

# Genetics of the polymicrogyria syndromes

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Polymicrogyria is a relatively common malformation of cortical development, characterised by multiple small gyri with abnormal cortical lamination. The different forms of polymicrogyria encompass a wide range of clinical, aetiological, and histological findings. Advances in imaging have improved the diagnosis and classification of the condition. The molecular basis of polymicrogyria is beginning to be elucidated with the identification of a gene, *GPR56*, for bilateral frontoparietal polymicrogyria. Functional studies of the *GPR56* gene product will yield insights not only into the causes of polymicrogyria but also into the mechanisms of normal cortical development and the regional patterning of the cerebral cortex. Based on imaging studies, several other region specific patterns of polymicrogyria have been identified, and there is increasing evidence that these may also have a significant genetic component to their aetiology. This paper reviews current knowledge of the different polymicrogyria syndromes, with discussion of clinical and imaging features, patterns of inheritance, currently mapped loci, candidate genes, chromosomal abnormalities, and implications for genetic counselling.

## PATHOGENESIS OF POLYMICROGYRIA

The development of human cerebral cortex can be divided into three overlapping stages. During the first stage, stem cells proliferate into neuroblasts or glial cells deep in the forebrain, in the ventricular and subventricular zones lining the cerebral cavity. In the second phase, after their final mitotic division, cortical neurones migrate away from their place of origin in a radial or tangential fashion towards the pial surface, where each successive generation passes one another and settles in an inside-out pattern within the cortical plate. The third phase represents cortical organisation within six layers associated with synaptogenesis and apoptosis. This is a dynamic process and more than one stage may occur simultaneously during several gestational weeks. In humans, the proliferation stage ranges from weeks 5–6 to weeks 16–20, migration from weeks 6–7 to weeks 20–24, and organisation from week 16 until well into postnatal life.<sup>5–8</sup>

Polymicrogyria is causally and histologically heterogeneous and its pathogenesis remains poorly understood. Based on excitotoxic animal models, polymicrogyria results from a developmental disorder or injury that occurs toward the end of the period of neuronal migration and in the early phase of cortical organisation.<sup>9–10</sup> In humans, there is some evidence that cytotoxic factors<sup>11</sup> or hypoperfusion<sup>12</sup> in the second trimester (between approximately 16 and 24 weeks of gestation) can lead to polymicrogyria. However, analysis of the expression pattern of *GPR56*, the first gene identified in polymicrogyria, suggests that the disorder may result from mutations in genes that are involved in the regional patterning of the cerebral cortex at early stages of development, during neuronal proliferation and migration.<sup>13</sup> These findings imply that polymicrogyria is the end point of different aetiological processes, not necessarily occurring at the same time in cortical development. It is likely that most bilateral polymicrogyria subtypes and generalised forms reflect an early rather than a late abnormality. Cytotoxic and hypoperfusion models in which the malformation is often focal or asymmetrical may originate at later stages of cortical development.

Microscopically, two types of polymicrogyria are recognised: a simplified four layered form

**Abbreviations:** BFP, bilateral frontal polymicrogyria; BFPP, bilateral frontoparietal polymicrogyria; BGP, bilateral generalised polymicrogyria; BPOP, bilateral parasagittal parietooccipital polymicrogyria; BPP, bilateral perisylvian polymicrogyria; CBPS, congenital bilateral perisylvian syndrome; ESES, electrical status epilepticus during sleep; FISH, fluorescence in situ hybridisation

Polymicrogyria is a malformation of cortical development in which the brain surface is irregular and the normal gyral pattern is replaced by an excessive number of small and partly fused gyri separated by shallow sulci.<sup>1</sup> It should be distinguished from sclerotic microgyria or ulegyria, which represents an encephaloclastic lesion resulting in atrophic, often mushroom shaped, small gyri and relatively broad intervening sulci.<sup>2</sup>

The incidence of polymicrogyria is unknown, the failure to obtain accurate data on incidence and prevalence being largely the result of the clinical and aetiological heterogeneity of this malformation. The diagnosis of polymicrogyria was often missed because of limitations in imaging techniques and it was often confounded with pachygyria<sup>3</sup> and even with schizencephalic clefts.<sup>4</sup> Advances in imaging studies have improved the diagnosis and classification of this condition, which now appears to be relatively common, and several region specific polymicrogyria syndromes have been identified.<sup>5</sup> Studies to delineate the genetic basis of these different polymicrogyria syndromes have just begun during the past few years.

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and an unlayered form.<sup>14</sup> In unlayered polymicrogyria, the external molecular layer is continuous and does not follow the profile of the convolutions. The underlying neurones have radial or vertical distribution but no laminar organisation. The unlayered form reflects an early disruption of normal neuronal migration with subsequent disordered cortical organisation. Four layered polymicrogyria has characteristics suggestive of a late disruption of neuronal migration or a disruption of cortical organisation, as demonstrated in placental perfusion failure occurring between 20 and 24 weeks of gestation. The two types of polymicrogyria may co-occur in contiguous cortical areas, indicating that they may comprise a continuum rather than distinct malformations.<sup>14</sup>

### AETIOLOGY OF POLYMICROGYRIA

Little is known about the factors that contribute to the development of polymicrogyria. There is evidence that extrinsic factors, such as intrauterine cytomegalovirus infection, can be involved in the pathogenesis.<sup>11</sup> In patients with confirmed prenatal infection with cytomegalovirus, the brain regions close to the polymicrogyria can contain viral inclusions, foci of necrosis, calcifications, heterotopia, and infarctions. Thus several simultaneously occurring mechanisms—including direct cell loss, loss of integrity at the pial border, hypoxia-ischaemia, and other local vascular insults mediated through endothelial damage at the capillary level—might influence cortical development.<sup>15</sup> Fetal cerebral ischaemia from placental perfusion failure,<sup>12</sup> twin–twin transfusion,<sup>16</sup> loss of a twin in utero,<sup>17,18</sup> and maternal drug ingestion<sup>12</sup> have been described in association with polymicrogyria. The association of polymicrogyria with several genetically determined syndromes such as Zellweger,<sup>19</sup> Aicardi,<sup>20</sup> and Walker-Warburg syndrome,<sup>21</sup> the presence of polymicrogyria in patients with chromosomal abnormalities, and the occurrence of familial cases of polymicrogyria all strongly indicate a genetic component in its development.

### CLINICAL AND IMAGING FEATURES OF POLYMICROGYRIA

Polymicrogyria can be focal or diffuse, unilateral or bilateral. It can occur as an isolated lesion, in association with other brain malformations such as heterotopia or white matter lesions, or as part of several multiple congenital anomaly/mental retardation syndromes. Schizencephalic clefts, whether open or closed, are lined by polymicrogyric cortex, implying that polymicrogyria is a necessary component of schizencephaly. Unilateral clefts are often accompanied by contralateral polymicrogyria.<sup>22</sup> Schizencephaly and polymicrogyria are therefore considered to represent different aspects of the same spectrum, but as the exact aetiologies of both polymicrogyria and schizencephaly are still not completely clarified, it is impossible to make a final statement about their exact relationship.

