A familial syndrome of unilateral polymicrogyria affecting the right hemisphere

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Abstract—A number of familial syndromes of bilateral polymicrogyria (PMG) have been described, but reported unilateral PMG cases have generally been sporadic. The authors identified four families in which unilateral right-sided PMG on MRI was present in more than one individual, with pathologic confirmation in one. Core clinical features included contralateral hemiparesis, developmental delay, and focal seizures. The authors' findings suggest that unilateral PMG exists in a familial syndrome of probable germline genetic origin.

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Polymicrogyria (PMG) is a malformation of cortical development characterized by an excessive number of small gyri with abnormal lamination.[1] A number of bilateral region-specific PMG syndromes of genetic origin have been well described.[2] The clinical spectrum of unilateral PMG has also been described in multiple series.[3] Most reported unilateral cases have been sporadic, with no indication of an obvious genetic cause, but the existence of families in which unilateral and bilateral PMG coexist raises the possibility of shared genetic influences.[4,5]

We sought to identify and study families in which unilateral PMG was present in more than one individual.

Methods. For all subjects, the diagnosis of PMG was made based on brain MRI; in one case, PMG was also confirmed pathologically. MRI was performed on 1.5-T scanners according to standard clinical protocols. All images were reviewed by a pediatric neuroradiologist (A.J.B.) who diagnosed PMG based on an irregular, scalloped gray-white junction, an irregular cortical surface, and/or an apparent increase in cortical ribbon thickness. Only cases in which the PMG appeared exclusively unilateral (within the limits of radiologic detection) were included, but the possibility of microscopic abnormalities in the contralateral hemisphere could not be excluded. Informed consent was obtained according to protocols approved by the institutional review board of Children's Hospital, Boston.

The binomial proportion test was used to analyze the significance of the right-left disproportion among our reported families. A significance threshold of $p < 0.05$ was used.

Results. Four families were identified in which more than one individual was affected by unilateral PMG (figure 1). In all cases, the PMG was right-sided. In three families, two siblings born to unrelated healthy parents were affected, while in the fourth, a mother and son were both affected. Salient clinical and radiologic findings are presented in the table.

Statistical analysis demonstrated that the observed proportion of right-sided families (1.0) in our sample had a low likelihood (two-tailed $p = 0.12$, one-tailed $p = 0.06$) of being due to chance alone, assuming expected equal proportions of left- and right-sided cases.

Family 1. Two affected brothers (III:1 and III:2) were born at full term to unrelated parents of European and Native American descent. Both developed a mild left spastic hemiparesis in early childhood, while other aspects of development were normal. The older boy began having seizures at age 4 years, and an EEG demonstrated right frontocentral epileptiform discharges; the younger boy has not had any seizures. Both boys had chronic dysphagia. A distant maternal cousin had febrile seizures.

MRI of both boys demonstrated unilateral right PMG (figure 2A). The cortex of the left hemisphere appears entirely normal.

Family 2. The younger of two affected siblings in this family (II:2) presented at 22 months of age with macrocephaly and developmental delay. He had a mild left hemiparesis, as well as cutaneous stigmata of neurofibromatosis type 1 (NF-1). Similar signs of NF-1 were present in multiple family members, but genetic mutation testing was negative. At 2 years of age he developed epilepsy that in time became refractory to medications. After invasive EEG recording, he underwent a limited cortical resection at 16 years of age with pathologic confirmation of PMG. Full-scale IQ was 64. The boy's older brother (II:1) had one seizure at 10 years of age. He also had a mild left hemiparesis but no signs of NF-1. Full-scale IQ was 87. MRI of the younger boy (figure 2B) demonstrates PMG involving the right frontal and perisylvian cortex. In the older boy (fig-

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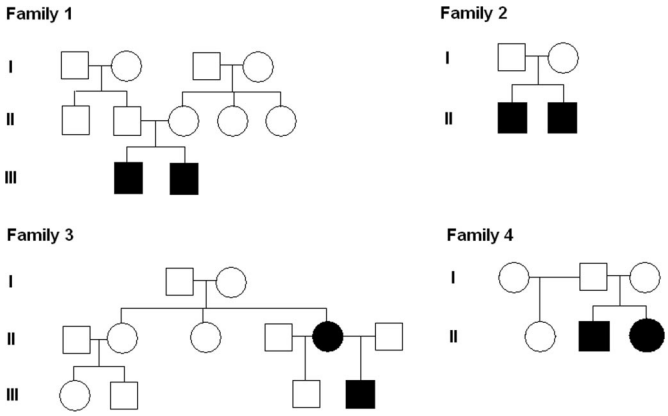

