be present in 50% of the reads (an alternate allele frequency [AAF] of 50%), and a somatic mutation is expected to be present in less than 50% of the reads. However, it is important to discriminate true somatic

mutations from false positives that arise from library preparation and sequencing errors. Bioinformatics tools are continually being developed to optimally detect mutations at low AAF in tissue samples containing normal and mutant cells. Depth of coverage is also an important consideration, as higher coverage provides higher power to detect mutations at lower AAF. Finally, independent validation using techniques such as digital droplet polymerase chain reaction (PCR) or resequencing is essential to confirm potential mutations.

In 2012, three groups initially reported mutations in mTOR pathway genes associated with HME and related megalencephaly syndromes. Poduri and colleagues studied surgically resected brain tissue from eight HME patients and identified one patient with a somatic activating point mutation in *AKT3* and two patients with somatic chromosome 1q copy number increases (which includes the *AKT3* locus) (Poduri et al., 2012). For the two patients where blood samples were available, the somatic mutations were not detectable in the blood samples. Interestingly, the point mutation identified in *AKT3* in HME, p.E17K, is paralogous to the mutation identified in *AKT1* in Proteus syndrome and in *AKT2* associated with left-sided overgrowth and hypoglycemia (Poduri et al., 2012). Lee and colleagues studied 20 HME patients with paired brain and blood samples using whole exome sequencing (WES) and mass spectrometry analysis and identified another patient with the *AKT3* p.E17K mutation, one patient with an activating somatic point mutation in *MTOR* itself, p.C1483Y, and four patients with the same activating somatic mutation in *PIK3CA*, p.E545K (Lee et al., 2012). These mutations were similarly detected in brain tissue but not in blood. Finally, Rivière and colleagues identified germline and somatic activating point mutations in *AKT3*, *PIK3CA*, and *PIK3R2* in the related megalencephaly-capillary malformation syndrome and megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (Riviere et al., 2012). *AKT3*, *PIK3CA*, and *PIK3R2* encode positive regulators of mTOR; thus, the activating mutations identified in these genes lead to abnormal activation of the mTOR pathway.

In 2015, somatic activating mutations in positive regulators of the mTOR pathway were initially identified in FCD. Lim and colleagues used deep sequencing to initially identify 8 different somatic activating point mutations in *MTOR* in brain tissue from 12 out of 77 FCD II patients, which were not detected in available blood samples (Lim et al., 2015). Multiple studies have now confirmed the role of "single-hit" activating mutations associated with FCD and HME. Three more studies have reported the p.E17K mutation in *AKT3* in four additional HME patients, and overall the six patients carry the mutation in 7.8%−56.6% of cells; moreover, the p.E17K mutation in *AKT1* has been reported in a patient with HME and likely Proteus syndrome (Alcantara et al., 2017; D'Gama et al., 2017; Jansen et al., 2015). Conti and colleagues identified a somatic chromosome 1q21.1-q44 copy number increase (which includes the *AKT3* locus) associated with FCD Ib (Conti et al., 2015). For *PIK3CA*, three studies have reported two additional somatic activating point mutations, p.E542K and p.H1047R, in four additional HME patients and one FCD IIa patient (D'Gama et al., 2015, 2017; Jansen et al., 2015). The three HME patients with p.E542K mutations carry the mutation in 32.3%−62.2% of cells, and the four HME patients with p.E545K mutations carry the mutation in approximately 60% of cells. Finally, for *MTOR*, 8 more studies have reported many of the same somatic activating point mutations as well as 6 additional somatic activating point mutations in 21 additional FCD patients and 5 HME patients (D'Gama et al., 2015, 2017; Griffin et al., 2017; Hanai et al., 2017; Leventer et al., 2015; Mirzaa et al., 2016; Moller et al., 2016; Nakashima et al., 2015). The five FCD patients with p.L1460P mutations carry the mutation in 3.8%−9.7% of cells and the three FCD patients with p.L2427P/Q mutations carry the mutation in 7.3%−16.5% of cells.

The recurrent activating somatic mutations thus far identified in FCD and HME demonstrate a relationship between the allele frequency of a mutation and the severity of the phenotype. For the p.H1047R mutation in *PIK3CA*, one patient with FCD IIa carries the mutation in 10.4% of cells and one patient with HME carries the mutation in 16.2% of cells (D'Gama et al., 2015; Jansen et al., 2015). For the p.A1459D mutation in *MTOR*, one patient with FCD IIb carries the mutation in 2.9% of cells and one patient with HME carries the mutation in 22.2% of cells (Hanai et al., 2017; Nakashima et al., 2015). For the p.C1483R/Y mutations in *MTOR*, two patients with FCD IIb carry the mutation in 15.2%−20.6% of cells, two patients with HME carry the mutation in 12%−34.3% of cells, and patients with multisystemic megalencephaly syndromes, who unfortunately die within the first few years of life, have been reported to carry the mutation in 100% of cells (D'Gama et al., 2015, 2017; Griffin et al., 2017; Lee et al., 2012; Lim et al., 2015; Kingsmore et al., 2013). For the p.T1977K/R mutations in *MTOR*, three patients with FCD carry the mutation in 3%−7.4% of cells and a patient with HME carries the mutation in 19.4% of cells (D'Gama et al., 2017; Lim et al., 2015). Finally, for the p.S2215Y/F mutation in *MTOR*, 14 patients with FCD carry the mutation in 2.1%−18.6% of cells, and 2 patients with HME carry the mutation in 15.4%−38.9% of cells (D'Gama et al., 2017; Lim et al., 2015; Mirzaa et al., 2016; Moller et al., 2016; Nakashima et al., 2015) (Table 12.2).

In addition to activating mutations in positive regulators of the mTOR pathway, studies have also demonstrated a role for loss-of-function mutations in negative regulators of the mTOR pathway associated with FCD and HME. An initial study by Schick and colleagues in 2006 used laser capture microdissection and Sanger sequencing to identify a somatic

TABLE 12.2 Mutations identified in positive regulators of the mTOR pathway.

