I, Lauren M Maynard, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Predictors of Epilepsy Severity in MRI-Identified Focal Cortical Dysplasia

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Predictors of Epilepsy Severity in MRI-Identified Focal Cortical Dysplasia

A thesis submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of

Master of Science

In the Department of Pediatrics of the College of Medicine

By

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Abstract

Focal cortical dysplasia is a malformation of cortical development that typically presents with epilepsy. Previous studies have used cohorts of patients with epilepsy who were found to have focal cortical dysplasia, thus limiting the data on “asymptomatic” or “atypically presenting” focal cortical dysplasia. The purpose of this study was to determine the prevalence of epilepsy and drug-resistant epilepsy in a cohort of pediatric patients with focal cortical dysplasia identified by magnetic resonance imaging. We hypothesized that there were clinical and imaging difference among those with focal cortical dysplasia who had drug-resistant epilepsy, drug-responsive epilepsy, and no epilepsy. A key word search of a hospital radiology database identified study participants. Participants were included if they were under 18 years of age at the time of the database query and had magnetic resonance imaging between 2004 to 2013 showing focal cortical dysplasia. Participants were excluded based on imaging and clinical characteristics. Data was gathered using a chart review and questionnaire. In the study cohort, 29% of patients with imaging findings compatible with focal cortical dysplasia did not have epilepsy. The prevalence of epilepsy was 71.13% (95% C.I. 61.05% to 79.89%) and the prevalence of drug-resistant epilepsy was 32.99% (95% C.I. 23.78% to 43.27%). Patients with epilepsy were more likely to have lesions located in the temporal (p=0.0293) or frontal lobes (p=0.0441) and a family history of seizures (p=0.0026) than those without epilepsy. The age of seizure onset was later in those with drug-responsive epilepsy than those with drug-resistant epilepsy (p=0.0002). For those with an epilepsy diagnosis, predictive factors for having drug-responsive epilepsy were age of seizure onset (OR=1.22, p=0.0441, 95% CI = 1.005 to 1.486) and lack of developmental delay (OR=3.624, p=0.0497, 95% CI = 1.002 to 13.110). For children with epilepsy, each one year increase in the age of seizure onset increased the odds of having drug-responsive epilepsy instead of drug-resistant epilepsy by 22%. Additionally, among children with epilepsy, patients who did not have developmental delay were 3.6 time more likely to have drug-responsive epilepsy instead of drug-resistant epilepsy. Identifying a novel cohort of children with focal cortical dysplasia without epilepsy helps define prognosis and inform clinical management of children with focal cortical dysplasia on imaging.
Acknowledgements

I would like to thank my research advisory committee for their time, guidance, and hard work on this research project. We would like to acknowledge and thank the families who participated in this study.

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Introduction

Focal cortical dysplasia (FCD) is a malformation of cortical development that typically presents with epilepsy in childhood (Sisodiya et al., 2009; Blümcke et al., 2011; Sarnat and Flores-Sarnat, 2014). Between 5-10% of patients who have epilepsy also have FCD; however, in cohorts with more severe forms of focal epilepsy such as children receiving surgery due to drug-resistant epilepsy, FCD is identified in up to 50% of patients (Bast et al., 2006; Leach et al., 2014a). Age of epilepsy onset in patients with FCD is variable with 60% of patients reporting seizure onset before the age of 5 years, 90% before 16 years, and 10% in adulthood (Bast et al., 2006; Fauser et al., 2006; Sisodiya et al., 2009). In a recent study, the mean age of epilepsy onset in a cohort who had drug-resistant epilepsy and FCD was 6.3 years, ranging from 0-60 years of age (Fauser et al., 2015).

Although histological examination is the only way to confirm FCD, brain magnetic resonance imaging (MRI) is a recognized and widely used diagnostic tool for identifying FCD (Leventer et al., 1999; Widdess-Walsh et al., 2006; Madan and Grant, 2009; Colombo et al., 2009; Mellerio et al., 2012; Lee and Kim, 2013; Leach et al., 2014a). Leach et al. conducted a study to correlate the features of FCD seen on MRI to the pathological features seen upon microscopic examination of surgical specimens (Leach et al., 2014b). Of the three types and multiple subtypes of FCD as classified by the current International League Against Epilepsy (ILEA) classification system (Blümcke et al., 2011), MRI abnormalities were seen in 30% of patients with FCD Type I, 55% of patients with Type IIa, and 80% of patients with Type IIb (Leach et al., 2014b).

Using a surgical cohort to study FCD is limited by the potential to miss those with atypically presenting or asymptomatic FCD (Widdess-Walsh et al., 2005; Bast et al., 2006; Fauser et al., 2006). Because most healthy individuals do not undergo a brain MRI, the prevalence of FCD in the general population is unknown and difficult to assess (Holthausen et al., 2014). Large studies performing brain MRIs on healthy individuals, such as the one by Vernooij et al. in 2007, have not identified FCD as an incidental finding (Sisodiya et al., 2009). However, there has been a case study reporting asymptomatic FCD identified as an incidental finding on MRI in an older individual (Tezer-Filik et al., 2010) and another reporting a patient who had two seizures and slow, progressive aphasia as an atypical clinical presentation of FCD (Forgacs et al., 2013).
We hypothesized that an “atypical clinical presentation” of FCD without epilepsy is not rare, just rarely reported. There have been no studies which describe the prevalence of epilepsy among those with MRI-identified FCD because all previous studies to our knowledge have used a cohort of individuals that have presented clinically with epilepsy and were found to have FCD. The purpose of this study was to determine the prevalence of epilepsy and drug-resistant epilepsy in patients with MRI-identified FCD and to describe a patient population with FCD without a diagnosis of epilepsy. We hypothesized that there are differences between patients with an MRI-identified FCD who have drug-resistant epilepsy, drug-responsive epilepsy and no epilepsy. We aimed to determine if there are clinical and imaging differences, such as comorbidities, family history and MRI features such as lesion location, that differentiate the epilepsy phenotype of children with FCD.

Materials and Methods

The Institutional Review Board approved this retrospective, case-control study. Participants were identified from a key word search of a radiology database (Illuminate Insight, Softek, Kansas City, KS, U.S.A.) and data was gathered using a chart review and a supplemental parent or guardian questionnaire.

Participants and Imaging Review

Potential participants were identified using a key word search of the radiology database at a large tertiary care pediatric medical center using the term “cortical dysplasia”. Individuals who were between the age of 0 and 17 years at the time of the query and received a brain MRI between January 1, 2004 and December 31, 2013 showing a single or multiple FCD(s) were included in the study. A board certified neuroradiologist with 20 years of experience interpreting MRIs for epilepsy surgery, reviewed and classified all participant MR images. For participants with more than one MRI available, all MR images were reviewed. He was blinded to the epilepsy phenotype of the potential participants.

