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Consistent Chromosome Abnormalities Identify Novel Polymicrogyria Loci in 1p36.3, 2p16.1–p23.1, 4q21.21–q22.1, 6q26–q27, and 21q2

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Polymicrogyria is a malformation of cortical development characterized by loss of the normal gyral pattern, which is replaced by many small and infolded gyri separated by shallow, partly fused sulci, and loss of middle cortical layers. The pathogenesis is unknown, yet emerging data supports the existence of several loci in the human genome. We report on the clinical and brain imaging features, and results of cytogenetic and molecular genetic studies in 29 patients with polymicrogyria associated with structural chromosome rearrangements. Our data map new polymicrogyria loci in chromosomes 1p36.3, 2p16.1–p23, 4q21.21–q22.1, 6q26–q27, and 21q21.3–q22.1, and possible loci in 1q44 and 18p as well. Most and possibly all of these loci demonstrate incomplete penetrance and variable expressivity. We anticipate that these data will serve as the basis for ongoing efforts to identify the causal genes located in these regions.

Key words: chromosome 1p36; chromosome 1q4; chromosome 2p; chromosome 4q2; chromosome 6q2; chromosome 18p; chromosome 21q2; deletion; duplication; polymicrogyria

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INTRODUCTION

Polymicrogyria (PMG), recognized since at least 1899 [Bresler, 1899], is characterized by an irregular brain surface, loss of the normal gyral pattern which is replaced by numerous small and infolded gyri separated by shallow sulci that are partly fused in their depths, and reduction of the normal 6-layered

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to a 4-layered or unlayered cortex [Crome, 1952; Levine et al., 1974; Ferrer, 1984; Leventer, 2007]. PMG most often occurs as an isolated cortical malformation, but may be associated with other brain malformations including agenesis of the corpus callosum (ACC), microcephaly (MIC) or megalencephaly, periventricular nodular heterotopia (PNH), hydrocephalus (HYD), cerebellar vermis hypoplasia (CVH) or more diffuse cerebellar hypoplasia (CBLH). It is a relatively common malformation with a rate of at least 0.01 per 1,000 livebirths in a population-based monitoring program (program personnel, Metropolitan Atlanta Congenital Defects Program, Birth Defects and Genetic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, GA, personal communication, 2001). The frequency is probably higher as affected individuals were ascertained only if the diagnosis was recorded in hospital records during the first six years of life, likely underestimating the true incidence.

Several subtypes of PMG have been recognized based on differences in topography, such as diffuse or generalized, frontal, perisylvian, mesial parieto-occipital, and multilobar forms [Kuzniecky et al., 1993; Guerrini et al., 1997, 1998, 2000; Barkovich et al., 1999]. We have recognized several other types including posterior PMG [Ferrie et al., 1995], parasagittal PMG, and diffuse (or perisylvian) PMG with abnormal white matter (both as yet unpublished), as well as frontal or posterior predominate PMG with PNH [Wieck et al., 2005]. The perisylvian form accounts for 60–70% of patients, with all other forms being uncommon [Leventer et al., 2001; Leventer, 2007]. Several forms of severe congenital microcephaly have PMG including MIC with PMG and PNH [Wieck et al., 2005], with diffuse PMG only, and with asymmetric PMG (see Figures H–L in Dobyns and Barkovich [1999]). Similarly, several forms of megalencephaly have been associated with PMG including megalencephaly with mega-corpus callosum and PMG [Gohlich-Ratmann et al., 1998], MPPH [Mirzaa et al., 2004], and the CMTC-macrocephaly syndrome [Moore et al., 1997; Giuliano et al., 2004].

Despite numerous descriptions over many years, the pathogenesis of PMG remains poorly understood and likely heterogeneous. Many older reports support extrinsic in utero causes—most supporting a vascular pathogenesis—such as intrauterine cytomegalovirus infection, placental perfusion failure often related to twinning, and maternal exposure to warfarin in the second trimester, and point to a period of risk between 13 and 24 weeks gestation [Norman, 1980; Barth and van der Harten, 1985; Hayward et al., 1991; Barth, 1992; Barkovich and Lindan, 1994; Iannetti et al., 1998; Curry et al., 2005].

A genetic basis for some forms of PMG has been proposed based on reports of familial recurrence consistent with autosomal dominant, autosomal recessive or X-linked inheritance [Hilburger et al., 1993; Ferrie et al., 1995; Bartolomei et al., 1999; Borgatti et al., 1999; Caraballo et al., 2000; Guerreiro et al., 2000], and from association with several chromosome abnormalities, such as deletion 22q11.2 or DiGeorge syndrome [Robin et al., 2006]. While PMG has been reported in patients with deletion or duplication of other chromosome regions, documentation has typically been limited.

Here, we describe the clinical and brain imaging features, and results of molecular genetic analysis in a series of 29 patients with PMG associated with various unbalanced chromosome constitutions ascertained from more than 800 patients with PMG in our large Brain Malformation and Deletion 1p36 databases. We have excluded patients with PMG and deletion 22q11.2 as these were reported previously [Robin et al., 2006]. Our data support the existence of 5 novel PMG loci in chromosomes 1p36.3, 2p16.1–p23, 4q21.21–q22.1, 6q26–q27, and 21q2, as well as possible loci in 1q44 and 18p. Other recent papers or abstracts suggest additional loci in 2p15–p16, 11q12–q13, and 13q14.1–q31.2 as well [Dupuy et al., 1999; Kogan et al., 2008].

METHODS

Subjects

We searched our primary brain malformation subject database (W.B.D.) for all patients with PMG including those with known chromosome deletion or duplication, and our deletion 1p36 database (L.G.S.) for patients with PMG. Some were ascertained following our specific requests for referral of patients with chromosome abnormalities, so that ascertainment in both groups of patients was biased. We reviewed clinical summaries, brain imaging studies, and clinical photographs, and requested blood or other samples following Informed Consent with appropriate institutional approval. Clinical data were entered into a spreadsheet, with additional records requested when needed.

All brain imaging studies were reviewed (W.B.D., R.J.L.) looking for characteristic changes of PMG including irregular or pebbled brain surface, abnormal gyral pattern, microgyri within the cortex, and irregular gray-white border. The severity of the cortical malformation was assessed using a grading system we developed for perisylvian PMG, in which the cortical malformation is most severe in the perisylvian region even when it extends to involve other regions of the cortex [Leventer et al., 2001; Leventer, 2007]. Grade 1 PMG involves the entire perisylvian region with extension to include one or both poles. Grade 2 involves the entire perisylvian region with extension to other brain regions but not involving either pole. Grade 3 PMG involves the entire perisylvian region without further extension, and grade 4 involves only the posterior perisylvian

region. We assessed whether the cortical malformation was more severe on the right versus left side by visual inspection.

Breakpoint Mapping

The 29 patients have been ascertained over many years, so that the methods of analysis have changed. Chromosome analysis was done at the referring institution for all patients, and was reported as abnormal in all but one patient, although for a few patients (i.e., the LP87-010 family) this required several attempts. No further studies were done for eight patients. We performed fine mapping of the breakpoints by fluorescence in situ hybridization (FISH) in 11 patients. BAC clones from the regions of interest were identified from the Ensembl (www.ensembl.org) and UCSC Genome Bioinformatics Site (http://genome.ucsc.edu/) genome databases. FISH was performed using standard methods [Shaffer et al., 1994].

We performed array comparative genome hybridization (aCGH) in 10 patients using four platforms. Five patients with deletion 1p36.3 were studied using either an array containing 97 clones covering the most distal 10.5 Mb of 1p36 [Yu et al., 2003], or the SignatureChip® from Signature Genomic Laboratories, LLC (Spokane, WA; http://www.signaturegenomics.com/). The remaining patients were studied using a ~19,000 whole genome BAC microarray available from the Roswell Park Cancer Institute [Cowell, 2004; Cowell et al., 2004], the Human Genome CGH Microarray Kit 44B® from Agilent Technologies (Palo Alto, CA) [Barrett et al., 2004], or the Genome-Wide Human SNP GeneChip® Array 5.0 from Affymetrix (Santa Clara, CA) [Ogawa et al., 2007]. In all 10 patients, copy number changes were seen in multiple contiguous BACs or clones. To confirm these results, metaphase FISH was performed with probes selected from the deleted or duplicated segments found on the microarrays. Deletion sizes (Table I) were estimated in accordance with the UCSC Genome Bioinformatics Site (Human March 2006 assembly; hg18).

