Polymicrogyria and Deletion 22q11.2 Syndrome: Window to the Etiology of a Common Cortical Malformation

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Several brain malformations have been described in rare patients with the deletion 22q11.2 syndrome (DEL22q11) including agenesis of the corpus callosum, pachygyria or polymicrogyria (PMG), cerebellar anomalies and meningo-myelocele, with PMG reported most frequently. In view of our interest in the causes of PMG, we reviewed clinical data including brain-imaging studies on 21 patients with PMG associated with deletion 22q11.2 and another 11 from the literature. We found that the cortical malformation consists of perisylvian PMG of variable severity and frequent asymmetry with a striking predisposition for the right hemisphere ($P = 0.008$). This and other observations suggest that the PMG may be a sequela of abnormal embryonic vascular development rather than a primary brain malformation. We also noted mild cerebellar hypoplasia or mega-cisterna magna in 8 of 24 patients. Although this was not the focus of the present study, mild cerebellar anomalies are probably the most common brain malformation associated with DEL22q11. © 2006 Wiley-Liss, Inc.

Key words: cerebellar hypoplasia; chromosome 22; deletion 22q11.2; perisylvian polymicrogyria

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INTRODUCTION

Deletion 22q11.2 (DEL22q11) is among the most common microdeletion syndromes in humans, with an estimated birth prevalence of 1–2/4,000 [Shprintzen, 2004]. Several hundred papers have documented the great clinical variability that has come to characterize this disorder, with over 180 different manifestations having been reported. Abnormalities of the central nervous system (CNS) are common and prominent, including neurobehavioral and psychiatric disorders such as learning disabilities, attention deficit disorder, and depression. Although much less common, brain malformations have also been described with DEL22q11 involving every level of the CNS including agenesis of the corpus callosum [Kraynack et al., 1999], pachygyria [Ehara et al., 2003; Koolen et al., 2004], polymicrogyria (PMG) [Cramer et al., 1996], cerebellar atrophy [Lynch et al., 1995], and meningo(myelo)cele [Nicken et al., 1994; Forrester et al., 2002]. Of these, the cortical malformation PMG has received the most attention.

While 12 patients with DEL22q11 associated with cortical malformations have now been described in case reports [Cramer et al., 1996; Bingham et al., 1998; Bird and Scambler, 2000; Worthington et al., 2000; Gharani et al., 2002; Kawame et al., 2000; Ehara et al., 2003; Koolen et al., 2004; Sztriha et al., 2004], the type, location and severity of the cortical malformation, and the presence of associated brain malformations have not been clarified. In a recent trio of Letters to the Editor in this journal, de Wit et al. [2005] suggested that the published images in two recent papers [Ehara et al., 2003; Koolen et al., 2004] showed PMG and not pachygyria or combined pachygyria and PMG as stated. The authors’ replies maintained that the malformation was in fact pachygyria, with one stating that “the final diagnosis requires neuropathological findings” [de Vries, 2005; Ehara et al., 2005]. However, many reports have shown that PMG may indeed be recognized by magnetic resonance imaging [Kuzniecky et al., 1994; Barkovich et al., 1999; Guerrini et al., 2003].

To address these questions, we analyzed clinical data on 21 patients with PMG and DEL22q11 from our subject databases, and another 11 from the literature. We found a cortical malformation consistent with perisylvian PMG—each time, every time—that was further associated with frequent asymmetry, a striking predisposition for the right hemisphere, and often mega-cisterna magna or mild cerebellar vermis hypoplasia.

METHODS

We searched our large brain malformation research databases (D.T.P., R.G., R.J.L., and W.B.D.) and found 21 patients with PMG and DEL22q11 among more than 1,000 patients with PMG of all types. All patients were deleted for the TUPLE1 probe by FISH, and one had additional molecular genetic studies performed. Many were ascertained after specific requests to colleagues, so that the prevalence of DEL22q11 among patients with PMG cannot be determined from these data. We also obtained additional clinical data for three previously reported patients [Bingham et al., 1998; Sztriha et al., 2004].