Participants with a known genetic diagnosis associated with syndromic FCD (such as tuberous sclerosis complex and neurofibromatosis) and those with non-English speaking parents or guardians were excluded. Participants were also excluded if the imaging review showed 1) lesions in the brain stem and/or cerebellum, 2) lesions that potentially represented a tumor as defined by mass effect, growth over time, radiologist
recommendations for follow-up, and associated enhancement, 3) lesions that were typical for remote insult as defined by cortical thinning and marked localized volume loss, or 4) lesions that were gyral malformations involving greater than one brain quadrant or typical of lissencephaly, bilateral extensive polymicrogyria or hemimegalencephaly.

During the imaging review of participant MRIs, lesion location and FCD classification were determined. FCD was defined as localized disorder of the cortex and/or subjacent white matter typical of pathologically proven Type II cortical dysplasia seen in patients with drug-resistant epilepsy undergoing surgical resection. The criteria used to determine FCD by MRI were adapted from those previously developed and reported (Leach et al., 2014b). MRI characteristics of cortical dysplasia included the following features: 1) localized increased cortical signal without other known cause, 2) localized increase in cortical thickness, 3) ill-defined or irregular cortical-white matter junction, 4) localized subcortical signal located at the bottom of a sulcus, 5) asymmetric gyral pattern and/or depth, 6) transmantle signal changes related to a gyrus, and 7) subcortical heterotopic gray matter. FCD by MRI was designated as “Definite” when feature 6 was seen with any two other features, “Probable” when feature 6 was seen with either feature 2, 3, 5, or 7 or when any three features were seen without feature 6, and “Possible” when any two features were seen without feature 6.

Data Collection

Following participant identification and review of participant MRI(s), data were collected using a retrospective chart review coupled with a supplemental questionnaire. Study data were collected and managed using REDCap electronic data capture tools hosted at the hospital (Harris et al., 2009).

A review of the medical record was used to capture clinical data and family history for each participant. Clinical characteristics included epilepsy diagnosis, comorbidities of epilepsy, and possible etiologies of epilepsy development. Use of physical therapy, occupational therapy, or speech therapy was used as a proxy for developmental delay. Family history was defined as a first or second degree relative or first cousin with a history of epilepsy or seizures. Family history and clinical characteristics were assessed as dichotomous variables. Data not included in the chart were recorded as missing; however, clinical and family history data were assumed to be
negative if providers in Neurology, Neurosurgery, Genetics, Pediatric Rehabilitation, or Developmental and Behavioral Pediatrics did not document it as present.

For patients with a diagnosis of epilepsy, clinical data were also gathered about epilepsy features and management. ILAE pathology classification (Blümcke et al., 2011) and surgical outcome classification (Wieser et al., 2001) were determined for participants who previously had surgical resection of the lesion. According to the ILAE classification scheme for FCD, Type I is characterized by abnormal radial cortical lamination (Type 1a), abnormal tangential cortical lamination (Type 1b), or both (Type 1c) (Blümcke et al., 2011). FCD Type II is characterized by dysplastic neurons with (Type IIb) or without (Type IIa) balloon cells (Blümcke et al., 2011). FCD type III is characterized by cortical lamination abnormalities in conjunction with hippocampal sclerosis (Type IIIa), a tumor (Type IIIb), a vascular malformation (Type IIIc), or an acquired lesion (Type IIId) (Blümcke et al., 2011). The ILAE surgical outcome classifications 1-6 are defined as 1) seizure free; no auras, 2) only auras; no other seizures, 3) one to three seizure days per year with or without auras, 4) four seizure days per year to 50% reduction of baseline seizure days with or without auras, 5) less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days with or without auras, and 6) more than 100% increase of baseline seizure days with or without auras (Wieser et al., 2001).

In addition, date of seizure onset, date of FCD identification by MRI, and length of clinical follow-up was abstracted from the medical record. Clinical follow-up length was defined as the time interval between the date of FCD identification on MRI and the date of last clinical visit. For participants whose parent or guardian completed the questionnaire, the date of questionnaire completion was used in place of the date of last clinical visit. Demographics of the participant and contact information for parent or guardian were also obtained.

For each participant, parents or guardians interested in participating in research were contacted by email, mail, and/or phone and asked to complete a short questionnaire. Current clinical characteristics, treatments, medical history and family history of the participant were gathered in order to supplement the data gathered from the review of the medical records and to determine the current epilepsy status of the participant. Factors were assessed as dichotomous variables based on parental report.
Statistical Analysis

Data were categorized into two groups based on the epilepsy phenotype of the participant. The classification scheme for epilepsy phenotype was as follows: a) epilepsy, drug-resistant—recurring unprovoked seizures despite at least two appropriately trialed antiepileptic drugs, b) epilepsy, drug-responsive—recurring unprovoked seizures, controlled for minimum of 12 months on antiepileptic drug(s), c) seizure but not epilepsy—single seizure or recurring provoked seizures, d) no history of seizures or epilepsy. These four groups were then combined so that Group 1—FCD with epilepsy represented a) and b) and Group 2—FCD without epilepsy represented c) and d).

The prevalence and 95% confidence interval of epilepsy and drug-resistant epilepsy was calculated for children with an MRI-identified FCD. Descriptive statistics were used to describe the groups. Fisher’s Exact Test was used to compare proportions of clinical characteristics (use of therapies, diagnosis of cerebral palsy, diagnosis of autism, headaches, and migraines), imaging characteristics (location of the lesion and FCD classification), and family history (first or second degree relative or cousin with seizures and/or epilepsy) between the groups. For continuous-type variables (e.g. age) the Wilcoxon rank sum test was used to compare groups. For each test the p-value was calculated. A p-value that was corrected for multiple testing based on the false discovery rate was also calculated for the clinical characteristics comparisons. Survival analysis was performed using the product limited estimator (Kaplan-Meier) to estimate the age of onset of epilepsy. Survival curves were compared using the log-rank test. Logistic regression was used to determine predictive factors of epilepsy and drug-resistant epilepsy. The discordance between the epilepsy status gathered by chart review and the parent or guardian questionnaire was measured.

The threshold of significance for this study was p=0.05. We powered for the difference between Groups 1 and 2 in their proportions of subjects with a family history of seizures. With 100 subjects, assuming that 70% are in Group 1 and 30% are in Group 2, there was 86% power to detect a difference in the proportions of those with a family history of seizures using a two-sided Fisher's exact test. This assumes that the proportions of those with a family history of seizures is 0.40 and 0.10 for Groups 1 and 2, respectively (nQuery Advisor (R) 7.0 software). All statistical analysis were performed using SAS ® version 9.3 (SAS Institute Inc., Cary, NC).
Results

Key word search of the radiology database identified 1,380 MRIs with the term “cortical dysplasia” in the report. Filtering by age of participant, date of MRI, and false positives of the keyword in the MRI reports, 328 potential participants were identified for this study. Fifty-three were excluded based on genetic diagnosis, lack of access to the medical record, status of deceased, or language spoken by parent or guardian. Imaging was reviewed for the 275 remaining individuals and identified 100 potential participants. Three individuals were excluded based on genetic diagnosis following a more detailed review of the medical record. The remaining 97 participants with MRI-identified FCD were included in the study.

