The Genetic Landscape of Polymicrogyria

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Abstract

Polymicrogyria (PMG) is a relatively common complex malformation with cortical development, characterized by an exorbitant number of abnormally tiny gyri separated by shallow sulci. It is a neuronal migration disorder. Familial cases of PMG and the manifestation of PMG in patients with chromosomal aberrations and mutations indicate their important role of genetics in this disorder. The highly stereotyped and well-conserved nature of the cortical folding pattern in humans is suggestive of the genetic regulation of the process. The chromosomal abnormalities observed in PMG include deletions, duplications, chromosomal rearrangements, and aneuploidies. Two of the most common deletions in PMG are 22q11.2 deletion and 1p36 deletion. Further, mutations in several genes such as GPR56, TUBB2B, SRPX2, PAX6, EOMES, WDR62, TUBA8, KIAA1279, and COL18A1 are known to be associated with PMG. Intriguingly, these genes are responsible only for a small number of cases of PMG. The protein products of these genes are implicated in diverse molecular and cellular functions. Taken together, PMG could be the result of the disruption of several biological pathways. Different modes of Mendelian inheritance and non-Mendelian inheritance are seen in PMG. We have suggested a gene panel that can be used for the detection of malformations of cortical development.

Keywords: 22q11.2 deletion, cortical folding, GPR56, polymicrogyria, tubulins

Polymicrogyria (PMG) is a relatively common complex malformation of cortical development, characterized by an exorbitant number of abnormally tiny gyri separated by shallow sulci, leading to an irregular and lumpy cortical surface. PMG may be unilateral or bilateral, symmetrical or asymmetrical, focal, multifocal or diffuse, and may affect the whole brain or part of the brain [Table 1; Figure 1]. The most frequently affected brain region in PMG is the perisylvian cortex.

PMG is a neuronal migration disorder wherein the normal process of cerebral cortical development is perturbed in the late stage of neuronal migration or in the early stage of cortical organization.[9] The signs and symptoms of PMG vary, based on the brain region and how much surface of the brain is involved [Table 1]. PMG previously remained underdiagnosed owing to the limitations in imaging techniques. However, the recent use of high-resolution radiological imaging approach has paved the way to improved diagnosis and classification. PMG can occur in association with other malformations of the brain such as microcephaly, megalencephaly, ventriculomegaly, and grey matter heterotopia.[15] In children, the clinical manifestations of PMG include delayed motor and language milestones, mild/moderate mental retardation, spastic hemiparesis/quadriplegia, and epilepsy.[1] It has been suggested that PMG is the culmination of a range of aberrations of cortical development.[4]

The incidence and prevalence of PMG are not accurately known due to the etiological and clinical heterogeneity of PMG. There is very little information on the factors leading to the development of PMG. Some of the factors that have been suggested to be associated with PMG include intrauterine cytomegalovirus infection,[1] maternal drug ingestion (Barkovich et al.,[6] 1995), fetal cerebral ischemia from placental perfusion failure, a twin-twin transfusion,[7] loss of a twin in utero,[8] mutations,[3] and chromosomal aberrations.[9]

The occurrence of familial cases of PMG,[10,11] the manifestation of PMG in patients with chromosomal abnormalities and mutations,[12-15] and the association of PMG with genetically determined syndromes such as Zellweger,[16] Aicardi,[17] and Walker-Warburg syndrome,[18] all indicate an important role of genetic factors in the pathogenesis of PMG. Efforts to elucidate the molecular genetic underpinnings of PMG are underway.

Genetic Underpinnings of Cortical Folding

Cortical folding is the process by which the massive cortex is fitted into a limited cranial volume. This occurs during embryonic development and is essential for the optimization of genetic and environmental factors. The occurrence of familial cases of PMG,[10,11] the manifestation of PMG in patients with chromosomal abnormalities and mutations,[12-15] and the association of PMG with genetically determined syndromes such as Zellweger,[16] Aicardi,[17] and Walker-Warburg syndrome,[18] all indicate an important role of genetic factors in the pathogenesis of PMG. Efforts to elucidate the molecular genetic underpinnings of PMG are underway.

