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FULL-LENGTH ORIGINAL RESEARCH

Polymicrogyria-associated epilepsy: A multicenter phenotypic study from the Epilepsy Phenome/Genome Project

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Summary

Purpose: **Polymicrogyria (PMG) is an epileptogenic malformation of cortical development. We describe the clinical epilepsy and imaging features of a large cohort with PMG-related epilepsy.**

Methods: **Participants were recruited through the Epilepsy Phenome/Genome Project, a multicenter collaborative effort to collect detailed phenotypic data on individuals with epilepsy. We reviewed phenotypic data from participants with epilepsy and PMG.**

Key Findings: **We identified 87 participants, 43 female and 44 male, with PMG and epilepsy. Median age of seizure onset was 3 years (range <1 month to 37 years). Most presented with focal epilepsy (87.4%), some in combination with seizures generalized from onset (23.0%). Focal seizures with dyscognitive features were most common (54.3%). Of those presenting with generalized seizure types, infantile spasms were most prevalent (45.2%). The most common topographic pattern was perisylvian PMG (77.0%), of which the majority was bilateral (56.7%). Generalized PMG presented with an earlier age of seizure onset (median age of 8 months) and an increased prevalence of developmental delay prior to seizure onset (57.1%). Of the unilateral, and asymmetric bilateral groups where PMG was more involved in one hemisphere, the majority (71.4%) of participants had seizures that lateralized to the same hemisphere as the PMG or the hemisphere with greater involvement.**

Significance: **Participants with PMG had both focal and generalized onset of seizures. Our data confirm the involvement of known topographic patterns of PMG and suggest that more extensive distributions of PMG present with an earlier age of seizure onset and increased prevalence of developmental delay prior to seizure onset.**

KEY WORDS: **Epilepsy, Polymicrogyria, Perisylvian, Epilepsy Phenome/Genome Project.**

Malformations of cortical development are increasingly recognized as the basis for epilepsy, intellectual disability, autism, and a spectrum of neurologic deficits (Guerrini et al., 1999; Wegiel et al., 2012). Polymicrogyria (PMG) refers to the excessive gyration or microfolding of the cerebral cortex and is a common clinically encountered cortical malformation, especially in patients with epilepsy (Leventer et al., 1999). PMG may be bilateral or unilateral and may occur in a variety of topographic regions, the most common of which is the perisylvian region (Hayashi et al., 2002; Leventer et al., 2010). Other topographic patterns have previously been described (Guerrini et al., 2000; Hayashi et al., 2002; Chang et al., 2003, 2004; Leventer et al., 2010). The etiology of PMG is likely heterogeneous because multiple environmental and genetic factors may play critical roles.

In a large past series, epilepsy was present in roughly 78% of cases of PMG, suggesting that PMG is a highly epileptogenic lesion (Leventer et al., 2010). However, detailed clinical characteristics of epilepsy related to PMG have not previously been reported in large numbers of patients. Furthermore, few descriptions of epilepsy lateralization and localization in regard to PMG distribution have been published. In this study, we report the clinical features of a cohort of 87 individuals with epilepsy in the setting of PMG. We evaluated whether the suspected region of seizure onset, based on ictal semiology and electroencephalography (EEG) data, corresponds to the location of PMG seen on magnetic resonance imaging (MRI). Finally, we report outcomes in the small subset of participants who underwent epilepsy surgery.

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[1]See Appendix.

Methods

Ascertainment

Participants were recruited through the Epilepsy Phenome/Genome Project (EPGP), a multicenter collaborative effort to collect detailed phenotypic data and DNA on a large number of individuals with epilepsy, including a cohort with symptomatic epilepsy related to PMG, with the ultimate goal of establishing genotype–phenotype correlations in epilepsy (The EPGP Collaborative, 2013). We retrospectively reviewed phenotypic data, including EEG and MRI data, from participants with epilepsy and PMG from 26 centers in the United States, Argentina, Australia, and New Zealand. Each site's local institutional review board approved the study, and site-specific screening procedures identified prospective participants. Participants with PMG and epilepsy were among those recruited from the clinical centers participating in EPGP.

