Bilateral Frontoparietal Polymicrogyria: Clinical and Radiological Features in 10 Families with Linkage to Chromosome 16

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Polymicrogyria is a common malformation of cortical development characterized by an excessive number of small gyri and abnormal cortical lamination. Multiple syndromes of region-specific bilateral symmetric polymicrogyria have been reported. We previously have described two families with bilateral frontoparietal polymicrogyria (BFPP), an autosomal recessive syndrome that we mapped to a locus on chromosome 16q12-21. Here, we extend our observations to include 19 patients from 10 kindreds, all linked to the chromosome 16q locus, allowing us to define the clinical and radiological features of BFPP in detail. The syndrome is characterized by global developmental delay of at least moderate severity, seizures, dysconjugate gaze, and bilateral pyramidal and cerebellar signs. Magnetic resonance imaging demonstrated symmetric polymicrogyria affecting the frontoparietal regions most severely, as well as ventriculomegaly, bilateral white matter signal changes, and small brainstem and cerebellar structures. We have refined our genetic mapping and describe two apparent founder haplotypes, one of which is present in two families with BFPP and associated microcephaly. Because 11 of our patients initially were classified as having other malformations, the syndrome of BFPP appears to be more common than previously recognized and may be frequently misdiagnosed.

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Malformations of cortical development are increasingly being recognized as a common cause of developmental delay and epilepsy.[1] Polymicrogyria, one of the most common cortical malformations, is characterized by multiple small gyri with abnormal cortical lamination.[2,3] With the advent of improved magnetic resonance imaging (MRI) technology, abnormalities of gyration have been easier to detect by neuroimaging, and some patients previously believed to have pachygyria or lissencephaly are now recognized to have polymicrogyria.[4]

Although environmental insults including intrauterine hypoxia-ischemia and congenital infections have been implicated in the pathogenesis of some forms of polymicrogyria,[5,6] several syndromes of bilateral polymicrogyria have been described[7–11] and some have been successfully mapped to specific genetic loci.[12,13] To date, the described bilateral polymicrogyria syndromes are mostly symmetric and region-specific and include, for example, bilateral frontal polymicrogyria,[8] bilateral perisylvian polymicrogyria (also known as congenital bilateral perisylvian syndrome),[9,10] and bilateral parasagittal parietooccipital polymicrogyria.[11]

We previously have described the genetic analysis of two families, one of which was originally reported by Straussberg and colleagues,[14] with an autosomal recessive syndrome of bilateral frontoparietal polymicrogyria (BFPP), a disorder we mapped to a locus on chromosome 16q12-21.[13] Two sporadic cases of BFPP also have been reported.[15] Here, we describe in detail the

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clinical and radiological features of autosomal recessive BFPP in 19 patients from 10 families, linked to chromosome 16q12-21 in all cases, and report on further genetic analysis of this disorder. We find that BFPP is a highly distinctive and stereotyped disorder both clinically and radiologically.

Subjects and Methods

Patients were examined at several medical centers worldwide. Detailed medical histories were obtained, and complete neurological examinations were performed by clinical neurologists in all cases. Informed consent was obtained in accordance with human studies protocols approved by the institutional review board of the Beth Israel Deaconess Medical Center, the Office of Human Research Protection, and the institutional review boards of many other participating institutions.

MRI was performed according to standard clinical protocols of each participating institution and generally consisted of axial, coronal, and sagittal T1- and T2-weighted images obtained on 1.5T scanners. Additional protocols including fluid-attenuated inversion recovery, proton-density, and gradient-echo sequences also were used in most cases. All films were reviewed by two neurologists (B.S.C., C.A.W.) and by one of two neuroradiologists (P.E.G., A.J.B.) for the extent of the cortical malformation and the presence or absence of additional abnormalities. Serum screening tests for chromosomal abnormalities and inborn errors of metabolism were performed in most cases, and in selected patients electroencephalography, evoked potentials, and electromyography/nerve conduction studies were performed if clinically appropriate.

Genetic analysis was performed on DNA isolated from peripheral blood lymphocytes from affected patients and their unaffected relatives. Genotyping was performed at multiple microsatellite markers on chromosome 16q, based on the mapping data obtained previously and using the techniques described.[13] Analysis of homozygosity was used[16] for consanguineous pedigrees, and statistical linkage analysis was performed by calculating multipoint logarithm of odds (LOD) scores using locally derived software and Genehunter.[17,18] We assumed a susceptibility allele with frequency 0.001 and a recessive mode of inheritance with 99% penetrance. For simplicity of calculation, the number of alleles at each marker was assumed to be one greater than the number present in the family analyzed, and each allele was assumed to occur with equal frequency, because previous analysis at this locus has failed to show a significant effect of allele frequencies on multipoint LOD scores.[13] For Family 10, the parents of the third affected child were assumed to be second cousins for the purpose of approximate LOD score calculation (see text below).

Results

Pedigrees of the affected families are presented in Figure 1. Clinical and radiological features are summarized in Table 1.