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of brain wiring and functional organization of the brain.\[^{[19]}\]

The intricate mechanisms underlying the gyrification of the human cerebral cortex have been a topic of immense interest to neurobiologists. Understanding this mechanism is key to recognizing the functional organization of the brain and how it is affected in neurological disorders. The highly stereotyped and well-conserved nature of cortical folding patterns in humans is suggestive of strong genetic regulation of the process.\[^{[19],[20]}\]

In mice and humans, the fibroblast growth factor (FGF) signaling has been implicated in cortical development, gyrification, and patterning. Fgf2 has been demonstrated to induce cortical gyrification in mice brains.\[^{[21]}\] In humans, strong activating mutations in FGFR3 caused expansion of the surface area of the occipitotemporal region leading to excessive gyrification.\[^{[22]}\] The WNT–\(\beta\)-catenin pathway (also referred to as canonical WNT signaling) is also shown to be important in gyrification.\[^{[23],[24]}\] It was shown to regulate rostral-caudal and medial-lateral patterning in the developing cortex, and in establishing the radial inside to outside organization of the cerebral cortex.\[^{[25]}\] The hominoid-specific gene TBC1D3 was

| Table 1: Common polymicrogyria syndromes |
|-----------------------------------------|
| **Type**                              | **Brain region affected** | **Symmetrical or not** | **Clinical features**                                                                 | **Incidence of seizures** | **Reference** |
|----------------------------------------|---------------------------|------------------------|--------------------------------------------------------------------------------------|--------------------------|---------------|
| Bilateral frontal polymicrogyria (BFP) | Frontal region            | Symmetrical            | Delayed motor and language milestones, mild to moderate mental retardation, seizures, spastic hemiparesis or quadriparesis, |
| Bilateral frontoparietal polymicrogyria (BFPP) | Frontal and parietal lobes | Symmetrical            | Global developmental delay, moderate to severe intellectual disability, dysconjugate gaze, ataxia, finger dysmetria, seizures |
| Bilateral perisylvian polymicrogyria (BPP) | Perisylvian cortex        | Usually, symmetrical   | Pseudobulbar palsy with diplegia of the facial, pharyngeal, and masticatory muscles, dysphagia, dysarthria, mild to severe intellectual disability, seizures |
| Bilateral parasagittal parieto-occipital polymicrogyria (BPPOP) | Parastagittal and mesial aspects of the parieto-occipital cortex | Symmetrical            | IQ scores ranging from average to mild mental retardation, cognitive slowing, seizures |
| Bilateral generalized polymicrogyria (BGP) | Generalized distribution; most severe in the perisylvian regions | Symmetrical            | Cognitive and motor delay, spastic hemiparesis or quadriparesis, seizures |
| Unilateral polymicrogyria              | Different cortical areas  | Asymmetrical            | Variable degree of mental retardation, spastic hemiparesis with primary involvement of the upper extremity, seizures |

Figure 1: MRI images of various patterns of polymicrogyria. Source: http://www.genereviews.org/. Copyright © 1993-2022 University of Washington.
shown to promote the generation of basal neural progenitor cells and induce cortical folding.[26] The gene GPR56, which encodes a member of the G protein-coupled receptor family, is known to regulate cortical progenitor proliferation and cortical patterning.[27] A 15-base pair deletion in the regulatory region of GPR56, which results in dysregulation of GPR56 expression, disrupts human cortical folding around the Sylvian fissure.[28] Heterozygous missense mutations in TUBB3, which encodes beta-tubulin isotype 3, a neuron-specific component of microtubules, are reported to cause dysmorphic cortical folding patterns.[29] Mutations in the regulatory region of human T-box transcription factor TBR2 have adverse effects on cortical size and folding.[30] In gyrencephalic mammals, the expression of Cdk5 in the upper-layer neurons was found to be essential for the effective folding of the cerebral cortex.[31]

**Role of Genetics in PMG**

Familial recurrence has been reported for several types of PMG, especially, bilateral frontoparietal PMG[32] and bilateral perisylvian PMG.[33] Chromosomal abnormalities (deletions and duplications) and gene mutations have been reported in PMG patients.

**Chromosomal Abnormalities**

Cytogenetic and molecular genetic studies in 29 patients with PMG identified several candidate loci in 1p36.3, 2p16.1-p23, 4q21.21-q22.1, 6q26-q27, and 21q21.3-q22.1, 1q44 and 18p. However, most of these loci demonstrated incomplete penetrance and variable expressivity.[30] Deletions, duplications, chromosomal rearrangements, and chromosomal aneuploidies have been observed in PMG.

**Deletions and duplications:** Two of the most common deletions in PMG, 22q11.2 deletion and 1p36 deletion, are discussed in detail below. Other deletions and duplications identified in PMG are listed in Table 2.

