Bilateral generalized polymicrogyria (BGP)

A distinct syndrome of cortical malformation

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Abstract—*Background:* Syndromes of bilateral symmetric polymicrogyria include an autosomal recessive form of bilateral frontoparietal polymicrogyria (BFPP), in which the malformation is most severe rostrally. The authors describe a new syndrome they have termed "bilateral generalized polymicrogyria" (BGP), in which the malformation occurs in a generalized distribution but is often most severe in the perisylvian regions. *Methods:* Patients with bilateral polymicrogyria were identified from multiple medical centers worldwide. The diagnosis of BGP was based on findings from conventional spin echo MRI and, in one case, postmortem neuropathologic findings. Genetic analysis was performed for those patients from consanguineous pedigrees and those with multiple affected siblings to rule out linkage to the BFPP locus on chromosome 16q. *Results:* Twelve patients were identified with BGP. Clinical features included cognitive and motor delay as well as seizures. Some specific features characteristic of other known bilateral polymicrogyria syndromes, such as pseudobulbar palsy and dysconjugate gaze, were not commonly seen in these patients. Radiologically, polymicrogyria appeared widespread but was often most severe in the perisylvian regions. Pathologic examination in one case revealed a diffusely thin and excessively folded cerebral cortex lacking normal six-layered architecture. Seven patients subjected to genetic analysis did not demonstrate linkage to the BFPP locus. *Conclusions:* BGP is a distinct syndrome of cortical malformation. Several features allow BGP to be distinguished from other disorders on the growing list of bilateral symmetric polymicrogyria syndromes.

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Polymicrogyria is a common malformation of cortical development (MCD) characterized by an excessive number of small gyri with abnormal cortical lamination.[1] Polymicrogyria can appear as either a focal lesion or a more widespread cortical abnormality and is often seen in association with other developmental brain malformations such as schizencephaly.[1,2] Potential environmental etiologies of polymicrogyria have been reported,[3,4] but many cases occur in the setting of known gene disorders and chromosomal abnormalities.[5,6]

The presence of bilateral symmetric polymicrogyria, in particular, is often taken to suggest a genetic etiology, and multiple such syndromes have been described.[7-13] The fact that all such syndromes to date have been region specific raises the possibility that underlying genetic factors may influence cortical development in a topologically specific manner (e.g., along an anatomic gradient). These bilateral syndromes have fairly distinct clinical and radiologic presentations and include some that are sporadic, such as bilateral frontal polymicrogyria (BFP)[7] and bilateral parasagittal parieto-occipital polymicrogyria,[8] and some that are familial, such as bilateral perisylvian polymicrogyria (BPP)[9,10] and bilateral frontoparietal polymicrogyria (BFPP).[11,12]

In BFPP, an autosomal recessive disorder we mapped to chromosome 16q12.2-21,[11,12] polymicrogyria is typically present in a generalized distribution but with a descending anterior–posterior gradient of severity, such that frontoparietal regions are most significantly affected. Many BFPP patients

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Table 1 *Clinical and radiologic features of bilateral generalized polymicrogyria*

	Clinical features				Radiologic features†			
Patient no./ age*/sex	Cognitive delay	Motor delay	Seizures	HC	PMG distribution	Ventricles	White matter	Brainstem and cerebellum
1/5 y/F	Severe	Severe	Refractory	Normal	Bilateral generalized	Severely enlarged	Reduced volume	Prominent extra-axial spaces
2/12 y/M	Mild	Yes	Refractory with myoclonic seizures	>98th percentile	Bilateral generalized, worst perisylvian	Severely enlarged	Reduced volume	—
3/10 y/F	Mild	Yes	Febrile seizure	Normal	Bilateral generalized	Severely enlarged	Signal change	Normal
4/7 y/F	Yes	Yes	In neonatal period	Normal	Bilateral generalized, worst perisylvian	Moderately enlarged	Patchy signal change	Small vermis
5/11 mo/M	Yes	Yes	No	Normal	Bilateral generalized	Mildly to moderately enlarged	Reduced volume	Normal
6/3 y/M	Yes	Yes	No	—	Bilateral generalized, worst perisylvian	Normal	Patchy signal change	Mega cisterna magna
7/8 y/M	Moderate to severe		Generalized tonic clonic	Macrocephalic	Bilateral generalized, worst perisylvian	Enlarged	Reduced volume	Normal
8/3 y/F	Yes	Yes	Generalized tonic clonic	Macrocephalic	Bilateral generalized, worst perisylvian	Enlarged	Reduced volume, signal change	Normal
9/32 y/M	Severe	Severe	Symptomatic generalized epilepsy	—	Bilateral generalized, worst perisylvian	Moderately enlarged	Reduced volume	Normal