Diagnosis	Gene	Mutation	AAF (%)	Study
HME/Proteus	*AKT1*	p.E17K	8.66	D'Gama et al. (2017)
HME	*AKT3*	Chr 1q tetrasomy	SM	Poduri et al. (2012)
HME	*AKT3*	Chr 1q CN increase	SM	Poduri et al. (2012)
FCD Ib	*AKT3*	Chr 1q21.1-q44 dup	SM	Conti et al. (2015)
HME	*AKT3*	p.E17K	3.91	D'Gama et al. (2017)
HME	*AKT3*	p.E17K	13.25	Alcantara et al. (2017)
HME	*AKT3*	p.E17K	13.83	Jansen et al. (2015)
HME	*AKT3*	p.E17K	17.39	Poduri et al. (2012)
HME	*AKT3*	p.E17K	28.29	Lee et al. (2012)
FCD IIa	*MTOR*	p.R624H	3.11	Lim et al. (2015)
FCD IIb	*MTOR*	p.Y1450D	3.2	Lim et al. (2015)
FCD IIa	*MTOR*	p.W1456G	8.78	Leventer et al. (2015)
FCD IIb	*MTOR*	p.A1459D	1.46	Nakashima et al. (2015)
HME	*MTOR*	p.A1459D	11.1	Hanai et al. (2017)
FCD IIb	*MTOR*	p.L1460P	1.9	Nakashima et al. (2015)
FCD IIb	*MTOR*	p.L1460P	2.44	D'Gama et al. (2017)
FCD IIb	*MTOR*	p.L1460P, p.A1459S	2.46	Moller et al. (2016)
FCD IIa	*MTOR*	p.L1460P	3.37	Mirzaa et al. (2016)
FCD IIb	*MTOR*	p.L1460P	4.87	Nakashima et al. (2015)
HME	*MTOR*	p.C1483R	6	Griffin et al. (2017)
FCD IIb	*MTOR*	p.C1483R	7.59	Lim et al. (2015)
FCD IIb	*MTOR*	p.C1483R	10.3	D'Gama et al. (2017)
HME	*MTOR*	p.C1483Y	17.14	Lee et al. (2012)
FCD IIa	*MTOR*	p.R1709H	1.58	Lim et al. (2015)
FCD IIb	*MTOR*	p.T1977K	1.49	Lim et al. (2015)
FCD IIb	*MTOR*	p.T1977K	3.09	Lim et al. (2015)
FCD	*MTOR*	p.T1977R	3.72	D'Gama et al. (2017)
HME	*MTOR*	p.T1977K	9.7	D'Gama et al. (2017)
FCD IIa	*MTOR*	p.R2193C	2.13	Lim et al. (2015)
FCD IIa	*MTOR*	p.S2215F	1.03	Moller et al. (2016)
FCD IIb	*MTOR*	p.S2215F	2.26	Lim et al. (2015)
FCD IIb	*MTOR*	p.S2215F	2.42	Nakashima et al. (2015)
FCD IIb	*MTOR*	p.S2215F	2.58	Lim et al. (2015)
FCD IIb	*MTOR*	p.S2215F	2.89	Moller et al. (2016)
FCD IIa	*MTOR*	p.S2215F	4.61	Mirzaa et al. (2016)
FCD IIa	*MTOR*	p.S2215F	6.41	Mirzaa et al. (2016)
FCD IIb	*MTOR*	p.S2215F	6.56	Moller et al. (2016)
FCD IIa	*MTOR*	p.S2215F	6.83	Mirzaa et al. (2016)
HME	*MTOR*	p.S2215F	19.44	D'Gama et al. (2017)

Continued

TABLE 12.2 Mutations identified in positive regulators of the mTOR pathway.—cont'd

Diagnosis	Gene	Mutation	AAF (%)	Study
FCD IIa	*MTOR*	p.S2215Y	1.33	Moller et al. (2016)
FCD IIb	*MTOR*	p.S2215Y	1.35	Nakashima et al. (2015)
FCD	*MTOR*	p.S2215Y	2.66	D'Gama et al. (2017)
FCD IIb	*MTOR*	p.S2215Y	3.65	Moller et al. (2016)
HME	*MTOR*	p.S2215Y	7.7	D'Gama et al. (2017)
FCD IIb	*MTOR*	p.S2215Y	9.31	Nakashima et al. (2015)
FCD IIb	*MTOR*	p.L2427Q	3.67	Lim et al. (2015)
FCD IIa	*MTOR*	p.L2427P	5.56	Lim et al. (2015)
FCD IIa	*MTOR*	p.L2427P	8.24	Lim et al. (2015)
HME	*PIK3CA*	p.E542K	16.13	D'Gama et al. (2017)
HME	*PIK3CA*	p.E542K	18.15	D'Gama et al. (2015)
HME	*PIK3CA*	p.E542K, p.T544N	31.11	Jansen et al. (2015)
HME	*PIK3CA*	p.E545K	28.6	Lee et al. (2012)
HME	*PIK3CA*	p.E545K	28.9	Lee et al. (2012)
HME	*PIK3CA*	p.E545K	29.03	Lee et al. (2012)
HME	*PIK3CA*	p.E545K	30.2	Lee et al. (2012)
FCD IIa	*PIK3CA*	p.H1047R	5.21	Jansen et al. (2015)
HME	*PIK3CA*	p.H1047R	8.1	D'Gama et al. (2015)

SM, somatic (AAF unknown).

point mutation in *PTEN* in an FCD IIb patient (Schick et al., 2006). A germline mutation in *PTEN* was subsequently reported in an HME patient (Jansen et al., 2015). Recently, mutations in genes encoding the GATOR1 complex, which are the most common mutations identified in inherited focal epilepsies, have been identified in FCD and HME. Scheffer and colleagues initially reported loss-of-function germline mutations in *DEPDC5* in familial focal epilepsy with four affected individuals carrying three different mutations showing FCD on MRI (Scheffer et al., 2014). Subsequently, 9 more studies have reported 15 additional germline loss-of-function mutations in *DEPDC5* in 17 additional patients with FCD and 1 patient with HME (Baulac et al., 2015; Carvill et al., 2015; D'Gama et al., 2015, 2017; Mirzaa et al., 2016; Ricos et al., 2016; Scerri et al., 2015; Weckhuysen et al., 2016; Ribierre et al., 2018). Interestingly, two of the FCD patients carry both germline and somatic loss-of-function mutations in *DEPDC5*, with the somatic mutations detected in brain tissue and not blood (Baulac et al., 2015; Ribierre et al., 2018). For the other components of the GATOR1 complex, two germline loss-of-function mutations in *NPRL2* have been reported in two FCD patients, and five germline loss-of-function mutations in *NPRL3* have been reported in six FCD patients (D'Gama et al., 2017; Sim et al., 2016; Weckhuysen et al., 2016).