Inclusion and exclusion criteria

Participants were enrolled in the EPGP study if they met general inclusion and exclusion criteria. All participants had epilepsy (two or more unprovoked seizures, or one unprovoked seizure with epileptiform EEG confirming epilepsy diagnosis); were at least 4 weeks of age at time of enrollment; and had high quality clinical, imaging, and laboratory data. Specific criteria for PMG participants included having an MRI showing PMG of any type reviewed by the EPGP MRI Core, as well as the absence of a confirmed genetic syndrome or metabolic disease. Participants with mild developmental delay prior to seizure onset, defined as any delay 50% or less of expected milestones in one area (motor, social, language, cognition, or activities of daily living), or 30% or less of milestones across more than one area, were included in the study. Participants with more severe developmental delay prior to seizure onset were excluded from the EPGP study. Individuals with PMG reported to have been caused by cytomegalovirus or other acquired etiologies were also excluded. According to the developmental and genetic classification for malformations of cortical development (Barkovich et al., 2012), this cohort of sporadic PMG thus comprises a subset of group IIIB, which includes cases of presumed genetic or disruptive PMG without clefts or calcifications. Of the 100 PMG participants enrolled within the EPGP cohort, 13 were excluded from our analysis due to insufficient records or poor quality MRI.

Clinical data

Participants underwent structured interviews to collect demographic information, as well as characteristics of their seizure history and additional medical conditions. In addition, data were abstracted from participants' medical records to support the epilepsy diagnosis and provide additional phenotypic information, including details about seizure semiology and laterality, clinical diagnostic evaluation, and presurgical evaluation, when applicable. Information on the number of antiepileptic drug (AED) trials was obtained from the participants' medical records. At each EPGP Clinical Center, the site principal investigator reviewed all collected clinical data (participant interviews, medical record abstraction, and EEG data) to classify participants' epilepsy according to seizure type, seizure semiology, and epilepsy syndrome derived from the 2010 International League Against Epilepsy (ILAE) classification criteria (Berg et al., 2010). For this report, sites were specifically queried for additional data regarding surgery evaluation. Presurgical evaluation data were available for 61 participants.

MRI review

After the initial standard EPGP MRI Core review, participant MRI studies were reviewed by three MRI Core reviewers (ZF, RK, and Ruben Kuzniecky) independently and later as a group to arrive at a consensus for eligibility, localization of PMG, and additional findings. Topographic extent of the PMG, and symmetry and laterality when applicable, were assessed for each participant, as well as details about white matter, basal ganglia, posterior fossa, and other abnormalities that might be relevant to future genotype–phenotype correlation. Any incidental findings were also documented.

Data analysis

Descriptive statistics were calculated for demographic and clinical data. Data are presented as frequencies and percentages for categorical data, and as means and medians for continuous variables including age at enrollment and age at seizure onset. We compared the location of PMG on MRI to the lateralization of epilepsy based on a synopsis of clinical and EEG data. The relationship between age of seizure onset and extent of PMG found on MRI was examined using a Wilcoxon two-sample test. Epilepsy classification, seizure semiology, and presence of developmental delay were also compared by extent of PMG found on MRI using frequency distributions and chi-square test of independence. For the nine participants who underwent epilepsy surgery, the Engel scoring system was used to characterize surgical outcome (Engel et al., 1993).

Results

Descriptive results

One hundred participants constituted the EPGP PMG cohort. We describe 87 cases for which good quality MRI data were available. Representative cases are shown in Figure 1. Forty-three participants (49.4%) were female and 44 were male. The median age at enrollment was 10 years, with age ranging from <1 year to 55 years. The majority of patients were of non-Hispanic ethnicity (81.6%) and Caucasian (73.6%). Head circumference data were available for