We reviewed clinical records, photographs and brain MRI (in 20 patients), or CT scan (in 1 patient) in these 21 patients and another 11 reported in the literature for whom adequate brain imaging figures were available (Table I and see the online Table III at http://www.interscience.wiley.com/jpages/1552-4825/ suppmat/index.html), with attention to the well-known abnormalities associated with the DEL22q11 syndrome. PMG consists of abnormally small gyri that do not follow the normal gyral pattern, regions of deeply infolded cortex, and shallow partly fused sulci [Crome, 1952; Barth, 1987; Barkovich et al., 2001]. We identified this on MRI by looking for regional loss of the normal gyral pattern, visible microgyri, irregular brain surface and white-gray border, and mildly thick (6–10 mm) cortex [Barkovich et al., 2001]. Pachygyria (one form of lissencephaly) consists of absent or abnormally wide gyri with reduced numbers of gyri and sulci, widely open sulci, and very thick 10–20 mm cortex. We looked for these changes on MRI. The severity of the cortical malformation was assessed using a system we developed for use with perisylvian PMG [Leventer et al., 2001]. Grade 1 PMG involves the entire perisylvian region with extension to other brain regions including one or both poles. Grade 2 involves the entire perisylvian region with extension to other brain regions but not involving either pole. Grade 3 involves the entire perisylvian region, and Grade 4 involves the posterior perisylvian region only. We assessed whether the malformation was more severe in anterior versus posterior, and right versus left-brain regions by visual inspection. The results were analyzed using the Chi-square test.
RESULTS

Our series of 21 patients plus the 11 patients reported in the literature together comprise 13 females and 19 males. While data were not available for all subjects, the types and severity of anomalies and developmental problems were typical for the DEL22q11 syndrome (see the online Table III at http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html). Conotruncal congenital heart defects were reported in 17 of 31, and typical facies in 21 of 27 patients in which these were noted. Other findings included cleft palate (4), hypocalcemia (2), and low T-cell count (3). Interestingly, 11 of 30 had microcephaly, and 3 of those with a normal OFC were at the 2nd centile. Most had a far greater degree of developmental delay than is typical for DEL22q11: 20 had severe, 6 moderate or mild-moderate, and 6 mild developmental delay or mental retardation, including one with only isolated speech and motor delay. Of the 12 subjects with moderate to mild involvement, 11 had asymmetric neurologic findings. In all, 16 subjects manifest neurologic asymmetry, and all but 3 had “hard” neurologic signs such as hypertonia or hypotonia.

On review of brain MRI (and a single CT scan), we recognized typical changes of PMG in all 32 patients (Table I). The figures show representative images of four patients with symmetric PMG (Fig. 1) and four with asymmetric PMG (Fig. 2), the latter including three more severe on the right and one more severe on the left. The extent of PMG varied considerably among hemispheres, but was always most severe in the perisylvian region. Among the 31 brains (62 hemispheres) that we were able to assess for severity, we observed severe Grade 1 perisylvian PMG in 28 hemispheres, Grade 2 in 17, Grade 3 in 5, Grade 4 in 6, and no visible PMG in six hemispheres (Table I). When the PMG extended beyond the perisylvian region, the frontal lobes were usually more severely affected than posterior regions. In three patients with severe bilateral Grade 1 perisylvian PMG, all regions appeared similarly involved (A = P gradient). In 26 of the 27 remaining patients with Grade 1 or 2 PMG in at least one hemisphere, the frontal lobes were more severely involved than

<table>
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N, normal; A = P, anterior same as posterior; A > P, anterior more severe than posterior; P > A, posterior more severe than anterior (A-P gradients only apply to more severe Grades 1 and 2); L, left; R, right; L > R, left more severe than right; R > L, right more severe than left; SYM, symmetric; CSP, cavum septum pellucidum; CVH, cerebellar vermis hypoplasia; MCM, mega-cisterna magna; RBG, right basal ganglia small; —, data not available. Patient numbers were given to reported patients when additional clinical information and complete brain imaging studies were obtained from the authors.
The cortical malformation was symmetric in 15 of the 32 patients. Surprisingly, the PMG was clearly asymmetric in the remaining patients, with the right hemisphere more severely affected than the left in 14 of 17. The right-sided predominance reached statistical significance by Chi-square analysis under the assumption that any asymmetry should involve the two sides equally (Table II). The more severely affected hemisphere had Grade 1 or 2 perisylvian PMG in all but one patient with Grade 3 PMG, while the less affected side had variable Grade 2–4 perisylvian PMG or no visible PMG. We also found mild cerebellar malformations that we classified as mild cerebellar vermis hypoplasia or as mega-cisterna magna in 8 of the 24 patients whom we were able to assess (the published figures did not include midline sagittal images), and cavum septum pellucidum in 5 patients.