Prevalence of Epilepsy and Drug-resistant Epilepsy

The prevalence of epilepsy in the study cohort was 69/97 or 71.13% (95% C.I. 61.05% to 79.89%) and the prevalence of drug-resistant epilepsy was 32/97 or 32.99% (95% C.I. 23.78% to 43.27%). There was no statistically significant difference in the age and race/ethnicity of participants with drug-resistant epilepsy, drug-responsive epilepsy, and no epilepsy (Table 1). The 32 participants who had drug-resistant epilepsy had an average age of 10 (SD=3.8), the 37 who had drug-responsive epilepsy had an average age of 11.9 (SD=3.2), and the 28 who had no diagnosis of epilepsy had an average age of 12 (SD=3.4). Two out of the 28 participants without epilepsy had a single or recurring provoked seizure(s). There were 60 males and 37 females, the majority of whom were of Caucasian decent (Table 1).

Participants who had drug-resistant epilepsy had a longer clinical follow-up time (4.5 vs. 3.1, p=0.038) and were younger when FCD was first identified on MRI (5.1 vs. 7.7, p=0.016) than those who did not have epilepsy (Table 1). The clinical follow-up time was longer for those who had epilepsy than those who did not have epilepsy, (4.1 vs. 3.1, p=0.044; Table 1). Four participants, 2 without epilepsy and 2 with epilepsy, had had no clinical follow-up after MRI-identification of FCD. Figure 1 shows the age of seizure onset for those with drug-resistant epilepsy, drug-responsive epilepsy, and no epilepsy.
MRI Indication and Features

FCD classification by imaging features on MRI was definite (n=27), probable (n=60), or possible (n=10). There were no statistically significant differences in FCD classification by MRI (“definite”, “probable” or “possible”) among those with drug-resistant epilepsy, drug-responsive epilepsy, and no epilepsy (Table 2). Additionally, there were no statistically significant differences in the seven features used to identify FCD by MRI across groups (Table 3). Treatment data for those with epilepsy are summarized in Table 4. For 22 of the 24 participants who had surgical resection, pathology information was available (Table 5). Across our patient population, FCD lesions were located in all lobes and both sides of the brain (Table 6). Seven participants, 4 with drug-resistant epilepsy and 3 with drug-responsive epilepsy, had lesions located in more than one lobe.

Epilepsy or seizures was the main MRI indication for those who had epilepsy, whereas participants without epilepsy received an MRI for a variety of indications including developmental or learning delays, headaches or migraines, a previously detected structural brain abnormality, head trauma, and psychosis (Figure 2). Miscellaneous MRI indications for those without epilepsy included precocious puberty, abdominal pain and swallowing difficulties, hypotropia, right hemiplegia, and truncal ataxia.

Predictors of Epilepsy and Drug-resistant Epilepsy

Several imaging and clinical features differed among those with drug-resistant epilepsy, drug-responsive epilepsy, and no epilepsy. Individuals with diagnoses of epilepsy were more likely to have lesions located in the temporal (26 vs. 4, p=0.0293) or frontal lobes (28 vs. 18, p=0.0441) than those did not have epilepsy (Table 6). Patients who used speech, occupational, or physical therapies were more likely to have drug-resistant epilepsy than drug-responsive epilepsy (26 vs. 13, p=0.006) or no diagnosis of epilepsy (26 vs. 10, p=0.0154; Table 7). Individuals with a family history of seizures were more likely to have epilepsy (26 vs. 2, p=0.0026); however, there was no statistical difference in family history of seizures between those who had drug-resistant epilepsy when compared to those with drug-responsive epilepsy (Table 7).

The strongest predictive factor for not having epilepsy was age of seizure onset (OR=1.48, p=<0.0001, 95% CI = 1.263 to 1.739; Table 8). The age of onset of seizures was later in those with drug-responsive epilepsy than those with drug-resistant epilepsy (p=0.0002; Figure 3). Predictive factors for having drug-responsive
epilepsy instead of drug-resistant epilepsy were age of seizure onset (OR=1.22, p=0.0441, 95% CI = 1.005 to 1.486) and no developmental delay (OR=3.624, p=0.0497, 95% CI = 1.002 to 13.110; Table 8).

**Questionnaire**

The parents or guardians of 33 participants indicated in the medical record that they were not willing to be contacted for research purposes. The parents or guardians of the remaining 64 participants received a questionnaire invitation and a reminder notification by email (n=33) or mail (n=31). A second questionnaire invitation was sent by email, mail, or phone. A total of 25 of the participant’s parents or guardians responded by email (n=7), mail (n=13), or phone (n=5), for a response rate of 39%.

Out of the 25 questionnaires returned, there was discordance of epilepsy status between the data from the participant’s medical record and the parentally reported information from the questionnaire for 2 participants. The discordance for one participant indicated clinical progression from a phenotype of no epilepsy to drug-resistant epilepsy between the date of the last clinic visit and the date that the questionnaire was completed, a time span of approximately 4 years and 4 months. This participant was classified as drug-resistant for all analysis. From parental report the other participant did not have epilepsy; however, the data in the medical record indicated a diagnosis of epilepsy, therefore data from the chart was used. Due to the low response rate, other data collected via the questionnaire was not used in the study.

**Discussion**

**Prevalence of Epilepsy and Drug-resistant Epilepsy**

This study is the first to report the prevalence of epilepsy in a patient population with FCD identified by MRI. Surprisingly, nearly 1/3 our participants did not have epilepsy. The prevalence of epilepsy and drug-resistant epilepsy in children with an MRI-identified FCD was 71% and 33%, respectively.

There are reasons to believe that this number may be an underestimate of the prevalence of individuals with FCD who do not have epilepsy. Due to the study design, the cohort was comprised of individuals for whom FCD was suspected. Those who had such subtle imaging features that FCD was not considered in a differential diagnosis or children who did not have seizures or other health concerns that would merit an MRI would not be included in this study. It is also true that, while MRI is by far the best noninvasive test for detection of FCD, its
sensitivity for type II FCD is between 56% and 88% based on series reporting both imaging detection and pathology (Krsek et al., 2008; Kim et al., 2009; Lerner et al., 2009; Mellerio et al., 2012; Leach et al., 2014b). Combined with our data demonstrating that all patients who had surgical resection did indeed have FCD, this suggests that sensitivity of MRI for FCD is likely lower than specificity.