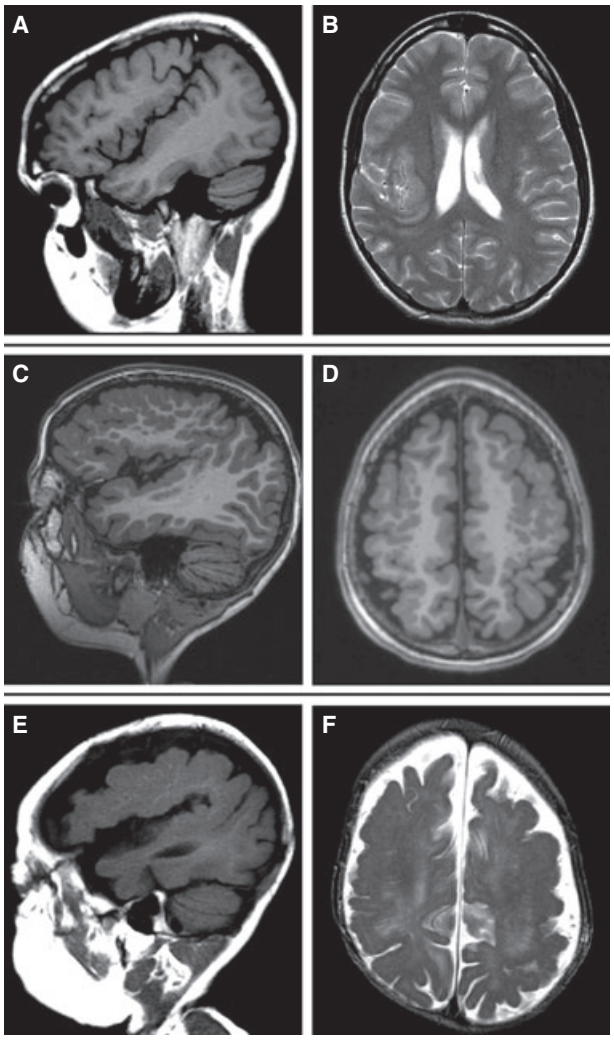

Figure 1.
Polymicrogyria—focal, bilateral, and generalized. We present representative images from the MRIs of three cases with PMG. First, sagittal T_1-weighted (**A**) and axial T_2-weighted (**B**) images from an 18-year-old woman with unilateral right-sided PMG involving the perisylvian region are shown. Epilepsy began at 18 years with focal seizures with dyscognitive features. There had been no history of developmental delay prior to seizure onset. Sagittal T_1-weighted (**C**) and axial T_1-weighted (**D**) images from a 5-year-old boy with bilateral perisylvian PMG. Extensive involvement of the frontal lobes can be seen in the axial image (**D**), and bilateral enlargement of ventricles is also present. Seizures presented at 1 year of age with focal seizures with dyscognitive features and secondary generalization. The participant had developmental delay prior to seizure onset. Finally, sagittal T_1-weighted (**E**) and axial T_2-weighted (**F**) images from an 18-month-old male illustrate generalized PMG. Ventricular enlargement and hypoplastic brainstem are also noted. Focal seizures with secondary generalization seizures presented at 1 month of age in the setting of severe chronic static encephalopathy.

56 participants, among whom the majority were normocephalic (40 of 56, 71.4%); the remaining participants were divided equally among microcephalic and macrocephalic (n = 8 for each). Developmental delay prior to the onset of seizures was present in 32 participants (36.8%). Further details regarding descriptive data are presented in Table 1.

The median age of seizure onset was 3 years, ranging from <1 month to 37 years. Focal seizure semiology, either exclusive or in conjunction with seizures generalized from onset, was the most common form of presentation (64.4%). Focal seizures with dyscognitive features, defined as a focal seizure with impairment of consciousness or awareness, were most common and documented in half of the entire cohort. Of the participants presenting with generalized seizure types, infantile spasms was the most prevalent (45.2%). Six participants had epilepsy that could not be definitively classified as focal or generalized. A history of febrile seizures was present in 11.5% of participants. Further details regarding epilepsy localization and seizure semiology are presented in Table 1. The proportion of participants with developmental delay did not differ significantly by gender (34.1% in female and 39.5% in male participants). In addition, we did not find any significant differences between female and male participants for age of seizure onset or the extent of PMG on MRI.

Imaging results

MRI findings in this cohort are presented in Table 2. Many participants presented with bilateral PMG (49.4%) and had a perisylvian topographic pattern (77.0%).

Unilateral PMG

Thirty-seven participants had unilateral PMG lesions. We divided these into cases with only a single lobe involved versus multilobar involvement. There were 11 participants with focal PMG involving a single lobe. All but one of these participants presented with focal epilepsy (n = 10, 90.9%); this individual had a combined focal and generalized epilepsy presentation. One participant had unclassified epilepsy localization. The median age of seizure onset in this series was 11 years (range 1 month to 28 years). Of the six participants with lesions in the left hemisphere, four had concordant epilepsy lateralization. Of the five lesions on the right, three had concordant lateralization. Lesions were localized to the perisylvian region in five, dorsolateral parietal lobe in two, dorsolateral frontal lobe in one, frontoparietal lobe in one, mesial temporal lobe in one, and lateral temporal lobe in one. Focal seizures with dyscognitive features predominated (n = 7, 63.6%). Fewer participants had nonconvulsive focal seizures with unknown evolution (n = 4, 36.4%) or focal seizures without dyscognitive features (n = 3, 27.3.%). Developmental delay prior to seizure onset was noted in two participants (18.2%).