The extent of polymicrogyria varies from focal polymicrogyria in otherwise normal brain to diffuse polymicrogyria with multiple other brain abnormalities. Similarly, the spectrum of clinical manifestations ranges from normal individuals with only selective impairment of cognitive function and no or easily controlled epilepsy to patients with severe encephalopathies and intractable epilepsy.

The diagnosis of polymicrogyria can be made confidently if irregularity of the cortical–white matter junction is detected by thin section magnetic resonance imaging (MRI).<sup>23</sup> MRI sequences to characterise polymicrogyria include axial spin echo T2 weighted images and spin echo T1 weighted images with 4 mm section thickness. Thin section (1.5 mm) coronal images obtained either by T1 weighted, three dimensional Fourier transformed, gradient recalled echo or by T2 weighted fast spin echo sequences

usually enable differentiation between polymicrogyria and pachygyria by allowing the irregular cortical–white matter junction to be identified.<sup>23</sup> In some patients with polymicrogyria the cortex appears very thin while in others it appears thick. It is likely that the two appearances of the cortex in polymicrogyria on MRI represent the same process, and that the apparent difference is the result of myelination in subcortical and intracortical fibres that causes a change in the appearance and apparent thickness of polymicrogyria on T2 weighted images.<sup>24</sup>

The topographic distribution of polymicrogyria does not always appear to be completely at random. The perisylvian regions are affected most often. Several distinct patterns of bilateral polymicrogyria have been described, including frontal,<sup>25</sup> frontoparietal,<sup>26–28</sup> perisylvian,<sup>29</sup> lateral parietal,<sup>30</sup> parasagittal parieto-occipital,<sup>31</sup> and generalised polymicrogyria.<sup>32</sup> Unilateral polymicrogyria has also been reported.<sup>33,34</sup> The underlying mechanisms for this regional distribution of polymicrogyria require further clarification.

### Polymicrogyria syndromes

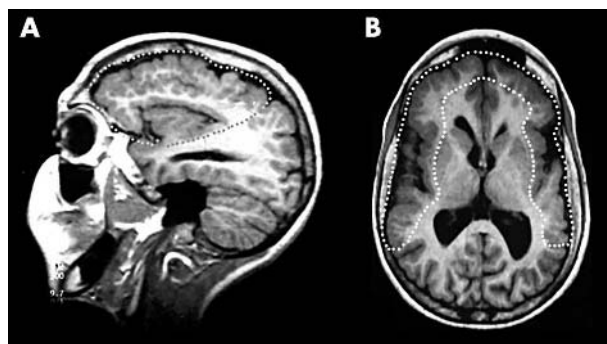
#### Bilateral frontal polymicrogyria (BFP)

Symmetrical polymicrogyria extending from the frontal poles anteriorly to the precentral gyrus posteriorly and to the frontal operculum inferiorly (fig 1) was reported in a series of 13 unrelated patients.<sup>25</sup> Typical features included delayed motor and language milestones, spastic hemiparesis or quadriparesis, and mild to moderate mental retardation. No bulbar signs were reported and head circumference was normal. Seizures were present in 38% of patients and varied in type, age at onset, and severity.<sup>25</sup>

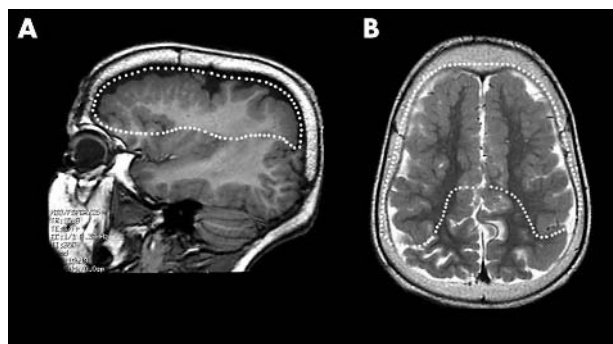
#### Bilateral frontoparietal polymicrogyria (BFPP)

Apart from symmetrical polymicrogyria affecting the frontoparietal regions, MRI in BFPP patients shows bilateral white matter abnormalities and atrophy of the brain stem and cerebellum (fig 2).<sup>28</sup> These additional features are not a consistent finding in any other bilateral polymicrogyria syndrome. Polymicrogyria associated with white matter lesions, on the other hand, is a common finding in congenital muscular dystrophies such as Walker–Warburg syndrome, muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy.<sup>21</sup> Thus it is not surprising that BFPP had previously been termed cobblestone lissencephaly with normal eyes and muscle.<sup>35</sup>

The main clinical features of BFPP include global developmental delay, dysconjugate gaze (esotropia), pyramidal and cerebellar signs, and seizures, which occur in 94% of patients and are mostly generalised.<sup>26–28</sup>



**Figure 1** Bilateral frontal polymicrogyria. Sagittal (A) and axial (B) T1 weighted magnetic resonance images displaying irregular, bumpy appearance of the hemispheric contour, shallow sulci, and nodular appearance of the cortex. The dotted contour shows the extent of the abnormal cortex, with predominant frontal involvement. Photograph courtesy of Professor Renzo Guerrini.



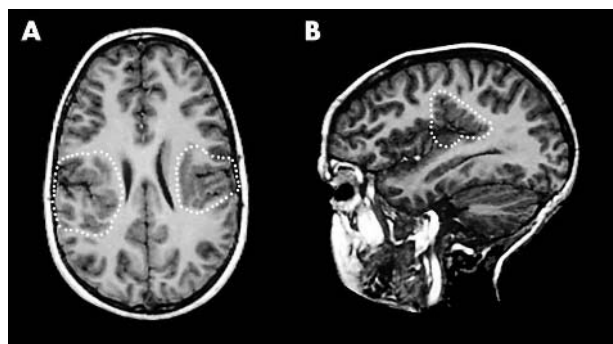
**Figure 2** Sagittal T1 weighted (A) and axial T2 weighted (B) magnetic resonance images showing bilateral frontoparietal polymicrogyria. The sagittal image reveals thin white matter digitations within multiple small gyri of corrugated appearance in the frontal lobes, having a cauliflower-like aspect in the axial image. The posterior margins of abnormal cortex in the parietal lobes show cortical thickening, most probably reflecting histological heterogeneity with fusion of microsulci. Photograph courtesy of Dr R Leventer.