The diagnosis of DEL22q11 syndrome was established by finding a deletion of the TUPLE1 or N25 probe by FISH in all patients, and three patients had further studies done. Array comparative genome hybridization using a full coverage chromosome 22 array containing 354 BAC clones demonstrated the common 3 Mb deletion in one patient [Koolen et al., 2004]. The common 3 Mb deletion was documented in patient UKMC-4 (LR00-036) and one reported patient [Ghariani et al., 2002] using a panel of FISH probes within and flanking the DEL22q11 region (data not shown).
Our detailed review confirms several prior reports in identifying the cortical malformation in DEL22q11 as PMG, and further demonstrates that the perisylvian area is invariably involved, although this was not specifically mentioned in all published reports. This distribution is by far the most common type, affecting two-thirds of all patients with PMG [Leventer et al., 2001]. The published images shown in the reports describing the cortical malformation as “pachygyria” [Ehara et al., 2003; Koolen et al., 2004] also have the distinct imaging characteristics of PMG, leading us to conclude that pachygyria (lissencephaly) is not a cortical malformation found in association with the DEL22q11 syndrome.

The characteristic neurological features of perisylvian PMG are cognitive defects, oromotor dysfunction (dyspraxia) consisting of nasal speech, dysarthria, dysphagia and drooling, and other signs of pseudobulbar palsy [Kuzniecky et al., 1993]. This phenotype was described by Worster-Drought long before brain imaging became available as a form of cerebral palsy with pseudobulbar paresis that

TABLE II. Analysis of PMG Gradients

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<tr>
<th>Type</th>
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<tr>
<td>R &gt; L</td>
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he designated “congenital suprabulbar paresis” [Worster-Drought, 1956], so it has also been designated Worster-Drought syndrome. The association between congenital suprabulbar paresis and perisylvian PMG has been noted in several reports [Kuzniecky et al., 1993; Clark et al., 2000; Nevo et al., 2001].

**Neurological Abnormalities in DEL22q11 with PMG**

Velopharyngeal insufficiency and articulation problems are frequent in DEL22q11, and are usually attributed to structural anomalies of the palate. However, most patients with this syndrome do not have brain imaging performed, so that subtle PMG might be under-ascertained among patients with velopharyngeal insufficiency. All of the children in our series for whom we had adequate information had oromotor dysfunction. One of them (UKMC-03) was actually diagnosed with Worster-Drought syndrome before the diagnoses of asymmetric PMG and DEL22q11 were made, and several others with either unilateral or bilateral PMG had drooling and choking consistent with oromotor dyspraxia. Enlargement of the Sylvian fissures without PMG was reported in 10 of 17 patients with DEL22q11 with oromotor dysfunction, but only two were recognized to have PMG [Bingham et al., 1997, 1998]. This suggests that widening of the Sylvian fissures could be an indication of an underlying cortical abnormality not visible on MRI.

Other neurological problems were also more common in our series. In the European collaborative study of DEL22q11, 21% had seizures that were usually attributed to hypocalcemia, and only 8% had other neurological features [Ryan et al., 1997]. In contrast, over half of our patients presented with neurological problems prior to diagnosis of DEL22q11, with abnormalities consisting of developmental delay, hemiplegia, microcephaly, or seizures. About half (15) of our patients had seizures despite limited follow-up, and none of these were associated with hypocalcemia.

We also found mild cerebellar vermis hypoplasia or mega-cisterna magna in about a third of the patients in our series. Thus, both PMG and the cerebellar malformation exhibit incomplete penetrance and variable expressivity, similar to many other malformations associated with DEL22q11 [Ryan et al., 1997]. In further support of this, two patients with PMG inherited their deletion from a mildly affected parent [Bingham et al., 1998; Worthington et al., 2000].

**Volumetric Brain Imaging in DEL22q11**

The DEL22q11 syndrome has been associated with subtle abnormalities on volumetric brain imaging including reduction of overall brain volume especially white matter, decreased volume of parietal and temporal gray matter, abnormalities of midline structures such as the corpus callosum and reduced size of the cerebellum [Bearden et al., 2004; van Amelsvoort et al., 2004; Simon et al., 2005; Zinkstok and van Amelsvoort, 2005]. Both agenesis of the corpus callosum and cerebellar “atrophy” (more likely cerebellar hypoplasia as we found in our series) have been reported in a few patients with DEL22q11 [Lynch et al., 1995; Chow et al., 1999; Kraynack et al., 1999], and could represent severe expression of these subtle brain volume abnormalities. However, the PMG is more difficult to explain this way.