Figure 1. Pedigrees of families affected by unilateral right-sided polymicrogyria. Shaded symbols represent individuals with the syndrome of unilateral right-sided polymicrogyria. Individuals designated by clear symbols are neurologically normal but may not have had neuroimaging.

ure 2B), the malformation is slightly less severe but occurs in a nearly identical distribution.

Family 3. This mother-and-son pair with unilateral right PMG (II:5 and III:4) has been previously described in detail.[6] Briefly, the boy had low-normal intelligence (full-scale IQ 80), a congenital left hemiparesis, and a seizure disorder that began at age 7. MRI (figure 2C) demonstrates that the right frontoparietal cortex is polymicrogyric and the right hemisphere is smaller than the left. The boy's mother also had low-normal intelligence (full-scale IQ 85) and a congenital hemiparesis, but did not have seizures. Her MRI (figure 2C) appears similar to her son's. Karyotype testing in both patients was normal.

Family 4. In this family, two affected siblings (II:2 and II:3) were born at full term to healthy nonconsanguineous parents. Both had cognitive delay, left hemianopia, and left hemiparesis with hemiatrophy. Both had the onset of refractory complex partial seizures at age 10.

MRI of both siblings demonstrates unilateral right PMG with severe ipsilateral cerebral hemihypoplasia (figure 2D). In the boy, the frontal/perisylvian region is most prominently affected, with relative sparing of the inferior and medial areas of cortex. The girl has similar but slightly more severe MRI findings. Both parents were neurologically normal and had normal brain MRI and EEG.

Discussion. Here we describe the familial occurrence of unilateral right-sided PMG in four pedigrees, each with two affected members. The core clinical features include developmental delay, contralateral (left) hemiparesis, and focal seizures. Radiologically, the PMG in each family has a stereotyped MRI appearance, with the right perisylvian cortex affected in all cases and only minimal variability in the distribution and severity of PMG among the different families. The most severely affected individuals clinically (Family 4) had left body hemiatrophy and hemianopia as well, but radiologically their malformation was consistent with the others', albeit more severe. Further investigation with higher resolution neuroimaging or pathologic study, if appropriate, would be necessary to rule out the presence of microscopic malformations in the contralateral hemisphere.

Our findings strongly suggest that unilateral PMG can have a germline genetic etiology. However, there may be more than one causative locus because the presence of multiple affected siblings with unaffected parents raises the possibility of autosomal recessive inheritance or dominant inheritance with germline mosaicism, while the mother-son pair suggests autosomal dominant or X-linked inheritance. None of our cases had a history of recognized environmental insults or signs of inborn metabolic errors.

Unilateral PMG can be seen in patients with dele-

Table *Clinical and radiologic features of patients with unilateral right-sided PMG*

Family/ patient	Age at latest follow-up, y	Intellectual development	Motor development	Epilepsy	Extent of PMG
1/III:1	4.5	Normal	Mild left hemiparesis	Partial seizures	Lateral hemisphere, sparing frontal and occipital poles
1/III:2	3	Speech delay	Mild left hemiparesis	No	Lateral hemisphere, sparing occipital and temporal poles
2/II:2	18	Mental retardation	Mild left hemiparesis	Refractory; had surgery	Frontal/perisylvian cortex
2/II:1	20	Mild learning difficulties	Mild left hemiparesis	Single seizure	Frontal/perisylvian cortex
3/III:4	9	Low-normal intelligence	Left hemiparesis	Focal motor, atonic	Frontoparietal cortex
3/II:5	35	Low-normal intelligence	Left hemiparesis	No	Frontoparietal cortex
4/II:2	20	Cognitive delay	Left hemiparesis and hemiatrophy	Refractory partial	Frontal/perisylvian cortex, sparing inferomedial cortex
4/II:3	15	Language delay	Left hemiparesis and hemiatrophy	Refractory partial	Frontal/perisylvian cortex

PMG = polymicrogyria.