Although *TSC1* and *TSC2* mutations are usually associated with TSC, recent studies have identified loss-of-function mutations in these genes associated with isolated FCD and HME. D'Gama and colleagues initially identified a germline mutation in *TSC2* in an HME patient and subsequently used higher coverage sequencing to identify a "second hit" somatic mutation in *TSC2* in the same patient as well as "two-hit" germline and somatic mutations in *TSC2* in a second HME patient (D'Gama et al., 2015, 2017). Lim and colleagues identified two somatic mutations in *TSC1* in four FCD II patients and a somatic mutation in *TSC2* in an FCD IIa patient, and two subsequent studies reported an additional somatic mutation in *TSC1* in an FCD IIb patient, a germline mutation in *TSC1* in an FCD IIb patient, and an additional somatic mutation in *TSC2* in an FCD patient (D'Gama et al., 2017; Hoelz et al., 2018; Lim et al., 2017). Given that *DEPDC5*, *NPRL2*, *NPRL3*, *PTEN*, *TSC1*, and *TSC2* are negative regulators of the mTOR pathway, it has been hypothesized that the "two-hit" model, originally described by Knudson for tumor pathogenesis, also applies to mutations in these genes to lead to focal MCDs. The "two-hit" mechanism has long been hypothesized for TSC and has been demonstrated in nonnervous system tumors as well as cortical tubers from TSC patients. Thus far, four examples of such a model have been reported in the literature for FCD and HME: two FCD patients with *DEPDC5* mutations and two HME patients with *TSC2* mutations (Baulac et al., 2015; D'Gama et al.,

2015, 2017; Ribierre et al., 2018). Future studies need to further investigate the validity of the "two-hit" model, especially for patients with only one identified loss-of-function mutation in a negative regulator (Table 12.3).

Overall, mutations that lead to abnormal activation of the mTOR pathway have been demonstrated to be a major cause of FCD, mainly FCD II, and HME (Fig. 12.2). Based on the mutations identified thus far, somatic activating mutations in *MTOR* are the most commonly identified mutations associated with FCD, and somatic activating mutations in *AKT3* and *PIK3CA* are the most commonly identified mutations associated with HME. Somatic mutations have been identified at AAFs as low as approximately 1% and 4% for FCD and HME, respectively. This suggests that abnormal mTOR activation in as few as 8% of cells is sufficient to disrupt an entire cerebral hemisphere and highlights the importance of neural circuits in brain development and function. Interestingly, the somatic mutations are generally detected in brain but not in nonbrain tissues where available. Thus, the mutations occur relatively late during embryonic development, after gastrulation and potentially neurulation. In addition, the mutations appear to confer a proliferative advantage. For mutations identified at AAFs as high as approximately 10% and 30% for FCD and HME, respectively, the mutation is only detected in the brain. However, functionally silent somatic mutations in normal human brain and disease-causing somatic mutations in non-proliferative MCDs are generally detectable in both brain and nonbrain tissues at AAF ≥5% (Jamuar et al., 2014; Lodato et al., 2015). Although the average AAF for somatic mutations associated with FCD (approximately 4%) is significantly lower than the average AAF for somatic mutations associated with HME (approximately 16%), there is overlap. This suggests that FCD II and HME represent part of a continuum, and the phenotype severity depends on the developmental time and progenitor cell in which the somatic mutation occurs (Fig. 12.3).

TABLE 12.3 Mutations identified in negative regulators of the mTOR pathway.

Diagnosis	Gene	Mutation	AAF (%)	Notes	Study
FCD	*DEPDC5*	c.279+1G>A	GL		Scheffer et al. (2014)
FCD	*DEPDC5*	c.481-1G>A	GL		Baulac et al. (2015)
FCD IIb	*DEPDC5*	c.624+1G>A	GL		D'Gama et al. (2015)
FCD	*DEPDC5*	p.Y7*	GL		Scheffer et al. (2014)
HME	*DEPDC5*	p.N45Qfs*3	GL		D'Gama et al. (2015)
FCD	*DEPDC5*	p.Q140*	GL		Scheffer et al. (2014)
FCD	*DEPDC5*	p.Q140*	GL		Scheffer et al. (2014)
FCD	*DEPDC5*	p.R239*, p.R422*	GL, SM	Two hit	Baulac et al. (2015)
FCD	*DEPDC5*	p.R239*	GL		Baulac et al. (2015)
FCD	*DEPDC5*	p.R239*	GL		Baulac et al. (2015)
FCD IIb	*DEPDC5*	p.N261Kfs*11	GL		D'Gama et al. (2015)
FCD	*DEPDC5*	p.Y281F	GL		Carvill et al. (2015)
FCD IIa	*DEPDC5*	p.R286*, p.Q289*	GL, 10.3	Two hit	Ribierre et al. (2018)
FCD	*DEPDC5*	p.R422*	GL		Baulac et al. (2015)
FCD IIa	*DEPDC5*	p.R555*	GL		Scerri et al. (2015)
FCD IIa	*DEPDC5*	p.R555*	GL		Scerri et al. (2015)
FCD	*DEPDC5*	p.R587*	GL		Baulac et al. (2015)
FCD	*DEPDC5*	p.Q797Rfs*18	GL		Carvill et al. (2015)
FCD IIa	*DEPDC5*	p.R874*	GL		D'Gama et al. (2017)
FE/FCD	*DEPDC5*	p.R1332*	GL		Ricos et al. (2016)
FCD IIa	*DEPDC5*	p.A1396Vfs*78	GL		Mirzaa et al. (2016)
FCD	*DEPDC5*	p.E1421Rfs*153	GL		Weckhuysen et al. (2016)
FCD Ia	*NPRL2*	p.I23Nfs*6	GL		Weckhuysen et al. (2016)

Continued

TABLE 12.3 Mutations identified in negative regulators of the mTOR pathway.—cont'd