Families 1 and 2

Clinical and radiological features of both these families have been reported previously.[13] Family 1 originally was described as having pachygyria,[14] although subsequent neuroimaging demonstrated that the malformation present was in fact polymicrogyria.[13] Family 2 is from the same village as Family 1, but there is no known relationship between them.

Family 3

There are two affected children (II-1, II-2) born to unrelated Pakistani parents. The boy (II-1) suffered from developmental delay first noted in infancy and died recently at age 4 years, apparently of pneumonia. Seizures began at approximately 3 years and were characterized by stiffening and eye deviation with blinking. His sister (II-2), last seen at 13 months, appeared to be less delayed. She had limited language development and could walk unsteadily. Both children were normocephalic and had strabismus.

In both children, MRI demonstrated polymicrogyria symmetrically affecting both the frontal lobes and the medial parietal-occipital lobes (Fig 2a, b). Ventricles were enlarged and the corpus callosum was dysplastic. White matter volume was decreased and T2 hyperintensities were seen bilaterally. The brainstem and superior vermis were small.

Family 4

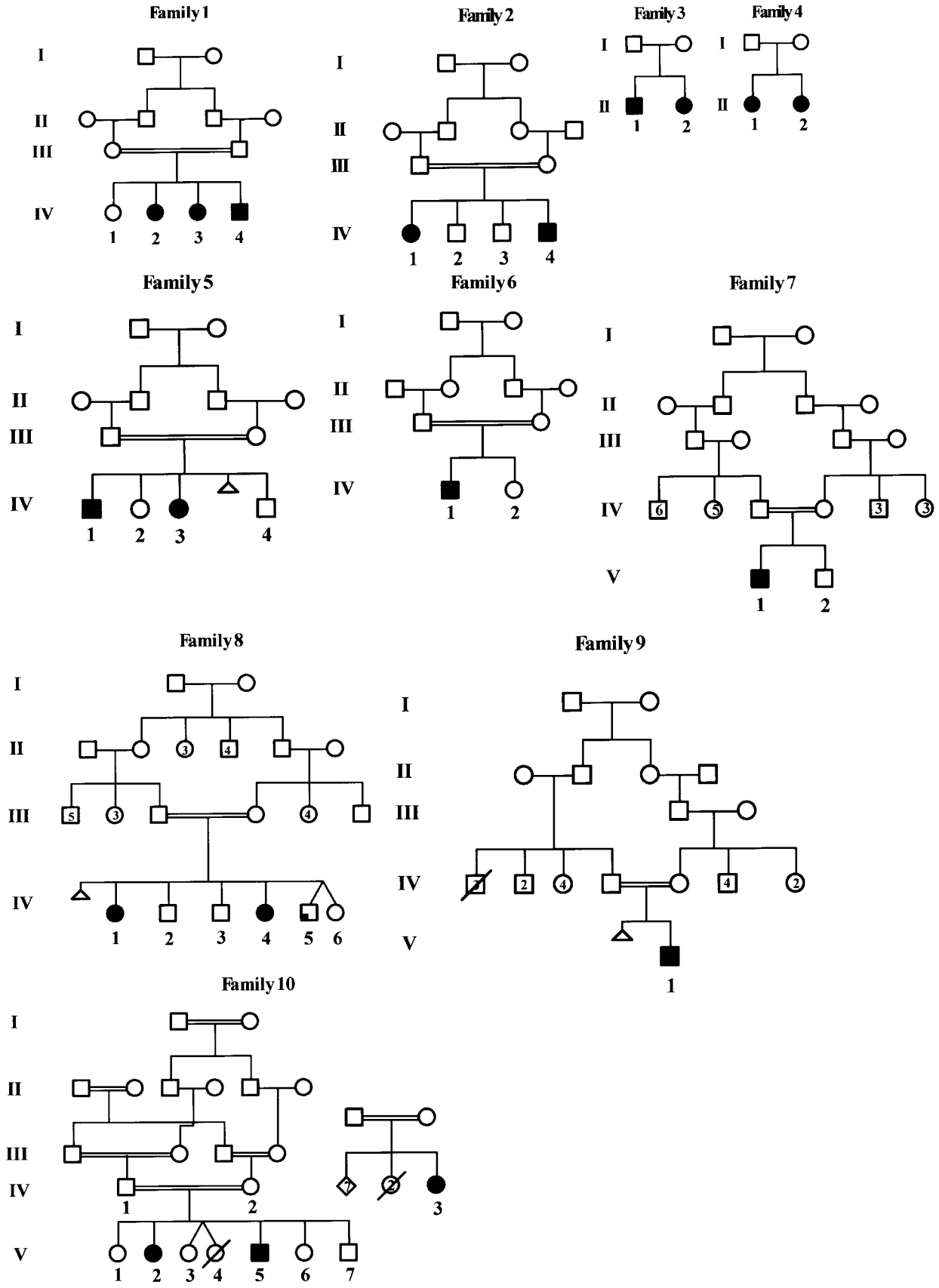
Clinical features of this family have been reported elsewhere,[19] but the MRI of one affected child, initially interpreted as a "neuronal migration abnormality" without further specification, is characteristic of the syndrome described here (Fig. 3a,e).