**Penetrance and Expressivity of PMG**

Unfortunately, our data does not allow us to determine either the prevalence of DEL22q11 among patients with PMG, or the prevalence of PMG among patients with DEL22q11. We estimate that the PMG was recognized before the 22q11.2 deletion was found in ~8 of the 32 patients in our series. In contrast, PMG was recognized before the chromosome abnormality was found in ~4 of nine patients with PMG and deletion 1p36.3 and in ~2 of six patients with PMG and deletion 6q26-qter (W.B.D., unpublished data). This suggests that DEL22q11 is the most common of the chromosomal loci associated with PMG. The frequency of PMG among patients with DEL22q11 is probably low as abnormalities of the Sylvian fissure were not seen in a series of ~100 DEL22q11 patients with MRIs available for review [Shprintzen, 2000], although in our experience subtle PMG can be missed.

These observations, particularly the consistent pattern, low penetrance, variable expressivity and asymmetry of the malformation, raise interesting questions regarding the mechanism that we will consider by reviewing other studies of DEL22q11 and PMG.

**Presumed Causes of PMG**

PMG consists of small, irregular gyri separated by shallow partly fused sulci and frequent areas of infolded cortex, and by loss of neurons in middle cortical layers with reduction from six to four or no recognizable layers [Crome, 1952; Levine et al., 1974]. It can be recognized on MRI from the microgyri, moderately thick cortex (usually 6–10 mm), and irregular or pebbled brain surface and gray-white interface [Barkovich et al., 2001]. Many different types of PMG have been described based on distribution and associated malformations, but the most common by far is centered in the perisylvian regions [Barkovich et al., 1999; Leventer et al., 2001; Barkovich et al., 2005]. Many causes of PMG are known, and include both extrinsic effects on the fetus and genetic disorders. Both PMG and the
related malformation schizencephaly have been associated with conditions proposed to disrupt the fetal vascular supply; such as twinning and intrauterine cytomegalovirus infection [Norman, 1980; Graff-Radford et al., 1986; Hayward et al., 1991; Larroche et al., 1994; Sugama and Kusano, 1994; Baker et al., 1996; Van Bogaert et al., 1996, 1998; Sener, 1998; Hung and Wang, 2003; Curry et al., 2005].

Numerous genetic causes of PMG have been documented, including familial PMG with autosomal dominant, autosomal recessive, or X-linked inheritance [Bartolomei et al., 1999; Borgatti et al., 1999; Caraballo et al., 2000; Guerreiro et al., 2000; Hung and Wang, 2003; Villard et al., 2002]. Several small deletions or duplications have been associated with PMG, most reported only in abstracts, including deletion 1p36, 1q44, 9p24-pter, and 13q14.1-q31.2 [Shapira et al., 1999; Zollino et al., 2003; Callier et al., 2005; Kogan et al., 2005] and duplication 11q12-q13 and 22q11.2 [Dupuy et al., 1999; Callier et al., 2005].

Typical PMG has been seen in several multiple congenital anomaly syndromes, especially Adams-Oliver, Aicardi, Goldberg-Shprintzen, (Warburg) Micro, and oculo-cerebro-cutaneous (Delleman) syndromes [Ferrer et al., 1986; Billette de Villemeur et al., 1992; Amor et al., 2000; Graham et al., 2004; Brooks et al., 2005; Moog et al., 2005; Pascual-Castroviejo et al., 2005]. Two syndromes with atypical PMG resembling the cobblestone cortical malformation of muscle-eye-brain disease have also been described [Chang et al., 2004; Piao et al., 2005; Sprecher et al., 2005], and another variant occurs in patients with thanatophoric dysplasia [Hevner, 2005].

**Pathogenesis of PMG in the DEL22q11 Syndrome**

While the basis of the infrequent PMG in this syndrome is unknown, enough data has accumulated to consider possible mechanisms. Our most interesting finding is the frequent asymmetry between hemispheres and the striking predisposition for the right hemisphere. This leads us to hypothesize that the gene or genes predisposing to PMG may be asymmetrically expressed between the hemispheres. But which gene or genes?

The existing data suggest several possible mechanisms, the first being haploinsufficiency of a gene expressed in embryonic brain that regulates cortical development. However, mutations of only a few genes have been associated with PMG. The first is RAB3GAP, which regulates the Rab3 pathway implicated in excitatory release of neurotransmitters, hormones, and possibly trophic factors, and is mutated in some patients with Micro syndrome [Aligianis et al., 2005]. The next is KIAA1279, a gene of unknown function that is mutated in Goldberg–Shprintzen syndrome [Brooks et al., 2005]. In addition, heterozygous and especially homozygous mutations of PAX6 have been associated with PMG [Glaser et al., 1994; Mitchell et al., 2003], suggesting that PMG may result from a cortical patterning abnormality such as proliferation defects involving specific subsets of neurons or cortical and thalamic pathfinding defects [Heins et al., 2002; Hevner et al., 2002; Muzzio et al., 2002; Muzzio and Mallamaci, 2003; Stenman et al., 2003; Englund et al., 2005]. However, no genes in the DiGeorge critical region stand out as strong functional candidates for this mechanism.