RESULTS

We found 29 patients with PMG and cytogenetic deletions or duplications at seven different loci

TABLE I. Cytogenetic Abnormalities in 30 Patients With PMG

Subject #[a]		Karyotype	Critical region[b]	Method	BP1[c]	BP2[c]	Size (Mb)
LR06-214	1p#52	46,XY,del(1)(p36.3)	1p36.3	FISH	RP11-340B24	1pter	10.9
LP99-072	1p#36	46,XX,del(1)(p36.3)	1p36.3	FISH	RP5-1113E3	1pter	10.4
LP98-109	1p#53	46,XX,del(1)(p36.3)	1p36.3	FISH	RP4-575L21	1pter	10.1
LR04-027	1p#92	46,XY,del(1)(p36.3)	1p36.3	aCGH/FISH	RP11-807G9	1pter	10.0
LP99-182	1p#54	46,XX,del(1)(p36.3)	1p36.3	FISH	RP5-963K15	1pter	9.0
LR01-161	1p#34	46,XX,del(1)(p36.3)	1p36.3	aCGH/FISH	RP5-892F13	1pter	7.9
LR01-160	1p#14	46,XX,del(1)(p36.3)	1p36.3	FISH	RP3-467L1	1pter	7.7
LR01-382	1p#47	46,XX,del(1)(p36.3)	1p36.3	FISH	RP11-92O17	1pter	7.5
LR06-133	1p#59	46,XY,del(1)(p36.3)	1p36.3	FISH	RP3-453P22	1pter	7.3
LR01-380	1p#66	46,XY,del(1)(p36.3)	1p36.3	aCGH/FISH	RP11-312B8	1pter	6.8
LR02-165	1p#91	46,XX,del(1)(p36.3)	1p36.3	aCGH/FISH	RP1-120G22	1pter	6.2
LR01-159	1p#05	46,XY,der(1)t(1;1)(p36.3;q44)	1p36.3	FISH	RP1-58B11	RP11-656O22	5.5, 1.3
LR01-383	1p#23	46,XX,del(1)(p36.3)	1p36.3	aCGH/FISH	RP5-1096P7	1pter	4.8
LP94-079		46,XX,der(1)t(1;11)(q44;p15.3)	1q44	FISH	RP11-518L10[d]	1qter	4.5
LR00-173		46,XY,dup(2)(p13-p23)	2p16.1-p23.1	Cyto	—	—	~50
LP99-112		46,XX,dup(2)(p16.1-p23.1)	2p16.1-p23.1	aCGH/FISH	RP11-162J17	RP11-373L24	30.7
LR04-022a2		46,XY,del(4)(q21.21q22.1)	4q21.21-q22.1	aCGH/FISH	RP11-90N19	RP11-49M7	9.3
LR07-256		46,XY,del(4)(q21.2q23)	4q21.21-q22.1	aCGH/Cyto	chr4:80,044,702	100,378,930	20
LP87-010a1		46,XY,−6,+der(6),t(6;21)(q25.3;p11)	6q26-qter	Cyto	—	6qter	—
LP87-010a2		46,XX,−6,+der(6),t(6;21)(q25.3;p11)	6q26-qter	Cyto	—	6qter	—
LP87-010a3		46,XY,−6,+der(6),t(6;21)(q25.3;p11)	6q26-qter	Cyto	—	6qter	—
LP87-010a4		46,XY,−6,+der(6),t(6;21)(q25.3;p11)	6q26-qter	Cyto	—	6qter	—
LR05-261		46,XX,del(6)(q25.3)	6q26-qter	aCGH/FISH	RP1-249F5	6qter	10.4
LR00-218		46,XY,del(6)(q26)	6q26-qter	aCGH/FISH	RP11-664L13[e]	6qter	9.49
LP99-104a1	Pt. 4	46,XX,del(6)(q26)	6q26-qter	FISH	RP11-57O22	6qter	7.35
LP99-104a2	Pt. 5	46,XX,del(6)(q26)	6q26-qter	FISH	RP11-57O22	6qter	7.35
LP99-062		46,XX,del(18)(p11.1)	18p	Cyto	—	18pter	—
LR00-219		45,XY,−21,der(18),t(18;21)(p11.2,q22.1)	18p, 21q2	Cyto	—, 21cen	18pter, —	—
LR05-078		46,XX,del(21)(q21.3-q22.1)	21q2	Cyto	—	21qter	—

[a]The first column numbers come from our Brain Malformation Database (Dobyns) and second column from our 1p- Database (Shaffer) or their patient number in the previous report.
[b]The critical regions indicate the shortest region of overlap among multiple patients when this could be determined.
[c]BP1 indicates the last non-deleted clone centromeric to the bp, while BP2 indicates the first non-deleted clone telomeric to the bp for interstitial deletions and duplications, or the last non-deleted clone on the other chromosome for translocations.
[d]This clone was split by FISH.
[e]This deletion was visible and assigned a breakpoint in 6q25.3 but non-deleted clone RP11-664L13 is located in 6q26.
Seventeen patients have been previously reported including 10 of 13 patients with deletion 1p36 [Heilstedt et al., 2003a,b], LP94-079 [Boland et al., 2007], the LP87-010 family [Curry et al., 2000], and LP99-104a1 and a2 [Eash et al., 2005].

(Table I). The deletions or duplications were large enough to be visible with sizes between 4.5 and 10.9 Mb, except for one 20 Mb deletion, and 30.7 and 50 Mb duplications. The largest group of patients consists of 13 children with deletion 1p36.3, and includes 13 of 64 patients from our deletion 1p36 database. The remainder consists of eight patients with deletion 6q26-qter, two with duplication 2p16–p23, two with deletion 4q21.21–q22.1, single patients with deletion 1q44, 18p, or 21q2, and one with deletion of both 18p and 21q2.

Details regarding the general, developmental and neurologic phenotypes are summarized in Tables II and III. As expected, these generally matched published reports with the addition of more details regarding the neurological problems and brain imaging. However, only limited data are available regarding deletion 4q2 or 21q2, or duplication 2p16.1–p23. The brain imaging findings are summarized in Table IV with representative images shown in Figures 1–5. All but deletion 6q26 are associated with perisylvian PMG, which is by far the most common subtype [Leventer et al., 2001; Leventer, 2007].

Additional Locus Specific Results

Deletion 1p36.3. We found PMG in 13 of 64 patients with brain imaging studies performed from our deletion 1p36 database (L.G.S.) with the smallest deleting the last 4.8 Mb of 1p36 and establishing a critical region between BAC RP5-1096P7 and the telomere (Table I). Because none of our eight subjects with interstitial deletions manifested PMG, and all of the interstitial deletions retained the distal 1 Mb of telomere sequence, we hypothesize that the putative PMG causal gene is localized between 1.0 and 4.8 Mb from the 1p telomere. We identified PMG in 6 of 18 patients with deletions larger than 4.8 Mb, and so estimate the penetrance to be about 33%. Another three patients from our 1p36 database had possible areas of PMG, but the scan resolution was too low for us to be certain. Among the 13 patients with confirmed PMG, the malformation was symmetric in seven and asymmetric in six patients, with five more severe on the right and only one more severe on the left (Table IV, Fig. 1). The asymmetry is slightly skewed to the right hemisphere but does not reach statistical significance ($P = 0.18$), primarily due to the small numbers. We found similar asymmetry with the right hemisphere more often and more severely affected among patients with PMG associated with deletion 22q11.2 that did reach statistical significance [Robin et al., 2006]. Most patients with deletion 1p36 had abnormal white matter signal, and a few had other malformations such as PNH, enlarged lateral ventricles or mild CVH, but none had HYD.

Duplication 2p16.1p23. Both of our patients had symmetric perisylvian PMG extending to involve most of the brain, and the boy with the larger deletion also had HYD (Table IV, Fig. 2). We confirmed the abnormality in LR00-173 by FISH (Fig. 6), and used aCGH in patient LP99-112 to amend the cytogenetic breakpoints from p13–p15 to p16.1–p23.1, and mapped the putative PMG locus to a large 30 Mb region (Table I).

Deletion 4q21.21–q22.1. Our first patient (LR04-022a2) and an older half-sister with Dandy-Walker malformation were both conceived by in vitro fertilization; his sister does not share the 4q2 deletion. He was born following a pregnancy complicated by polyhydramnios and enlarged ventricles on prenatal ultrasound. His birth weight and head circumference were normal, and he had onset of seizures at 3 months. By 3 years, he had HYD managed with a shunt, and a non-communicating suprasellar cyst compressing the optic chiasm that was treated by fenestration of the cyst. His vision deteriorated following a shunt revision, but gradually improved to near normal. On exam at age 4.5 years, his OFC was 51 cm (50th centile). He had a triangular facial appearance with a relatively large head, prominent forehead, narrow nose, low-set and posteriorly rotated ears, flat philtrum and pointed chin. His balance was poor with probable ataxia, but he had minimal spasticity and normal reflexes. Abdominal ultrasound has not been done. Initial chromosome analysis was reported as normal, but array CGH detected a 9.3 Mb deletion in chromosome 4q21.1–q22.1 that was confirmed on repeat chromosome analysis.

The second child (LR07-256) with this deletion is a boy with severe developmental delay, hypotonia, normal head circumference, poor visual attention, conductive hearing loss, pale optic nerves, facial dysmorphism, atrial septal defect, and renal cysts. He also had a congenital juvenile-type granulosa cell tumor of the testes. Brain MRI in both boys (Fig. 2) shows PMG in the mid- and posterior frontal plus perisylvian regions and mildly enlarged lateral ventricles. The MRI was done prior to development of HYD and shunt insertion in the first boy. The second did not have HYD. Both had mild to moderate CVH, and the first also had an enlarged posterior fossa consistent with so-called mega-cisterna magna.