Family 5

This family includes two affected children described previously as having "cobblestone lissencephaly."[20] The MRI of the affected male child (IV-1) initially was thought to demonstrate generalized pachygyria, although frontal polymicrogyria was also seen. Subsequent interpretation shows radiological features characteristic of the syndrome described here.

Family 6

The affected boy in this family, born to Pakistani parents who are first cousins, also has been described previously and diagnosed with "cobblestone lissencephaly" based on head computed tomography (CT).[20] Although pachygyria and agyria were reported, these can be indistinguishable from polymicrogyria on CT (and even on low-resolution MRI). His other CT findings, including patchy areas of radiolucency in the white matter, hypoplasia of the cerebellar vermis and hemispheres, and enlarged ventricles all are consistent with the imaging of our other patients.


Family 1
I
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IV
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Family 2
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Family 3
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Family 8
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1 2 3 4 5 6
Family 9
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Family 10
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II
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IV
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1 2 3 4 5 6 7

Figure 1

Table 1. Clinical and Radiological Features of Patients with Bilateral Frontoparietal Polymicrogyria

Family/ Patient	Age[a]/Gender	Clinical Features					
		Cognitive Delay	Motor Delay or Pyramidal Signs	Cerebellar Signs	Dysconjugate Gaze	Seizures	Head Circumference
1/IV-2	14 yr/F	Moderate	Yes	Yes	Esotropia	GTC, absence	Normal
1/IV-3	9 yr/F	Yes	Yes	Yes	Esotropia	FS, atonic-drop	Normal
1/IV-4	7 yr/M	Severe	Severe	NA	Esotropia	FS, GTC	Normal
2/IV-1	13 yr/F	Severe	Yes	Yes	Esotropia	GTC, atonic	Normal
2/IV-4	4 yr/M	Severe	Yes	Yes	Esotropia	No	Normal
3/II-1	4 yr/M	Yes	Yes	NA	Strabismus	Episodes of stiffening, eye deviation, and startles	Normal
3/II-2	13 mo/F	Yes	Yes	NA	Strabismus	Episodes of startles	Normal
4/II-1	24 yr/F	Yes	Yes	Yes	Exotropia	Blank episodes	Normal
4/II-2	20 yr/F	Yes	Yes	Yes	No	Absence	Normal
5/IV-1	13 yr/M	Moderate-severe	Yes	NA	Esotropia, vertical divergence	Tonic, GTC, myoclonic, CPS	Normal
5/IV-3	6 yr/F	NA	Yes	Yes	Esotropia	Yes	Normal
6/IV-1	5 yr/M	Severe	Severe	Yes	Esotropia	Generalized	>98th percentile
7/V-1	8 yr/M	Moderate	Yes	NA	Esotropia	NA	NA
8/IV-1	11 yr/F	Yes	Yes	NA	NA	NA	<2nd percentile
8/IV-4	2 yr/F	NA	Yes	NA	NA	NA	<2nd percentile
9/V-1	20 mo/M	Severe	Yes	NA	Esotropia	Yes	<3rd percentile
10/V-2	29 yr/F	Severe	Yes	NA	No	Myoclonic, GTC	Normal
10/V-5	22 yr/M	Severe	Yes	NA	Exotropia	Myoclonic, GTC	NA
10/IV-3	21 yr/F	Severe	Yes	No	Yes	Myoclonic, GTC	Normal

[a]Age at most recent follow-up.

PMG = polymicrogyria; GTC = generalized tonic-clonic seizures; LV = lateral ventricle; FS = febrile seizure; NA = information not available; CPS = complex partial seizures; CT = computed tomography.

Family 7

In this family, the affected boy (V-1) was born to Afghani parents who are second cousins. He did not walk independently until 3 years. At 8 years of age, he had moderate language and mental delay. A convergent squint was present.

MRI (Figs 3b, d and 4b) demonstrated polymicrogyria extending from the frontal poles bilaterally back to the occipital poles medially and the motor strip laterally. The posterior body and splenium of the corpus callosum were thin. Ventricles were enlarged and white matter volume decreased. The superior vermis and pons were small.

Family 8

This family consists of six children born to Palestinian parents who are first cousins. They live in a village 5 to 10km away from the one in which Families 1 and 2 reside. Two children (IV-1, IV-4) are clinically affected and have the characteristic MRI pattern of BFPP. A younger sibling (IV-5) has suggestive clinical abnormal-

Fig 1. Pedigrees of bilateral frontoparietal polymicrogyria (BFPP) families. Completely shaded symbols designate those with the clinical and radiological syndrome of BFPP. The partially shaded symbol in Family 8 designates a child who has consistent clinical features but has not had magnetic resonance imaging performed (see text). In the pedigree of Family 10, which has been simplified for sake of clarity, the father of affected child IV-3 is a third cousin once removed of both parents of affected children V-2 and V-5.