**22q11.2 deletion:** Deletion 22q11.2 (DEL22q11.2), with a reported incidence as high as 1:4000 live births, is one of the most common microdeletions in humans.[33] Among the various brain malformations described with DEL22q11.2, PMG is the most frequently reported condition.[35] DEL22q11.2 is the most common chromosomal abnormality associated with PMG. However, owing to the low penetrance and variable expressivity of this microdeletion, the underlying molecular mechanisms are unknown.[38]

In DEL22q11.2, PMG is observed mostly in the perisylvian areas and most often is asymmetrical with a predisposition for the right hemisphere of the brain.[39] This asymmetric presentation has led to the hypothesis that the candidate genes of PMG may be asymmetrically expressed between the two hemispheres of the brain.[38] In a fetal brain, the haploinsufficiency of a gene, that could be responsible for cortical development, in this deleted region could lead to PMG.[39] However, there is no strong functional candidate gene, within or around the critical deleted region, currently known to be associated with PMG. Another hypothesis suggests asymmetric hypoperfusion of the developing brain, resulting from the haploinsufficiency of a gene expressed in the fetal vascular brain tissue.[38] Bingham[40] postulated that DEL22q11.2 may influence one or more of the predisposing factors of PMG such as fetal cerebral vasculature, a tendency toward thrombosis, regulation of energy metabolism, and post-migrational cortical maturation. In children with DEL22q11.2 syndrome, brain magnetic resonance imaging (MRI) should be performed to look for PMG. The prognosis might depend on the presence of PMG.[39]

**1p36 deletion:** PMG has been reported in patients with 1p36 monosomy.[41] However, this shows only incomplete penetrance.[42] Even though 1p36 harbors several genes involved in brain development or function, the gene whose insufficiency leads to PMG has not yet been identified. Some of the potential candidate genes in this region are TP73, PEX10, SKI, GABRD, PRDM16, PRKCZ, MMP23B, MMP23A, and PRDM16.[42,43] 1p36 duplications are rare. The smallest 1p36 microduplication was reported in a patient with bilateral perisylvian PMG.[44] Functional validation studies of the genes in this duplicated region revealed that ENO1 could be the most likely causative gene for the brain malformation.[44]

**Chromosomal rearrangements:** The following unbalanced rearrangements have been observed in PMG:

- Deletion of segment 1q44-1qter and duplication of segment 12p13.3-12pter in two patients with unilateral perisylvian PMG[45]

| Type of PMG                                      | Chromosomal abnormality | Number of patients | Reference |
|-------------------------------------------------|-------------------------|--------------------|-----------|
| Symmetric perisylvian PMG                       | Deletion of 1q44        | 1                  | [9]       |
| Bilateral centro-temporo-parietal PMG, periventricular nodular heterotopia, arachnoid cyst, hypoplasia of falx, and agenesis of the corpus callosum | Deletion of 2q31-2q33    | 1                  | [34]      |
| Symmetric perisylvian PMG                       | Deletion of 4q21.21-q22.1 | 2                 | [9]       |
| Extensive PMG                                   | Deletion of 6q26-q27    | 7                  | [9]       |
| Bilateral frontotemporal PMG and left parietooccipital PMG | Deletion of 13q14.1-13q31.2 | 1                  | [35]      |
| Symmetric perisylvian PMG                       | Deletion of 18p         | 1                  | [9]       |
| Symmetric perisylvian PMG                       | Duplication of 2p16.1-p23.1 | 2                 | [9]       |
| Bilateral perisylvian PMG                       | Duplication of 17p13.3-p13.2 | 1                  | [36]      |

PMG: Polymicrogyria
• Deletion of segments 18p11.2-18pter and 21pter-21q22.1 in a patient with localized PMG.
• Duplication of segments 9pter-9q22.2 and 7q35-7pter in a patient with bilateral parietooccipital PMG and caudal hypoplasia of cerebellar vermis.

A balanced translocation by breakpoints at 1p12 and 6p12.2 that leads to locus disruption was observed in a patient with bilateral perisylvian PMG, bilateral periventricular nodular heterotopia, and hypoplasia of corpus callosum.

**Chromosomal aneuploidies:** Trisomy 13 in bilateral perisylvian PMG, duplication of the short arm of the X chromosome in unilateral hemispheric PMG, and turner mosaicism in bilateral frontal PMG have been reported.