Deletion 6q26-qter. We reviewed brain-imaging studies of six patients (Fig. 3), and found extensive PMG that was sometimes difficult to appreciate in all of them. The PMG was most severe in the posterior frontal, perisylvian and temporal regions in three patients, and appeared limited to the temporal lobe in the other three. Other abnormalities included PNH of the trigones or temporal horns in four patients, HYD in three with less marked ventricular enlargement in the others, partial ACC in one and thin corpus

TABLE II. Congenital Anomalies in PMG Syndromes

Subject #		Age	Sex	Locus	Facial features	Heart	Hearing	Eye	Other
LR06-214	1p#52	4 y	F	1p36.3	—	Dilated Ao root	SNHL, severe	Normal	—
LP99-072	1p#36	8 y	F	1p36.3	DYSM	—	—	—	—
LP98-109	1p#53	13 y	F	1p36.3	DYSM, cleft palate	CM, VSD, ASD, PDA	SNHL	Blind, retinal COL, ESO, hyperopia, astigmatism	Horeshoe kidney, kyphosis, scoliosis, GR
LR04-027	1p#92	(6 m)	M	1p36.3	DYSM	PDA, ASD, PFO, Ao coarctation	—	Mild L ptosis	Finger contractures, clinodactyly
LP99-182	1p#54	9 y	F	1p36.3	DYSM	PDA, ASD, VSD	SNHL	—	HipD, PylS
LR01-161	1p#34	8 y	F	1p36.3	DYSM	Bicuspid AV, PDA, PFO, trivial TR, MiR, PR, AR	SNHL	Nystagmus, large angle exotropia, hyperopia	Achalasia
LR01-160	1p#14	10 y	F	1p36.3	DYSM, cleft lip	Dilated CM, PFO, Ao tubular hypoplasia	CHL, SNHL	Exotropia	—
LR01-382	1p#47	3 y	F	1p36.3	DYSM	Normal	SNHL, L > R	Mild L ptosis	Cricoid cleft, clinodactyly
LR06-133	1p#59	6 y	M	1p36.3	—	VSD x2, PFO, thick mitral valve leaflets	SNHL, mild	Visual inattention, o/w normal	Borderline growth hormone deficiency
LR01-380	1p#66	6 m	M	1p36.3	DYSM	VSD	—	Lamellar CAT (R > L)	BPD, poorly developed lungs, diastasis recti
LR02-165	1p#91	4 y	F	1p36.3	DYSM	PDA, ASD, PFO, long QT	SNHL	B cystic retinal COL, hyperopia	UMB wall defect and hernia
LR01-159	1p#05	16 y	M	1p36.3	DYSM	—	—	—	—
LR01-383	1p#23	2 y	M	1p36.3	—	—	—	—	—
LP94-079		(11 d)	F	1q44	DYSM, large tongue	VSD, PDA, TR	—	—	—
LP99-112		19 y	F	2p1–p2	DYSM, HYP	—	—	Strabismus	—
LR00-173		6 y	M	2p1–p2	DYSM, HYP	—	—	—	Ambiguos genitalia, chordee, hypospadius, cryptorchidism
LR04-022a2		4.5 y	M	4q2	DYSM	N	N	—	Suprasellar cyst
LR07-256		8 m	M	4q2	DYSM	ASD	CHL	Pale ON	Renal cysts, juvenile granulosa cell tumor
LP87-010a1		22 y	M	6q26	DYSM	VSD	—	B microcornea, ON COL, nystagmus	Hyperextensible joints, UMB hernia
LP87-010a2		9 y	F	6q26	DYSM	—	—	Strabismus	Scoliosis, lipoma of filum terminale, tethered cord
LP87-010a3			M	6q26	DYSM	ASD	—	N	Skin soft and hyperextensible
LP87-010a4		(3 m)	M	6q26	—	N	—	N	—
LR05-261		6 m	F	6q26	DYSM	—	—	B iris, retinal, and ON COL	Rocker bottom feet
LR00-218		5 y	M	6q26	—	—	—	—	Intestinal volvulus
LP99-104a1		12 y	F	6q26	DYSM	—	—	Esotropia	R kidney cyst, tethered cord
LP99-104a2		5 y	F	6q26	DYSM	—	—	Blind, roving eye movements, midline gaze paresis	Tethered cord
LP99-062		8 y	F	18p	DYSM	—	—	Ptosis, myopía, esotropia, ambylopia	Hyperextensible knees
LR00-219			M	18p, 21q2	—	—	—	—	—
LR05-078		12 y	F	21q2	DYSM	—	—	—	—

Ao, aortic; AR, aortic valve regurgitation; ASD, atrial septal defect; AV, aortic valve; B, bilateral; BPD, broncho-pulmonary dysplasia; CAT, cataract; CHL, conductive hearing loss; CL, cleft lip; CM, cardiomyopathy; COL, coloboma; CP, cleft palate; DYSM, dysmorphic facial features; ESO, esotropia; GR, growth deficiency; HipD, hip dysplasia; HYP, hypertelorism; m, months; MiR, mitral valve regurgitation; ON, optic nerve; PDA, patent ductus aretriosus; PFO, patent foramen ovale; PR, pulmonary valve regurgitation; PylS, pyloric stenosis; R, right; SNHL, sensorineural hearing loss; TR, tricuspid valve regurgitation; UMB, umbilical; VSD, ventricular septal defect; y, years. Ages in parenthesis are age at death.

TABLE III. Neurologic Abnormalities in PMG Syndromes

Subject #		OFC		Neurological exam	DD/MR	Seizures age of onset, type
		First	Last			
LR06-214	1p#52	—	—	—	Severe	Yes, age and type unknown
LP99-072	1p#36	—	10 mo: 40.3 cm (−3.75 SD)	HYPER L ankle, paresis L arm	Yes	3 mo, type unknown
LP98-109	1p#53	—	10 mo: 45 cm (50th centile)	HYPO, chorea, athetosis	Severe	2 mo, TC, myoclonic
LR04-027	1p#92	—	6 mo: 41.5 cm (−2 SD)	HYPO, head lag	Yes	2 mo, type unknown
LP99-182	1p#54	Birth: 35 cm (+0.25 SD)	3 mo: 39.1 cm (50th centile)	HYPO, weak feet	Yes	Apnea-bradycardia soon after birth
LR01-161	1p#34	Birth: 36 cm (+1.75 SD)	10 mo: 44.5 (∼50th centile)	HYPO, increased DTR	Yes	No info
LR01-160	1p#14	1 mo: 34 cm (−2 SD)	19 mo: 44 cm (−2.5 SD)	HYPO	Yes	Yes, age and type not available
LR01-382	1p#47	Birth: 33 cm (−1 SD)	3 y: 47 cm (−2 SD)	HYPO, HYPER at ankles only, DTR 3+ at knees, weak gag	Severe	None by 3 y
LR06-133	1p#59	—	—	HYPO	Severe	2 mo, myoclonic, TC
LR01-380	1p#66	Birth: 33.3 cm (−1.75 SD)	1 y: 44.3 cm (−2 SD)	HYPO diffuse	—	1 mo, jaw jerking and quivering
LR02-165	1p#91	6 mo: 41 cm (−1 SD)	1 y: 44 cm (−1.75 SD)	HYPO, decreased DTR	Yes	3 mo, TC
LR01-159	1p#05	3.5 mo: 40.5 cm (∼50th centile)	6 y: 48 cm (−2.25 SD)	HYPO diffuse, paresis R arm, hyperactive, autistic features	Yes	3 mo, TC
LR01-383	1p#23	—	—	—	—	—
LP94-079		Birth: 31.75 cm (−2 SD)	—	HYPO	Yes	4 hr, TC
LP99-112		12 y: 52.2 cm (−1 SD)	15 y: 53 cm (−1.75 SD)	Unsteady gait	Yes	10 y, behavior outbursts of uncertain cause
LR00-173		Birth: 32.5 cm (−2 SD)	—	—	—	—
LR04-022a2		Normal	4.5 y: 51 cm (50th centile)	Ataxia, poor vision after shunt failure, spasticity at ankles	Severe	3 mo, probable ISS
LR07-256		3 mo: 40.5 cm (20th centile)	7 mo: 45 cm (60th centile)	HYPO, poor visual attention	Yes	No
LP87-010a1		Birth: 35.5 cm (∼50th centile)	14.5 y: 51.25 cm (−2.25 SD)	Poor muscle bulk, especially legs	Yes	6 mo, TC
LP87-010a2		9 mo: 38.25 cm (−4.5SD)	1.5 y: 41.5 cm (−4 SD)	Mixed HYPER and HYPO, mild tremor, brisk DTR	Yes	—
LP87-010a3		—	—	—	—	—
LP87-010a4		3 mo: 42 cm (∼75th centile)	—	—	—	—
LR00-218		22 mo: 45 cm (−3 SD)	—	HYPO, HYPER at ankles	Yes	Yes, TC
LP99-104a1		Birth: 31.8 cm (−2 SD)	4.5 y: 45.7 cm (−4 SD)	HYPO, repetitive behavior, poor coordination, gait ataxia	Yes	9 mo, PC
LP99-104a2		Birth: 41 cm (+5.5 SD)	11 mo: 46 cm (+0.25 SD)	HYPO diffuse	Yes	2 mo, absence-like
LR05-261		Birth: 31.0 cm (−2.25 SD)	—	—	—	—
LP99-062		8.5 mo: 46 cm (+1.75 SD)	5.5 y: 51.5 cm (+1.25 SD)	HYPO	Yes	—
LR00-219		—	—	—	—	—
LR05-078		10 y: 48.5 cm (−2 SD)	11 y: 48.5 cm (−3 SD)	Slight HYPER, wide-based gait	Yes	10 y, head drops

AB, apnea-bradycardia; DTR, deep tendon reflexes; HYPER, hypertonia (spasticity); HYPO, hypotonia; L, left; mo, months; PC, partial complex; R, right; SD, standard deviations; TC, tonic-clonic; y, years.