When defining the study cohort, those with other types of malformations of cortical development or more extensive lesions were excluded even though the term “cortical dysplasia” commonly occurs in the MRI reports. In this way, the focus of the study was narrowed to children who had exclusively FCD identified on imaging. Because the participants were identified by a hospital radiology database, this is not a true population study. These results do not address the still unknown population prevalence of FCD, but rather the prevalence epilepsy and drug-resistance in those with FCD who are brought to clinical attention. Large population studies have not identified healthy individuals with MRI-identified FCD (Sisodiya et al., 2009), which means that both natural history studies of FCD and studies which focus on the clinical management of patients with asymptomatic or atypical FCD who are brought to clinical attention are important.

The retrospective study design in a pediatric population is a limitation of this study since some participants who do not currently have epilepsy could develop epilepsy or those with drug-responsive epilepsy could develop drug-resistant epilepsy in the future. The average age of the participants was 10-12 years old and the average length of clinical follow-up was 3-4.5 years, but 4 participants did not have any follow-up after identification of FCD by MRI. The low response rate of the supplemental questionnaire influenced the short clinical follow-up time period. However, while 1 out of 25 participants showed a progression from no diagnosis of epilepsy to drug-resistant epilepsy between the time of the last clinic note and response to the parent questionnaire, the vast majority (92%) reported an epilepsy status that was consistent with the information in their medical record. Additionally, our data shows that some individuals in the study cohort are in their late teens and have not developed epilepsy supporting the finding that there are a subset of children with MRI-identified FCD who do not have epilepsy. Future studies, such as a follow-up study of this cohort or a study of an adult population with MRI-identified FCD, are needed to support the prevalence of epilepsy and drug-resistant epilepsy in patients with FCD.
MRI Indication and Features

Advances in MR imaging have revolutionized detection of FCD (Widdess-Walsh et al., 2006; Colombo et al., 2009; Gaillard et al., 2009; Madan and Grant, 2009; Lee and Kim, 2013). In our study we aimed to determine MRI biomarkers that could predict epilepsy severity. We found that temporal lobe localization was a significant predictor of epilepsy. More detailed brain parcellation maps were not performed for this study, but could be useful for identifying particular anatomic structures more often involved in epilepsy and drug-resistant epilepsy related to FCD. Severity was not predicted by classification of FCD based on imaging features, such that those with “definite FCD” did not have drug-resistant epilepsy significantly more often than those with “possible FCD”. Additionally, there were participants who did not have epilepsy that had an imaging classification of “definite FCD”. The independence between epilepsy severity and FCD classification provides evidence for the validity of the imaging review process.

Although MRI is clinically used to identify FCD, pathology is the gold standard of FCD diagnosis. Pathology reports were available for the 22 participants who had surgical resection for epilepsy treatment and the majority were consistent with FCD. As expected, over half of these participants had FCD type II, which is the subtype of FCD that is most commonly identified via imaging (Leach et al., 2014b). A limitation of this study is that a diagnosis of FCD via pathology is missing from much of the study cohort, including all of the patients without epilepsy. A diagnosis of FCD by pathology was present for 22% of participants, all of whom had drug-resistant epilepsy which is an anticipated clinical outcome for patients with FCD.

Participants without epilepsy received an MRI for a variety of indications. The most common indication was developmental or learning delay, which affects approximately 3.3% of the population in the United States (Shevell et al., 2003). Other MRI indications included headaches or migraines, head trauma, psychosis, and various abnormalities found on neurologic exam. There is no evidence to support that these health concerns represent an expanding phenotype of FCD; however, more studies are required to explore these novel reasons to identify FCD by imaging.
Predictors of Epilepsy and Drug-resistant Epilepsy

The strongest predictor of having no epilepsy or drug-responsive epilepsy instead of drug-resistant epilepsy was age of seizure onset. Children who had drug-resistant epilepsy had earlier seizure onset than those who had drug-responsive epilepsy. For those with epilepsy, each one year increase in the age of seizure onset increased the odds of having drug-responsive epilepsy by 22%. For those with an MRI-identified FCD but no diagnosis of epilepsy, each one year seizure-free increase in age increased the odds of not developing epilepsy by 48%.

Location of the lesion and clinical features were also predictors of epilepsy. Those with temporal or frontal lobe lesions were more likely to have epilepsy; however, the lobe in which the lesion was located did not predict if a patient would develop drug-responsive epilepsy instead of drug-resistant epilepsy. Patients with developmental delay were more likely to have drug-resistant epilepsy than drug-responsive epilepsy or no epilepsy. Patients with epilepsy who did not have developmental delay were 3.6 time more likely to have drug-responsive epilepsy. Lastly, participants with epilepsy were more likely to have a family history of seizures than those who did not have epilepsy, but there was no difference in family history between those with drug-resistant epilepsy and drug-responsive epilepsy.

Data for this study was gathered using both a review of medical records and parental report. Inaccuracies intrinsic to both of these data collation methods contribute to information bias. For example, one of the findings of the study is that patients who had a family history of seizures were more likely to have epilepsy. It may be that parents of children who have seizures are more likely to report to a family history of seizures to a healthcare professional than those whose child has always been seizure-free.

Conclusions

Twenty-nine percent of children with an MRI-identified FCD did not have epilepsy. Identification of a portion of children with FCD without epilepsy is a novel finding that brings into question prognosis information and clinical management of children with incidental findings of “asymptomatic FCD”. The American Academy of Pediatrics recommends neurological evaluation for all children with unexplained intellectual disability or developmental delay (Moeschler and Shevell, 2006), which was the most common MRI indication for patients
without epilepsy in our study. The widespread and increasing use of MRI in the clinical evaluation of pediatric and even prenatal patients may increase the identification of “asymptomatic” or “pre-symptomatic” FCD.

This study showed that the age at which a child with “asymptomatic FCD” is brought to clinical attention and the lobar location (temporal v. other) can be used to predict likelihood of developing epilepsy. Likewise, the age of seizure onset can be used to predict the chance of developing drug-resistant epilepsy for children with drug-responsive epilepsy. Further predictive factors of epilepsy phenotype for children with MRI-identified FCD should be explored in future studies.