Table 1. Continued

Radiological Features			
PMG Distribution	Ventricles	White Matter	Brainstem and Cerebellum
Frontoparietal	Slightly enlarged LVs	Patchy signal change	Slightly small pons and superior vermis
Frontoparietal	Enlarged 4th	Periventricular signal change	Small pons
Frontoparietal	Slightly enlarged LVs	Periventricular signal change	Slightly small pons
Frontoparietal	Enlarged LVs	Periventricular signal change	Slightly small pons and vermis
Diffuse	Enlarged LVs	Patchy signal change	Small pons and superior vermis
Frontal and medial parietooccipital	Enlarged	Reduced volume, periventricular signal change	Small pons and superior vermis
Frontal and medial parietooccipital	Slightly enlarged	Reduced volume, patchy signal change	Small pons and vermis
Frontoparietal	Enlarged	Reduced volume, patchy signal change	NA
Diffuse, most severe frontally	NA	Patchy signal change	Slightly small pons and vermis
Frontal	Enlarged	Patchy signal change	Small brainstem
Diffuse, most severe in frontoparietal regions	Enlarged	Patchy signal change	Small pons and vermis
Diffuse agyria and pachygyria (CT)	Enlarged	Patchy radiolucency (CT)	Small cerebellum
Frontal and medial parietooccipital	Enlarged	Reduced volume, patchy signal change	Small pons and superior vermis
Frontoparietal	Enlarged	Reduced volume, patchy signal change	Small pons and cerebellum
Frontoparietal	Enlarged	Reduced volume, patchy signal change	Small pons and cerebellum
Frontal	Enlarged LVs	Reduced volume, frontal subcortical signal change	Small brainstem and cerebellum
Frontoparietal	Enlarged	Reduced volume	Small vermis
Frontoparietal	Enlarged	Reduced volume	Small vermis
Frontoparietal	Enlarged	Reduced volume	Small vermis

ities, although neuroimaging has not yet been performed.

The older affected child (IV-1), now 11 years old, has mental retardation and motor delay. She had spasticity and exaggerated deep tendon reflexes on examination. Her head circumference (HC) was less than the second percentile. Her mother also had a small HC (50cm, less than the second percentile). Her younger sister (IV-4), now 2 years old, had fairly normal development until this year, at which point some motor delay and spasticity were noted. HC was 44.5cm (less than second percentile) at 21 months. The youngest possibly affected child (IV-5), 4 months old at latest follow-up, had spasticity and exaggerated deep tendon reflexes on examination. HC was 41cm (90th percentile) at 2 months.

MRI of the oldest child (see Figs 3c and 4c) demonstrated polymicrogyria symmetrically extending from the frontal lobes back to the parietal-occipital sulcus. The ventricles were large and white matter volume was reduced. Large subcortical perivascular spaces were present. The superior vermis, cerebellar hemispheres, and ventral pons were small, as was the splenium of the corpus callosum. MRI of the younger affected child appeared similar.

Family 9

This Palestinian family is from the same village as Family 8, but there is no known relationship between them. The parents are first cousins once removed and electively terminated a previous pregnancy because of anencephaly diagnosed by prenatal ultrasound.

The affected child (V-1) has severe developmental delay and seizures with onset at 1 month of age. Es-

otropia was present on examination, but vision and fundoscopic examination were normal. Although at birth HC was 35cm (50th percentile), by 10 months it had fallen to less than the third percentile. Parental HC were normal.

MRI (see Figs 2c and 4a, d) demonstrated polymicrogyria most severely affecting the frontal lobes. The frontal horns of the lateral ventricles were large, and the white matter was of reduced volume bilaterally, with large perivascular spaces. The cerebellar hemispheres, vermis, pons, and splenium were all small.

Family 10

This family initially was described as having lissencephaly with cerebellar hypoplasia.[21] Although clinical findings have been reported previously, recent examinations demonstrated that the affected boy (V-5) had a divergent squint of the right eye and the third affected child (IV-3) had mildly dysconjugate gaze and marked nystagmus on horizontal endgaze. This girl was born to parents who are believed to be consanguineous, although their exact relationship is not known; her father is a third cousin once removed of the other affected children's parents (see Fig 1).

CT of the affected patients, described previously,[21] demonstrated apparently thickened gyri in the bilateral anterior head regions, although close observation shows that the gray-white junction is irregular and scalloped. Subsequent MRI confirmed that bilateral symmetric polymicrogyria was present with a decreasing anterior-posterior gradient of severity. In addition, thin white matter with foci of T2 prolongation, enlarged ventricles, and a small cerebellar vermis were seen in these three cases.