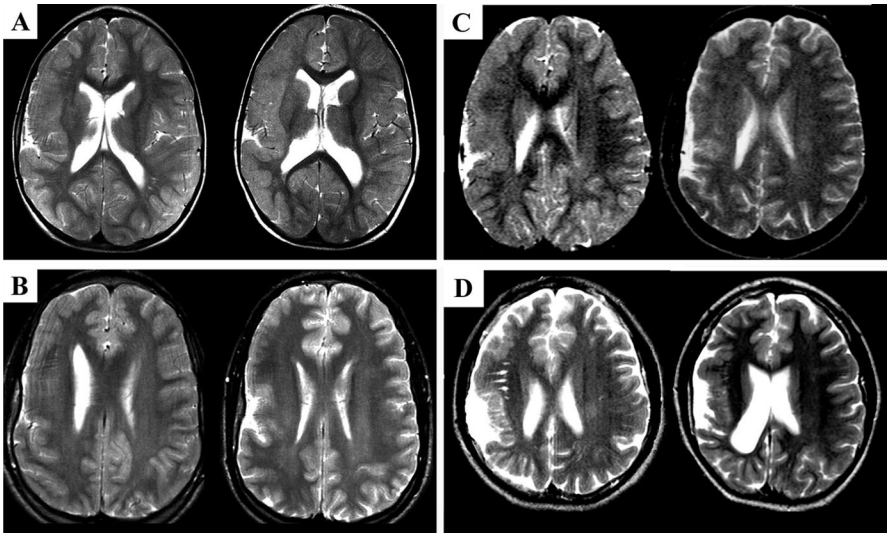

Figure 2. MRI appearance of unilateral right-sided polymicrogyria (PMG). Conventional T2-weighted spin-echo brain MRI in these families demonstrates that the PMG is quite stereotyped between the two members of each family but differs slightly between families. In all cases, the affected right hemisphere is smaller in size than the left. (A) MRI of the older brother (III:1; left) and younger brother (III:2; right) from Family 1 demonstrates unilateral right-sided PMG, characterized by an apparent increase in cortical thickness and an irregular, scalloped gray-white junction extending from near the frontal pole to the posterior end of the abnormally oriented, open sylvian fissure. (B) MRI of the younger brother (II:2; left) and older brother (II:1; right) from Family 2 demonstrates PMG with a similar distribution, although the degree of PMG appears less severe than in Family 1. (C) MRI of the son (III:4; left) and mother (II:5; right) from Family 3 demonstrates PMG of a largely similar extent and severity as that seen in Family 2. (D) MRI of the brother (II:2; left) and sister (II:3; right) from Family 4 demonstrates PMG largely restricted to the perisylvian region, as well as significant right cerebral hemihypoplasia in both cases.

tions at chromosome 22q11, the locus for DiGeorge syndrome and velocardiofacial syndrome, but it appears to be quite uncommon in these cases and is typically seen in association with other syndromic abnormalities,[7] which were not present in our subjects. An unbalanced translocation resulting in 1q44qter monosomy and 12p13.3pter trisomy has been associated with unilateral right PMG, severe mental retardation, congenital hypotonia, dysmorphic facial features, and hypogenitalism,[8] but none of our cases fit this clinical syndrome. Finally, although cutaneous signs of NF-1 were seen in one of our subjects, other family members showed evidence of NF-1 without brain malformation and the subject's affected brother had PMG without NF-1.

Candidate genes for unilateral PMG might include those that have differential expression or function between the two hemispheres during cortical development. For example, the transcription factor *LMO4* is reproducibly expressed more highly in the right perisylvian region of human embryonic brains than in the left.[9] The uniform right-sided laterality in our families has a low likelihood of being due to chance alone, and there may be specific reasons for a differential hemispheric susceptibility to PMG. For example, the right cerebral hemisphere in the fetus demonstrates gyral complexity earlier than the left, particularly in the perisylvian region.[10]

The identification of genes underlying this and other unilateral cortical malformation syndromes can potentially offer molecular insights into interhemispheric differences in cortical patterning. Lateralization and asymmetry in the mature human brain have been subjects of interest for decades, and the exploration of unilateral or asymmetric aspects of prenatal brain development is likely to provide important insights as well.

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