Tables and Figures

Table 1: Demographics

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (n=69)</th>
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<tr>
<td></td>
<td>Drug-resistant (n=32)</td>
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<tr>
<td></td>
<td>15</td>
<td>5.1 (3.6)‡</td>
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<td>2</td>
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<tr>
<td></td>
<td>32</td>
<td>6.9 (3.7)</td>
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<tr>
<td>Other</td>
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<td>1</td>
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<tr>
<td></td>
<td>2</td>
<td>4.1 (2.7)§</td>
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<tr>
<td>Age at time of chart review in years, Mean (SD)</td>
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<td>11.9 (3.2)</td>
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<td>Age of FCD diagnosis in years, Mean (SD)</td>
<td>6.1 (3.8)</td>
<td>7.7 (3.7)²</td>
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<tr>
<td>Length of clinical follow-up in years, Mean (SD)</td>
<td>4.5 (2.7)¹</td>
<td>3.9 (2.8)</td>
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<tr>
<td>p=0.038, Wilcoxon rank sum</td>
<td>p=0.016, Wilcoxon rank sum</td>
<td>p=0.044, Wilcoxon rank sum</td>
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</table>
Figure 1: Age of Seizure Onset

Table 2: FCD Classification

<table>
<thead>
<tr>
<th></th>
<th>Drug-resistant Epilepsy (n=32)</th>
<th>Drug-responsive Epilepsy (n=37)</th>
<th>No Epilepsy (n=28)</th>
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<tr>
<td>Possible</td>
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<td>4</td>
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</table>

Comparison among the three epilepsy phenotypes for FCD classification (p=0.8974, Fisher’s Exact Test)
### Table 3: MRI features of FCD

<table>
<thead>
<tr>
<th>Feature Description</th>
<th>Drug-resistant (n=32)</th>
<th>Drug-responsive (n=37)</th>
<th>No Epilepsy (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature 1: Localized increased cortical signal without other known cause</td>
<td>54</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Feature 2: Localized increase in cortical thickness</td>
<td>25</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Feature 3: Ill-defined or irregular cortical-white matter junction</td>
<td>64</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Feature 4: Localized subcortical signal located at the bottom of a sulcus</td>
<td>22</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Feature 5: Asymmetric gyral pattern and/or depth</td>
<td>20</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>Feature 6: Transmantle signal changes related to a gyrus</td>
<td>6</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Feature 7: Subcortical heterotopic gray matter</td>
<td>3</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 4: Epilepsy Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Drug-resistant (n=32)</th>
<th>Drug-responsive (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Anti-Epileptic Drugs, Mean (SD)</td>
<td>4.7 (1.9)</td>
<td>2.0 (1.1)</td>
</tr>
<tr>
<td>Ketogenic Diet</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surgery</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Surgical Resection</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Vagus Nerve Stimulator Placement</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Two patients had surgical resection and vagus nerve stimulator placement
<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Surgical Type</th>
<th>Pathology</th>
<th>ILAE Surgical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>012</td>
<td>Multi-lobar surgery</td>
<td>FCDIa</td>
<td>4</td>
</tr>
<tr>
<td>021</td>
<td>Corticectomy</td>
<td>FCDIib</td>
<td>1</td>
</tr>
<tr>
<td>029</td>
<td>Multi-lobar surgery</td>
<td>FCDIib</td>
<td>1</td>
</tr>
<tr>
<td>032</td>
<td>Corticectomy</td>
<td>FCDIla</td>
<td>4</td>
</tr>
<tr>
<td>033</td>
<td>Hemispherotomy</td>
<td>FCDIla, FCDIIIa</td>
<td>1</td>
</tr>
<tr>
<td>034</td>
<td>Anterior Temporal Lobectomy</td>
<td>FCDIIIa</td>
<td>1</td>
</tr>
<tr>
<td>037</td>
<td>Hemispherotomy</td>
<td>FCDIib</td>
<td>3</td>
</tr>
<tr>
<td>038</td>
<td>Multi-lobar surgery</td>
<td>FCDIa</td>
<td>5</td>
</tr>
<tr>
<td>040</td>
<td>Anterior Temporal Lobectomy</td>
<td>FCDIIIa</td>
<td>4</td>
</tr>
<tr>
<td>041</td>
<td>Hemispherotomy</td>
<td>FCDIla</td>
<td>1</td>
</tr>
<tr>
<td>042</td>
<td>Anterior Temporal Lobectomy</td>
<td>FCDIIIa</td>
<td>5</td>
</tr>
<tr>
<td>047</td>
<td>Hemispherotomy</td>
<td>FCDIla</td>
<td>3</td>
</tr>
<tr>
<td>048</td>
<td>Anterior Temporal Lobectomy, Corticectomy</td>
<td>FCDIib</td>
<td>1</td>
</tr>
<tr>
<td>052</td>
<td>Hemispherotomy</td>
<td>FCDIib</td>
<td>1</td>
</tr>
<tr>
<td>053</td>
<td>Hemispherotomy</td>
<td>FCDIa</td>
<td>1</td>
</tr>
<tr>
<td>055</td>
<td>Hemispherotomy</td>
<td>Other- neuronal loss</td>
<td>5</td>
</tr>
<tr>
<td>060</td>
<td>Hemispherotomy</td>
<td>FCDIib</td>
<td>1</td>
</tr>
<tr>
<td>069</td>
<td>Lesionectomy</td>
<td>FCDIla</td>
<td>1</td>
</tr>
<tr>
<td>090</td>
<td>Anterior Temporal Lobectomy</td>
<td>FCDIc</td>
<td>1</td>
</tr>
<tr>
<td>091</td>
<td>no data</td>
<td>FCDIla</td>
<td>5</td>
</tr>
<tr>
<td>092</td>
<td>Lesionectomy</td>
<td>FCDIib</td>
<td>4</td>
</tr>
<tr>
<td>097</td>
<td>Hemispherotomy</td>
<td>FCDIIIId</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 6: Location of Lesion by MRI

<table>
<thead>
<tr>
<th>Location</th>
<th>Epilepsy (n=69)</th>
<th>No Epilepsy (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug-resistant (n=32)</td>
<td>Drug-responsive (n=37)</td>
</tr>
<tr>
<td>Temporal</td>
<td>26$^1$</td>
<td>13$^2$</td>
</tr>
<tr>
<td></td>
<td>13$^2$</td>
<td>13</td>
</tr>
<tr>
<td>Parietal</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Occipital</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Frontal</td>
<td>28$^3$</td>
<td>10</td>
</tr>
<tr>
<td>Insula</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Left</td>
<td>38</td>
<td>11$^4$</td>
</tr>
<tr>
<td>Right</td>
<td>21$^4$</td>
<td>17</td>
</tr>
<tr>
<td>Both</td>
<td>10$^4$</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1$^4$</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Seven participants had more than 1 lesion (4 with drug-resistant and 3 with drug-responsive)

$^1$ p=0.0293, Fisher’s Exact Test
$^2$ p=0.0428, Fisher’s Exact Test
$^3$ p=0.0441, Fisher’s Exact Test
$^4$ p=0.0368, Fisher’s Exact Test

Figure 2: MRI Indication

MRI Indication

- Epilepsy or seizures
- Structural brain abnormality
- Headaches or migraines
- Developmental delay, autism, or learning disability
- Head trauma
- Psychosis
- Miscellaneous

Participants with Epilepsy (n=69)  Participants without Epilepsy (n=28)
### Table 7: Clinical Characteristics and Family History