Genetic Analysis

Genotyping at multiple microsatellite DNA markers at chromosome 16q12-21 showed that all 10 families showed positive evidence of linkage to the BFPP locus, as demonstrated both by analysis of homozygosity and by statistical analysis (LOD score calculation). Affected patients from consanguineous families were homozygous across multiple consecutive markers, and these regions of homozygosity shared a common overlapping interval. LOD scores (Table 2) were calculated for each family individually. Because the presence of common founder mutations in multiple pedigrees is not in-

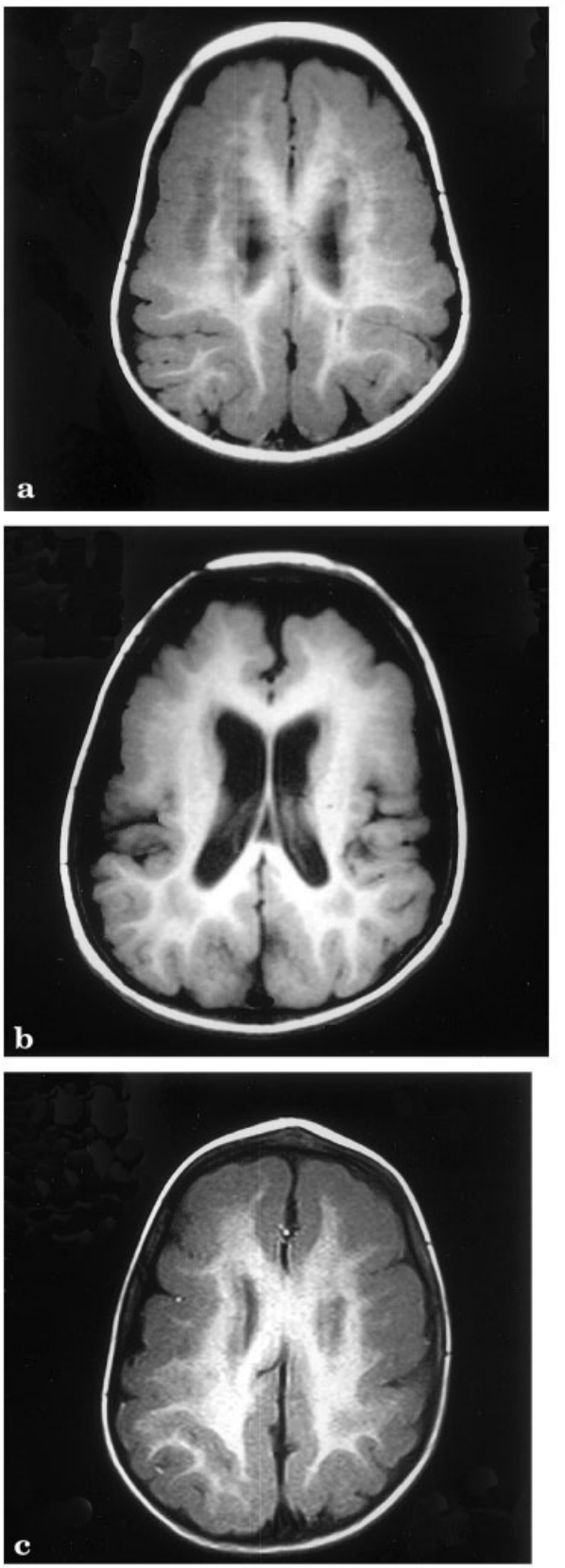

Fig 2. Representative T1-weighted axial magnetic resonance imaging of bilateral frontoparietal polymicrogyria patients. The gyri appear thickened in the frontal and parietal regions, but the irregular, scalloped appearance of the gray-white junction indicates the presence of polymicrogyria rather than pachygyria. Scans a to c are from Patient II-2 in Family 3, Patient II-1 in Family 3, and Patient V-1 in Family 9, respectively.

volved in the LOD calculation, in some cases these scores greatly underestimate the likelihood of linkage. For example, the common haplotypes of Families 1 and 2 and of Families 8 and 9 make linkage to this locus far more likely for these pedigrees than LOD scores would indicate.

We have previously described the common founder mutation of Families 1 and 2 at the BFPP locus.[13] In addition, the affected members of Families 8 and 9, the only BFPP patients who have associated microcephaly, were homozygous for a shared allele at multiple consecutive markers over a 7cM region that overlapped the haplotype of Families 1 and 2 extensively. Surprisingly, these two founder haplotypes, from Palestinian families originating in villages 5 to 10km apart, were distinct from one another. The two pedigrees (Families 3 and 4) who denied consanguinity showed no evidence of homozygosity near the BFPP locus. Thus, these affected children presumably carry different mutant alleles in their two copies of the responsible gene.

Discussion

Here, we describe 19 patients who share an apparently common genetic malformation of the brain with highly stereotyped clinical, radiological, and genetic features. The salient clinical findings of BFPP include global developmental delay, dysconjugate gaze (typically esotropia), seizures, and bilateral pyramidal and cerebellar signs. The disorder appears to be consistent with survival into adulthood, although affected adults usually do not live independently. The distinctive radiological finding is bilateral symmetric polymicrogyria most prominent in the frontoparietal regions, with a decreasing anterior-posterior gradient of severity. In addition, the white matter is typically thin and demonstrates foci of T2 prolongation, the ventricles are enlarged, and the pons and cerebellar vermis are frequently small (likely hypoplastic) as well. BFPP is inherited in an autosomal recessive manner, and all of our affected families map to a common locus on chromosome 16. We have not seen so far any patients with the clinical and radiological features of BFPP map to other loci.