Diagnosis	Gene	Mutation	AAF (%)	Notes	Study
FCD	*NPRL2*	p.Q188*	GL		D'Gama et al. (2017)
FCD IIa	*NPRL3*	c.1352-4 delACAGInsTGACCCATCC	GL		Sim et al. (2016)
FCD IIa	*NPRL3*	p.R92Q	GL		Sim et al. (2016)
FCD	*NPRL3*	p.P357Hfs*56	GL		Weckhuysen et al. (2016)
FCD IIa/HS	*NPRL3*	p.R424*	GL		Weckhuysen et al. (2016)
FCD IIa	*NPRL3*	p.S460Pfs*20	GL		Sim et al. (2016)
FCD IIa	*NPRL3*	p.S460Pfs*20	GL		Sim et al. (2016)
HME	*PTEN*	p.Y68H	GL		Jansen et al. (2015)
FCD	*PTEN*	p.F278L	SM		Schick et al. (2006)
FCD IIb	*TSC1*	p.A22W	1.79		Lim et al. (2017)
FCD IIa	*TSC1*	p.A22W	2.25		Lim et al. (2017)
FCD IIa	*TSC1*	p.A22W	2.41		Lim et al. (2017)
FCDIIb	*TSC1*	p.E31Afs*12	GL		Hoelz et al. (2018)
FCD IIb	*TSC1*	p.Q55*	5.92		D'Gama et al. (2017)
FCD IIa	*TSC1*	p.R204C	1.38		Lim et al. (2017)
FCD	*TSC2*	p.R751*	1		D'Gama et al. (2017)
HME	*TSC2*	p.L631P, p.E1558K	GL, 9.56	Two hit	D'Gama et al. (2017)
FCD IIa	*TSC2*	p.Val1547Ile	1.37		Lim et al. (2017)
HME	*TSC2*	p.R1713H, p.Y587*	GL, 3.46	Two hit	D'Gama et al. (2017)

FCD, focal cortical dysplasia; *GL*, germline; *SM*, somatic (AAF unknown); shaded rows indicate family members.

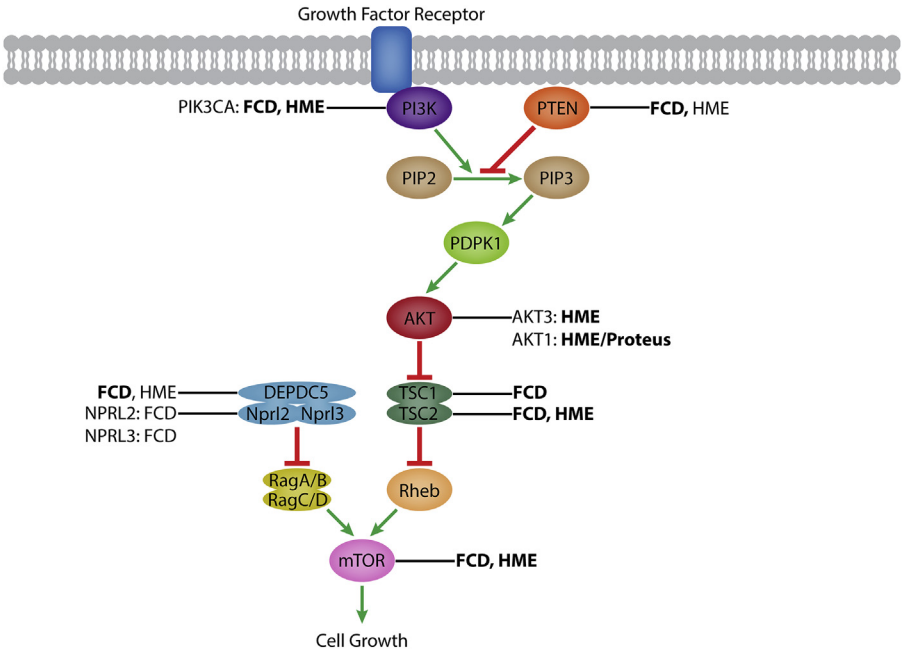

FIGURE 12.2 Schematic of the mammalian target of rapamycin (mTOR) pathway indicating genes for which pathogenic mutations have been identified in FCD and/or HME. Somatic mutations are indicated by boldface. *FCD*, focal cortical dysplasia; *HME*, hemimegalencephaly. *Legend and figure adapted with permission from D'gama, A.M., Woodworth, M.B., Hossain, A.A., Bizzotto, S., Hatem, N.E., Lacoursiere, C.M., Najm, I., Ying, Z., Yang, E., Barkovich, A.J., Kwiatkowski, D.J., Vinters, H.V., Madsen, J.R., Mathern, G.W., Blumcke, I., Poduri, A., Walsh, C.A., 2017. Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias. Cell Rep. 21, 3754–3766.*