**Gene Mutations Associated With PMG**

Different modes of Mendelian inheritance such as autosomal dominant, autosomal recessive, and X-linked are seen in PMG. Several genes including GPR56, TUBB2B, SRPX2, Pax6, Eomes, WDR62, Tuba48, Col18a1, and KIAA1279 are known to be associated with PMG. The proteins products of these genes are involved in diverse molecular and cellular functions. Thus, PMG could be the result of the disruption of several biological pathways. Some of the well-studied genes are discussed below.

**GPR56:** GPR56 is an orphan G protein-coupled receptor that regulates the migration of neural progenitors via a G alpha 12/13 and Rho pathway, suggesting its importance in the development of the central nervous system (CNS). Autosomal recessive mutations in the GPR56 gene located on chromosome 16q13 are shown to be associated with bilateral frontoparietal PMG. GPR56 expression levels are suggested to regulate cortical progenitor proliferation by affecting neuronal migration and cell fate. GPR56 mutations tend to disrupt human cortex folding around the Sylvian fissure. A homozygous germline nonsense mutation (p.R271*) in GPR56 contributes to phenotypic variability in bilateral frontoparietal PMG. Intriguingly, GPR56 knockout mice suggest that GPR56-related bilateral frontoparietal PMG shares certain features of the cobblestone brain malformation. Detailed studies are needed to elucidate the range of phenotypic features associated with GPR56 mutations.

**Tubulins:** Tubulins, present in the postmitotic cells of the human CNS, are involved in the formation of microtubules that are vital for neuronal proliferation, migration, differentiation, and axonal guidance during cortical development. Mutations of tubulin genes (Tuba1a, Tubb2B, Tuba8) are seen in PMG. Neuropathological examination of the pattern of PMG in a 27-gestational-week fetus with Tubb2B mutation revealed ruptures in the pial basement membrane, cerebellar nodular heterotopias, over-migration of neurons, and disorganization of radial glial fibers. The cortical malformations associated with mutations of tubulin genes encompass a broad spectrum of cerebral anomalies ranging from lissencephalic to polymicrogyric cortical dysplasias, suggesting common underlying pathogenic mechanisms that involve microtubular function, reinforcing the role of microtubule-related proteins in cortical development.

PMG is strongly associated with epilepsy, the incidence being 33% to 87%. Mutations in the tubulin genes Tuba1a, Tubb2B, and Tubb3 are known to be associated with epilepsy. Mutations of Tuba1a and Tubb2B genes are most frequently associated with epilepsy compared with Tubb3 mutations. When the distribution of epilepsy-associated mutations in

| Type of PMG | Gene | Mode of inheritance | Reference |
|------------|------|---------------------|-----------|
| Bilateral frontoparietal PMG | ADGRG1, GPR56 | AR | [27,50] |
| Bilateral perisylvian PMG | PIK3R2, SRPX2 | Maternal | [54] |
| Bilateral temporooccipital PMG | FIG4 | AR | [54] |
| Bilateral asymmetric PMG | TUBB2B | AD | [13] |
| Bilateral asymmetric PMG and lissencephaly | TUBA1A, TUBB2B | De novo | [60,61,62] |
| Bilateral PMG | MECP2 | De novo | [63] |
| Unilateral PMG | Pax6 | Maternal | [64] |
| PMG and lissencephaly | TUBA1A | AD | [65] |
| PMG and agenesis of corpus callosum, microcephaly | EOMES | AD | [38] |
| PMG and microcephaly | WDR62, RTTN | AR | [66,67] |
| PMG and optic nerve hypoplasia | TUBA8 | AR | [68] |
| PMG and band-like calcification | OCLN | AR | [14] |
| PMG and Warburg Micro syndrome | RAB18 | AR | [69] |
| PMG and Goldberg-Shprintzen syndrome | KIAA1279 | AR | [70] |
| PMG and CK syndrome | NSDHL | X-linked | [71] |
| PMG and Knobloch syndrome | COL18A1 | AR | [71] |
| Warburg Micro syndrome (characterized by ocular and neurodevelopmental abnormalities, including PMG) | RAB3GAP | AR | [73] |