Although dysconjugate gaze is common in patients with severe static encephalopathy, it may help to distinguish BFPP from other bilateral polymicrogyria syndromes, in which it has not been described. Patients with exclusively frontal polymicrogyria who lack these ocular symptoms do not link to the locus described for the BFPP families (Piao X, Walsh C, unpublished observations cited in Chang *et al*, 2003<sup>28</sup>). Interestingly, esotropia was recently described in a family with autosomal recessive frontotemporal pachygyria without polymicrogyria.<sup>36</sup> These patients lack the cerebellar and pyramidal features described in BFPP and their seizure phenotype is less severe. However, linkage to the BFPP locus has not been ruled out in this family.

### Bilateral perisylvian polymicrogyria (BPP)

In bilateral perisylvian polymicrogyria, the cerebral cortex on the borders and in the depth of the sylvian fissures is thickened and abnormally infolded, as shown by MRI (fig 3). The sylvian fissures are often more vertically oriented and extend more posteriorly up to the parietal lobes compared with normal controls. The abnormality is usually symmetrical but varies in extent among patients.<sup>29</sup> Polymicrogyria limited to the perisylvian regions has been confirmed in neuropathological reports.<sup>29 37 38</sup>

Leventer *et al*<sup>39</sup> developed a grading system to describe the variations in severity encountered among patients with BPP:



**Figure 3** Axial (A) and sagittal T1 weighted (B) magnetic resonance images showing bilateral perisylvian polymicrogyria. The axial slice displays bilateral inward folding of abnormal cortex in the posterior segments of the sylvian fissure bilaterally. The multiple small gyri are better demonstrated in the sagittal plane. Photograph courtesy of Dr R Leventer

- *grade 1*: perisylvian polymicrogyria extending to one or both poles;
- *grade 2*: perisylvian polymicrogyria extending beyond the perisylvian region but not to either pole;
- *grade 3*: polymicrogyria of the perisylvian region only;
- *grade 4*: polymicrogyria of the posterior perisylvian region only.

Despite normal MRI findings, neurological abnormalities characteristic of BPP have been found in some family members of patients with proven BPP. This may be explained by a spectrum of histological findings in polymicrogyria, in which subtle cortical disorganisation may result in structural changes not detectable by current imaging techniques.<sup>40 41</sup>

BPP was the first bilateral polymicrogyria syndrome to be described<sup>29</sup> and is the most common form of polymicrogyria. BPP has also been referred to as bilateral opercular polymicrogyria<sup>37</sup> and bilateral perisylvian dysplasia.<sup>42</sup> The clinical phenotype in patients with BPP was initially defined as the congenital bilateral perisylvian syndrome (CBPS),<sup>29</sup> but recent studies have broadened the phenotypic spectrum beyond that of CBPS. Interfamilial and intrafamilial variability has been reported.<sup>41</sup> Clinical manifestations of BPP include pseudobulbar palsy with diplegia of the facial, pharyngeal, and masticatory muscles (facio-pharyngo-glosso-masticatory paresis), pyramidal signs, and seizures. The pseudobulbar involvement results in restricted tongue movements, drooling, feeding problems, and dysarthria. Voluntary and emotional facial movements can be dissociated. Developmental language disorder can be associated with BPP, and its severity depends on the extent of the cortical damage.<sup>43</sup> Patients with marked dysarthria are often labelled as severely retarded, although they may have normal comprehension (<sup>29</sup> and Jansen A *et al*, in preparation). Patients with BPP may have pyramidal signs of variable severity, which can be either unilateral<sup>44</sup> or bilateral.<sup>41</sup> Associated malformations such as arthrogryposis, club feet, and micrognathia are more frequent in sporadic BPP (30%)<sup>29 45</sup> than in familial BPP (12%).<sup>41</sup>

Epilepsy was found in almost 90% of cases in the series reported by Kuzniecky *et al*,<sup>29</sup> in contrast to only 43% in that reported by Guerreiro *et al*.<sup>41</sup> The lower prevalence of epilepsy in the Guerreiro series could result from family based recruitment, which also includes family members with milder phenotypes. As was demonstrated for double cortex syndrome,<sup>46</sup> the milder phenotypes observed in familial BPP cases might result from missense mutations that are compatible with reproduction rather than from the more severe protein truncating mutations often seen in sporadic cases. Infantile spasms may be the presenting seizure type<sup>47</sup> but, in general, seizures develop only toward the end of the first decade or later. Most patients develop multiple seizure types, and seizure control is poor in more than half the cases. Frequent seizures may aggravate speech dysfunction and result in progressive deterioration. In patients with severe and disabling seizures, especially drop attacks, callosotomy can be considered.<sup>47</sup>

Similar symptoms and signs have been described as the Foix–Chavany–Marie syndrome in adults with bilateral anterior opercular infarctions.<sup>48</sup> The congenital form of BPP was first described by Worster-Drought as congenital suprabulbar paresis.<sup>49</sup> Since the introduction of MRI, BPP has been demonstrated in several cases of familial Worster-Drought syndrome.<sup>50</sup> The BPP phenotype could also be confounded with a syndrome of specific language impairment called “speech and language disorder with orofacial dyspraxia” or “developmental verbal dyspraxia.” In these patients, mutations in the *FOXP2* gene on 7q31 affect intellectual, linguistic, and orofacial praxic functions.<sup>51</sup>



However, these patients do not have BPP on MRI, and epilepsy is not part of the phenotype.

#### Bilateral parasagittal parieto-occipital polymicrogyria (BPOP)

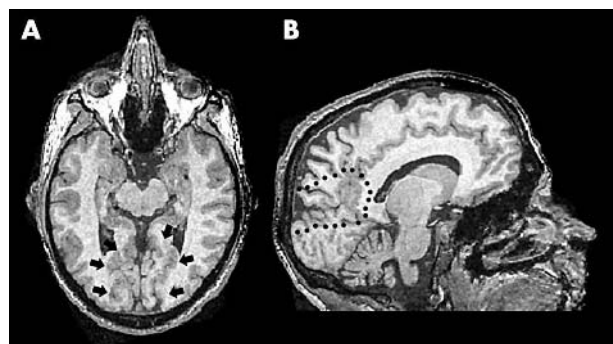
Polymicrogyria centred in the parasagittal and mesial aspects of the parieto-occipital cortex (fig 4) was reported in a series of nine sporadic patients with seizures, cognitive slowing, and IQ scores ranging from average intelligence to mild mental retardation. Neurological examination was otherwise normal. Age at seizure onset varied between 20 months and 15 years. Focal seizures with or without automatisms were the most frequent ictal pattern, and in most patients seizures were intractable.<sup>31</sup>