Table 1. Clinical and demographic history of the EPGP PMG cohort

Number of participants	87	
Number female	43	
Number male	44	
Median age at enrollment	10 years (1–55)	
Head circumference data (n = 56) (%)		
Microcephalic[a]	8 (14.3)	
Normocephalic	40 (71.4)	
Macrocephalic[a]	8 (14.3)	
Developmental delay prior to seizure onset (%)		
Present	32 (36.8)	
Absent	46 (52.9)	
Unknown	9 (10.3)	
Epilepsy-related data		
Median age of seizure onset (range)	3 years (<1 month–37 years)	
Mean age of seizure onset	6 years	
Number of participants with febrile seizures (%)	10 (11.5)	
Broad epilepsy classification	**Participants**	**Percent**
Focal	56	64.4
Generalized	6	6.9
Both focal and generalized	20	23.0
Unclassified	5	5.7
Epilepsy laterality	**Participants**	**Percent (out of n = 76)**
Left	20	26.3
Right	28	36.8
Bilateral	11	14.5
Multifocal	7	9.2
Focal, unknown laterality	10	13.2
Seizure type, generalized[b]	**Participants**	**Percent (out of n = 31)[c]**
Generalized tonic–clonic	6	19.4
Generalized tonic	7	22.6
Generalized convulsive[d]	6	19.4
Absence	2	6.5
Atypical absence	3	9.7
Myoclonic	13	41.9
Infantile spasm	14	45.2
Atonic	2	6.5
Generalized nonconvulsive, unclassifiable	3	9.7
Seizure type, focal[b]	**Participants**	**Percent (out of n = 81)[c]**
Focal evolving to secondary GTC	9	11.1
Focal seizures with dyscognitive features, evolving to secondary GTC	16	19.8
Focal evolving to focal with dyscognitive features evolving to secondary GTC	3	3.7
Secondary GTC, evolution unclassifiable	25	30.9
Focal with dyscognitive features, no evolution	44	54.3
Focal, no evolution	20	24.7
Partial, nonconvulsive, unknown whether focal or focal with dyscognitive features	18	22.2
GTC, unclear whether generalized from onset or secondarily generalized	2	6.5
Nonconvulsive seizure, unclear whether partial or generalized from onset	2	2.5
Antiepileptic medications		
Median number of AED trials, n = 83 (range)	3 (0–14)	

[a]2 or more standard deviations from the norm.
[b]Some participants may have multiple seizure semiologies. Participants with "unclassified" seizure onsets may have contributed to both focal and generalized semiologies.
[c]Generalized seizure group does not include participants with focal epilepsy only. Focal group does not include participants with generalized epilepsy only.
[d]Generalized convulsive indicates a tonic and/or clonic semiology which cannot be further classified.

Table 2. Topographic description of polymicrogyria in EPGP cohort

Topographic description of polymicrogyria	frequencies (%)
Perisylvian	67 (77.0)
Bilateral	38 (56.7)
Symmetric	20 (52.6)
Asymmetric	18 (47.4)
Unilateral	29 (43.3)
Generalized	7 (8.05)
Frontal	4 (4.6)
Frontal only	3 (75.0)
Frontoparietal	1 (25.0)
Parasagittal parietooccipital, bilateral	2 (2.3)
Other	7 (8.05)
Total	87

Of the 37 unilateral cases, 26 had multilobar PMG lesions. Twenty-five (96.2%) had focal epilepsy, of whom four also had seizures generalized from onset. One participant had unclassified seizures. The median age of onset was 3 years (range <1 month to 21 years). Nineteen participants had right-sided lesions (73.1%), of whom 16 had concordant laterality of seizure onsets (84.2%). Seven had left-sided lesions (26.9%), of which six were concordant (85.7%). Again, focal seizures with dyscognitive features predominated (n = 14, 53.9%). Other seizure types observed included secondary generalized seizures with unknown evolution (n = 9, 34.6) and focal seizures without dyscognitive features (n = 8, 30.8%). Of note, the most common generalized seizure type was infantile spasms (n = 3). Developmental delay prior to seizure onset was present in six participants (23.1%).