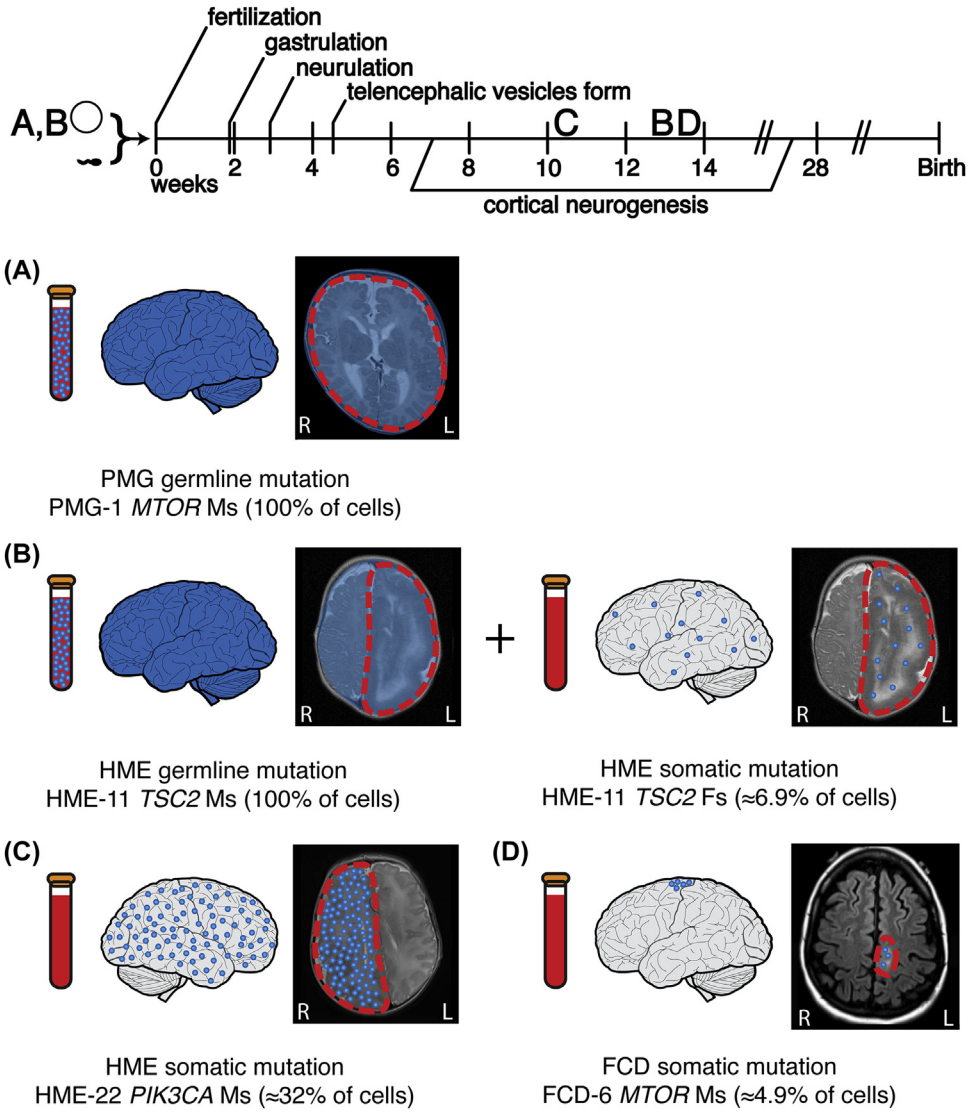

FIGURE 12.3 FCD and HME represent a continuum, with lesion differences reflecting the time and place of origin of the mutation. (A) Germline mutations occur before fertilization and are detectable in the brain and a clinically accessible blood sample. Germline activating mutations in the mammalian target of rapamycin (mTOR) pathway can lead to megalencephaly, as seen in case PMG-1 with a de novo germline *MTOR* mutation. (B) "Two-hit" germline and somatic mutations in negative regulators of the mTOR pathway can lead to focal malformation of cortical development (MCDs). In some cases, such as HME-11 with two *TSC2* mutations, we have identified both a germline and a somatic mutation leading to HME. The germline mutation was detectable in the brain and blood, while the somatic mutation occurred later during embryonic development and was detectable only in the brain. (C) Activating somatic mutations in positive regulators of the mTOR pathway can also lead to focal MCDs. Those mutations present at a higher AAF, suggesting they arose earlier during cortical neurogenesis, appear more likely to lead to HME; for example, we identified a somatic activating point mutation in *PIK3CA* present in ≈32% of the cells in the abnormal hemisphere of case HME-22. (D) Mutations present at a lower AAF, suggesting they arose later during cortical neurogenesis, appear more likely to lead to FCD; for example, we identified a somatic activating point mutation in *MTOR* present in ≈4.9% of the cells in the abnormal cortical tissue of case FCD-6. *AAF*, alternate allele frequency; *FCD*, focal cortical dysplasia; *HME*, hemimegalencephaly, *PMG*, polymicrogyria. *Legend and figure adapted with permission from D'Gama, A.M., Woodworth, M.B., Hossain, A.A., Bizzotto, S., Hatem, N.E., Lacoursiere, C.M., Najm, I., Ying, Z., Yang, E., Barkovich, A.J., Kwiatkowski, D.J., Vinters, H.V., Madsen, J.R., Mathern, G.W., Blumcke, I., Poduri, A., Walsh, C.A., 2017. Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias. Cell Rep. 21, 3754–3766.*

While progress has been made in understanding the genetic etiology of FCD II and HME, many cases of FCD II remain unsolved and little is known about the genetic etiology of FCD I and FCD III. For FCD I, an association has been reported with recessive mutations in *CNTNAP2* in Old Order Amish children. Strauss and colleagues identified homozygous mutations in *CNTNAP2* in nine Old Order Amish children with cortical dysplasia-focal epilepsy syndrome (Strauss et al., 2006). Focal malformations were seen on MRI in three of the seven children for whom MRI was available. Three of the

children underwent surgical resection (two of those three had focal malformations visible on MRI), and neuropathology for all three cases was consistent with FCD 1. Recently, Winawer and colleagues reported somatic mutations in *SLC35A2* in five patients with intractable focal epilepsy, and two of the five had pathologically confirmed FCD Ia (Winawer et al., 2018). There have been several studies reporting an association between FCD and additional genes, but it is unclear if the identified mutations and FCD are coincidental occurrences or if the mutations are truly causative of FCD. Kurian and colleagues identified mutations in *PCDH19* in four patients with early infantile epilepsy and MRI showing FCD, including FCD I and FCD IIa (Kurian et al., 2018). Barba and colleagues identified mutations in *SCN1A* in three patients with epileptic encephalopathies and MRI showing FCD, with neuropathology confirming FCD Ia and IIa in the two patients who underwent surgery (Barba et al., 2014). Weckhuysen and colleagues identified a mutation in *STXBP1* in a patient with epileptic encephalopathy and normal MRI, but neuropathology after surgery revealed FCD 1a (Weckhuysen et al., 2013). Uddin and colleagues recently reported additional *STXBP1* mutations in three patients with various neurodevelopmental phenotypes and MRI suggesting FCD, with one patient undergoing surgery and neuropathology most consistent with FCD Ib (Uddin et al., 2017). Finally, Griffin and colleagues recently reported somatic uniparental disomy of chromosome 16p in an HME patient, and they speculated that abnormal expression of *ZNF597*, which is on 16p, may contribute to disease pathogenesis (Griffin et al., 2017).

There has been interest in the role of HPV infection in FCD IIb, but the overall evidence does not appear to support causation. The E6 oncogene of HPV is known to activate the mTOR pathway, and in 2012, Crino and colleagues initially reported detection of HPV16 infection and E6 in FCD IIb, studying 50 brain samples from FCD IIb patients using PCR or in situ hybridization (Chen et al., 2012). In utero electroporation of E6 into mice resulted in a focal MCD and increased mTOR pathway activation. Another study confirmed detection of HPV as well as additional viruses in FCD IIb, studying 20 brain samples from FCD IIb patients using PCR and IHC (Liu et al., 2014). However, three additional studies have been unable to replicate these findings and raised questions about the original methods, such as the interpretation of antibody staining in paraffin-embedded brain samples (Coras et al., 2015; Shapiro et al., 2015; Thom et al., 2015). Moreover, the association with HPV infection would be hard to explain clinically; for example, HPV16 carries high cancer risk but FCD is not known to malignantly transform into cancer. Thus, while an association between HPV infection and FCD IIb remains possible, the balance of evidence currently does not support such an association.