#### Bilateral generalised polymicrogyria (BGP)

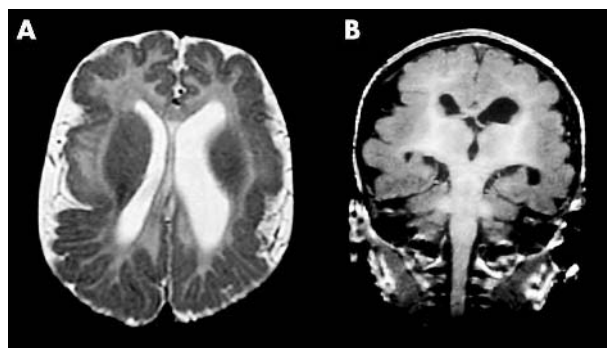
In BGP, polymicrogyria occurs in a generalised distribution but is most severe in the perisylvian regions (fig 5). Ventriculomegaly and reduced white matter volume are commonly associated. Pathology findings in one case showed an abnormally thin cerebral cortex with excessively folded and fused gyri and an absence of the usual six layered architecture.<sup>32</sup> BGP patients mostly have a variable degree of cognitive and motor delay, spastic hemiparesis or quadriplegia, and seizures. In the series reported by Chang *et al*,<sup>32</sup> seizures were present in 10 of 12 patients and varied in age at onset, type, and severity. Most patients had associated congenital abnormalities such as macrocephaly, scalp and limb defects, low set ears, macrostomia, hypothyroidism, and sensorineural hearing loss. Pseudobulbar signs were reported in one family, in which the proband had BGP on MRI but no pseudobulbar signs. Three siblings in this family did have pseudobulbar signs, but MRI data were not available. As pseudobulbar signs are commonly seen in patients with BPP, the question arises as to whether there is overlap between patients with BGP and those with the most severe form of BPP (grade 1). However, the presence of different polymicrogyria patterns in the same family has previously been reported.<sup>41 52</sup> Thus it is not excluded that BGP and BPP co-exist in the family reported by Chang *et al*.<sup>32</sup>

#### Unilateral polymicrogyria

Unilateral polymicrogyria has been reported in different cortical areas (fig 6).<sup>34 53-56</sup> Typical features include spastic hemiparesis with primary involvement of the upper extremity, a variable degree of mental retardation, and seizures. Additional clinical features depend on the site and the extent of the cortex affected by the polymicrogyria.<sup>55</sup> Most patients have generalised seizures and develop focal seizures in the



**Figure 4** Axial T1 weighted (A) and sagittal T1 weighted (B) magnetic resonance images, showing bilateral parieto-occipital polymicrogyria. The arrows point to irregular, bilateral deep sulci, extending from the posterior occipital surface toward the ventricular trigones. The cortex had a smooth appearance. The dotted lines (sagittal) delineate the lesion extent and local anatomical distortion.



**Figure 5** Axial T2 weighted (A) and coronal T1 weighted (B) magnetic resonance images showing bilateral generalised polymicrogyria. The frontal and parietal lobes present multiple small gyri interspaced with thin layers of white matter, whereas the central region has a smooth appearance. The T1 weighted image (coronal) shows a rather pachygyric appearance, related to thick slices and abnormal myelination. Photograph courtesy of Dr R Leventer.

course of the disease. Seizure control is variable.<sup>54 55</sup> Guerrini *et al* reported a series of nine patients (two bilateral, seven unilateral) with polymicrogyria and electrical status epilepticus during sleep (ESES) with a favourable seizure prognosis.<sup>53</sup> In a series of 15 patients, Ohtsuka *et al* confirmed that patients with unilateral localised polymicrogyria tend to have ESES or localisation related epilepsy with a relatively favourable prognosis.<sup>56</sup>

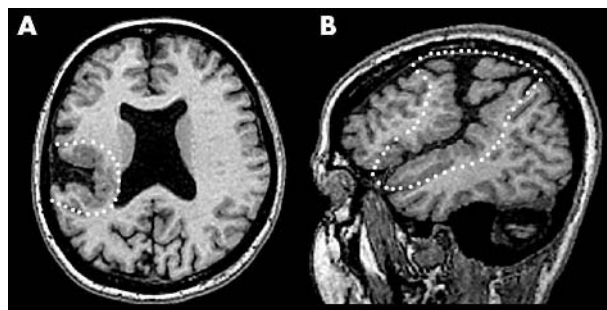
Caraballo *et al* described the development of an age specific, drug responsive syndrome of negative myoclonus in a series of 12 children with unilateral polymicrogyria.<sup>34</sup>

#### Summary

Polymicrogyria seems to develop in specific locations within the brain (frontal, perisylvian, parietal, and occipital) and in combinations of those regions, and the clinical manifestations appear to correlate with the parts of the cortex that are involved.<sup>30</sup>

#### GENETICS OF POLYMICROGYRIA SYNDROMES

Familial recurrence has been reported for bilateral fronto-parietal,<sup>3 27 28</sup> bilateral perisylvian,<sup>4 29 40 41 45 57-62</sup> and bilateral generalised polymicrogyria<sup>32</sup> (table 1, A-C). Bilateral frontal polymicrogyria was reported only in sporadic patients, but parental consanguinity was found in two families, suggesting possible autosomal recessive inheritance<sup>25</sup> (table 1D).



**Figure 6** Unilateral polymicrogyria. (A) Axial slice shows inward folding in the right central region. The cortex displays nodular, bumpy appearance. Note also absent septum pellucidum and septum cavum vergae. The sylvian fissure, better demonstrated in the sagittal image (B), is lined by polymicrogyric cortex, extending upward toward the interhemispheric fissure. Photograph courtesy of Alexandre Bastos.