1PMG: Polymicrogyria; AD: Autosomal dominant; AR: autosomal recessive
these genes was examined, the mutations in TUBB2B were equally distributed, while the N-terminal domain harbored most of the mutations in TUBA1A.\(^{[83]}\) Structural abnormalities of the cortex, fractured pyramidal layer of the hippocampus, and defects due to impairment of neuronal migration were revealed in histological examinations of Tuba1a-mutant mice brains.\(^{[82,83]}\) TUBB2B mutations are known to affect tubulin heterodimer folding and incorporation into microtubules, leading to impairments in neuronal migration, radial glia dysfunction, and impaired cortical development.\(^{[113]}\) These malformations of cortical development are recognized as a cause of early-onset epilepsy.\(^{[84]}\) Epileptogenicity associated with tubulin gene mutations is a complex phenomenon, depending on the mechanism by which the mutations alter the dynamic properties and functions of microtubules. Epilepsy frequently occurs when the mutations lead to malformations of cortical development, while it is less frequent when mutations are associated with axonal guidance disorders. Early-onset epilepsy is often generalized and considered as an expression of diffuse cortical malformation.\(^{[89]}\) A role of TUBB3 in regulating epileptic seizures via GABA-A receptor-mediated synaptic transmission has been reported, explaining the rare epileptic cases in patients with TUBB3 mutations.\(^{[86]}\)

**SRPX2:** SRPX2, expressed in the neurons of the adult human brain, is a secreted protein that modulates synapse density.\(^{[87]}\) SRPX2 serves as a target of the FOXP2 transcription factor and is associated with epilepsy and language development.\(^{[58,88]}\) Mutations in SRPX2 have been linked to bilateral perisylvian PMG.\(^{[58]}\) In the developing rat cerebral cortex, Srpx2 downregulation led to the altered position of projection neurons.\(^{[89]}\) Detailed studies into the role of SRPX2 in neuronal migration and brain development are warranted.

**PAX6:** PAX6 is a developmentally regulated highly conserved gene. Located on 11p13, this gene encodes a transcription factor. In an MRI study involving 24 subjects heterozygous for PAX6 mutations, Mitchell et al.\(^{[64]}\) observed widespread structural abnormalities including unilateral PMG and absence of the pineal gland. Extensive PMG was reported in an infant who was a compound heterozygote for two of PAX6.\(^{[90]}\) Being a transcription factor, PAX6 could be involved in regulating gene expression during corticogenesis.\(^{[91,92]}\) Murine models have demonstrated a significant role of PAX6 in brain development. Pax6 plays a key role in the doroventral patterning of telencephalon,\(^{[114]}\) modulating the proliferation and differentiation of neural progenitor cells,\(^{[94-96]}\) specification of neuronal identity,\(^{[97]}\) radial glia differentiation,\(^{[98]}\) and neuronal migration.\(^{[99]}\) PAX6 mutations could lead to disruption of these functions leading to PMG.

**TBR2 (EOMES):** TBR2 is a transcriptional factor that serves an important role during development. It is a crucial modulator of neurogenesis in the subventricular zone.\(^{[99]}\) It is involved in neuronal proliferation and migration,\(^{[99]}\) and in implementing regional identity in the cortex.\(^{[100]}\) In humans, a homozygous chromosomal translocation that disrupts the expression of TBR2 was found to be associated with microcephaly, PMG, agenesis of the corpus callosum, cognitive deficits, and severe motor delay.\(^{[100]}\) Tbr2 is known to regulate the transcriptome by upregulating or downregulating the expression of numerous target genes.\(^{[101]}\) Interestingly, the TBR2 protein acts immediately downstream of Pax6 and regulates the division of intermediate progenitor cells. Pax6, Tbr2, and Tbr1 are expressed sequentially by the radial glia, intermediate progenitor cells, and postmitotic neurons in the developing neocortex.\(^{[102]}\) This sequential expression suggests that each of these transcription factors regulates specific steps in neuron differentiation. The altered fate of neurons due to mutations of TBR2 can be one of the causes of PMG.\(^{[9]}\)

**WDR62:** The protein encoded by WDR62 localizes to the centrosome and the nucleus, depending on the cell type and cell phase.\(^{[103]}\) Recessive mutations of WDR62 are identified as one of the causes of a broad range of severe cerebral cortical malformations including PMG, pachygyria, lissencephaly, microcephaly, schizencephaly, and cerebellar hypoplasia.\(^{[104]}\) Downregulation of Wdr62 in mice has revealed neuronal migration abnormalities.\(^{[105]}\) WDR62 transcripts and protein are abundant in the neural progenitors in ventricular and subventricular zones.\(^{[104]}\) Thus, progenitor abnormalities have been suggested as a cause of PMG.