Bilateral PMG

Of the 43 participants with bilateral lesions, 37 had focal epilepsy (86.0%). Thirteen of these participants also pre-

sented with seizures generalized from onset. Four participants had generalized epilepsy (9.3%) and two had unclassified seizure onsets. The median age of onset was 3 years (range <1 month to 37 years.) Twenty-four participants had symmetric lesions (55.8%). Of note, 10 of these participants presented with focal epilepsy. Of the nineteen with asymmetric lesions, 11 (57.9%) had more extensive PMG on the right side. Six (54.5%) of these participants had concordant epilepsy laterality. Eight (42.1%) had more extensive PMG on the left. Epilepsy was localized to the same side in five (62.5%) of these participants. Focal seizures with dyscognitive features were most common (n = 20, 46.5%), followed by secondarily generalized seizures with unknown evolutions (n = 15, 34.9%). The most common generalized seizure types were infantile spasms and myoclonic (n = 7 for each type.) Twenty participants had developmental delay prior to seizure onset (46.5%).

Generalized PMG

Seven participants had generalized PMG, among whom one had white matter abnormalities. Four had generalized epilepsy (57.1%), two of whom also presented with seizures with focal onset. Two participants had focal epilepsy (28.6%) and one had unclassified epilepsy. The median seizure onset was 8 months (range 1 month to 7 years). Myoclonic seizures were noted in four, infantile spasms were noted in three, and focal seizures with dyscognitive features were noted in three participants. Developmental delay prior to seizure onset was documented in four (57.1%) of the seven participants.

Other MRI findings

Additional subcortical findings included unilateral (n = 16) and bilateral (n = 14) enlarged ventricles, small or hypoplastic brainstem (n = 3), small or hypoplastic cerebellum (n = 2), hypoplastic basal ganglia (n = 1), and corpus callosum abnormalities (n = 3). A proportion of PMG malformations included relative hypoplasia of cortical volume in the cortex of affected regions (n = 10). Other MRI findings noted were white matter abnormalities (n = 4) and cavum septum pellucidum (n = 3). Two participants had periventricular heterotopia (n = 2), one of whom also had subcortical heterotopia. Nonperiventricular subcortical heterotopia was noted in two. One participant had evidence of encephalomalacia.

Epilepsy concordance and surgery

We defined "concordance" as an agreement between epilepsy laterality based on seizure semiology and EEG (with most weight given to ictal EEG, when available) and cerebral hemisphere with PMG based on MRI. Of the focal, unilateral, and asymmetric bilateral groups where PMG was lateralized to one hemisphere, the majority (71.4%) of participants had seizures with laterality concordant with the laterality of the PMG involved exclusively or predominantly.

Of the participants with data available regarding surgery evaluation (n = 61), 25 underwent formal presurgical evaluation. Four of these participants had focal PMG, for which surgery was completed in three. One participant did not undergo surgery, as adequate medical control of seizures was obtained. Nine participants had unilateral PMG, five of whom underwent surgery. Of those who did not, surgery was not done due to extensive malformation and lack of anticipated efficacy (n = 3), or because evaluation was underway at time of data collection (n = 1). Eleven participants had bilateral PMG, of whom one underwent surgery. Surgery was not done in this group due to bilateral/multifocal seizure onsets (n = 5), adequate medical seizure control (n = 2), extensive malformation without a single seizure focus (n = 2), or concern for risk of deficits (n = 1). One participant with generalized PMG underwent presurgical evaluation but was not considered a good candidate for surgery due to the extensive malformation and lack of a single seizure focus.

Nine participants underwent epilepsy surgery. In these participants, surgery consisted of partial or total lesionectomy. The median follow-up duration was 1 year (range 1 month to 21 years). Among those who had surgery, seven had an outcome consistent with an Engel classification score of I, with significant postsurgery seizure reduction. One of these participants presented with bilateral PMG, but the source of ictal onset was sufficiently localized to a single region. One participant had no improvement of seizures after surgery (Engel class III). One, who underwent a minimal resection considering the extent of malformation on MRI, had worsening of seizures after surgery (Engel class IV). Additional data related to the presurgical evaluation of these participants is available in the Table S1.

Discussion

In a large cohort of patients with PMG, we found that bilateral distributions were most common, with a perisylvian pattern predominating. There was a trend toward more right-sided involvement in unilateral and bilateral asymmetric cases. We found that most participants with lateralized PMG have seizure onset with concordant lateralization. Generalized PMG patterns tended to have an earlier seizure onset, and we observed a later age of seizure onset for unilateral PMG involving a single lobe. There was also a trend toward increasing prevalence of developmental delay prior to seizure onset as PMG distribution becomes more extensive. In contrast to a previously published case series of PMG, however, we did not find any overall gender differences in our series of epilepsy participants (Hayashi et al., 2002; Leventer et al., 2010).