* Age at death or at latest follow-up.

† For Patient 9, postmortem pathologic features are presented. Patients 10 and 11 did not have radiologic studies, and Patient 12 had a head CT, but this was not available for review.

HC = head circumference; PMG = polymicrogyria.

had been previously misdiagnosed with a different MCD, owing mostly to limited neuroimaging technology and overlapping clinical features. BFPP is distinguished from its most closely similar syndrome, BFP, both clinically (by the presence of dysconjugate gaze in BFPP) and radiologically (by the extent and distribution of the malformation and by the associated white matter and posterior fossa abnormalities).

In our examination of potential BFPP cases, it became clear that yet another distinct syndrome existed in which bilateral polymicrogyria was present in a generalized distribution, with the perisylvian regions often predominantly affected. We present 12 patients with this syndrome, including 1 with postmortem neuropathologic findings. This disorder, which we have termed "bilateral generalized polymicrogyria" (BGP), appears to be distinct clinically, radiologically, and genetically from BFPP, BPP, and the other bilateral symmetric polymicrogyria syndromes. We review these bilateral syndromes and discuss their distinguishing features.

Methods. *Subjects and clinical data.* Patients were examined by clinical neurologists at different medical centers. Detailed medical histories and complete neurologic examinations were performed. Informed consent was obtained in accordance with human study protocols approved by the Institutional Review Board of Beth Israel Deaconess Medical Center. Spin echo MRI was performed according to standard clinical protocols of each participating institution and included the acquisition of T1- and T2-weighted images in the axial, coronal, and sagittal planes. In some cases, fluid-attenuated inversion recovery (FLAIR) and proton density sequences were also obtained. All films were interpreted by two neurologists and one of two pediatric neuroradiologists. Postmortem examination was performed on one subject (Patient 9) according to standard pathologic protocols at the receiving medical center, including both gross and microscopic study of brain tissue.

Genetic analysis. Genetic analysis was performed on pedigrees with evidence of either consanguineous parents or multiple affected siblings (Patients 2, 3, 4, and 9 through 12). DNA was isolated from peripheral lymphocytes of affected patients and unaffected relatives according to standard techniques. Genotyping was then performed at multiple microsatellite markers across the BFPP locus on chromosome 16q12.2-21, based on the mapping data previously reported.[12] Analysis of homozygosity was used for consanguineous pedigrees[14] (Patients 2, 3, and 4) to assess for linkage to this locus.