**RAB3GAP:** RAB3GAP is a heterodimeric complex that serves as a guanine-nucleotide exchange factor for RAB18. Mutations of RAB18 cause Warburg Micro syndrome, which is characterized by several neurodevelopmental abnormalities, including PMG.\(^{[73,106]}\) The Rab proteins are key regulators of vesicular membrane transport in both the exocytic and endocytic pathways.\(^{[107]}\) Members of the Rab3 subfamily have been implicated in the regulated exocytosis of neurotransmitters and hormones.\(^{[108]}\) But how this contributes to PMG is yet to be elucidated.

**KIAA1279:** The KIAA1279 gene encodes a ubiquitously expressed protein that interacts with the microtubules. A homozygous nonsense mutation in KIAA1279 causes Goldberg-Shprintzen syndrome, which is characterized by an enteric nervous disorder, mental retardation, microcephaly, and bilateral generalized PMG.\(^{[109,110]}\) KIAA1279 is found to be involved in neurite outgrowth.\(^{[109]}\)

**Deep Sequencing Approach**

Recently, to identify the monogenic causes of PMG, Stutterd et al.\(^{[111]}\) recruited 123 patients with PMG for a deep sequencing study using gene panels containing 377 known candidate genes for malformations of cortical development. Pathogenic or likely pathogenic variants were identified in 20.3% of the patients. TUBA1A and PIK3R2 were the most common causal genes. The other causal genes were NEDD4L, PIK3CA, COL4A1, COL4A2, GRIN2B, GPSM2, TUBB3, WDR62, TUBB2B, FH, and ACTG1.

Among the causative/candidate variants, 30.7% were in the tubulin-related genes (TUBA1A, TUBB2B, TUBB3), and the
patients harboring a tubulin gene variant were diagnosed with tubulopathies. The mTOR-PI3K-AKT pathway was the second most frequently implicated molecular pathway, with causative variants identified in the PIK3R2 or PIK3CA genes in 26.9% of the patients who were diagnosed with mTORopathies. The PIK3R2 variant p.Gly373Arg itself contributed 20% of all the identified variants. Collagenopathies were diagnosed in 2.4% of the patients harboring causative variants in COL4A1 and COL4A2.

Between the male and female patients, there was no significant difference in the genetic causes identified. The possibilities of identifying a genetic cause were high in patients with abnormal head growth. A genetic cause could be identified in 58.3% of the patients with macrocephaly and 30.8% of the patients with microcephaly. The diagnostic yield of 20.3% shows that PMG may be associated with non-genetic factors, somatic mutations that are brain-specific, or other genes that were not included in the gene panel.

**De novo Mutations**

*De novo* variations have been identified in PMG. In a whole-exome sequencing (WES) study of 124 patients with PMG, *de novo* variations were observed in the ATP1A3 gene of eight patients. These patients had a severe form of PMG with developmental delay and epilepsy.[112] In mice, *Atp1a3* variants were associated with defects in brain architecture.[112] In another WES study of 57 PMG patients, *de novo* mutations in GRIN1 were observed in 11 patients.[113] GRIN1 encodes an essential subunit of the N-methyl-D-aspartate (NMDA) receptor. The PMG-associated GRIN1 mutations significantly altered the *in vitro* activity of the receptor, denoting an important role of NMDA signaling in the pathogenesis of PMG.[113] A *de novo* PIK3R2 variation has been reported in a patient with asymmetrical bilateral PMG.[114] *De novo* variants of PIK3R2, which is an upstream component of the mTOR pathway, have also been identified in patients with megalencephaly–polymicrogyria–polydactyly–hydrocephalus syndrome (MPPH).[115] In mice, Pik3r2 mutations were associated with brain overgrowth.[116] Interestingly, *de novo* variants of CCND2 have been identified as another pathogenic cause of brain overgrowth and severe cortical malformations including MPPH. The variants can lead to pathological stabilization of cyclin D2, which in turn lead to malformations in the developing cerebral cortex.[117] It has been suggested that mutations of PIK3R2 and CCND2 result in a common functional endpoint- increased cyclin D2 activity in neural precursors leading to cortical malformations.[117] *De novo* variations in MAPK8IP3, which is a crucial component of the retrograde axonal transport system, are associated with intellectual disability and brain anomalies such as perisylvian PMG, cerebral/cerebellar atrophy, and hypoplasia of the corpus callosum.[118] A recurrent *de novo* BICD2 missense mutation is associated with PMG and severe arthrogryposis.[119] A novel *de novo* DDX3X missense variant was reported in a female with delayed psychomotor development, delayed myelination, brachycephaly, and PMG.[120] Ddx3x regulates neuron generation and cortical development. Pathogenic DDX3X mutations lead to impaired RNA helicase activity, stimulate ectopic RNA-protein granules in neurons, and disrupt translation.[121] In the aforementioned deep sequencing study, *de novo* variations were observed in ACTG1, COL4A1, GRIN2B, NEDD4L, PIK3R2, TUBA1A, TUBB2B, and TUBB3.[111]