Single-cell experiments have provided further insight into FCD and HME disease pathogenesis. Laser capture microdissection allows isolation of specific cell types from resected brain tissue samples, and several cells of the same type can be pooled to generate sufficient DNA for further analysis. For example, in the study by Schick and colleagues discussed above, laser capture microdissection was used to isolate dysplastic neurons and balloon cells from the brain tissue of an FCD IIb patient, and PCR and single-strand conformation polymorphism analysis on pooled cells identified the somatic mutation in *PTEN* (Schick et al., 2006). Baek and colleagues used laser capture microdissection to isolate phospho-S6+ and phospho-S6− cells from the brain tissue of an FCD patient carrying the p.E17K mutation in *AKT3* (Baek et al., 2015). Subsequent analysis of pooled cells demonstrated that the mutation was detected and enriched in the phospho-S6+ cell population and not detected in the phospho-S6− cell population. In addition, methods have been developed to isolate single neuronal and nonneuronal nuclei from frozen brain tissue using an antibody against the neuronal marker NeuN and fluorescence-activated nuclear sorting (Evrony et al., 2012). After whole genome amplification using φ29-mediated multiple displacement amplification, sufficient DNA is generated for genotyping and further analysis. As mentioned above, Poduri and colleagues initially reported somatic chromosome 1q copy number increases in two HME patients and a somatic activating point mutation in *AKT3* in a third HME patient (Poduri et al., 2012). Subsequent single-cell copy number variant analysis revealed that at least one of the somatic chromosome 1q copy number increases was actually a somatic chromosome 1q tetrasomy, present in both neuronal and nonneuronal cells, and single-cell genotyping showed that the somatic point mutation in *AKT3* was similarly present in both neuronal and nonneuronal cells (Cai et al., 2015; Evrony et al., 2012). Recently, D'Gama and colleagues studied seven FCD and HME patients with identified somatic point mutations, including the HME patient initially reported by Poduri and colleagues, using single-cell genotyping of neuronal and nonneuronal cells (D'Gama et al., 2017). In all seven cases, the somatic mutations were present in neuronal cells, suggesting that abnormal activation of the mTOR pathway in the neuronal lineage is necessary for FCD and HME pathogenesis. However, the somatic mutations were variably present in nonneuronal cells. In the two FCD cases carrying mutations with the lowest AAFs, single-cell genotyping showed that the mutations were limited to the neuronal lineage, suggesting that in some cases abnormal activation of the mTOR pathway in the neuronal lineage is sufficient for pathogenesis and the somatic mutation occurs after separation of the neuronal and glial lineages.

Multiple groups have recently generated mouse or rat models of FCD and HME using in utero electroporation, cre recombination, or genome editing techniques, which recapitulate many aspects of the human phenotype and provide insight into underlying mechanisms and potential treatments. *TSC1* and *TSC2* models will not be discussed here, as there is

another chapter on TSC. In utero electroporation at E14.5 of *Akt3* p.E17K, which has been recurrently identified in HME, leads to abnormal cortical architecture and abnormal neuronal migration with neuronal heterotopias and cytomegalic dysmorphic neurons, as well as electrographic seizures (Baek et al., 2015). Administration of the mTOR inhibitor rapamycin rescued the phenotype when administered prenatally, but not when administered postnatally. In utero electroporation at E14 of *Mtor* p.L2427P, which has been recurrently identified in FCD II, leads to abnormal neuronal migration, cytomegalic neurons, and spontaneous seizures, and rapamycin treatment suppressed cytomegalic neurons and seizures (Lim et al., 2015). Two studies have recently used cre recombination techniques to express mutant *Pik3ca* in various cell lineages. Roy and colleagues conditionally expressed *Pik3ca* p.H1047R or p.E545K in subsets of neural progenitors starting from early embryonic, late embryonic, or neonatal age using different cre drivers, and D'Gama and colleagues conditionally expressed *Pik3ca* p.H1047R in dorsal telencephalic progenitors using *Emx1-Cre* and in interneurons using *Nkx2.1-Cre* (D'Gama et al., 2017; Roy et al., 2015). Megalencephaly, abnormal cortical organization, and cytomegalic neurons were observed when p.H1047R was expressed embryonically in neural progenitors (but not when expressed neonatally) and when p.E545K was expressed early embryonically in neural progenitors (but not when expressed late embryonically or neonatally). These phenotypes were not observed when p.H1047R was expressed embryonically in the interneuron lineage; however, there was a subtle decrease in cortical interneuron number. Seizures were observed with abnormal mTOR activation starting embryonically or neonatally. Administration of BKM120, a PI3K inhibitor, suppressed seizures in the mouse model expressing *Pik3ca* p.H1047R from early embryonic age. Several mouse models have been developed with *Pten* conditionally knocked out in neurons or astrocytes using different cre drivers, and the mutant mice generally develop megalencephaly, cytomegalic neurons, and seizures, and administration of rapamycin suppressed the seizures (Kwon et al., 2006; Ljungberg et al., 2009). Although *Nprl2*$^{-/-}$ mice, *Nprl3*$^{-/-}$ mice, and *Depdc5*$^{-/-}$ mice and rats are embryonic lethal, *Depdc5*$^{-/-}$ rats show increased mTOR activation and prenatal administration of rapamycin rescued the growth phenotype (Marsan et al., 2016). *Depdc5*$^{+/-}$ rats show cytomegalic dysmorphic neurons and balloon-like cells, which were suppressed by prenatal administration of rapamycin (Marsan et al., 2016). Yuskaitis and colleagues conditionally knocked out *Depdc5* in neurons using *Syn1-Cre*, and the mutant mice developed megalencephaly, cytomegalic neurons, and spontaneous seizures (Yuskaitis et al., 2018). Finally, Park and colleagues used a genome-edited cell line and mouse models with brain somatic mutations in *Mtor* to demonstrate that these mutations lead to defective neuronal ciliogenesis, specifically by disrupting autophagy (Park et al., 2018). The animal model studies together with the NGS and single-cell sequencing studies suggest that FCD II and HME are caused by somatic mutations in dorsal cerebral cortical progenitors that abnormally activate the mTOR pathway and that mTOR inhibitors may be effective for treatment.

12.6 Management and outcomes

The management of FCD generally begins with AEDs for focal epilepsy, with the specific AED for each patient chosen based on the types of seizures present and side effect profiles. Multidisciplinary approaches involving physical, occupational, and/or speech therapy are important for patients with neurological or cognitive deficits. It should not be assumed that all patients with focal epilepsy and FCD have medically refractory epilepsy. However, focal epilepsy associated with FCD is often refractory to medical management, potentially due to the intrinsic epileptogenicity of FCD brain tissue and/or activation of multidrug transporters (Bast et al., 2006). The rate of medically refractory epilepsy has remained unclear because surgical studies report only on patients who failed medical management and thus were evaluated for surgical resection (Guerrini et al., 2015). Based on surgical studies, approximately one-quarter to one-third of FCD patients have a transient response to AEDs, commonly carbamazepine and oxcarbazepine, usually within the first year of treatment and lasting for more than 2 years (Guerrini et al., 2015). A recent study of almost 100 patients with MRI-positive FCD found that 46% of the patients with FCD and epilepsy developed intractable epilepsy (Maynard et al., 2017).