Dysconjugate Gaze

Dysconjugate gaze is a common clinical feature of BFPP. Fifteen of 17 patients (88%) in whom gaze was described had either esotropia observed on examination (most commonly) or a known history of a "squint" or strabismus; in some cases, this was repaired surgically in childhood. In a few cases, however, detailed descriptions of the precise gaze abnormality were not available. The presence of horizontal dysconjugate gaze suggests the possibility of primary pontine pathology, which is consistent with the small pons seen on MRI in some cases. Alternatively, some have theorized that congenital esotropia can stem from cerebral abnormalities that result in a decreased potential for binocular fusion.[22] In fact, esotropia can be seen in patients with periventricular leukomalacia[23] or other white matter disorders,[24] as well as in those with unspecified forms of hydrocephalus or cerebral palsy.[25] Although dysconjugate gaze thus is not uncommon in patients with severe static encephalopathies, we believe it may help clinicians to distinguish BFPP from other bilateral polymicrogyria syndromes, in which it has not been reported.

Seizures

Polymicrogyria is a highly epileptogenic malformation,[26] and seizures were reported in 15 of 16 (94%) BFPP patients. (Most of those without reported seizures were younger than age 5 years at latest follow-up, however, raising the possibility that seizures could develop later.) Although details of epilepsy history were not available in all cases with documented seizures, most appeared to suffer from symptomatic generalized epilepsy.[27] This is most likely because of the symmetric and diffuse extent of the cortical abnormality in BFPP, as well as the fact that epilepsy of frontal lobe origin often can appear to be generalized in origin.[28,29] Complex partial seizures were reported in only one of our patients, in contrast with their frequent appearance in patients with bilateral parasagittal parietooccipital polymicrogyria, a more localized malformation that spares the frontal regions.[11]

Polymicrogyria Syndromes

An appreciation of the radiological appearance of polymicrogyria is critical to its proper diagnosis. Although the cortical surface may appear smooth, the gyri broad, and the thickness of the cortical ribbon may appear increased in polymicrogyria because of the folding of the cortex; in fact, the irregular, scalloped appearance of the gray-white junction allows for differentiation from most cases of pachygyria.[4] Eleven of our patients previously had been diagnosed with another

Fig 3. Representative T2-weighted axial magnetic resonance imaging of bilateral frontoparietal polymicrogyria patients. The apparently increased cortical thickness and irregular gray-white junction in the bilateral frontoparietal regions are particularly evident in images a to c. Scans a to c are from Patient II-2 in Family 4, Patient V-1 in Family 7, and Patient IV-1 in Family 8, respectively. Scan d, from Patient V-1 in Family 7, demonstrates well the patchy foci of T2 prolongation in the white matter, resembling enlarged perivascular spaces. Ventriculomegaly is notable in scan e, from Patient II-2 in Family 4.