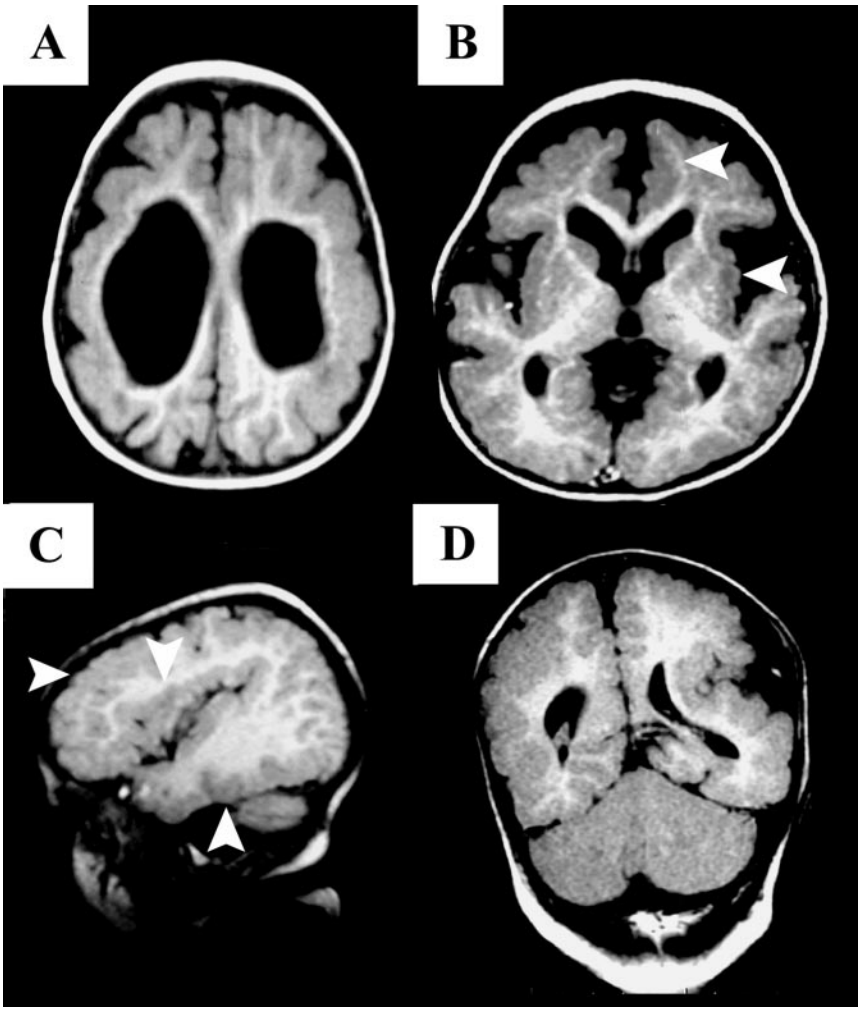

Figure 1. Representative T1-weighted MRI from patients with bilateral generalized polymicrogyria. (A) Axial image from Patient 3 at 13 months of age. The apparent increase in cortical thickness and irregular, scalloped gray–white junction indicate the presence of polymicrogyria in almost all regions of cortex. Markedly enlarged ventricles and reduced white matter volume are also evident. (B) Axial image from Patient 4 at 11 months of age. Generalized polymicrogyric cortex is apparent in this image, including the perisylvian and medial frontal regions bilaterally (indicated on left by arrowheads). (C) Sagittal image from Patient 7 at 2 years of age. The frontal, inferior temporal, and perisylvian regions of cortex are most obviously affected (arrowheads). (D) Coronal image from Patient 5 at 4 months of age. In addition to generalized polymicrogyria, this image also demonstrates that the posterior end of the left Sylvian fissure is "uncovered" and abnormally oriented.

Results. Twelve patients were identified with BGP. Salient clinical and radiologic features are presented in table 1. Representative T1-weighted (figure 1) and T2-weighted (figure 2) MRI of BGP are shown.

Patient 1. This Australian girl was the third child of nonconsanguineous parents. She had profound global delay and mental retardation as well as refractory partial epilepsy that began in infancy. She had a dysmorphic appearance with low-set ears and generalized spasticity. EEG demonstrated focal epileptiform discharges from the right midtemporal and frontal region. She died of pneumonia at age 5 after a femoral fracture from a fall.

MRI (see figure 2C) demonstrated BGP, particularly affecting the frontal, temporal, and parietal lobes. The cerebral ventricles were enlarged, and the white matter volume was markedly reduced. The olfactory sulci appeared dysplastic. The corpus callosum was fully formed but thin. The inferior cerebellar vermis was hypoplastic.