**Somatic Mosaicism**

Somatic mosaicism has been reported in PMG. In the deep sequencing study of 123 PMG patients, five variants (c.1117G>A variant of PIK3R2 in three patients, and two PIK3CA variants) were mosaic with allele fractions less than 0.33, the lowest allele fraction being 0.09.[111] Mosaic mutations in the PIK3R2 gene are associated with bilateral perisylvian PMG.[117] Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) is caused by somatic mosaicism of the PIK3CA gene.[112] Mosaic trisomy of chromosome 1q in the human brain is associated with unilateral PMG, very early-onset focal epilepsy, and severe developmental delay.[123]

Identification of somatic mosaicism is extremely challenging. Recent advances in high-depth next-generation sequencing (NGS) have made possible the detection of disease-associated somatic mosaicism.[124] The detection requires high depth sequence coverage, preferably 500× (giving alternate-allele coverage of >20×, assuming the allele is present in ~10% of cells), as against the 40 to 80× coverage of clinical exome sequencing or WES. Deep sequencing using targeted gene panels are a good option in this regard as they facilitate a higher depth of coverage and cost-efficient detection of somatic mosaicism.[125]

**Copy Number Variations**

PMG has been observed in genetic syndromes associated with copy number variations (CNVs), such as the 22q11.2 deletion syndrome.[126] Dobyns et al.[9] identified six PMG loci associated with pathogenic CNVs (1p36.3, 2p16.1-p23.1 4q21.21-q22.1, 6q26-q27, 21q21.3-q22.1, 22q11.2 and another five possible loci (1q44, 2p15-p16.1, 11q12-q13, 13q14.1-q31.2, 18p). Two patients were included in the deep sequencing study of Stutterd et al.,[111] who had chromosome copy number variants of uncertain significance that could be relevant to their PMG. Kobow et al.[123] identified a somatic duplication of the entire long arm of chromosome 1 in the surgical brain tissue of 7 out of 26 PMG patients studied. Duplication of 2p16 is associated with perisylvian PMG.[126] Gene pathway analysis suggested several developmentally relevant genes and gene clusters in this region. Further, a rare locus for PMG was narrowed to a region of 2p16.1-p16.3, which contained 23 genes that expressed in the cerebral cortex during fetal development. Several of the duplicated genes contributed to neurodevelopmental pathways including cytokine, growth factor, and hormonal signaling, modulation of cell cycle progression, neuronal migration, and intellectual disability.
and axonal guidance. Microduplication of 22q11.2 and inverted 9p duplication/deletion was observed in a child with asymmetrical PMG predominantly affecting the right occipital lobe.

WHAT DO THE GENES TELL US ABOUT THE PATHOGENESIS OF PMG?

PMG is a disorder of neuronal migration in which normal cortical development is disrupted during the later stages of neuronal migration or the earlier stages of cortical organization. Precise tuning of neuronal proliferation, differentiation, migration, and connectivity are pivotal in the normal development of the cerebral cortex. PMG can be considered as the culmination of multiple diverse pathological processes, occurring at different time points during cortical development. It can result from mutations in multiple genes or different mutations in the same gene with pleiotropic effects. The low/incomplete penetrance of mutations and variable expressivity pose problems in understanding the underlying molecular mechanisms. Further, it needs to be noted that these genes still account for only a small percentage of the cases of PMG. The potential influence of epigenetic factors (e.g., DNA methylation, histone acetylation, microRNAs) in the pathogenesis of PMG has not yet been studied. Since epigenetic processes play a crucial role during cortical development by regulating neurogenesis, proliferation, and cell specification, a study into the role of epigenetic factors in PMG could constitute a topic for future research.

TREATMENT AND MANAGEMENT OF PMG

PMG is diagnosed by brain MRI, which will reveal the abnormalities in brain structure, and the location and severity of the abnormality. In individuals with seizures, an electroencephalogram will help to confirm the type of seizure. The possibilities of genetic testing should also be explored by a detailed study of the medical history of the patient and his/her family members. Knowing the cause of the disease might help to formulate efficient therapeutic strategies.