TABLE IV. Polymicrogyria and Other Brain Anomalies

Subject #		Locus	PMG Type	PMG Grade	PMG Sym.	HET location	LV	Midline	CBL	WM	Prior references
LR06-214	1p#52	1p36.3	PS	R2	R > L	None	DIL	N	N	—	Heilstedt et al. [2003a,b]
LP99-072	1p#36	1p36.3	PS	L4-R1	R > L	None	R > L	Thin	N	Abn	Heilstedt et al. [2003a,b]
LP98-109	1p#53	1p36.3	PS	L2-R1	R > L	L FH	DIL	Thin	CVH	—	Heilstedt et al. [2003a,b]
LR04-027	1p#92	1p36.3	PS	4	SYM	None	N	N	N	—	
LP99-182	1p#54	1p36.3	PS	4	R > L	None	DIL	Thin, CSP	N	N	Heilstedt et al. [2003a,b]
LR01-161	1p#34	1p36.3	PS	2	SYM	None	DIL	N	N	Abn	Heilstedt et al. [2003a,b]
LR01-160	1p#14	1p36.3	PS	4	SYM	None	DIL	Thin, CSP	N	Abn	Heilstedt et al. [2003a,b]
LR01-382	1p#47	1p36.3	PS	R4	R > L	None	N	N	N	Abn	Heilstedt et al. [2003a,b]
LR06-133	1p#59	1p36.3	PS	4	L > R	None	R > L	N	CBLH	Abn	Heilstedt et al. [2003a,b]
LR01-380	1p#66	1p36.3	PS	1	SYM	None	DIL	N	N	Abn	
LR02-165	1p#91	1p36.3	PS	R4	R > L	None	DIL	N	N	N	
LR01-159	1p#05	1p36.3	PS	L1-R4	L > R	none	L > R	N, CSP	N	—	Heilstedt et al. [2003a,b]
LR01-383	1p#23	1p36.3	PS	4	R > L	R FH, L TRI	DIL	ACC	N	Abn	Heilstedt et al. [2003a,b]
LP94-079		1q44	PS	2	SYM	—	N	N	CBLH		Boland et al. [2007]
LP99-112		2p16.1–p23.1	PS	1	SYM	None	N	N	N		
LR00-173		2p16.1–p23.1	PS	1	SYM	None	HYD	N	N		
LR04-022a2		4q21.21–q22.1	PS	1	SYM	None	HYD	N	MCM		
LR07-256		4q21.21–q22.1	PS	1	SYM	None	DIL	N	CVH		
LP87-010a1		6q26	PS-TL	—	SYM	—	HYD	N	N		Curry et al. [2000]
LP87-010a2		6q26	PS-TL	2	SYM	L > R TRI	DIL	Thin	CVH		Curry et al. [2000]
LP87-010a3		6q26	+++	—	—	—	HYD	Thin, ASP	CBLH		Curry et al. [2000]
LP87-010a4		6q26	+++	—	SYM	None	HYD	Thin	CBLH	Thin	Curry et al. [2000]
LR05-261		6q26	PS-TL	—	SYM	TH	R TH	ACC	CBLH		
LR00-218		6q26	PS-TL	2	SYM	None	HYD	Thin	CBLH		
LP99-104a1	Pt. 4	6q26	PS-TL	n.a.	SYM	TH	DIL	N	N		Eash et al. [2005]
LP99-104a2	Pt. 5	6q26	PS-TL	n.a.	SYM	TH	HYD	Thin[a]	N		Eash et al. [2005]
LP99-062		18p	PS	R1	R > L	None	DIL	N	N		
LR00-219		18p, 21q2	PS	1	SYM	None	DIL	Thin	CVH		
LR05-078		21q2	PS	3	SYM	None	N	ACC	N		

Abn, abnormal white matter signal; ACC, partial agenesis of the corpus callosum; CBL, cerebellum; CBLH, diffuse cerebellar hypoplasia; CSP, cavum septi pellucidi et vergae; CVH, cerebellar vermis hypoplasia; DIL, dilated; HYD, hydrocephalus; L, left; L > R, left more severe than R; Midline, corpus callosum and septum pellucidum; N, normal; n.a., not applicable; PS, perisylvian; R, right; R > L, right more severe than left; SYM, symmetric; TH, temporal horns; TL, temporal lobe; TRI, trigone of lateral ventricles; WM, white matter; —, too few or suboptimal images to determine. See text for explanation of PMG grades.
[a]Unclear if primary partial ACC or secondary destruction due to hydrocephalus.

callosum in three more, and CBLH in three patients. Autopsy in one boy (LP87-010a4) demonstrated extensive PMG, reduced volume of white matter, enlarged lateral ventricles, and cerebellar hypoplasia or atrophy.

Several patients were assigned breakpoints in 6q25.3 by cytogenetic analysis, with one (LR00-218) corrected to 6q26 by aCGH. The deletions ranged from 7.35 to 10.4 Mb in size. The sisters with the smallest deletion had fewer anomalies outside of the brain, but were otherwise similar [Eash et al., 2005]. One of the two sisters had HYD.

DISCUSSION

Our results and reports from the literature provide strong support for six PMG loci associated with pathogenic copy number variants, and weaker support for another five loci, which should be considered tentative from the data available (Table V). Several more loci associated with autosomal recessive or X-linked inheritance are known as well.

Confirmed PMG loci

Deletion 1p36.3. Deletion 1p36.3 is the most commonly observed terminal deletion syndrome in humans [Heilstedt et al., 2003a]. The phenotype consists of developmental delay, mental retardation, hypotonia, speech delay, seizures, cardiomyopathy, congenital heart defects, hearing loss, eye anomalies, and gastrointestinal problems. The most frequent dysmorphic features are flat nasal bridge, deep-set eyes, large anterior fontanel, pointed chin, microcephaly, clinodactyly, and midface hypoplasia [Reish et al., 1995; Shapira et al., 1997; Slavotinek et al., 1999; Knight-Jones et al., 2000; Heilstedt et al., 2003a,b]. Previous mapping studies defined critical regions for hearing loss, moderate to severe mental retardation (D1S243 to D1S468) and seizures [Shapira et al., 1999; Wu et al., 1999], while brain imaging studies typically show abnormal white matter signal, especially on Flair sequences. Autopsy in one patient included in our series confirmed PMG [Shapira et al., 1999], as did a recent report of another patient [Ribeiro Mdo et al., 2007]. Our