Patients 2 and 3. These are two affected siblings born to Australian parents who are first cousins. Their clinical features, including several congenital anomalies consistent with Adams–Oliver syndrome, have been reported in detail previously.[15] Patient 2, a boy, exhibited a scalp defect at the site of the anterior fontanelle, a reduction defect of the left toes, shortened digits, and bilateral inguinal hernias. Global developmental delay was noticed as early as the first year. Startle epilepsy and drop attacks began at age 16 months; myoclonic seizures were prominent, and rare afebrile convulsions occurred. Macrocephaly was noted beginning at age 1 year, and by age 9, his head circumference was >98th percentile. On exam, prominent lymphedema and mild generalized spasticity were seen in addition to the above anomalies.

Patient 2's head CT was initially felt to show a simple thickened cortex with thinned periventricular white matter (suggestive of pachygyria); further review, however, suggested that the actual disorder was generalized polymicrogyria, appearing most prominently in the suprasylvian regions bilaterally. Polymicrogyria can be mistaken for pachygyria on CT owing to poor resolution of the gray–white junction.[16,17] The cerebral ventricles were markedly enlarged and white matter volume markedly reduced. The cerebellar vermis appeared hypoplastic, although interpretation was limited, given the presence of a CT scan only.

Patient 3, the younger sister of Patient 2, was noted to have brachydactyly of all toes at birth and mild shortening of the fingers. She had global developmental delay (apparent at age 1 year) and spasticity. A single prolonged febrile convulsion, more marked on the left side, occurred at age 9 months. Her head circumference was normal. Neurologic examination at age 7 showed mild generalized spasticity, worse on the left, and lymphedema, more prominent on the right.

MRI (see figure 1A) demonstrated BGP most severe in

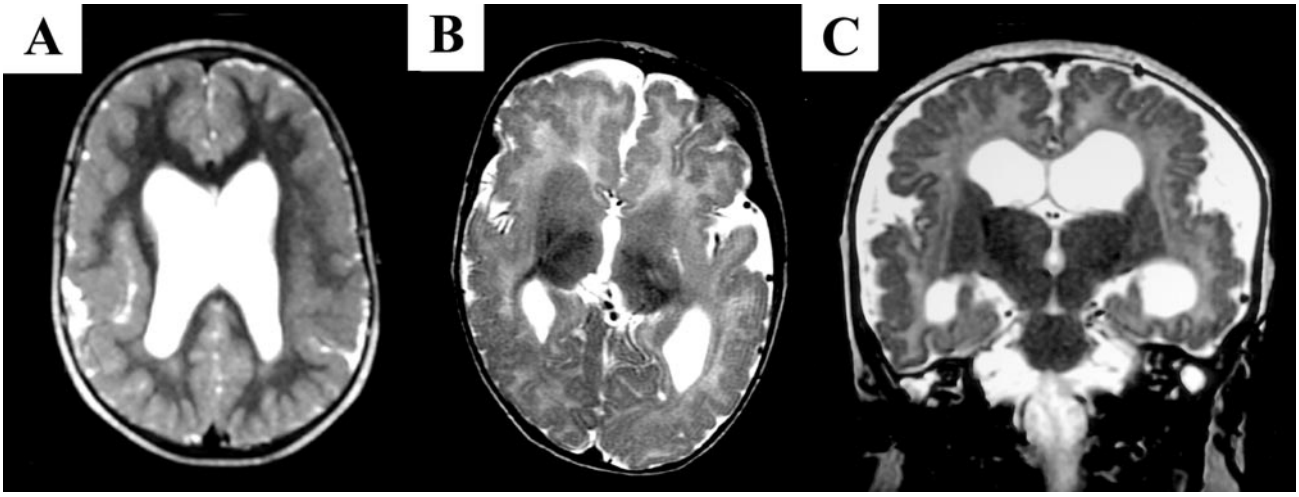

Figure 2. Representative T2-weighted MRI from patients with bilateral generalized polymicrogyria. (A) Axial image from Patient 7 at 2 years of age. (B) Axial image from Patient 5 at 4 months of age. The high gray–white contrast of these two T2-weighted images highlights the polymicrogyric folding of the cortex. Enlarged ventricles are also present. (C) Coronal image from Patient 1 at 4 months of age. In addition to generalized polymicrogyria, this image also demonstrates abnormally rotated hippocampi, enlarged ventricles, and enlarged extra-axial CSF spaces.

the suprasylvian regions and frontoparietal convexities, with a slight increase in apparent cortical thickness. The cerebral ventricles were markedly enlarged, and the white matter had markedly reduced volume and abnormal bright signal on T2-weighted images.