PMG is a lifelong disorder. The brain malformation cannot be reversed, but the symptoms may be treated in children and adults. Thus, only symptomatic treatment is possible for PMG at present. The first-line treatment for those with seizures is anti-seizure medications. Individuals with unilateral PMG affecting only a small region could be considered for resective surgery. Advanced neuroradiologic and neurophysiologic techniques are required to provide an effective and safe resection of the epileptogenic cortex. Patients with bilateral PMG are not good candidates for resective surgery. Occupational therapy, physiotherapy, and speech therapy may help some of the affected individuals.

GENETIC TESTING AND COUNSELING FOR PMG

A flow chart that provides the guidelines for genetic testing and counseling of families with brain malformations is provided in Figure 2. Familial PMG has shown an autosomal dominant, autosomal recessive, or X-linked mode of inheritance. In such familial cases, risk assessment and genetic counseling depend on the genetic cause of PMG in the affected individual. The phenotypic heterogeneity of PMG, low/incomplete penetrance of mutations, and the occurrence of de novo variants, somatic mosaicism, CNVs challenge the conventional genetic testing strategies and have important implications for genetic counseling. If a typical Mendelian inheritance pattern is observed in the family of the proband, a WES approach will help to identify the inherited monogenic causative variant. On the other hand, if a Mendelian pattern of inheritance is not observed in the family, the possibilities of de novo variants, CNVs, or somatic mosaicism should be looked into. CNVs can be tested using chromosomal microarrays, while mosaicism can be tested by deep sequencing. Table 4 shows a suggested gene panel for the NGS testing of malformations of cortical development.
**Table 4: A gene panel for the genetic testing of malformations of cortical development**

| ACTB | ACTG1 | ADGRG1 | AKT3 | ARHGAP31 | ARFGEF2 | ARX | ASPM |
|------|-------|--------|------|-----------|----------|-----|-------|
| ATP6V0A2 | B3GALNT2 | B4GAT1 | BMPER | CCDC88A | CCND2 | CIT | COL1A1 |
| CPT2 | CUL4B | DAG1 | DCCH1 | DCX | DOCK6 | DYNCH1 | CML1 |
| ERCC1 | FAT4 | FH | FIG4 | FKRP | FKTN | FLNA | GMP11 |
| GPHN | GPM2 | HSD17B4 | IA57 | ISPD | KATNB1 | KIAA0586 | KIAA1279 |
| KIF2A | KIF5C | KIF1L15 | LAGE3 | LAMBI | LAMC3 | LARGE1 | MBOAT7 |
| MECP2 | MTO | NANS | NDE1 | NEDD4L | NSDLH | OCLN | PAFAH1B1 |
| PAX6 | PEX1 | PEX13 | PEX2 | PEX26 | P14KA | PIK3CA | PIK3R2 |
| POMGNT1 | POMGNT2 | POMK | POMT1 | POMT2 | PFBP1 | RAB18 | RABGAP1 |
| RAB3GAP2 | RAC1 | RELN | RTTN | SF3B4 | SMO | SNAP29 | SRD5A3 |
| SRPX2 | TBC1D20 | TCTN2 | TME5 | TMTC3 | TP53RK | TUBA1A | TUBA8 |
| TUBB | TUBB2A | TUBB2B | TUBB3 | TUBB4A | TUBBG1 | USP18 | VLDLR |
| TUBB4A | TUBB2B | TUBB3 | TUBB3 | TUBB4A | TUBBG1 | USP18 | VLDLR |
| WDR62 | | | | | | | |

**Conclusions**

Despite several clinical and pathological studies, there is very limited understanding of the etiological mechanisms of PMG. It has not been possible to identify the primary brain insult that leads to each type of PMG. Studies indicate that disruption of neuronal migration and differentiation could lead to abnormalities of cortical gyration. In-depth molecular genetic studies will further shed light on the molecular basis of normal cortical development, contribute to genotype-phenotype correlations in PMG, and determine whether the different types of PMG are genetically heterogeneous or share a common molecular mechanism. We have suggested a panel of 96 genes that can be used for targeted NGS to detect the malformations of cortical development. Some of the important genes included in the panel are ADGRG1, AKT3, GPM2, KIAA1279, LAMC3, OCLN, RAB18, TBC1D20, tubulins, and WDR62. This will help to improve the diagnosis and treatment of PMG and can be made use of in early detection and genetic counseling. The integration of advanced neuroimaging, genetics, and animal model studies will assist in finding answers to the many unanswered questions.

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**Conflicts of interest**

There are no conflicts of interest.

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