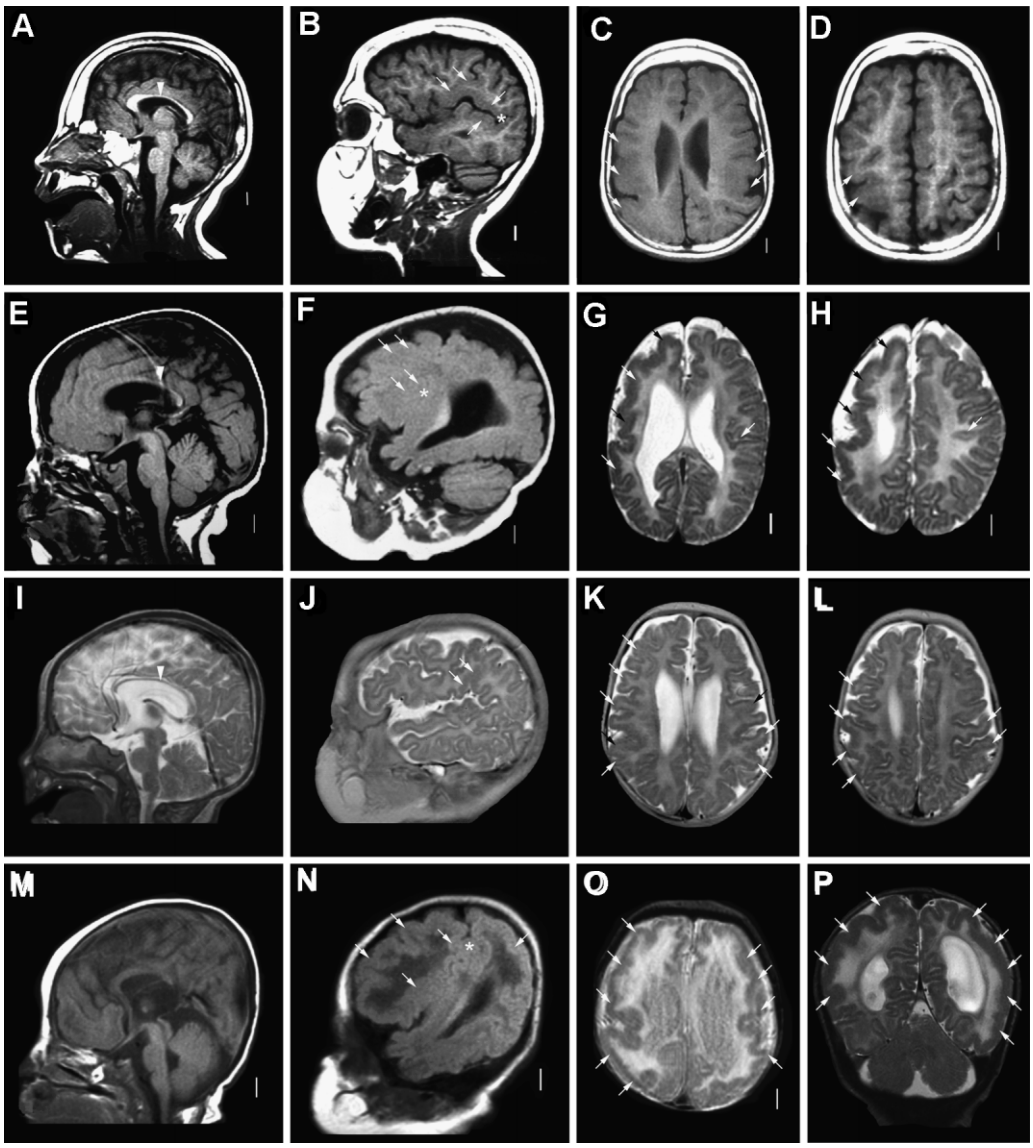

FIG. 1. Brain images from four patients with deletion 1p36 including LP98-109 (**A–D**), LP99-072 (**E–H**), LP99-182 (**I–L**), and LR01-380 (**M–P**). These images demonstrate extensive areas of polymicrogyria (PMG, white or black arrows in many images) characterized by an irregular gyral pattern with abnormally wide sulci that are often too shallow or deep, as well as variably thick cortex. The PMG appears most severe in the posterior frontal and perisylvian regions and may be asymmetric. Here, the cortical malformation appears symmetric in two patients (C,D, O,P), mildly asymmetric in one (K,L) and strikingly asymmetric in another (G,H). In both asymmetric patients, the PMG is more severe on the right (left side of image as shown). Midline sagittal images show a mildly thin corpus callosum (arrowheads in A,E,I), and parasagittal images demonstrate an extended sylvian fissure (asterisks in B,F,N).

genotype–phenotype analysis revealed brain abnormalities on MRI in 60% of patients with deletion 1p36, with patchy signal abnormalities in white matter (leukoencephalopathy) and PMG being the most common (unpublished data). Other abnormalities found in more than one subject include generalized atrophy, prominent ventricles, delayed myelination, and thinning of the corpus callosum.

Duplication 2p16.1–p23. The syndrome resulting from duplication of proximal 2p has not previously been delineated, although we found old reports of two patients [Yunis et al., 1979; Monteleone et al., 1981]. Adding these to our two patients (Tables II and III), we reviewed clinical data on one girl with dup 2p16.1–p23.1, two boys with dup 2p13–p23 or 2p14–p23, and a newborn girl with dup 2p13-pter. From these data, the proximal 2p duplication syndrome is characterized by normal head size, mental retardation, and facial dysmorphism consisting of hypertelorism, broad nasal bridge and low-set malformed ears. The two boys with dup 2p13–p23 also had growth deficiency and genital abnormalities consisting of hypospadius and cryptorchidism. One boy (LR00-173) had corneal clouding. The girl with dup 2p13-pter had intrauterine growth retardation, similar facial

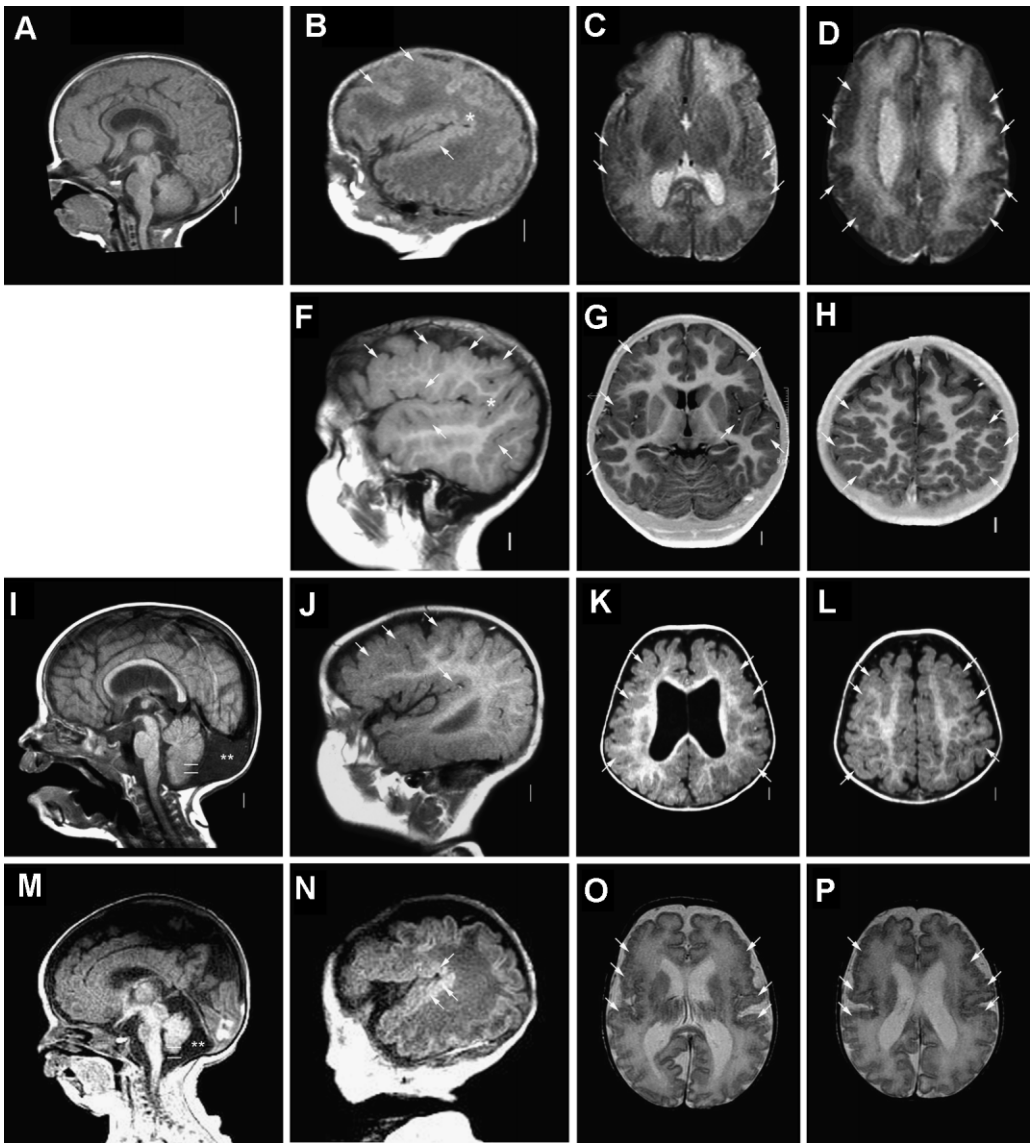

FIG. 2. Brain images from patients with dup 2p16–p23 (**A–D**, LP99-112 and **E–H**, LR00-173), and del 4q21–q22 or q23 (**I–L**, LR04-022a2 and **M–P**, LR07-256). These images show extensive areas of PMG (white arrows in many images) that appear most severe in the posterior frontal and perisylvian regions, but are symmetric in all patients shown. Midline sagittal images show mild (I) or moderate (M) cerebellar vermis hypoplasia (CVH), as the bottom of the vermis (top white line in I,M) does not extend down to the level of the obex (bottom white line in I,M). The cisterna magna (double asterisks) is mildly prominent in one (M) and enlarged with an enlarged posterior fossa consistent with so-called mega-cisterna magna (I) in the other.

changes plus cleft palate, skeletal anomalies and a complex heart malformation. Autopsy showed ovarian hypoplasia and dysplasia, as well as cerebellar hypoplasia with dysplastic foliar pattern and heterotopia that we presume were PNH [Monteleone et al., 1981]. The girl with the smallest deletion (LP99-112) has had seizures, behavior problems and sleep disturbances.

Deletion 4q21.21–q22.1. At least 10 children with deletion 4q21–q22 have been reported, with typical features including developmental delay, mental retardation, hypotonia, absolute or relative macrocephaly, frontal bossing, small nose, flat nasal bridge, malformed ears and small jaw. HYD was noted in 4 of 10 patients [Nowaczyk et al., 1997]. PMG has not been reported, but our review of the original brain MRI of Patient 1 from this report [Nowaczyk et al., 1997] shows partial ACC with a short corpus callosum, small rostrum and absent genu, moderate CVH, and small areas of PMG in the posterior perisylvian regions (courtesy of M. Nowaczyk and S. Blaser). Rare patients with deletion of this region have had polycystic kidney disease associated with deletion of *PKD2* [Velinov et al., 2005], or infantile hepatocellular carcinoma [Terada et al., 2001].