Patient 4. This girl was born to Turkish parents who are second cousins. She has two unaffected sisters, and her mother had one previous spontaneous abortion. She has had developmental delay, bilateral hearing loss, and recurrent pulmonary infections. She developed seizures on the third day of life, but none persisted beyond the neonatal period. On exam, her head circumference was normal, and deep tendon reflexes were brisk.

MRI (see figure 1B) demonstrated BGP most prominent in the frontal and perisylvian regions. The frontal horns of the lateral ventricles were moderately enlarged, with reduced volume and patchy T2 hyperintensity in the white matter bilaterally. The olfactory sulci were mildly dysplastic. The cerebellar vermis was mildly hypoplastic.

Patient 5. This boy was born to nonconsanguineous US parents of German descent. His mother had had one prior spontaneous abortion. He was born by cesarean section for failure to progress, but there were no other perinatal problems. He initially demonstrated poor visual behavior and diffuse hypotonia in the first months of life. He has never had any seizures. On examination, his head circumference was normal, and he initially demonstrated axial hypotonia and diffuse appendicular hypertonia, with increased flexor tone of both upper extremities and increased extensor tone in both lower extremities. The reflexes were brisk without clonus, and both plantar responses were extensor. He exhibited a tonic neck posture toward the right. Over time, he more clearly demonstrated a right hand preference, while his left hand tended to be kept fisted. Cytogenetic testing revealed a normal male karyotype.

MRI (see figures 1D and 2B) demonstrated BGP, sparing the orbitofrontal and occipital lobes. The apparent cortical thickness was increased. The cerebral ventricles were mildly to moderately enlarged, and the white matter volume was diminished.

Patient 6. This boy was born to nonconsanguineous Turkish parents. He has one unaffected sibling, but a first cousin shares similar clinical features. He was cyanotic at birth and had a low birth weight. There was no history of seizures. On examination, he was developmentally delayed and had a right hemiparesis. MRI demonstrated BGP with perisylvian predominance; the frontoparietal regions were somewhat less affected. Ventricular size was normal, but patchy T2 white matter hyperintensity was seen. A mega cisterna magna was present.

Patients 7 and 8. These are siblings born to nonconsanguineous Caucasian parents living in England. Patient 7, a boy, has moderate to severe mental retardation, marked autistic features, occasional generalized tonic-clonic (GTC) seizures, and macrocephaly. He had an early onset of hypothyroidism owing to an apparent organification defect and has also been noted to have very fast hair and nail growth. MRI (see figures 1C and 2A) demonstrated BGP centered in the perisylvian regions. The splenium of the corpus callosum was thin, and the rostrum was absent. The lateral ventricles were enlarged, and white matter volume was reduced.

Patient 8, the younger sister of Patient 7, has less severe mental retardation, more refractory seizures, and motor delay with moderate truncal hypertonia. She also has macrocephaly and hypothyroidism diagnosed within a few weeks of birth. Her MRI was similar to that of her brother.

Patients 9 through 12. Patient 9 was one of four affected siblings born to nonconsanguineous parents from Minnesota. He had severe mental retardation and chronic spastic quadriparesis since infancy and developed marked contractures of all extremities. He was treated for symptomatic generalized epilepsy. At age 32, he experienced sudden cardiac death.