Another possible and more intriguing mechanism for PMG involves hypoperfusion of the embryonic brain. Here we hypothesize that haploinsufficiency of a gene expressed in vascular tissue perfusing the embryonic brain, probably in concert with genetic modifying factors, leads to PMG and in particular to asymmetric PMG. Several lines of evidence support this hypothesis. First, disorders that disrupt the fetal vascular supply have been associated with PMG as noted above. Next, haploinsufficiency of TBX1 (the key cardiovascular patterning gene in the DiGeorge critical region, DGCR) results in a spectrum of distinct vascular and heart defects in both mouse and human that affects formation and growth of the pharyngeal arch arteries and related structures [Lindsay et al., 2004; Vitelli et al., 2002; Yagi et al., 2003]. In mouse mutants, the arterial growth deficiency affects all embryonic day (E) 10.5 mutants, but partial recovery occurs so that only 65% are affected at E11.5 and only 30% at E18.5 [Lindsay and Baldini, 2001]. At all ages studied, the right side is more frequently and severely affected than the left with significant P values. This fits well with our observations of PMG in DEL22q11, as we also found that the right side is more frequently and severely affected than the left with a significant P value. Little other data are available in humans with DEL22q11, although magnetic resonance arteriograms in 11 patients demonstrated unilateral hypoplasia of the posterior cerebral artery in two patients, both involving the right side [Chow et al., 1999].

These data suggest that the gene or genes predisposing to PMG may be asymmetrically expressed between the hemispheres. Several genes in the DGCR, including DGCR6, DGCR6L, and ZNF74 are differentially expressed in 12-week embryonic human cortex [Sun et al., 2005]. The former two are expressed at low levels in brain, while ZNF74 is expressed in neural crest-derived tissues and so could contribute to the vascular (and brain) phenotype.

Further, studies in mouse, human, and zebrafish have all demonstrated that the VEGF gene functions as a modifier of the cardiovascular birth defects in the DEL22q11 syndrome, including data demonstrating that a VEGF promoter haplotype is associated with an increased risk for cardiovascular malformations in humans [Stalman et al., 2003]. Conotruncal heart defects were recently reported in a boy with a
small 6p21 deletion that includes the VEGF gene, suggesting that haploinsufficiency of VEGF results in cardiovascular defects similar to haploinsufficiency of TBX1 [Izumi et al., 2006]. Interestingly, VEGF is asymmetrically expressed in 19-week human cortex [Sun et al., 2005]. Putting these together, the PMG in the DEL22q11 syndrome could result from a combination of haploinsufficiency of TBX1 and mutation or unfavorable promoter haplotype of VEGF or other modifying genes. These are potentially testable hypotheses.

Two other explanations seem less likely. The PMG could result from large deletions that extend beyond the common 3 Mb DiGeorge critical region, but this has been excluded in three patients. Alternatively, the deletion might uncover mutations in the undeleted homolog of a gene located in this region, as has been observed in the Bernard–Soulier syndrome [Budarf et al., 1995]. But this should be a rare mechanism, and would not easily explain our ascertainment of more than 30 patients.

CONCLUSIONS

This series of patients confirms that PMG is an associated manifestation for the DEL22q11 syndrome. The PMG is characterized by variable severity and frequent asymmetry of PMG, but the perisylvian cortex is always the most severely affected region. The typical DEL22q11 phenotype is difficult to recognize in the presence of PMG, as most patients manifest more severe developmental abnormalities and often have associated neurologic findings. These data suggest that DEL22q11 is a relatively common cause of perisylvian PMG, especially asymmetric PMG. In our series of 32 patients, all manifest either severe developmental delay or "hard" neurologic findings such as asymmetry, pseudobulbar palsy, or hypotonia. These are atypical for DEL22q11, and should prompt evaluation for PMG. Furthermore, we recommend that all patients with perisylvian PMG be tested for deletion 22q11.2, and that brain imaging be performed in patients with DEL22q11 who have more severe neurological abnormalities than are typical.

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