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (n=69)</th>
<th>No Epilepsy (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug-resistant (n=32)</td>
<td>Drug-responsive (n=37)</td>
</tr>
<tr>
<td>Use of speech, occupational, or physical therapy</td>
<td>39</td>
<td>26(^1)(^2)</td>
</tr>
<tr>
<td>Diagnosis of Cerebral Palsy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diagnosis of Autism</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Headaches</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Migraines</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Head trauma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Family history of seizures</td>
<td>26(^1)(^2)</td>
<td>13(^3)(^4)(^5)(^6)</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Note: For clinical characteristics, a p-value adjusted for multiple testing was calculated.
\(^1\)p=0.0154, Fisher’s Exact Test
\(^2\)p=0.006, Fisher’s Exact Test
\(^3\)p=0.0026, Fisher’s Exact Test
\(^4\)p=0.0031, Fisher’s Exact Test
\(^5\)p=0.0086, Fisher’s Exact Test
\(^6\)p=0.0058, Fisher’s Exact Test

### Table 8: Predictive Factors of Epilepsy Phenotype

<table>
<thead>
<tr>
<th></th>
<th>No epilepsy instead of epilepsy</th>
<th>Drug-responsive instead of drug-resistant epilepsy</th>
</tr>
</thead>
</table>
| Age of seizure onset, OR (95% C.I.)| 1.48 (1.263 to 1.739)
\(^1\) | 1.22 (1.005 to 1.486)
\(^2\) |
| No developmental delay, OR (95% C.I.) | 3.624 (1.002 to 13.110)
\(^3\) |

\(^1\)p=<0.0001, Logistic regression
\(^2\)p=0.0441, Logistic regression
\(^3\)p=0.0497, Logistic regression
Those with drug-resistant epilepsy had an earlier age of seizure onset than those with drug-responsive epilepsy (p=0.0002, Log-rank test).
References


# Appendices

## Appendix 1: Focal Cortical Dysplasia Imaging Review Form

<table>
<thead>
<tr>
<th>Assigned Identifier:</th>
<th>MRI Indication(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI Date(s):</td>
<td>See Excel spreadsheet</td>
</tr>
<tr>
<td>MRI Impressions:</td>
<td></td>
</tr>
</tbody>
</table>

### Patient Excluded
- [ ] Yes
- [ ] No

### Reason for Exclusion:
- Other Notes:

### Exclusion Criteria
- Larger gyral malformations involving greater than one brain quadrant
  - [ ] Yes
  - [ ] No
  - [ ] Data Missing
- Gyral malformations typical of lissencephaly, bilateral extensive polymicrogyria or hemimegalencephaly
  - [ ] Yes
  - [ ] No
  - [ ] Data Missing
- Lesions that could potentially represent tumor (mass effect, growth over time, associated enhancement)
  - [ ] Yes
  - [ ] No
  - [ ] Data Missing
- Lesions that are typical for remote insult (infarct, traumatic, encephalitis) including features of cortical thinning and marked localized volume loss
  - [ ] Yes
  - [ ] No
  - [ ] Data Missing

### Features

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localized increased cortical signal without other known cause</td>
</tr>
<tr>
<td>2</td>
<td>Localized increase in cortical thickness</td>
</tr>
<tr>
<td>3</td>
<td>Ill-defined or irregular cortical-white matter junction</td>
</tr>
<tr>
<td>4</td>
<td>Localized subcortical signal located at the bottom of a sulcus</td>
</tr>
<tr>
<td>5</td>
<td>Asymmetric gyral pattern and/or depth</td>
</tr>
<tr>
<td>6</td>
<td>Transmantle signal changes related to a gyrus</td>
</tr>
<tr>
<td>7</td>
<td>Subcortical heterotopic gray matter</td>
</tr>
</tbody>
</table>

### Overall Focal Cortical Dysplasia Classification

- **Definite** = Feature 6 with any other two features
- **Probable** = Feature 6 with Feature 2, 3, 5, or 7
- **Possible** = Any two features without Feature 6

- [ ] Definite FCD
- [ ] Probable FCD
- [ ] Possible FCD
- [ ] Not FCD
- [ ] Cannot be determined

### Location

- Location of the lesion (lobe): 
  - [ ] Temporal
  - [ ] Parietal
  - [ ] Occipital
  - [ ] Frontal
  - [ ] Data Missing

- Location of lesion (side):
  - [ ] Left
  - [ ] Right
  - [ ] Both
  - [ ] Data Missing
### Appendix 2: Data Abstraction Form

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<thead>
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<th>Record ID</th>
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<tbody>
<tr>
<td>Assigned Identifier</td>
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<tr>
<td>Known Genetic Diagnosis</td>
<td>○ Yes</td>
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<tr>
<td></td>
<td>○ No</td>
</tr>
<tr>
<td></td>
<td>○ Maybe</td>
</tr>
<tr>
<td></td>
<td>○ Data Missing</td>
</tr>
<tr>
<td></td>
<td>(If Yes, remove from study)</td>
</tr>
<tr>
<td>Specify Maybe</td>
<td></td>
</tr>
<tr>
<td>English speaking</td>
<td>○ Yes</td>
</tr>
<tr>
<td></td>
<td>○ No</td>
</tr>
<tr>
<td></td>
<td>○ Data Missing</td>
</tr>
<tr>
<td></td>
<td>(If No, remove from study)</td>
</tr>
<tr>
<td>MRI Indication(s)</td>
<td></td>
</tr>
<tr>
<td>MRI date(s)</td>
<td></td>
</tr>
<tr>
<td>Date of first MRI</td>
<td>(Month, Day, Year)</td>
</tr>
</tbody>
</table>
| Larger gyral malformations involving greater than one brain quadrant | ○ Yes |}
| Gyral malformations typical of lissencephaly, bilateral extensive polymicrogyria or hemimegalencephaly | ○ Yes |}
| Lesions that could potentially represent tumor (mass effect, growth over time, associated enhancement) | ○ Yes |}
| Lesions that are typical for remote insult (infarct, traumatic, encephalitis) including features of cortical thinning and marked localized volume loss | ○ Yes |}
| Participant Excluded             | ○ Yes                                |
|                                  | ○ No                                 |
| Reason for Exclusion             |                                      |
| Feature 1: Localized increased cortical signal without other known cause | ○ Yes |}
| Feature 2: Localized increase in cortical thickness | ○ Yes |}
| Feature 3: Ill-defined or irregular cortical-white matter junction | ○ Yes  
|                                                                | ○ No  
|                                                                | ○ Data Missing  |
| Feature 4: Localized subcortical signal located at the bottom of a sulcus | ○ Yes  
|                                                                | ○ No  
|                                                                | ○ Data Missing  |
| Feature 5: Asymmetric gyral pattern and/or depth | ○ Yes  
|                                                                | ○ No  
|                                                                | ○ Data Missing  |
| Feature 6: Transmantle signal changes related to a gyrus | ○ Yes  
|                                                                | ○ No  
|                                                                | ○ Data Missing  |
| Feature 7: Subcortical heterotopic gray matter | ○ Yes  
|                                                                | ○ No  
|                                                                | ○ Data Missing  |
| Imaging Classification for FCD | ○ Definite FCD  
|                                                                | ○ Probable FCD  
|                                                                | ○ Possible FCD  
|                                                                | ○ Not FCD  
|                                                                | ○ Cannot be determined  
(Definite=Feature 6 with any other two features;  
Probable=Feature 6 with Features 2, 3, 5, or 7 OR any three features without Feature 6; Possible=any two features without Feature 6. If Not FCD, remove from study)  
| Location of the lesion (lobe) |  
|                            | □ Temporal  
|                            | □ Parietal  
|                            | □ Occipital  
|                            | □ Frontal  
|                            | □ Insula  
|                            | □ Data Missing  |
| Location of the lesion (side) |  
|                            | ○ Left  
|                            | ○ Right  
|                            | ○ Both  
|                            | ○ Data Missing  |
| Date of Data Collection |  
|                            | ((Month, Day, Year))  
| Child's name |  
|                            | ((Last, First Middle))  
| Patient MRN |  
|                            |  
| Date of Birth |  
|                            | (Month, Day, Year)  
| Gender |  
|                            | ○ male  
|                            | ○ female  |
Race/Ethnicity