Postmortem examination demonstrated a right ventricular cardiomyopathy, thought to be arrhythmogenic and responsible for his death, as well as macroglossia, severe scoliosis, chronic mild portal hepatitis, and cachexia. Gross examination of the brain surface and coronal sections (figure 3) revealed the presence of BGP. The perisylvian re-

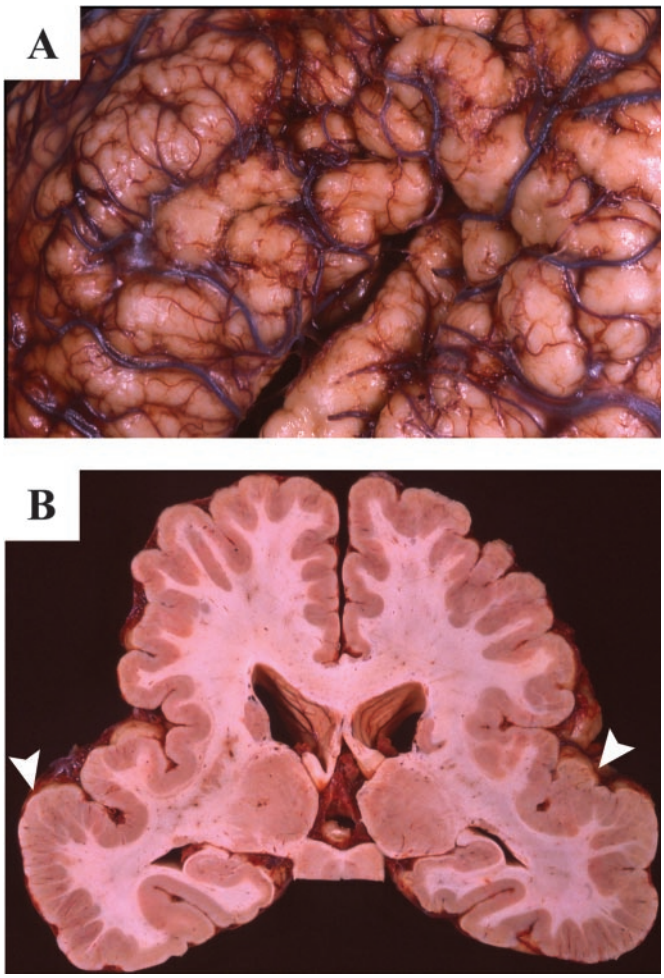

Figure 3. Neuropathologic findings of bilateral generalized polymicrogyria from Patient 9. (A) Gross appearance of brain surface in left perisylvian region. The gyri are small and excessive in number. (B) Coronal section through posterior thalamus. Polymicrogyria is evident throughout most visible regions of cerebral cortex, particularly in the perisylvian regions bilaterally. The tops of neighboring small gyri often appear fused, whereas the gray–white junction appears irregular and scalloped. Overall cortical thickness is reduced but appears increased in some areas owing to the fused appearance of multiple small gyri (see arrowheads).

gions, middle temporal gyri, and occipital lobes were predominantly affected. Microscopic examination revealed that the gyral abnormality was widespread. Cortical thickness was diffusely decreased, and a paucity of granular neurons was evident throughout. In some regions, four poorly delineated cortical layers were visible. The marginal zone extended downward in strips through clefts in the cortical surface, without accompanying pia to separate adjoining gyri (figure 4). No heterotopia or other malformations were seen.

Patients 10 through 12 are the three younger siblings of Patient 9. All have similar features and are thought likely to have BGP as well, but clinical details are incomplete for these individuals. The oldest sister (Patient 10) has mental retardation, spastic quadriparesis, and rare GTC seizures on phenobarbital. She has spastic dysarthria and dysphagia. Her EEG demonstrated generalized spike-and-wave discharges. Her echocardiogram was normal. Another sister (Patient 11) has mental retardation, spastic right hemiparesis, macrostomia, difficulty swallowing, no spontaneous speech, and excessive drooling. She experiences partial and GTC seizures that are well controlled on carbamazepine. EEG demonstrated left central and bilateral central spikes. Finally, a younger brother (Patient 12) also has mental retardation, spastic quadriparesis, spastic dysarthria, and macrostomia and does not talk. He has rare GTC seizures and was not on anticonvulsants at last follow-up. EEG and echocardiogram were normal. Head CT was reported to demonstrate large subarachnoid spaces in the frontoparietal regions as well as prominent third and fourth ventricles, potentially consistent with BGP, but the scan was not available for review.