**Table 1** Familial polymicrogyria

| Reference  | Syndrome                       | Fam | Cons | Aff | M  | F  | Includes      | Inheritance (most likely) | Locus      | Gene  |
|--|--------------------------------|-----|------|-----|----|----|---------------|---------------------------|------------|-------|
| <b>A Bilateral frontoparietal PMG (BFPP)</b>                   |                                |     |      |     |    |    |               |                           |            |       |
| Harbord <i>et al</i> <sup>68</sup>                             | Neuronal migration abnormality | 1   | –    | 2   | –  | 2  |               | AR                        |            |       |
| Dobyns <i>et al</i> <sup>35</sup>                              | Cobblestone lissencephaly      | 2   | 2    | 3   | 2  | 1  |               | AR                        |            |       |
| Straussberg <i>et al</i> <sup>3</sup>                          | Pachygyria                     | 1   | 1    | 3   | 1  | 2  |               | AR                        |            |       |
| Farah <i>et al</i> <sup>69</sup>                               | LIS + cerebellar hypoplasia    | 1   | 1    | 3   | 1  | 2  |               | AR                        |            |       |
| Piao <i>et al</i> <sup>27</sup>                                | BFPP                           | 2   | 2    | 5   | 2  | 3  | Ref 5         | AR                        | 16q12.2–21 |       |
| Chang <i>et al</i> <sup>28</sup>                               | BFPP                           | 10  | 8    | 19  | 8  | 11 | All previous  | AR                        | 16q12.2–21 |       |
| Piao <i>et al</i> <sup>13</sup>                                | BFPP                           | 12  | 9    | 22  | ?  | ?  | All previous  | AR                        | 16q12.2–21 | GPR56 |
| <b>B Bilateral perisylvian PMG (BPP)</b>                       |                                |     |      |     |    |    |               |                           |            |       |
| Graff-Radford <i>et al</i> <sup>57</sup>                       | BPP                            | 1   | –    | 2   | 2  | –  |               | Monozygotic twins         |            |       |
| Robinson <i>et al</i> <sup>4</sup>                             | Familial schizencephaly        | 1   | –    | 2   | 1  | 1  |               | AR or X linked (sibs)     |            |       |
| Kuzniecky <i>et al</i> <sup>29</sup> (1)                       | BPP                            | 1   | –    | 2   | 2  | –  | Ref 57        | Monozygotic twins         |            |       |
| Kuzniecky <i>et al</i> <sup>29</sup> (2)                       | BPP                            | 1   | –    | 3   | 2  | 1  |               | X linked                  |            |       |
| Gropman <i>et al</i> <sup>45</sup>                             | BPP                            | 1   | –    | 2   | ?  | ?  |               | AR or X linked (sibs)     |            |       |
| Yoshimura <i>et al</i> <sup>58</sup>                           | BPP                            | 1   | –    | 4   | 3  | 1  |               | X linked                  |            |       |
| van Bogaert <i>et al</i> <sup>59</sup>                         | BPP (1), UPP (1)               | 1   | –    | 2   | 1  | 1  |               | AR or X linked (sibs)     |            |       |
| Bartolomei <i>et al</i> <sup>60</sup>                          | BPP (1), UPP (1)               | 1   | –    | 2   | 0  | 2  |               | AR or X linked (sibs)     |            |       |
| Borgatti <i>et al</i> <sup>40</sup>                            | BPP                            | 1   | –    | 6   | 1  | 5  |               | X linked                  |            |       |
| Barkovich <i>et al</i> <sup>30</sup>                           | BPP                            | 1   | ?    | 3   | ?  | ?  |               | D or R?                   |            |       |
| Guerreiro <i>et al</i> <sup>41</sup>                           | BPP                            | 6   | –    | 18  | 7  | 11 | Ref 29 and 40 | X linked                  |            |       |
|  |                                | 4   | –    | 8   | 6  | 2  | Ref 59 and 60 | AR or X linked (sibs)     |            |       |
|  |                                | 1   | –    | 1   | 1  | –  |               | AD with DP                |            |       |
|  |                                | 1   | –    | 4   | 1  | 3  |               | AR with PsD               |            |       |
| Villard <i>et al</i> <sup>61</sup>                             | BPP                            | 5   | –    | 13  | 12 | 1  |               | X linked                  | Xq28       |       |
| Brandao-Almeida <i>et al</i> <sup>62</sup>                     | BPP                            | 3   | –    | 17  | 14 | 3  |               | AD                        |            |       |
|  |                                | 2   | –    | 11  | 8  | 3  |               | AD or X linked            |            |       |
|  |                                | 1   | 1    | 2   | –  | 2  |               | AR with PsD               |            |       |
| <b>C Bilateral generalised PMG (BGP)</b>                       |                                |     |      |     |    |    |               |                           |            |       |
| Chang <i>et al</i> <sup>32</sup>                               | BGP                            | 3   | 1    | 8   | 4  | 4  | Ref 64        | AR                        |            |       |
|  |                                | 1   | –    | 2   | 1  | ?  |               | AR                        |            |       |
|  |                                | 1   | 1    | 1   | –  | 1  |               | AR                        |            |       |
| <b>D Bilateral frontal PMG (BFP)</b>                           |                                |     |      |     |    |    |               |                           |            |       |
| Guerrini <i>et al</i> <sup>25</sup>                            | BFP                            | 2   | 2    | 2   | 2  | –  |               | AR                        |            |       |
| <b>E Unilateral frontoparietal PMG (UFPP)</b>                  |                                |     |      |     |    |    |               |                           |            |       |
| Caraballo <i>et al</i> <sup>63</sup>                           | UFPP                           | 1   | –    | 2   | 1  | 1  |               | X linked or AD            |            |       |
| <b>F Mixed PMG syndromes (BGP + BFPP)</b>                      |                                |     |      |     |    |    |               |                           |            |       |
| Hung and Wang <sup>52</sup>                                    | BGP and BFPP                   | 1   | –    | 3   | 2  | 1  |               | AR or X linked (sibs)     |            |       |
| <b>G Familial PMG associated with congenital malformations</b> |                                |     |      |     |    |    |               |                           |            |       |
| De Bleecker <i>et al</i> <sup>64</sup>                         | Polymicrogyria + DM with PCI   | 1   | –    | 2   | –  | 2  |               | AR or X linked (sibs)     |            |       |
| Amor <i>et al</i> <sup>65</sup>                                | BGP + scalp and limb defects   | 1   | 1    | 2   | 1  | 1  |               | AR                        |            |       |
| Ciarlo <i>et al</i> <sup>66</sup>                              | BGP + limb defects             | 1   | –    | 2   | 1  | 1  |               | AR or X linked (sibs)     |            |       |

AD, autosomal dominant; Aff, number affected; AR, autosomal recessive; BFPP, bilateral frontoparietal polymicrogyria; BGP, bilateral generalized polymicrogyria; BPP, bilateral perisylvian polymicrogyria; Cons, number of consanguineous families; D, dominant; DM, dermatomyositis; DP, decreased penetrance; F, female; Fam, number of families; M, male; PCI, paracrystalline inclusions; PMG, polymicrogyria; PsD, pseudodominance; R, recessive; UFPP, unilateral frontoparietal polymicrogyria; UPP, unilateral perisylvian polymicrogyria.

Bilateral parieto-occipital polymicrogyria has been limited to sporadic patients so far.<sup>31</sup> A single family with unilateral frontoparietal polymicrogyria has been described<sup>63</sup> (table 1E). Hung and Wang reported different forms of polymicrogyria in monozygotic twins and in their older sibling<sup>52</sup> (table 1F). Mendelian forms of polymicrogyria in association with other congenital malformations have been described in three sibships<sup>64–66</sup> (table 1G).