Surgical resection is considered relatively early for patients with FCD and focal epilepsy because of the high rate of medically refractory epilepsy, and alternative approaches such as the ketogenic diet or vagus nerve stimulation are sometimes also considered (Guerrini et al., 2015). As discussed above, some patients with focal epilepsy and FCD, especially FCD I, have negative MRI. Thus, presurgical evaluation is generally started after a patient with focal epilepsy fails two or more AED trials, regardless of the presence or absence of FCD on initial MRI (Bast et al., 2006). If the initial MRI is negative, presurgical evaluation should include additional high-resolution MRI and optimal protocols to identify FCD or other structural abnormalities. Presurgical evaluation should also include neuropsychological evaluation, noninvasive approaches, and potentially invasive approaches to determine the location and extent of the lesion, the location and extent of the seizure onset zone (which may be larger than the lesion seen on MRI), possible deficits that may result from surgical resection (FCD is often near eloquent motor or language regions), and the concordance of various localization

approaches. Such approaches include EEG, FDG-PET, diffusion tensor imaging, magnetoencephalography, and invasive electrode monitoring (Kabat and Krol, 2012). Multiple studies have shown that completeness of the surgical resection is a key prognostic factor for seizure freedom (Choi et al., 2018; Rowland et al., 2012). Thus, a delicate balance exists between resection of the lesion and preservation of function. Deciding between partial resection to preserve function and a higher risk of failed seizure control versus complete resection to cure seizures and a higher risk of postoperative deficits (which may be somewhat reversible, especially in young children due to plasticity) should be discussed in advance with the patient and family (Palmini and Holthausen, 2013). The goal of surgery is to completely resect the epileptogenic lesion, and the surgical approach ranges from focal resection to partial or total lobectomy to anatomic or functional hemispherectomy (e.g., patients with multilobar FCD or HME). Postoperative mortality is low, and severe postoperative complications such as hydrocephalus are uncommon (Kabat and Krol, 2012).

Studies over the past several decades have investigated outcomes after FCD surgery and identified prognostic factors associated with favorable versus unfavorable outcomes. Although rates of seizure freedom vary widely, a 2012 meta-analysis of over 2000 patients with FCD who underwent surgical resection reported that the overall rate of seizure freedom (Engel class 1) was 55.8% ± 16.2% (Rowland et al., 2012). Patients with FCD II, especially FCD IIb (76% seizure freedom), appear to have better outcomes than patients with FCD I (21%−67% seizure freedom), and outcomes for patients with FCD III appear to depend on the associated pathology, although some studies have reported that surgical outcomes did not significantly differ between subtypes (Blumcke et al., 2009; Choi et al., 2018; Najm et al., 2018; Rowland et al., 2012). A recent study by Choi and colleagues analyzed characteristics and outcomes for 58 patients with FCD I or FCD II who underwent surgical resection and were followed postsurgery for at least 2 years (Choi et al., 2018). After 2 years, 62% of patients were seizure free (Engel class I) (58% after 5 years) and 48% were able to discontinue AEDs. However, patients with FCD IIb had a significantly higher rate of seizure freedom (88% at 5 years) compared to patients with FCD IIa (57%) and FCD I (21%). Identification of a lesion on MRI and complete resection were the most important prognostic factors for seizure freedom. About 63% of patients with complete resection achieved seizure freedom compared to 14% of patients with incomplete resection. For the 33% of patients with incomplete resection, the main reason for partial resection was lesion overlap with eloquent cortex, similar to previous studies reporting incomplete resection in approximately 30% of patients most commonly due to lesion overlap with eloquent cortex or lesion not visible on MRI (Kabat and Krol, 2012).

Overall, studies have shown that identification of a lesion by MRI or EEG, complete resection, Type II neuropathology (especially BOSD), severe neuropathological features, partial seizures (vs. secondarily generalized seizures), and temporal location are favorable prognostic factors (Choi et al., 2018; Rowland et al., 2012). Type II lesions and severe neuropathological features are more likely to be localized by MRI or EEG and thus more likely to be completely resected. Type I lesions are often diffuse and extensive (e.g., multilobar) and less likely to be precisely localized by MRI or EEG and thus more likely to be incompletely resected (Choi et al., 2018; Gaitanis and Donahue, 2013). Recent studies identifying mutations that lead to abnormal activation of the mTOR pathway in patients with FCD, especially FCD II, suggest that mTOR inhibitors have the potential to be targeted therapies. mTOR inhibitors have been studied in clinical trial for patients with TSC, and a clinical trial is currently ongoing to evaluate the mTOR inhibitor everolimus in patients with FCD and TSC (NCT02451696). Future studies may also develop drugs targeting other components of the mTOR pathway, such as the GATOR1 complex, which is frequently mutated in focal epilepsy and FCD.

12.7 Conclusion

In the past decade, we have made significant progress in understanding FCD. In 2011, the ILAE proposed a consensus three-tiered clinicopathologic classification for FCD, which has been applied to hundreds of studies (Blumcke et al., 2011; Najm et al., 2018). Recent studies have confirmed that FCD is a common cause of pediatric intractable epilepsy and the most common cause of surgically treated intractable pediatric epilepsy (Blumcke et al., 2017; Maynard et al., 2017). Although a significant percentage of FCD lesions, especially FCD I lesions, are not detected by standard MRI, recent studies have suggested that optimized high-resolution MRI and new imaging modalities provide better sensitivity (Lee and Kim, 2013; Veersema et al., 2017). Notably, recent studies have identified genetic causes of FCD and provided initial insight into FCD pathogenesis and potential targeted therapies. Many FCDs are caused by germline and somatic mutations that lead to abnormal activation of the mTOR pathway, and thus mTOR pathway inhibitors may be effective therapies for some patients (D'Gama et al., 2017; Lim et al., 2015; Poduri et al., 2012; Scheffer et al., 2014).