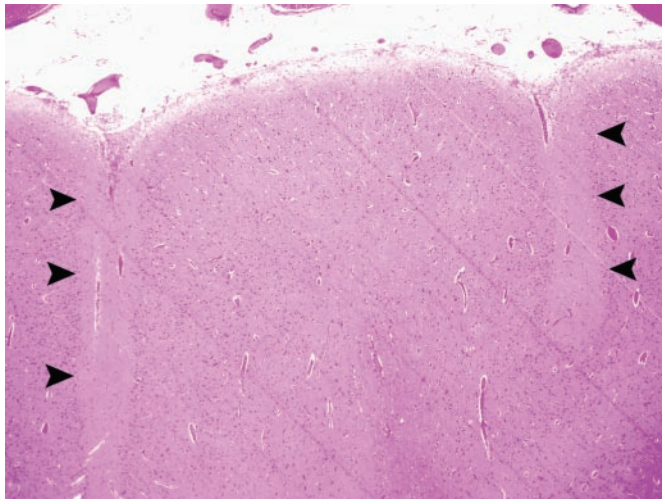

Figure 4. Histologic section of bilateral generalized polymicrogyria, taken from right occipital cortex of Patient 9. The cortex consists of poorly organized neurons without well-demarcated lamination. The marginal zone descends in fused strips through the entire thickness of cortical mantle (arrowheads), separating distinct "microgyri," but there is no intervening pia in these regions. Hematoxylin and eosin.

Genetic analysis. The two pedigrees demonstrating consanguinity (Patients 2, 3, and 4) were presumed to have autosomal recessive inheritance and were analyzed for linkage to the BFPP locus on chromosome 16q12.2-21, as that disorder is also characterized by widespread polymicrogyria (although the distribution of the cortical malformation and the gradient of severity are different). No region of homozygosity was seen across multiple microsatellite markers spanning the BFPP locus in these patients, making linkage to the locus extremely unlikely. The pedigree with four potentially affected siblings (Patients 9 through 12) was also studied. Affected individuals in this pedigree did not consistently share genotypes at the BFPP locus, and logarithm-of-the-odds scores were consistently negative, ruling out linkage to the BFPP locus.

Discussion. Here we describe 12 patients with a cortical malformation syndrome of BGP. Clinically, nearly all exhibit some degree of cognitive and motor delay, and most have seizures. Radiologically, the

Table 2 *Bilateral symmetric polymicrogyria syndromes*

Syndrome	Affected regions	Ref.	Clinical features	Radiologic findings	Genetic basis
Bilateral frontal polymicrogyria		7	Cognitive and motor delay, spastic quadriparesis, 5/13 with epilepsy	Symmetric PMG extending from frontal poles posteriorly to precentral gyrus and inferiorly to frontal operculum	All cases sporadic but 2/13 with consanguineous parents
Bilateral frontoparietal polymicrogyria		11,12	Severe cognitive and motor delay, seizures, dysconjugate gaze, 8/19 with cerebellar dysfunction	Symmetric generalized PMG with decreasing anterior–posterior gradient, most prominent in frontoparietal cortex	Autosomal recessive, with locus identified on 16q12.2-21
Bilateral perisylvian polymicrogyria		9,10	Pseudobulbar signs, 17/42 with cognitive impairment, 17/42 with epilepsy	PMG in the perisylvian region, usually bilateral	Likely heterogeneous, with five families linked to locus on Xq28
Bilateral parasagittal parieto-occipital polymicrogyria		8	Partial seizures, 4/9 with mental retardation	Bilateral PMG in parasagittal and mesial aspects of parieto-occipital cortex	All cases sporadic
Bilateral generalized polymicrogyria		This article	Cognitive and motor delay of variable severity, 10/12 with seizures	Symmetric generalized PMG, often most prominent in perisylvian regions	Most cases presumed to be autosomal recessive

PMG = polymicrogyria.

abnormality occurs in a generalized distribution but often affects the bilateral perisylvian regions most severely. In addition, ventriculomegaly and reduced white matter volume are often seen. Pathologic findings in one case demonstrate an abnormally thin cerebral cortex with excessively folded and fused gyri and an absence of the usual six-layered architecture.