### Familial polymicrogyria syndromes

#### Bilateral frontoparietal polymicrogyria (table 1A)

Bilateral frontoparietal polymicrogyria (BFPP) was first described in three unrelated patients.<sup>26–27</sup> Twelve further families with BFPP have been reported,<sup>3–13 27 28 35 68 69</sup> many of which were initially misdiagnosed. Nine families had close parental consanguinity suggesting autosomal recessive inheritance. Linkage analysis in two consanguineous families localised the responsible gene on chromosome 16q12.2–21.<sup>27 28</sup> Eight independent mutations in *GPR56*, a gene encoding an evolutionarily dynamic G protein coupled

receptor (GPCR), have been identified in 22 radiologically and clinically confirmed patients from 12 families of Middle Eastern and French Canadian origin.<sup>13</sup>

Analysis of the *GPR56* gene expression pattern suggests that GPCR signalling plays an essential role in regional patterning of the human cerebral cortex. *GPR56* is expressed in neuronal progenitor cells at all ages, but there is no clear expression in post-mitotic neurons. Expression of *GPR56* in neuronal progenitor cells and the observation that the most severely affected cortical regions in BFPP are extremely thin imply that *GPR56* may regulate cortical development by affecting cell fate. However, a role for *GPR56* in neuronal migration cannot be ruled out.<sup>13</sup> The identification of *GPR56* as a gene involved in the normal development of the frontoparietal cortex suggests that some genes in the human forebrain may underlie species specific programmes for the generation of cortical neurones that are destined for particular regions of the cerebral cortex.<sup>70</sup> It also illustrates how mutations in specific genes affect cell proliferation only in the regions of the embryonic ventricular zone subjacent to

these cortical areas. This in turn indicates that the proliferative zone consists of a heterogeneous population of progenitor cells that form a "protomap" rather than a uniform sheet of totally equipotent stem cells.<sup>71</sup>

The N-terminal domain that defines *GPR56* is unique to animals that have a cerebral cortex. This suggests that *GPR56* is not only essential during human cerebral cortical development and patterning, but may also have been a key target in the evolution of the cerebral cortex.<sup>13</sup>

How mutations in *GPR56* result in the white matter abnormalities and atrophy of brain stem and cerebellum seen on MRI in BFPP patients warrants additional study. Further mutation analysis in polymicrogyria patients is required to refine the phenotypic spectrum associated with mutations in *GPR56*.

### Bilateral perisylvian polymicrogyria (table 1B)

The first delineation of familial BPP was by Andermann and Andermann.<sup>72</sup> Familial occurrence has now been reported in 28 BPP families. Different patterns of inheritance, including X linked dominant,<sup>40 41</sup> X linked recessive,<sup>58 61</sup> autosomal recessive,<sup>4 41 45</sup> autosomal dominant with reduced penetrance,<sup>41</sup> autosomal recessive with pseudodominance,<sup>41 62</sup> and autosomal dominant<sup>62</sup> have been suggested, illustrating the genetic heterogeneity of BPP. However, 75% of BPP families are compatible with X linked inheritance.<sup>40 41 72</sup> To date, five families with X linked recessive BPP have been mapped to a locus on the distal long arm of the X chromosome (Xq28),<sup>61</sup> but the linkage has not yet been confirmed and no gene has been identified to date. It is still not clear if the remaining families with X linked inheritance map to the same locus, or if additional loci are involved.

In a few families, unilateral and bilateral perisylvian polymicrogyria co-exist, suggesting that a single genetic abnormality could be responsible for both.<sup>41 59 60</sup>

### Bilateral generalised polymicrogyria (table 1C)

BGP was reported in three sibships, one of which had consanguineous parents, as well as in one sporadic patient whose parents were second cousins. Another patient had a first cousin with a clinical picture characteristic of BGP.<sup>32</sup> These findings suggest autosomal recessive inheritance, although genetic heterogeneity cannot be ruled out.

In three BGP pedigrees, linkage to the BFPP locus was excluded. This strengthens the idea that BGP and BFPP are distinct entities with respect to both the genotype and the phenotype.

Although most families with BPP show X linked inheritance, autosomal recessive inheritance cannot be ruled out in a number of families. Further research is required to determine if there is overlap between BGP and a subgroup of BPP families, or if BGP and BPP are genetically distinct entities.

The above findings show that there are distinct forms of regional polymicrogyria which seem to be genetically determined. This is most likely to result from abnormalities in several developmental genes, each with a different area specific expression. Identification of *GPR56*, the first gene implicated in the development of polymicrogyria, provides a clue to understanding the molecular basis for the functional subdivision of the cerebral cortex.

### Chromosomal abnormalities

The chromosomal abnormalities associated with polymicrogyria are shown in table 2.

#### Chromosome 22q11 deletion syndrome (table 2A)

To date, polymicrogyria has been reported in 11 patients (nine male) with 22q11 deletion syndrome,<sup>73-80</sup> all of whom

had dysmorphic features to a variable extent. Seven also had a cardiac malformation. The deletion of chromosome 22q11 produces a phenotype encompassing the velocardiofacial syndrome, DiGeorge syndrome, and conotruncal heart malformations.<sup>81-83</sup>

The distribution of polymicrogyria in patients with 22q11 deletion syndrome is variable, and both unilateral and bilateral polymicrogyria have been reported. Possibly, the incidence and localisation of polymicrogyria in these patients is influenced by the size of the deletion or by deletion of contiguous genes. Two patients with polymicrogyria and 22q11 deletion syndrome had a parent with the deletion,<sup>74 77</sup> but neither of the parents had polymicrogyria. This illustrates the pleiotropy of the 22q11 deletion syndrome and suggests involvement of modifying factors. Although the frequency of polymicrogyria or other gross brain malformations in 22q11 deletion syndrome is low, it is very likely that polymicrogyria and chromosome 22q11 deletion in these patients are causally related. However, further investigations are required to determine whether the cerebral anomalies reflect a primary genetic defect or are secondary to the vascular and circulatory abnormalities encountered in 22q11 deletion syndrome.<sup>80</sup> The possible association of polymicrogyria with 22q11 deletion syndrome makes FISH analysis for 22q11 advisable in patients with polymicrogyria, especially in the presence of dysmorphic features or cardiac malformations.

#### Chromosomal rearrangements (table 2B)

Polymicrogyria was reported as part of the CNS abnormalities in eight patients with unbalanced chromosomal rearrangements,<sup>84-90</sup> occurring either de novo or inherited from a parent carrying a balanced translocation, and in one patient with a balanced chromosomal rearrangement.<sup>91</sup> In two patients, chromosomal abnormalities were associated with both polymicrogyria and periventricular nodular heterotopia (PNH).<sup>84 91</sup>

Leventer *et al*<sup>92</sup> reported a study of 220 patients with polymicrogyria, including nine with chromosomal abnormalities. Based on these findings, new loci for polymicrogyria were identified on chromosomes 2p13, 6q25, and 21q22. Loci on chromosomes 1p36 and 22q11 were confirmed, identifying del 1p36 and del 22q11 as the chromosomal abnormalities that are most frequently associated with polymicrogyria.<sup>92</sup> Apart from del 1p36 and del 22q11, it remains unclear whether the presence of polymicrogyria in patients with chromosomal rearrangements is coincidental or if any of these chromosomal abnormalities are involved in the development of the condition.

Zollino *et al*<sup>88</sup> described a family in which a t(1;12)(q44;p13.3) balanced translocation was detected in healthy carriers. In this family, two unbalanced segregation products were observed, each with a distinct phenotype.