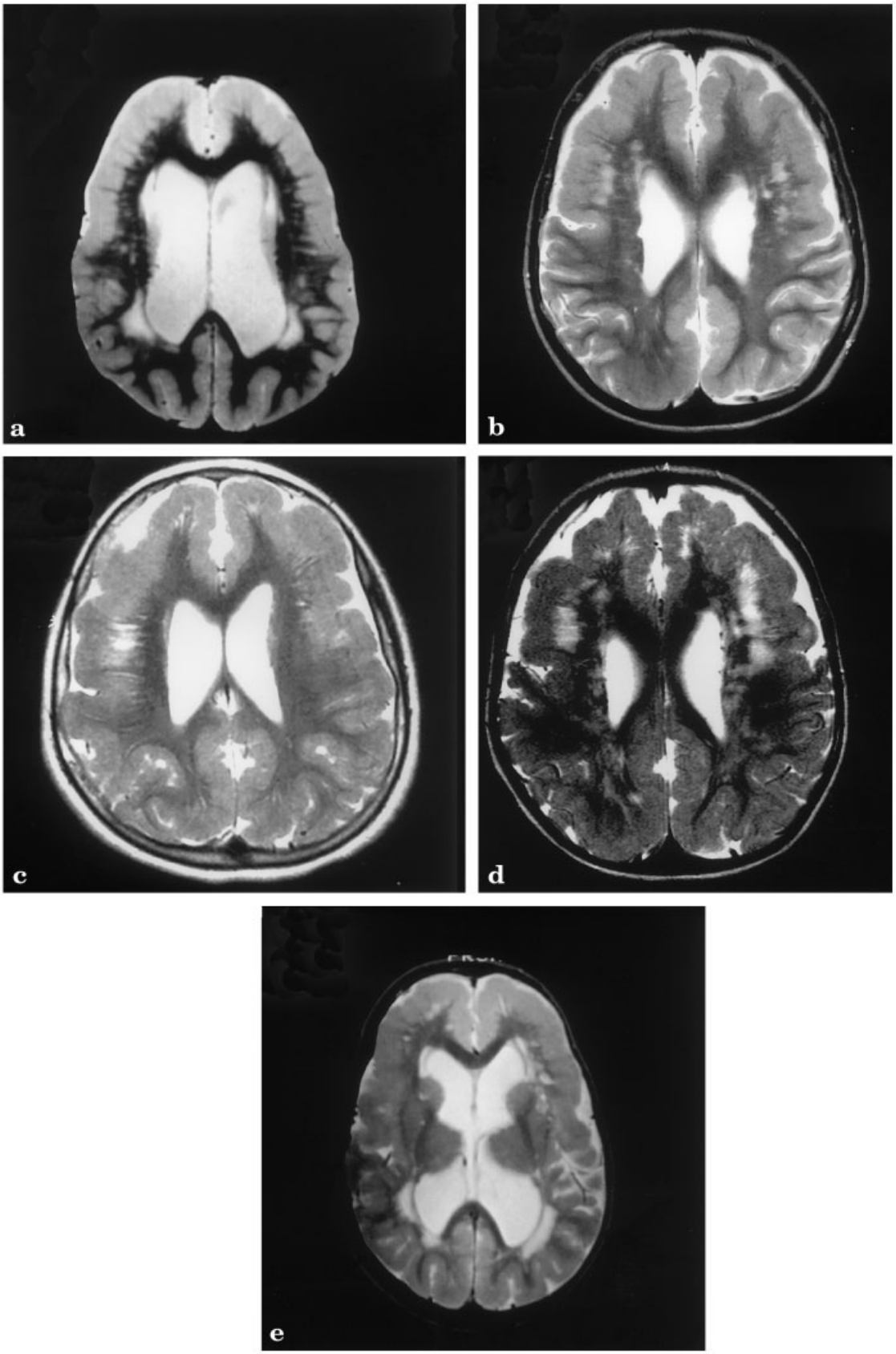

Figure 3

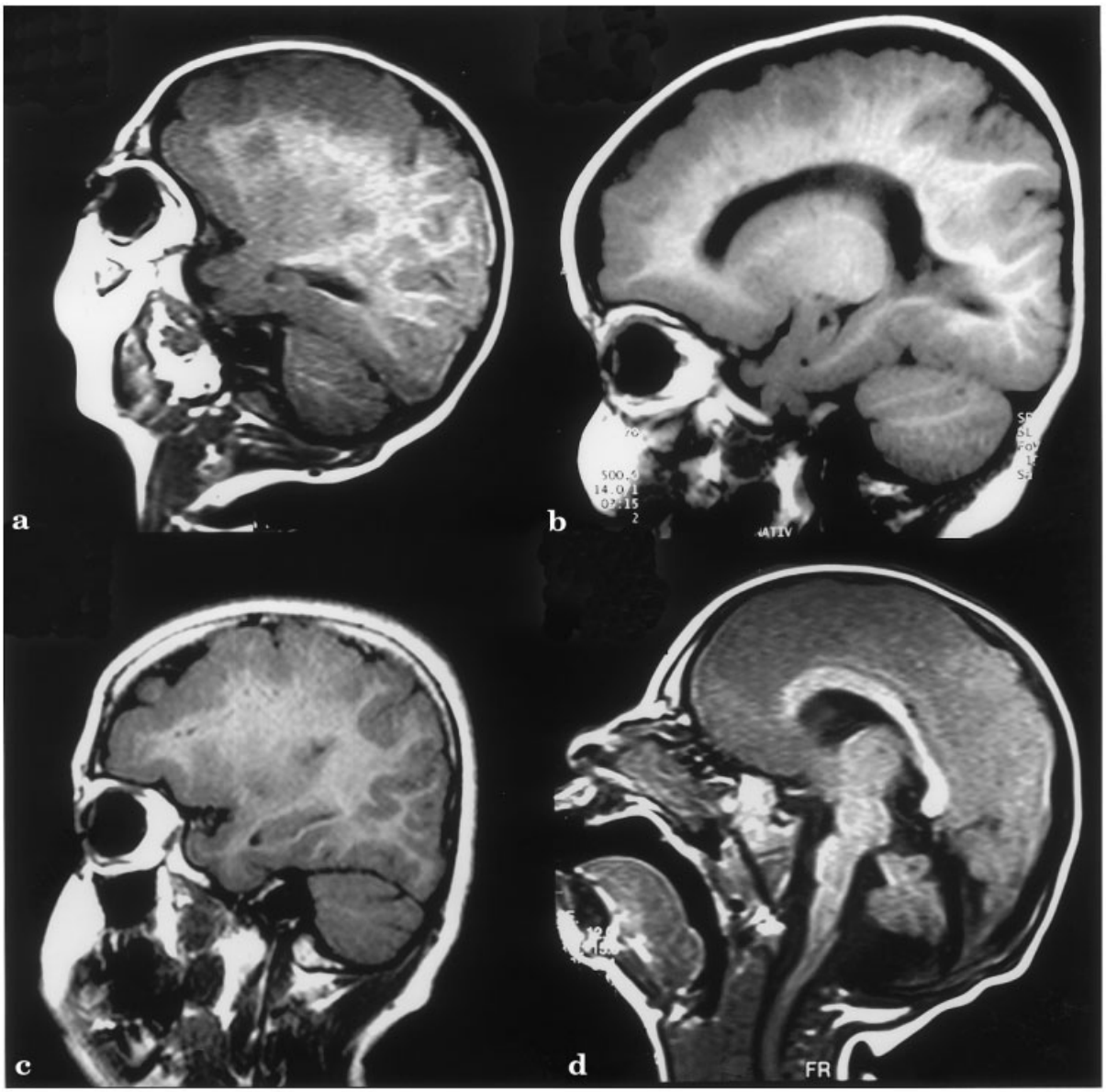

Fig 4. Representative T1-weighted sagittal magnetic resonance imaging of bilateral frontoparietal polymicrogyria patients. The anterior-posterior extent of the cortical malformation is best seen in these images. Scans a to c are from Patient V-1 in Family 9, Patient V-1 in Family 7, and Patient IV-1 in Family 8, respectively. In addition, characteristically small (likely hypoplastic) brainstem and cerebellar structures are evident in scan d, from Patient V-1 in Family 9.

malformation, most commonly, a form of pachygyria or lissencephaly. Careful attention to the acquisition of high-resolution MRI with thin sections and maximal contrast between cortex and white matter should make the accurate diagnosis of polymicrogyria in clinical practice increasingly straightforward.

BFPP joins a growing list of syndromes of bilateral symmetric polymicrogyria.[7] It can be distinguished from bilateral frontal polymicrogyria clinically in that it is familial and features esotropia and cerebellar dysfunction. Radiologically, the malformation extends more posteriorly than in bilateral frontal polymicrogyria and the brainstem and vermis are frequently small.[8] The white matter in BFPP is also distinctive, given the absence of reported white matter signal changes in bilateral frontal polymicrogyria.

Several radiological features help to distinguish BFPP from syndromes associated with cobblestone complex, such as Fukuyama congenital muscular dystrophy and Walker–Warburg syndrome.[30] These include the absence of cerebellar microcysts in BFPP, the prominent decreasing anterior-posterior gradient of the

Table 2. Degree of Linkage to the BFPP Locus on Chromosome 16q12–21

Family No.	Ethnicity/National Origin	Maximal Multipoint LOD Score
10	Bedouin (Kuwait)	2.92
1	Palestinian	2.48[a]
2	Palestinian	2.09[a]
8	Palestinian	2.05[b]
5	Qatar	2.05
9	Palestinian	1.49[b]
6	Pakistan	1.32
7	Afghanistan	0.88[c]
3	Pakistan	0.6[d]
4	India	0.6[d]

[a]These two families share a common haplotype at the BFPP locus.
[b]These two families share a second common haplotype at this locus.
[c]Two-point LOD score due to gaps in marker data.
[d]Not consanguineous.

BFPP = bilateral frontoparietal polymicrogyria; LOD = logarithm of odds.

cortical malformation in BFPP (in most cases of cobblestone complex the temporoparietooccipital cortex is more severely affected), the white matter signal changes suggestive of dilated perivascular spaces, and the scalloped appearance of the gray-white junction indicative of polymicrogyria rather than pachygyria.