PMG is strongly associated with epilepsy, with an incidence of 33–87% (Kuzniecky et al., 1994a; Teixeira et al.,

2007; Leventer et al., 2010; Castano de la Mota et al., 2011). As observed in our study, epilepsy in PMG typically begins in mid-childhood, although it can also present in infancy or adulthood, as has been observed previously (Guerrini et al., 1998; Luders et al., 1998). In addition, our finding of an association of PMG with epileptic spasms and myoclonic seizures is consistent with prior reports (Brodtkorb et al., 1992; Luders et al., 1998). This constellation of seizure types has been specifically associated with congenital bilateral perisylvian PMG (Kuzniecky et al., 1994b; Baykan-Kurt et al., 1997; De Coene et al., 2010). The overall distribution of PMG in our cohort closely resembles that of previous descriptive studies of PMG, including the prevalence of previously described PMG patterns (Guerrini et al., 2000; Hayashi et al., 2002; Chang et al., 2003, 2004; Leventer et al., 2010). However, previous reports of PMG patients have not shown a trend in more right-sided involvement in unilateral and bilateral asymmetric cases.

There was a general trend in our cohort toward having a younger age of seizure onset in more extensive PMG distributions, although the differences did not reach statistical significance. The median age of seizure onset was younger in participants with generalized PMG than those with other forms of PMG. Similarly, participants with focal PMG showed a trend toward an older age of seizure onset. Developmental delay before seizure onset also tended to be more common in participants with more extensive PMG, although not statistically significant. In a previously published series of 26 patients with PMG, patients with bilateral involvement had a higher prevalence of motor delay, intellectual disability, and speech problems than those with unilateral involvement and were also noted to have an earlier age of epilepsy onset (Mavili et al., 2012).

Initial concerns regarding the efficacy of surgery in PMG emerged following case reports of surgery failure in participants with this malformation (Brodtkorb et al., 1998; Guerrini et al., 1998). One source of debate concerns whether the site of cortical malformation corresponds to epileptogenic foci (Sisodiya, 2000). In contrast to these findings, a number of case reports have shown more favorable outcomes following surgery (RamachandranNair et al., 2006; Chang et al., 2011). Factors postulated to result in seizure free outcome in surgical treatments of cortical malformations, obtained from a retrospective study of 143 patients, include gray–white blurring on MRI, smaller lesion size, and complete resection of both structural and electrographically abnormal areas (Chang et al., 2011).

We assessed the degree of concordance between laterality of seizure onset based on semiology and EEG data and laterality of PMG on MRI. Because not all participants underwent formal presurgical evaluation, mostly due to assumed adequate seizure control, extensive malformation with lack of a single seizure focus, or lack of the possibility of undertaking a presurgical evaluation at the clinical site, precise seizure onset localization information for many cases was not available. In most cases, the laterality of the visible lesion and the epilepsy laterality were concordant. In addition, review of our surgical cases demonstrated that in carefully selected cases of epilepsy secondary to PMG, surgery may provide a favorable outcome. All but two participants who underwent surgery were seizure free or had a major reduction in seizure frequency following surgery at their most recent follow-up. For all of these participants, the area of resection included the PMG lesion. Future attempts at genetically defining individuals with PMG may lead to better predictions of outcome from epilepsy surgery.

The data from this study were collected from multiple tertiary care centers and may be subject to referral bias, as well as information bias. Misclassification of epilepsy localization may have occurred in a small fraction of cases. Because all participants in our cohort had epilepsy, the clinical and imaging features of PMG without epilepsy cannot be applied to all individuals with PMG. Because individuals with known genetic disorders were not included in the EPGP cohort, the PMG data thus acquired may not be applicable to these excluded participants.

In the future, these data should be correlated with genetic analysis of our PMG cohort to identify mutations that may correspond with specific phenotypes. In addition, prospective research should be conducted to evaluate the response of patients with PMG to medication based on both phenotypic and genotypic data. Further study is also needed to understand the specific association between the genetic mutations leading to PMG and their subsequent phenotypic expressions.

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Disclosures

Catherine Shain, Sriram Ramgopal, Zianka Fallil, Isha Parulkar, Richard Alongi, Robert Knowlton, and Annapurna Poduri have nothing to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix 1:

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Epilepsy surgery and outcomes within the EPGP PMG cohort