The observation of discordant phenotypes in patients with cytogenetically identical unbalanced familial translocations in three of the reported families<sup>84 88 89</sup> may have important consequences for genetic counselling and prenatal diagnosis. Potential mechanisms underlying these findings include breakpoint modifications, abnormal imprinting, and interaction with X inactivation, mosaicism, environmental factors, genetic background, and cross regulation.<sup>89</sup>

The translocation breakpoints defined in these families may lead to the identification of other genes involved in the development of polymicrogyria.

#### Chromosomal aneuploidies associated with polymicrogyria (table 2C)

Single case reports of polymicrogyria have been published in patients with a duplication of the short arm of the X chromosome,<sup>54</sup> trisomy 13,<sup>93</sup> and Turner mosaicism.<sup>94</sup>



**Table 2** Chromosomal abnormalities associated with polymicrogyria

| Reference   | Year | Chromosomal abnormality  | Aff | M | F | Brain abnormalities  |
|---|------|--|-----|---|---|--|
| <b>A Deletion 22q11.2</b>                             |      |  |     |   |   |  |
| Cramer <i>et al</i> <sup>73</sup>                     | 1996 | del 22q11.2  | 1   | 1 | – | Perisylvian (MCA) PMG  |
| Bingham <i>et al</i> <sup>74</sup>                    | 1998 | del 22q11.2  | 2   | 1 | 1 | Unilateral perisylvian PMG + heterotopia + CT syrinx (1); BPP (1)        |
| Bird <i>et al</i> <sup>75</sup>                       | 2000 | del 22q11.2  | 2   | 1 | 1 | Unilateral frontoparietal (1); unilateral parietal PMG + cleft (1)       |
| Kawame <i>et al</i> <sup>76</sup>                     | 2000 | del 22q11.2  | 1   | 1 | – | Unilateral frontoparietal PMG  |
| Worthington <i>et al</i> <sup>77</sup>                | 2000 | del 22q11.2  | 1   | 1 | – | Bilateral perisylvian PMG  |
| Ghariani <i>et al</i> <sup>78</sup>                   | 2002 | del 22q11.2  | 1   | 1 | – | Unilateral hemispheric PMG   |
| Ehara <i>et al</i> <sup>79</sup>                      | 2002 | del 22q11.2  | 1   | 1 | – | Bilateral perisylvian PMG  |
| Sztriha <i>et al</i> <sup>80</sup>                    | 2004 | del 22q11.2  | 2   | 2 | – | Unilateral/bilateral FTP PMG   |
| <b>B Chromosomal rearrangements</b>                   |      |  |     |   |   |  |
| Ramer <i>et al</i> <sup>84</sup>                      | 1990 | UR: deletion of segment 2q31–2q33  | 1   | 1 | – | Bilateral CTP PMG + PNH + arachnoid cyst + hypoplasia of falx and CC     |
| Shapira <i>et al</i> <sup>85</sup>                    | 1999 | Monosomy 1p36  | 1   | ? | ? | Extensive neuronal and glial heterotopia + PMG                           |
| Dupuy <i>et al</i> <sup>86</sup>                      | 1999 | UR: duplication of centromere of chr 11 and of segment 11q11–11q12           | 1   | 1 | – | Microcephaly, PMG and pachygyria   |
| Alkan <i>et al</i> <sup>87</sup>                      | 2002 | UR: deletion of segments 18p11.2–18pter and 21pter–21q22.1                   | 1   | 1 | – | Localised PMG  |
| Zollino <i>et al</i> <sup>88</sup>                    | 2003 | UR: deletion of segment 1q44–1qter and duplication of segment 12p13.3–12pter | 2   | 2 | – | Unilateral perisylvian PMG   |
| Leeflang <i>et al</i> <sup>91</sup>                   | 2003 | BR: locus disruption by breakpoints at 1p12 and 6p12.2                       | 1   | 1 | – | Bilateral perisylvian PMG + bilateral PNH + hypoplasia of CC             |
| Metzke-Heidemann <i>et al</i> <sup>89</sup>           | 2004 | UR: duplication of segments 9pter–9q22.2 and 7q35–7qter                      | 1   | – | 1 | Bilateral parieto-occipital PMG + caudal hypoplasia of cerebellar vermis |
| Kogan <i>et al</i> <sup>90</sup>                      | 2004 | UR: deletion of segment 13q14.1–13q31.2                                      | 1   | 1 | – | Bilateral frontotemporal PMG + left parieto-occipital PMG                |
| Leventer <i>et al</i> <sup>92</sup>                   | 2001 | Loci on chr 1p36, 2p13, 6q25, 21q22 and 22q11                                | 9   | ? | ? | PMG, not specified   |
| <b>C Chromosomal aneuploidies associated with PMG</b> |      |  |     |   |   |  |
| Sener <i>et al</i> <sup>93</sup>                      | 1996 | Trisomy 13   | 1   | 1 | – | Bilateral perisylvian PMG  |
| Pascual-Castroviejo <i>et al</i> <sup>54</sup>        | 2001 | Duplication short arm X  | 1   | – | 1 | Unilateral hemispheric PMG   |
| Tombini <i>et al</i> <sup>94</sup>                    | 2001 | Turner mosaicism   | 1   | – | 1 | Bilateral frontal PMG  |

Aff, number affected; BPP, bilateral perisylvian polymicrogyria; BR, balanced rearrangement; CC, corpus callosum; CT, cervico-thoracic; CTP, centro-temporo-parietal; del, deletion; F, female; FTP, fronto-temporo-parietal; M, male; MCA, middle cerebral artery; PMG, polymicrogyria; PNH, periventricular nodular heterotopia; UR, unbalanced rearrangement.

### Multiple congenital anomaly/mental retardation syndromes

Polymicrogyria has been described in association with multiple congenital anomaly/mental retardation syndromes including Adams–Oliver, Aicardi, Arima, Delleman, Galloway–Mowat, Micro,<sup>5</sup> Baller–Gerold,<sup>95</sup> Kabuki make up (Niikawa–Kuroki),<sup>96</sup> and Pena–Shokeir<sup>97</sup> syndrome, among others.

Galloway–Mowat syndrome is characterised by microcephaly, hiatus hernia, and nephrotic syndrome resulting from underlying microcystic dysplasia and focal glomerulosclerosis.<sup>98</sup> The presence of polymicrogyria as part of this syndrome raises the possibility of screening genes for glomerulosclerosis as candidate genes for polymicrogyria. However, as many of the patients with all the above syndromes do not have polymicrogyria, it is likely that the presence of polymicrogyria in these syndromes results from the influence of additional modifying genes or environmental insults.