Of the two sporadic cases of BFPP described,[15] one child was born to unrelated parents and exhibited developmental delay but not seizures, whereas the other child was born to consanguineous Middle Eastern parents and had both delay and generalized seizures, suggesting that the latter may in fact be a case of autosomal recessive BFPP. These families were not available for genetic testing.

Genetic Analysis

All of our families show evidence of autosomal recessive inheritance and demonstrate linkage to chromosome 16q, suggesting that BFPP may be a relatively uniform genetic entity. In fact, preliminary evidence suggests that other forms of frontal polymicrogyria without esotropia are not linked to chromosome 16 (X. Piao and C. Walsh, unpublished observations).

The presence of a distinct founder mutation in Families 8 and 9, who are the only BFPP patients who are microcephalic, raises the intriguing possibility that these two families carry either a more severe mutation in the same gene as BFPP patients with normal HC or a more extensive mutation that also affects a neighboring gene, resulting in a modified phenotype. Alternatively, because both families are consanguineous, there may be a recessive mutation in an entirely unrelated gene. The fact that the affected child in Family 6, who is relatively macrocephalic, maps to the same locus as the other patients suggests either some degree of phenotypic heterogeneity or an additional, as yet unidentified, genetic factor.

All of our patients with BFPP are originally from the Middle East or Indian subcontinent. To our knowledge, there are no published cases with similar features that originate from other parts of the world. However, especially because many of our patients initially were misdiagnosed with other malformations, it is unclear whether this syndrome is truly regionally distinctive. It may be that increased awareness of the clinical and radiological features of BFPP will allow for its identification in patients of European and other ancestries.

The presence of multiple syndromes of region-specific symmetric polymicrogyria suggests that there are likely to be distinct but potentially overlapping genetic influences on development of the telencephalon along a rostral-caudal axis. The genes for these disorders may, for example, be critical to proper development of the region-specific architecture of the cerebral cortex. Increased clinical awareness of these syndromes will aid in the identification of additional affected families and facilitate further genetic analysis.

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