Specify Other

Parents Willing to be Contacted?

Parent/Guardian Email Address

Parent/Guardian Mailing Address

Parent/Guardian Telephone Number

Have had a Seizure

Date of first seizure

Date of first seizure (estimated)

Diagnosis of Epilepsy

Date of epilepsy diagnosis

Date of epilepsy diagnosis (estimated)

Currently drug-resistant

Previously drug-resistant

Date of drug resistance

Date of drug resistance (estimated)

Number of anti-epileptic drugs tried over the course of the illness

Surgical Treatment
<table>
<thead>
<tr>
<th>Condition</th>
<th>Options</th>
</tr>
</thead>
</table>
| Type of Surgery                               | ☐ Resection  
☐ VNS placement  
☐ Other  
☐ Data Missing |
| Surgical Outcome                              | ☐ Outcome Classification 1  
☐ Outcome Classification 2  
☐ Outcome Classification 3  
☐ Outcome Classification 4  
☐ Outcome Classification 5  
☐ Outcome Classification 6  
☐ Data Missing |
| Ketogenic diet or other modified diet as a treatment for epilepsy | ☐ Yes  
☐ No  
☐ Data Missing |
| Use of Speech Therapy, Occupational Therapy, or Physical Therapy | ☐ Yes  
☐ No  
☐ Data Missing |
| Diagnosis of Cerebral Palsy                   | ☐ Yes  
☐ No  
☐ Data Missing |
| When diagnosis of Cerebral Palsy was reported | ☐ Pre-Seizure Onset  
☐ Post-Seizure Onset  
☐ Data Missing |
| Diagnosis of Autism Spectrum Disorder         | ☐ Yes  
☐ No  
☐ Data Missing |
| When diagnosis of Autism Spectrum Disorder was reported | ☐ Pre-Seizure Onset  
☐ Post-Seizure Onset  
☐ Data Missing |
| Headaches                                     | ☐ Yes  
☐ No  
☐ Data Missing |
| When headaches were first reported            | ☐ Pre-Seizure Onset  
☐ Post-Seizure Onset  
☐ Data Missing |
| Migraines                                     | ☐ Yes  
☐ No  
☐ Data Missing |
| When migraines were first reported            | ☐ Pre-Seizure Onset  
☐ Post-Seizure Onset  
☐ Data Missing |
| Head Trauma                                   | ☐ Yes  
☐ No  
☐ Data Missing |
| When Head Trauma was reported                 | ☐ Pre-Seizure Onset  
☐ Post-Seizure Onset  
☐ Data Missing |
| Encephalitis                                  | ☐ Yes  
☐ No  
☐ Data Missing |
<table>
<thead>
<tr>
<th>Category</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>When Encephalitis was reported</td>
<td>Pre-Seizure Onset, Post-Seizure Onset, Data Missing</td>
</tr>
<tr>
<td>Family members with seizures</td>
<td>Mother, Father, Brother, Sister, Child, Grandparent, Uncle, Aunt, Cousin, None, Data Missing</td>
</tr>
<tr>
<td>Family members with epilepsy</td>
<td>Mother, Father, Brother, Sister, Child, Grandparent, Uncle, Aunt, Cousin, None, Data Missing</td>
</tr>
<tr>
<td>Family members with abnormal brain MRI</td>
<td>Mother, Father, Brother, Sister, Child, Grandparent, Uncle, Aunt, Cousin, None, Data Missing</td>
</tr>
<tr>
<td>Family members with FCD</td>
<td>Mother, Father, Brother, Sister, Child, Grandparent, Uncle, Aunt, Cousin, None, Data Missing</td>
</tr>
<tr>
<td>Date of last follow up</td>
<td>Date of last follow up_q</td>
</tr>
<tr>
<td>Type of follow up</td>
<td>neuroscience provider, other provider, none, data missing</td>
</tr>
</tbody>
</table>
Appendix 3: Questionnaire

Brain MRI Follow Up Questionnaire

Purpose: These questions are a part of a study to follow up on individuals who have had a brain MRI (Magnetic Resonance Imaging) at Cincinnati Children's Hospital Medical Center (CCHMC).

Why you have been asked to participate: You are invited to participate in this study because you are the parent or guardian of a child who has had a brain MRI at CCHMC.

Description of the study: This is a survey that will take about 10 minutes to complete. The questions focus on the medical and family history of your child who has a MRI at CCHMC. The data from these questions will be used along with a review of your child's medical records. Participation in this study is optional and you may choose to contact us at any time to remove your child from this study. Participation in this study will not cost you anything.

Instructions: You can fill out this survey in several different ways.
   1. Email Lauren Maynard to receive access to an electronic copy of the survey
   2. Complete the paper copy of the survey below and mail survey using the envelop provided
   3. Contact Lauren Maynard to complete the survey by phone

Who to contact: If you have any questions, concerns, or would like us to remove your child from the study, please contact:

   Lauren Maynard
   Lauren.Maynard@cchmc.org
   (513) 636-1864
Possible Benefits:

- There are no direct benefits to you or to your child for participating in this study.
- By sharing the answers to the questions below, you will be adding to our knowledge of the brain.

Possible Risks:

- The only potential risk is that personal information about your child could be accidently disclosed.
- To prevent this only members of the research team will have access to data that contains personal identifiers:
  - Electronic records will be password protected and paper copies will be stored in a locked cabinet.
  - The name and other identifiers of your child will be removed when the data is analyzed and published.

Consent: It is your choice whether you participate in this study or not. Participation is completely voluntary. Your child’s care at CCHMC will not be affected by your choice to participate in this project.