Joubert syndrome<sup>99</sup> is an autosomal recessive disorder marked by absence of the cerebellar vermis and by prominent superior cerebellar peduncles that form the “molar tooth sign” on axial magnetic resonance imaging.<sup>100</sup> Joubert syndrome can be subdivided according to clinical and genetic findings into classical Joubert syndrome (JBTS1) mapped to chromosome 9q34.3,<sup>101–102</sup> cerebello-oculo-renal syndrome (CORS2 or JBTS2) linked to chromosome 11p12–q13.3,<sup>103–104</sup> and Joubert syndrome 3 (JBTS3), caused by mutations in the *AH11* gene on chromosome 6q23.2–23.3.<sup>105–106</sup> A subset of

patients with nephronophthisis was found to have mutations in the *NPHP1* gene on chromosome 2q13.<sup>107</sup> Two patients with polymicrogyria and Joubert syndrome have mutations in *AH11*, suggesting that this gene is required for both cerebellar and cortical development in humans.<sup>108</sup> However, polymicrogyria is not universally associated with Joubert syndrome. The phenotypic spectrum of *AH11* mutations as well as the function of its gene product, joubertin, remain to be clarified.

### Mutations in *MECP2*, *PAX6*, and *MTTL1*

BPP has been described in a male patient with severe neonatal encephalopathy whose sister had classical features of Rett syndrome. Both patients had a mutation in the *MECP2* gene on Xq28, suggesting that *MECP2* screening could be considered in males with severe neonatal encephalopathy and in males and females with bilateral polymicrogyria.<sup>109</sup>

*PAX6* is a highly conserved developmentally regulated gene on 11p13, encoding for a transcription factor. Murine models suggest that *PAX6* plays a role in human brain development. Bilateral polymicrogyria occurs in homozygous mutant mice. Unilateral polymicrogyria was demonstrated in a mother and son with mutations in the *PAX6* gene, making this a candidate gene for polymicrogyria.<sup>110</sup>

The A3243G mutation in the mitochondrial transfer RNA for the leucine 1 (*MTTL1*) gene accounts for 80% of patients with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes). A single sibship has been reported in which the female proband

presented with polymicrogyria, dysmorphic features, and raised lactic acid. Her elder brother presented with typical MELAS syndrome. Both were carriers of the A3243G mutation on *MTTL1*.<sup>111</sup>

Again, as these are isolated findings, further studies are required to investigate the possible importance of these genes in the development of polymicrogyria.

### Schizencephaly and mutations in *EMX2*

*EMX2* is a transcription factor that acts as a regulatory gene.<sup>112</sup> The mouse *EMX2* gene is homologous to the *Drosophila ems* (empty spiracles) gene which, when mutated, is responsible for a developmental defect in fly brain segmentation.<sup>113</sup> Heterozygous mutations in the homeobox gene *EMX2* on chromosome 10q26.1 were reported in some sporadic and familial patients with schizencephaly.<sup>114–116</sup> Although the mutations are presumed to be autosomal dominant, the pattern of inheritance remains unclear. A causative role of *EMX2* in the development of schizencephaly could not be reproduced by other research groups,<sup>5</sup> suggesting genetic heterogeneity or the involvement of modifying factors. However, if the role of *EMX2* in the development of schizencephaly can be confirmed, screening for mutations in the *EMX2* gene in patients with polymicrogyria could be pursued, as polymicrogyria and schizencephaly are considered to be part of the same clinical and developmental spectrum.

### Summary

The above findings illustrate the genetic heterogeneity of polymicrogyria. Many types seem to be inherited as single gene disorders whereas in some cases inheritance is multifactorial or complex, with interaction of several modifying genes, each with a small additive effect, and environmental factors. Polymicrogyria may also be associated with specific malformation syndromes as well as with chromosomal abnormalities, particularly unbalanced translocations. Finally, in some cases purely environmental causes may predominate, although it is likely that they occur in the presence of a predisposing genetic background.

### COUNSELLING

As illustrated above, polymicrogyria is a very heterogeneous condition, clinically as well as aetiologically and histologically, and it remains unclear if differences in the polymicrogyria patterns and phenotypes result from mutations in different genes, different mutations in the same gene that affect protein function differently, different dosage of the same mutation in the same gene, or different effects of the same mutation and dosage caused by unidentified modifying factors.<sup>5</sup>

The following investigations could be helpful in refining the diagnosis of polymicrogyria and improving counselling.

- Detailed personal history and neuroimaging can point to underlying environmental aetiologies such as infections in utero, twin–twin transfusion syndrome, or maternal drug toxicity during pregnancy.
- Family history with special attention to learning difficulties, mental retardation, speech problems, epilepsy, and dysmorphic features can give more information on the possible mode of inheritance. In the presence of known familial syndromes such as Rett or MELAS, mutation screening of *MECP2* and *MTTL1* can be pursued.
- High resolution karyotyping or microarray based comparative genomic hybridisation (CGH) should be carried out to identify chromosomal abnormalities. Apart from counselling issues, this will contribute to the identification of further loci or genes involved in the development of polymicrogyria.

- Fluorescence in situ hybridisation (FISH) for del 1p36 and del 22q11.2 should be done, especially in the presence of mental retardation or cardiac malformations in patients or family members.
- Serum creatine kinase should be measured to rule out the presence of subclinical congenital muscular dystrophy.
- Families with perisylvian polymicrogyria can be tested for linkage to Xq28. If linkage is confirmed, families can be counselled with respect to the X linked pattern of inheritance and the individual haplotypes.
- Patients with frontoparietal polymicrogyria can be screened for mutations in the *GPR56* gene on chromosome 16q12.2–21. If a mutation is found, family members can be screened and prenatal diagnosis becomes an option.

### FUTURE PERSPECTIVES

Elucidation of the cellular and molecular events underlying cortical development has come mainly from animal studies, which are amenable to experimental approaches, including the induction of genetic mutations. Another approach to studying the mechanisms of normal cortical development and cortical specification can come from the genetic analysis of inherited conditions such as polymicrogyria, in which specific regions of the cortex are preferentially disrupted.

The search for additional genes involved in the development of polymicrogyria will consist of collecting more pedigrees to identify new loci or confirm linkage to the loci described to date. Candidate gene screening will be directed by the results of animal studies, linkage studies, and information provided by cytogenetic studies in patients with polymicrogyria who have known chromosomal abnormalities such as deletions or unbalanced translocations. The association of two or more malformations of cortical development in the same patient or in family members also provides clues to candidate genes, as does association of polymicrogyria with known multiple congenital anomaly/mental retardation syndromes.

The results of the molecular studies will determine whether the various clinical and anatomical polymicrogyria syndromes defined above are genetically heterogeneous or whether some share a common genetic basis, thus contributing to genotype–phenotype correlations in polymicrogyria. We also expect that these findings will help to improve diagnosis and treatment of polymicrogyria, and to assist with genetic counselling and prenatal diagnosis.

Functional studies of genes associated with this condition will not only improve our understanding of its often region specific development, but will also further clarify the molecular basis of normal cortical development. Furthermore, it will be interesting to see how the genes implicated in the development of the disorder interact with other genes that have already been identified as regulators of cortical development.

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