The 9.3 Mb deletion in our patient LR04-022a2 contains 55 RefSeq genes including *PKD2*, while the deletion in LR07-256 is much larger, encompassing

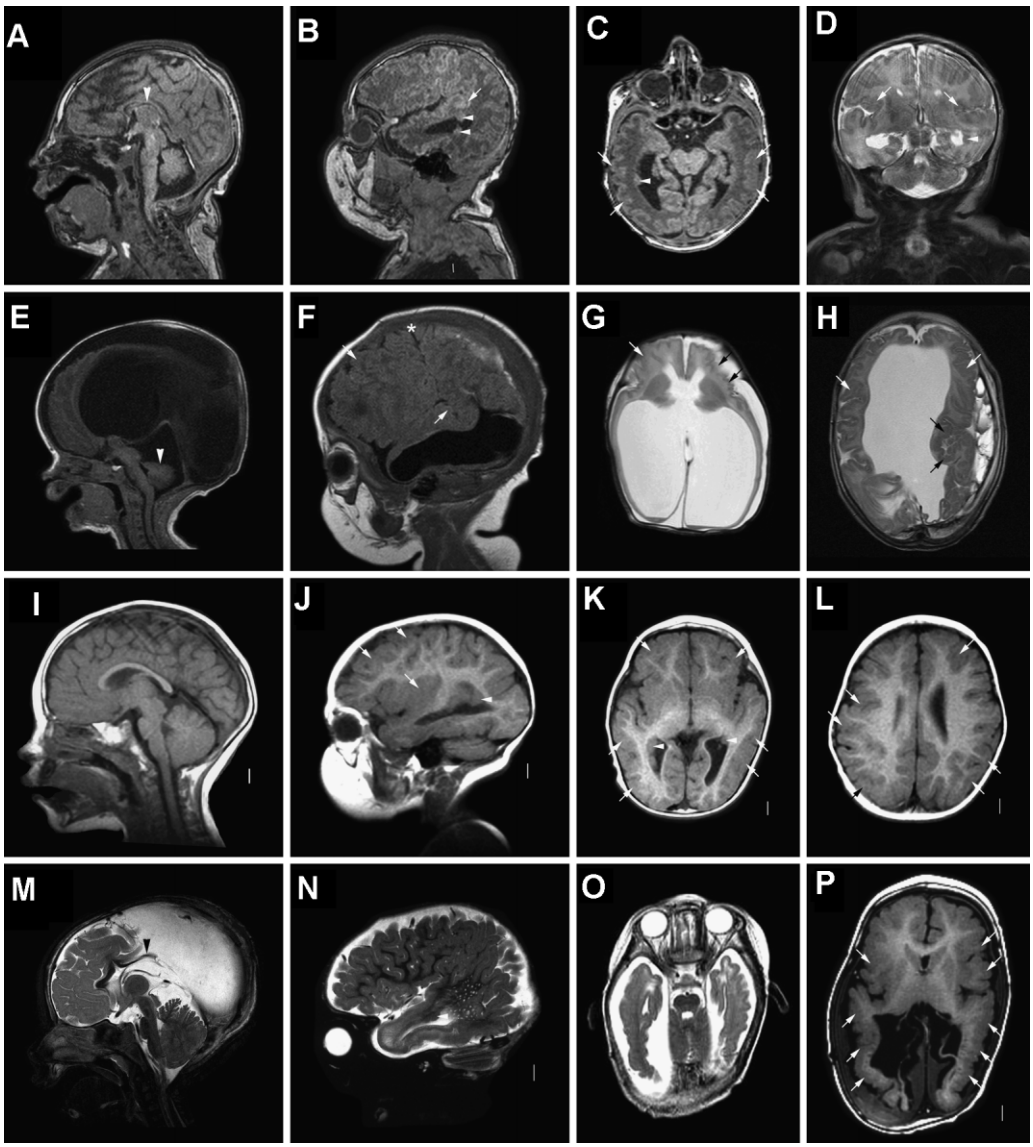

FIG. 3. Brain images from four patients with deletion 6q26 including LR05-261 (**A–D**), LR00-218 (**E–H**), LP99-104a1 (**I–L**) and LP99-104a2 (**M–P**). These images show extensive areas of PMG (white arrows in many images) that is more difficult to appreciate than in other figures, but appears most severe in the temporal lobes and perisylvian regions. Midline sagittal images show thin and short corpus callosum (arrowheads in A,M) and CVH (arrowhead in E but also mildly small in A). Two patients had hydrocephalus (G,H,P).

the entire region deleted in the first boy. The 9.3 Mb deletion overlaps with a region predisposing to hepatocellular carcinoma [Yeh et al., 2004; Nishimura et al., 2006], which when considered together with the granulosa cell tumor in LR07-256 supports the existence of one or more oncogenes in this region.

Deletion 6q26-qter. At least 30 patients with deletion 6q25-qter have been reported, most with deletion of the entire region. A review of 26 patients found mental retardation and facial dysmorphism in all, seizures in 88%, and short neck, retinal abnormalities, heart malformations and genital hypoplasia including cryptorchidism in about 50% each [Hopkin et al., 1997]. Three patients had HYD. The most consistent facial features were hypertelorism (30%), prominent nasal bridge (67%), epicanthal folds (66%), ear anomalies (88%), and small jaw (72%). The retinal changes were variously described as abnormal retinal vessels, retinal pits or macular disorders such as hypopigmentation, hypoplasia, or degeneration. Reports of about 17 patients with smaller deletions of distal 6q26–q27 describe less severe mental retardation but similar facial dysmorphism, mild MIC and short stature [Eash et al., 2005; Bertini et al., 2006]. None had short neck, retinal anomalies, heart malformations, or genital hypoplasia. One child with a small 400 kb subtelomeric deletion had HYD, but also other atypical anomalies such as tracheo-esophageal

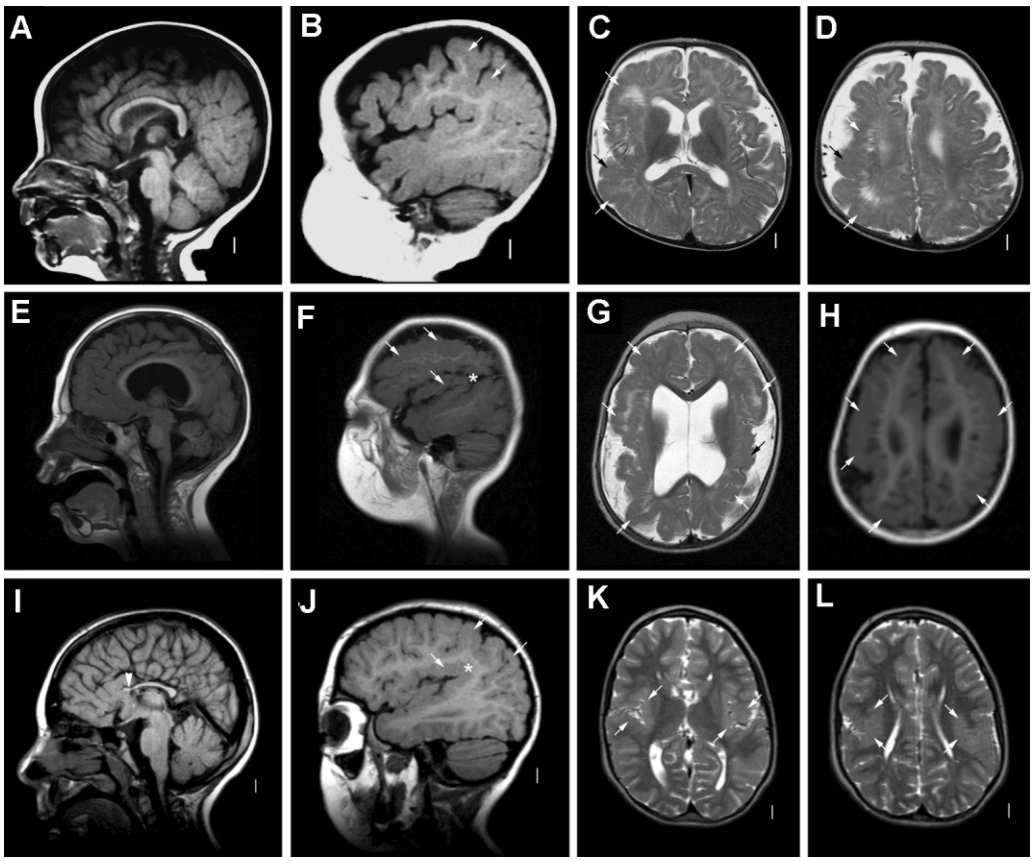

FIG. 4. Brain images from patients with del 18p (**A–D**, LP99-062), del 18p and 21q2 (**E–H**, LR00-219), and del 21q2 (**I–L**, LR05-078). These images show variable areas of PMG (white or black arrows in many images). In the girl with del 18p, the cortical abnormality involves the perisylvian and posterior regions on the right (C,D). In the boy with del 18p plus del 21q2, the PMG involves the entire cortex except for the mesial frontal lobes and appears most severe in the posterior frontal and perisylvian regions (G,H). In the girl with del 21q2, the PMG involves only the perisylvian regions (K,L). Midline sagittal images show dysplastic corpus callosum in one patient consisting of absent rostrum and small genu (arrowhead in I).

fistula suggesting VATER syndrome, so we suspect that this child has a separate etiology for these abnormalities.