If you complete this survey, the answers you provide will be used in the research project. You make choose to withdraw your answers or stop your participation in the study at any time by contacting Lauren Maynard.

Thank you for your time and for considering helping us with this study.
Here are some terms which you will see in the questions below.

- Epilepsy is a disease that is marked by seizures.
- A seizure is a sudden attack which is marked by abnormal motion or actions. A person can have a seizure without having epilepsy.

1. Name of your child (first, last)___________________

2. Child's date of birth (month, day, year)____________________

Family History Questions

For the purposes of this survey, the term “relatives” refers to biological or blood relatives

3. Have any of your child’s relatives listed below been told by a doctor that they had seizures or epilepsy? Please check all that apply.

- [ ] Mother
- [ ] Father
- [ ] Brother
- [ ] Sister
- [ ] Child
- [ ] Grandparent
- [ ] Uncle
- [ ] Aunt
- [ ] Cousin
- [ ] None
- [ ] Not sure

4. Have any of your child’s relatives listed below been told by a doctor that they had MRI with unusual findings? Please check all that apply.

- [ ] Mother
- [ ] Father
- [ ] Brother
- [ ] Sister
- [ ] Child
- [ ] Grandparent
- [ ] Uncle
- [ ] Aunt
- [ ] Cousin
- [ ] None
- [ ] Not sure

29
5. A focal cortical dysplasia is a possible unusual finding on MRI. Have any of your child’s relatives listed below been told by a doctor that they had a focal cortical dysplasia? Please check all that apply.

- Mother
- Father
- Brother
- Sister
- Child
- Grandparent
- Uncle
- Cousin
- Aunt
- None
- Not sure

Medical History Questions

6. Has your child been diagnosed with epilepsy?

- Yes
- No
- Not sure

If "Yes", please take Survey A starting on page 5
If "No", please proceed to the next question, question 7
If "Not Sure", please proceed to the next question, question 7

Please only continue to question 7 if you have answered “No” or “Not sure” on question 6. If you have answered “Yes” on question 6 please move to Survey A starting on page 5.

7. Have you been told by a doctor that your child has had a seizure?

- Yes
- No
- Not sure

If "Yes", please take Survey A starting on page 5
If "No", please take Survey B starting on page 8
If "Not sure", please take Survey B starting on page 8
SURVEY A

Please complete these questions if your child who has had a brain MRI at CCHMC:

- Has been diagnosed with epilepsy
  OR
- Has had a seizure

Note: If your child has NOT been diagnosed with epilepsy AND has NOT had a seizure, please complete SURVEY B starting on page 8.

8. Is your child currently using a medicine prescribed by a doctor to control seizures?
   □ Yes
   □ No
   □ Not sure

9. Over the course of your child's lifetime, has he or she taken medicine prescribed by a doctor to control seizures?
   □ Yes
   □ No
   □ Not sure

10. Over the course of your child's lifetime, how many different medicines prescribed by a doctor to control seizures has your child tried?
    □ 1
    □ 2
    □ 3
    □ More than 3
11. Between the time of your child's birth and his or her first seizure, did your child have any head trauma for which he or she needed to see a doctor?

☐ Yes
☐ No
☐ Not sure

12. Between the time of your child's birth and his or her first seizure, did your child have a brain infection?

☐ Yes
☐ No
☐ Not sure

13. Does your child have developmental delay?

☐ Yes
☐ No
☐ Not sure

14. When did you notice your child's developmental delay?

☐ Before his or her first seizure
☐ After his or her first seizure
☐ Not sure
☐ Question does not apply
Thank you for completing the questionnaire!

Please mail the completed questionnaire to Cincinnati Children’s Hospital Medical Center using the envelope provided.

Thank you for your time and willingness to participate in this survey. We appreciate your help with this project. Please do not hesitate to contact us with any questions, concerns, or if you would like us to remove your child from the study.

Lauren Maynard
Lauren.Maynard@cchmc.org
(513) 636-1864
SURVEY B

Please complete these questions if your child who has had a brain MRI at CCHMC:

- Has NOT been diagnosed with epilepsy
  AND
- Has NOT had a seizure

Note: If your child has been diagnosed with epilepsy OR has had a seizure, please complete SURVEY A starting on page 5.

8. Has your child ever had any head trauma for which he or she needed to see a doctor?
   - Yes
   - No
   - Not sure

9. Has your child ever had a brain infection?
   - Yes
   - No
   - Not sure

10. Does your child have developmental delay?
    - Yes
    - No
    - Not sure
11. How old was your child when you noticed your child's developmental delay?

- 0-1 years
- 1-2 years
- 2-3 years
- 3-4 years
- 4-5 years
- 5+ years
- Not Sure
- Question does not apply
Thank you for completing the questionnaire!

Please mail the completed questionnaire to Cincinnati Children’s Hospital Medical Center using the envelope provided.

Thank you for your time and willingness to participate in this survey. We appreciate your help with this project. Please do not hesitate to contact us with any questions, concerns, or if you would like us to remove your child from the study.

Lauren Maynard
Lauren.Maynard@cchmc.org
(513) 636-1864
Appendix 4: Phone Script for Questionnaire

“Hi, may I speak to Mrs. or Mr. {Parent or guardian name}. My name is Lauren Maynard. I am a student at Cincinnati Children’s Hospital. I am part of a team of hospital staff who are doing a research study to follow up on children who have had a brain MRI. According to our records your child is eligible to participate. You may have received an email or letter about this study. Would you like to hear more about the study?”

IF NO:

“OK. Thank you for your time. You will not be contacted again. I apologize for the inconvenience. Thank you again. Goodbye.”

IF YES:

“Participation involves a survey that will take less than 10 minutes to complete. The questions focus on the medical and family history of your child who has a MRI at CCHMC. The name and identifiers of you and your child will be kept confidential. It is your choice to take this survey or not. Your care at CCHMC will not be affected by your choice to participate in this project. There is no payment for your participation. By sharing, you will be adding to our knowledge of the brain. The data gathered in the survey will be used with a review of your child’s medical records. Participation is optional and you may request to remove your child from the study. Do you have any questions?”

“Would you like to take the survey today?”

IF NO:

“OK. Thank you for your time. You will not be contacted again. Thank you again. Goodbye.”

IF YES:

“Thank you. I am going to start by giving you the definition to some terms that will be used in the survey. Epilepsy is a disease that is marked by seizures. A seizure is a sudden attack which is marked by abnormal motion or actions. A person can have a seizure without having epilepsy.

Read and fill out questionnaire
“Thank you for completing the survey. We appreciate your help with this project. Do you have any questions at this time?”

“Let me give you my contact information just in case you have any questions, concerns, or would like us to remove your child from the study at any time. Are you ready?”

“My name is Lauren Maynard. My email address is Lauren.Maynard@cchmc.org and my phone number is (513) 636-1864. Thank you again for your time. Goodbye.”