In the future, there are several important research directions for the FCD field. First, the ILAE classification needs to be improved using knowledge gained from studies of the genetic mutations and pathogenic mechanisms underlying the different FCD subtypes. As discussed above, the 2018 update noted several challenges with the current classification of FCD I, II, and

III subtypes (Najm et al., 2018). Separating subtypes based on underlying etiology would likely improve the usefulness of the classification for both clinical practice and research studies. Second, the detection of FCD using brain imaging needs to achieve higher sensitivity. Currently, 37% of patients with FCD I and 15% of patients with FCD II have a negative MRI (Lee and Kim, 2013). Future studies need to continue investigating the application of MRI with higher field strength, the optimal protocols and postprocessing techniques, and the feasibility and application of new brain imaging modalities. Third, the genetic etiology underlying the many "unsolved" FCD cases needs to be identified. As NGS technologies improve, we will be able to detect somatic mutations present at very low alternate allele frequencies that are currently difficult to discriminate from false positive errors. In addition, as the cost of sequencing decreases, it will be feasible to perform WES or whole genome sequencing at high depth of coverage instead of focusing on targeted sequencing approaches. Thus, future studies will ideally investigate all types of genetic variation contributing to FCD pathogenesis, which may include somatic mutations in mTOR pathway genes at AAFs below the current level of detection, mutations in novel genes, and intronic or noncoding mutations. Moreover, epigenetic or other mechanisms may additionally contribute to FCD pathogenesis. Fourth, the genetic mutations identified need to be connected to the disease phenotype by studying underlying molecular, cellular, and system level mechanisms. For example, single-cell studies may provide further insight into the cell types critical for FCD pathogenesis. Finally, targeted therapies need to be developed and tested in vitro, in vivo in animal models, and eventually in clinical trials using the knowledge gained from identifying genetic mutations and understanding underlying disease mechanisms. In particular, it will be important to investigate if the efficacy of a potential therapy differs depending on the specific mutation carried by a patient and when the therapy is started.

12.8 Application

FCD affects approximately 1:1000 individuals. The most common clinical presentation is seizures, and recent data suggest that over 70% of patients with FCD develop epilepsy (Maynard et al., 2017). The seizures are usually focal, with the seizure semiology dependent on the location of the FCD, and sometimes secondarily generalize. FCD is one of the most common causes of intractable pediatric epilepsy, and recent data suggest that almost 50% of patients with FCD and epilepsy develop intractable epilepsy (Maynard et al., 2017). Thus, a clinician needs to have a high suspicion for FCD if a child presents with focal epilepsy, especially focal epilepsy refractory to medical management. MRI is the main imaging modality used for FCD diagnosis, and it is important to use proper MRI protocols with high field strength to optimally detect FCDs and to consider additional imaging modalities if the initial MRI is negative. For a child presenting with focal epilepsy, initial seizure control should generally be attempted with AEDs, with the specific AED choice based on the seizure type(s) present. If the child fails at least two AED trials, the clinician should consider presurgical planning. In some cases, presurgical planning will reveal FCD that was not detected on the initial MRI. If presurgical planning reveals that the lesion overlaps eloquent cortex, deciding between partial resection to preserve function and a higher risk of failed seizure control versus complete resection to cure seizures and a higher risk of postoperative deficits (which may be somewhat reversible, especially in young children because of plasticity) should be discussed in advance with the patient and family. Surgical outcome studies have demonstrated that completeness of resection is a key prognostic factor for favorable outcome, and thus a delicate balance exists between resection of the epileptogenic lesion and preservation of function (Choi et al., 2018; Rowland et al., 2012). Furthermore, patients with FCD II appear to have better outcomes than patients with FCD I (Choi et al., 2018; Rowland et al., 2012). In some cases, FCD will not be detected preoperatively, and postoperative neuropathology will reveal FCD. In the near future, genetic testing will likely play a larger role in FCD diagnosis. Based on current studies demonstrating that pathogenic somatic mutations detected in brain tissue are unable to be detected in clinically accessible tissues like blood or saliva, assaying DNA extracted from patient blood or saliva is unlikely to be high yield (D'Gama et al., 2017). If abnormal brain tissue is available from surgical resection, assaying DNA extracted from this brain tissue as well as DNA extracted from maternal and paternal blood or saliva may be helpful for detecting pathogenic germline and somatic mutations, and genetic counseling will be important to interpret the results. Clinical trials for new therapies for FCD, such as mTOR inhibitors, are just beginning, and hopefully efficacious targeted therapies based on a patient's FCD subtype and genetic mutation will eventually be available in the clinical setting.

Glossary

Balloon cell Abnormal cell type found in FCD IIb and HME with increased cell diameter, glassy eosinophilic cytoplasm, minimal neurite outgrowth, and accumulated intermediate filaments vimentin and nestin. Expresses neuronal, glial, and cellular immaturity markers.

Dysmorphic neuron Abnormal cell type found in FCD IIa and FCD IIb with increased cell diameter, increased nuclear diameter, abnormally distributed Nissl substance, and accumulated cytoplasmic neurofilament proteins. Generally expresses pyramidal neuronal markers.

Focal cortical dysplasia Malformation of cortical development characterized by a localized region of abnormal cerebral cortex with abnormal cortical lamination and in some subtypes specific abnormal cell types.

Germline mutation A mutation that is present in all of the cells of an individual.

Hemimegalencephaly Malformation of cortical development characterized by abnormal enlargement of most or all of a cerebral cortical hemisphere.

mTORopathies Spectrum of neurological diseases, including tuberous sclerosis, focal cortical dysplasia, and hemimegalencephaly characterized by epilepsy and abnormal activation of the mTOR pathway.

Somatic mutation A mutation that occurs post-zygotically and is present in only a subset of the cells of an individual.

Two-hit mechanism Originally described by Knudson in relation to tumor pathogenesis. An individual has a germline inherited or de novo mutation in one allele of a tumor suppressor gene and a somatic mutation of the second allele leads to disease manifestations.

List of acronyms and abbreviations

AAF alternate allele frequency
AEDs antiepileptic drugs
BOSD bottom of the sulcus dysplasia
CEDs continuous epileptiform discharges
CFDE cortical dysplasia-focal epilepsy
CNV copy number variant
CT computed tomography
ddPCR digital droplet polymerase chain reaction
DTI diffusion tensor imaging
EEG electroencephalogram
FANS fluorescence-activated nuclear sorting
FCD focal cortical dysplasia
FDG-PET 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography
HME hemimegalencephaly
IHC immunohistochemistry
ILAE International League Against Epilepsy
ISH in situ hybridization
MCAP megalencephaly-capillary malformation
MCD malformation of cortical development
MDA multiple displacement amplification
MEG magnetoencephalography
MPPH megalencephaly-polymicrogyria-polydactyly-hydrocephalus
MRI Magnetic resonance imaging
mTOR mammalian target of rapamycin
NGS next-generation sequencing
REDs rhythmic epileptiform discharges
SPECT single photon emission computed tomography
SSCP single-strand conformation polymorphism
T Tesla
TSC tuberous sclerosis complex
WES whole exome sequencing

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