The PMG and PNH seen with deletion 6q26 (Fig. 3) differs from other forms of PMG, somewhat resembling the posterior PNH and PMG syndrome that we recently described [Wieck et al., 2005]. Other reports provide limited information about the brain, although autopsy in a boy with ring chromosome 6 and presumed breakpoint in 6q26 demonstrated MIC, PMG, and HYD [Salamanca-Gonez et al., 1975]. Another child had PNH with no further brain imaging data provided [Bertini et al., 2006]. Our data maps the critical region to a 7.35 Mb region between BAC RP11-57O22 and the 6q telomere (Table I), with penetrance unknown.

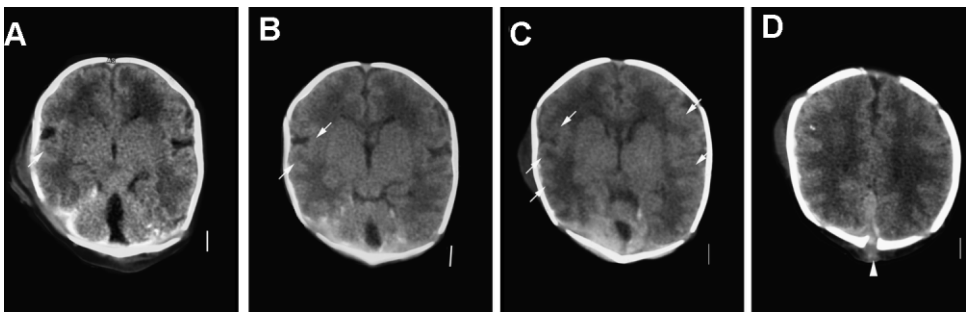

FIG. 5. Brain CT images from a girl with deletion 1q44 (**A–D**, LP94-079) show an open sylvian fissure, reduced sulcation and mildly thick cortex (white arrows in each image) that suggest a cortical malformation. The lowest image demonstrates severe CVH based on lack of any vermis at the level of the midbrain (A), and the highest image shows a small occipital cephalocele (arrowhead in D). Images (A,B,D) are re-printed from Boland et al. [2007].

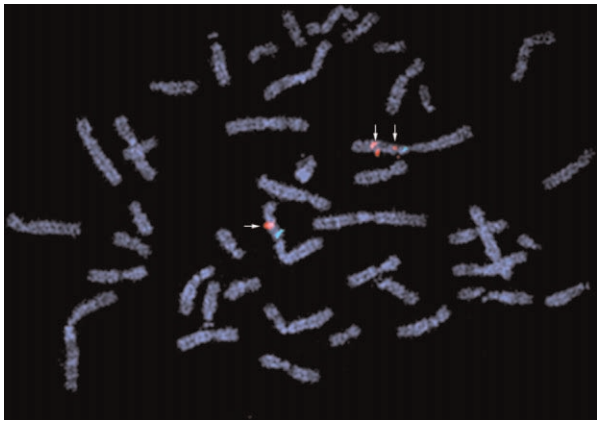

FIG. 6. FISH in patient LR00-173. Hybridization with BAC probe CTB-6J9 from 2p16.1 labeled in orange (white arrows) shows one signal on the normal chromosome 2 homolog, but two signals on the duplicated homolog. This BAC contains marker AFMB304YH1. Control probe RP11-113N17 from 2p12 labeled in aqua is not in the duplicated region and shows only one signal on each homolog. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Deletion 21q22.1. Only a few individuals with partial deletions of chromosome 21q have been reported, with three distinct phenotypes. First, six individuals from two families with small centromeric deletions of 21q11.1–q21.2 had normal intelligence [Korenberg et al., 1991; Aviv et al., 1997], and another whose deletion extended to 21q21.3 had mild mental retardation [Roland et al., 1990]. Next, at least five patients with deletion 21q22.3 had holoprosencephaly [Aronson et al., 1987; Estabrooks et al., 1990; Muenke et al., 1995], and one individual with a small telomeric deletion of 21q22.3 had normal intelligence [Falik-Borenstein et al., 1992]. Another six patients have had proximal, interstitial or distal deletions involving bands 21q22.1–q22.2, all with multiple congenital anomalies [Rethore and Dutrillaux, 1973; Theodoropoulos et al., 1995; Ahlbom et al., 1996; Yao et al., 2006].

A recent report of deletion 21q22.1–q22.2 listed many abnormalities including developmental delay, mental retardation, seizures, MIC and facial dysmorphism, as well as eye, heart, hand and feet, and genital anomalies with no further details provided [Yao et al., 2006]. Brain imaging in three patients was reported to show PMG, "pachygyria," thin white matter, hypoplasia of the corpus callosum and variable hypoplasia of the cerebellum [Yao et al., 2006]. Physical mapping in these three patients demonstrated a critical region of 8.4 Mb in 21q22.2–q22.3 flanked by the *KCNJ6* and *COL6A2* genes [Yao et al., 2006], a region that excludes the *ITSN1* gene that was suggested as a PMG causative gene in abstracts [Chen et al., 1999]. However, the published brain imaging studies were too small to review and confirm the malformations.

Our patient with deletion 21q2 has severe mental retardation, microcephaly (−3 standard deviations at 11 years), prominent eyes, low-set and posteriorly rotated ears, coarse voice, clinodactyly, long slender hands and feet, mild spasticity and multiple contractures leading her to walk with a crouched posture. She began having drop seizures at 10 years. Brain MRI demonstrates symmetric perisylvian PMG involving only the perisylvian cortex as well as partial agenesis of the corpus callosum (Fig. 4). Based on our observation of PMG in this girl and two boys with deletion of 18p plus 21q (see below), we hypothesize that deletion 21q2 is associated with PMG and hypoplasia of the corpus callosum, but not with lissencephaly or "pachygyria." Further studies will be needed to determine the critical region for PMG.

Deletion 18p11.2-pter plus deletion 21q22.1. We found one boy with deletion of both 18p and distal 21q, and unexpectedly found a report of another boy with the same karyotype [Alkan et al., 2002]. We obtained only limited data on our patient, while the reported boy had clinical features of both deletion 18p and deletion 21q. Brain imaging

TABLE V. Polymicrogyria Loci Identified by Cytogenetic Analysis

Locus	Mechanism	N		References
		LP	LIT	
Confirmed loci				
1p36.3	Del	15	1	Ribeiro Mdo et al. [2007] and Shapira et al. [1999]
2p16.1–p23.1	Dup	2	0	—
4q21.21–q22.1	Del	2	1	Nowaczyk et al. [1997]
6q26–q27	Del	7	1	Curry et al. [2000], Eash et al. [2005] and Salamanca-Gonez et al. [1975]
21q21.3–q22.1[a]	Del	2	4	Alkan et al. [2002], Chen et al. [1999] and Yao et al. [2006]
22q11.2	Del	21	11	Robin et al. [2006]
Possible loci				
1q44	Del	1	2	Zollino et al. [1992, 2003]
2p15–p16.1	Del	0	2	Rajcan-Separovic et al. [2007]
11q12–q13	Dup	0	1	Dupuy et al. [1999]
13q14.1–q31.2	Del	0	1	Kogan et al. [2008]
18p[a]	Del	1	0	—

Del, deletion; Dup, duplication; LIT, number reported in literature; LP, number identified in our subject database; N, number of subjects.
[a]Patients with combined del 18p and del 21q2 are included with the 21q locus.

demonstrated perisylvian PMG in both patients; our patient also had mild CVH (Fig. 4).

The PMG observed in these two children is open to at least two different interpretations. First, PMG could result from deletion 21q2, adding two more patients to the four described above. In this scenario, the PMG we report in a girl with deletion 18p might be coincidental. Alternatively, data from other PMG loci, especially 1p36.3 and 22q11.2, demonstrate incomplete penetrance and variable expressivity. In this scenario, deletion of two putative PMG loci would be predicted to increase the penetrance and severity of the cortical malformation.

Deletion 22q11.2. The deletion 22q11.2 (DiGeorge or velocardiofacial) syndrome is a common disorder that is associated with many rare manifestations, including PMG in 12 reported patients [Cramer et al., 1996; Bingham et al., 1998; Bird and Scambler, 2000; Kawame et al., 2000; Worthington et al., 2000; Ghariani et al., 2002; Ehara et al., 2003; Koolen et al., 2004; Sztriha et al., 2004]. We recently analyzed clinical data on 21 patients with PMG and deletion 22q11.2 from our subject database and 11 from the literature, finding perisylvian PMG associated with frequent asymmetry, a striking predisposition for the right hemisphere, and often mega-cisterna magna or mild CVH [Robin et al., 2006].