No environmental factors such as prenatal infections, twin gestations, or significant perinatal complications were reported in any of our cases. In addition, radiologic findings characteristic of congenital infections (such as widespread white matter signal abnormality, intraparenchymal cysts, and calcifications) are not present. None of the patients has affected parents, and two pedigrees show consanguinity, suggesting that the likely mode of genetic transmission is autosomal recessive.

With the growing number of recognized syndromes of bilateral symmetric polymicrogyria (table 2), it is critical to be able to delineate the distinguishing features of each so that families can be properly counseled and genetic studies properly undertaken, when appropriate. The syndrome of BGP appears distinct from several close relatives clinically, radiologically, and genetically.

BGP can be distinguished from BPP by the more severe clinical deficits, the more widespread radiologic distribution of the malformation, and the apparent autosomal recessive inheritance pattern. Most patients with BPP have prominent pseudobulbar signs (such as spastic dysarthria and dysphagia) as a hallmark of their disorder,[18] whereas these features have not been prominent in our BGP patients. (Patients 10 through 12 are reported to demonstrate these signs but have not been studied in detail by neuroimaging.) Conversely, developmental delay and epilepsy are more common in BGP than in BPP. Some authors have subclassified the perisylvian disorder according to radiologic severity[10]; using such a system, our BGP patients would be classified as having the most severe form of BPP. In fact, however, the malformation in BPP extends beyond the perisylvian region in only a small number of cases (12% in one series).[9] We also believe BGP is distinct from BPP based on the likely autosomal recessive inheritance pattern. Most cases of BPP appear to demonstrate either autosomal dominant or X-linked inheritance,[9] and a locus has been reported at Xq28.[10] The predilection for perisylvian involvement in polymicrogyria syndromes has been previously noted.[13] In one series, the Sylvian fissure was involved in 80% of polymicrogyria cases.[19] This predilection has been speculated to be due to a predisposition of the region to ischemic insults occurring in utero,[4,20] but its apparent occurrence in genetic syndromes remains unexplained.

Whereas BGP and BFPP are both probably autosomal recessive, they can be distinguished on several

grounds. First, although the malformation in BFPP is indeed present in a generalized distribution, it is invariably more severe rostrally and it relatively spares the infrasylvian regions. In addition, brainstem and cerebellar atrophy are characteristic of BFPP but uncommon in BGP. Dysconjugate gaze was seen in >80% of the original cases of BFPP in whom gaze was described, but was not noted in these BGP patients. Finally, for the three BGP pedigrees available for genetic analysis, none showed evidence of linkage to the BFPP locus on chromosome 16q. Therefore, we believe that patients with generalized polymicrogyria should receive close examination of eye movements and detailed radiologic attention to posterior fossa structures and may ultimately require genetic analysis to rule out linkage to the BFPP locus.

The genetic basis of BGP is still unknown. Most of our patients are presumed to have autosomal recessive inheritance, but we cannot be sure that the disorder is not genetically heterogeneous. Various forms of polymicrogyria have now been linked to a number of different loci,[5,6,10,12,21] suggesting that disparate genetic abnormalities may result in the same final outcome: an alteration in proper cortical lamination and folding. The identification of more families with multiple affected members will help to facilitate further genetic analysis and thus ultimately lead to a better understanding of the genetic influences on regional cortical development. Detailed pathologic study of gyral abnormalities, as described in one of our cases, may also yield potentially valuable clues to the mechanisms by which malformations can develop.

Clinically, MCD as a whole are increasingly being recognized as a common cause of mental retardation and refractory epilepsy.[22] Proper syndromic diagnosis based on high-resolution neuroimaging and recognition of distinguishing clinical features will allow not only for the acceleration of genetic studies but also for more accurate prognostication and counseling for those affected by these developmental disorders.

Addendum. Since this article went to press, our group has now identified the responsible gene for bilateral frontoparietal polymicrogyria (BFPP) as *GPR56*, which now encodes an orphan G-protein coupled receptor (Piao X, et al., Science 2004;303:2033–2036).

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