Possible PMG Loci

Deletion 1q44. At least 30 patients with deletion of 1q42q44 have been reported with constant but variable mental retardation, frequent seizures, and numerous congenital anomalies [van Bever et al., 2005]. The latter include facial dysmorphism especially upslanted palpebral fissures, ear anomalies, small jaw and cleft palate, heart malformations, abnormalities of the hands and feet, and genital anomalies such as hypospadius and cryptorchidism. The reported brain malformations include MIC in 25 of 27 and ACC in 22 of 25 affected individuals, both likely related to deletion of *AKT3*, as well as cerebellar hypoplasia or atrophy in 10 of 21 [Gentile et al., 2003; van Bever et al., 2005; Boland et al., 2007; Hill et al., 2007; van Bon et al., 2008].

The existence of a PMG causative gene in this region was first suggested by the report of PMG in two cousins with deletion 1q44 and duplication 12p13.3 resulting from the unbalanced state of a familial 1q;12p translocation [Zollino et al., 1992, 2003]. Both boys with the unbalanced derivative 1 chromosome had PMG, and a subsequent paper reported a 14 cM deletion of the 1q telomere by FISH [Rossi et al., 2001], but we could not confirm the location of the YAC probe used. The deletion presumably includes *AKT3* (5.5 Mb from the 1q telomere) due to the MIC and ACC. We previously reported probable perisylvian PMG in our patient LP94-079 (Fig. 5), but this girl also has an unbalanced duplication [Boland et al., 2007]. None of the remaining 20 patients with brain imaging findings reported had PMG [Boland et al., 2007; Hill et al., 2007; van Bon et al., 2008], leaving this putative locus in doubt.

Deletion 2p15-p16.1. Two children with a new deletion syndrome involving chromosome 2p were reported recently [Rajcan-Separovic et al., 2007]. Both of them had moderate to severe mental retardation with autistic features, poor attention, coordination and vision, MIC, dysmorphic appearance, camptodactyly and renal anomalies consisting of hydronephrosis or multicystic kidney. The facial features consist of flat occiput, widened inner canthal distance, small palpebral fissures, ptosis, long straight eyelashes, broad and high nasal root, prominent nasal tip, long smooth philtrum, and everted lower lips. Brain imaging demonstrated bilateral perisylvian cortical dysplasia (Patient 1) or "generally thickened cortex" (Patient 2) that probably represent perisylvian PMG, although no images were shown. BAC microarray analysis showed a critical region of 4.5 Mb between BACs RP11-81L7 and RP11-355B11.

Duplication 11q11–q12. Several patients with facial dysmorphism, atrioventricular canal and PMG associated with small duplications of 11q11–q12 were reported in an abstract several years ago [Dupuy et al., 1999]. No further information is available.

Deletion 13q14.1–q31.2. Interstitial deletions of proximal 13q that do not extend into 13q32 have most often been found with the retinoblastoma-mental retardation syndrome that results from heterozygous deletion of the *RB1* gene in 13q14.2 and other unknown brain development genes [Brown et al., 1993; Baud et al., 1999]. About 70% of patients have severe mental retardation that correlates with the size and location of the deletion [Baud et al., 1999]. The typical facial abnormalities consist of a high broad forehead, prominent philtrum, and anteverted ear lobes. Patients with larger deletions, such as 13q14.12–q31.2, have a similar non-specific phenotype with added severe growth and mental retardation [Slavotinek and Lacbawan, 2003], although brain imaging has not been reported.

One boy reported with deletion 13q14.1–q31.2 also had PMG [Kogan et al., 2008]. At 4 months, he had mental retardation, hypotonia, severe growth deficiency, facial dysmorphism, submucous cleft palate, hearing loss, bilateral inguinal hernias, and bilateral retinoblastomas. His facial abnormalities consisted of a triangular-shaped face, protuberant eyes, downslanting palpebral fissures, downturned mouth and small jaw. Brain imaging demonstrated severe and symmetric perisylvian PMG. Patients with more distal deletions involving 13q32 have had severe brain malformations including holoprosencephaly and Dandy-Walker malformation, but not polymicrogyria [Marcorelles

et al., 2002; McCormack et al., 2002; Alanay et al., 2005].

Deletion 18p. More than 150 patients with deletion 18p have been reported [Wester et al., 2006]. Typical features include mild to moderate mental retardation, short stature and facial dysmorphism, with less frequent malformations of the brain, heart, limbs, and genitalia. Facial changes consist of ptosis, broad flat nose, hypertelorism, large protruding ears, and small jaw. Other problems include strabismus, hypotonia, slow movements, autoimmune disorders, and pituitary insufficiency. A few have had holoprosencephaly [Overhauser et al., 1995], which may be associated with a single central incisor and pituitary insufficiency. One patient with Dandy-Walker malformation and hydrocephalus was recently reported but no images were provided [Wester et al., 2006]. Overall, brain-imaging studies have only rarely been described.

We identified a single patient with deletion 18p syndrome who has unilateral right perisylvian PMG (Fig. 4). This girl has a deletion of almost the entire short arm, so we cannot refine the location of the putative PMG gene. Penetrance is probably low as deletions of 18p are not rare, and we found no reports of this association. The only other supportive data for this locus are the two patients with combined del 18p and dup 21q22.1, which we think are more likely due to the chromosome 21q deletion with deletion 18p as a possible modifier locus.

The Genetic Basis of Polymicrogyria

Polymicrogyria genes. Reports to date have identified four human genes associated with PMG including *RAB3GAP* in 2q21.3, *TBR2* in 3p21, *KIAA1279* in 10q22.1 and *PAX6* in 11p13. The most interesting so far involve the interacting genes *PAX6* and *TBR2* (*EOMES*). High-resolution brain imaging in 2 of 24 patients with aniridia due to heterozygous *PAX6* mutations had focal and apparently unilateral temporal lobe PMG, in addition to hypoplasia or absence of the pineal gland and anterior commissure [Sisodiya et al., 2001; Mitchell et al., 2003]. More importantly, an infant who was a compound heterozygote for two different mutations of *PAX6* had a severe brain malformation consisting of ACC and extensive PMG [Glaser et al., 1994]. Studies in mouse mutants have shown that Pax6 is involved in dorsoventral patterning of the telencephalon [Stoykova et al., 2000], specification of neuronal identity [Briscoe et al., 1999], radial glia differentiation and intermediate progenitor cell division [Gotz et al., 1998; Englund et al., 2005], neuronal migration [Brunjes et al., 1998; Talamillo et al., 2003], and cortico-thalamic and thalamo-cortical pathfinding [Hevner et al., 2002]. Loss of regulation of some or all of these functions might leads to PMG, and $Pax6^{-/-}$ mutants may be the most appropriate animal models for study currently available. Importantly, a boy with homozygous mutation of *TBR2* had MIC, ACC, PMG, and persistent unexplained fevers [Baala et al., 2007]. The TBR2 protein functions immediately downstream of PAX6, and regulates intermediate progenitor cell division [Englund et al., 2005]. This suggests that deficiency or altered fate of neurons derived from intermediate progenitor cell division may be one cause of PMG.

Mutations of *RAB3GAP* were identified in 12 of 18 probands with Warburg Micro syndrome, an autosomal recessive disorder manifest by MIC, frontal PMG, eye malformations and genital hypoplasia [Graham et al., 2004; Aligianis et al., 2005]. The protein regulates the Rab3 pathway that functions in exocytic release of hormones, neurotransmitters and possibly trophic factors, but the mechanism by which this leads to PMG is not clear. Mutations of *KIAA1279* were found in patients with Goldberg-Shprintzen syndrome, an autosomal recessive disorder with MIC, mental retardation and Hirschsprung disease (absence of ganglion cells in the wall of the colon) as the major manifestations [Goldberg and Shprintzen, 1981; Hurst et al., 1988; Brooks et al., 1999, 2005]. A recent report recognized bilateral diffuse PMG as part of the phenotype. The gene encodes a protein with two tetratrico peptide repeats although little is yet known about gene or protein function [Brooks et al., 2005].

Polymicrogyria syndromes. PMG occurs as a major (and probably constant) component of several multiple congenital anomaly—mental retardation syndromes including Aicardi, oculo-cerebro-cutaneous (Delleman) and Warburg Micro syndromes [Ferrer et al., 1986; Billette de Villemeur et al., 1992; Nassogne et al., 2000; Graham et al., 2004; Brooks et al., 2005; Moog et al., 2005; Pascual-Castroviejo et al., 2005], and occasionally in Adams-Oliver syndrome [Amor et al., 2000]. Given the reduced penetrance of PMG found in these deletion syndromes, we expect the list of syndromes occasionally associated with PMG to expand, as demonstrated by a recent report for Aarskog-Scott syndrome [Bottani et al., 2007].

CONCLUSIONS

Despite numerous clinical and pathological studies, we still have very limited understanding of the causes of PMG, as both extrinsic (see Introduction Section) and genetic causes are known. Our data provides the first detailed documentation for PMG loci across the human genome, which we anticipate will serve as the basis for ongoing efforts to identify more PMG causal genes.

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