NEXRES 8 (2026) 101540

Contents lists available at ScienceDirect

Next Research

journal homepage: www.elsevier.com/locate/nexres

Research Paper

Differential expression of neurogenesis-relevant genes in the peripheral blood lymphocytes of children with polymicrogyria

Mary Iype [a,b,c], Mithran Omana Surendran [d], Jesmy James [e], Aadhira Raghu [e], Smriti Menon [e], Arya K. S [e], Gokul Babu [e], Rahul Kumminimana [f], Ayyappan Anitha [e,*]

[a] Department of Pediatric Neurology, Government Medical College, Thiruvananthapuram, Kerala 695 011, India
[b] Department of Neurology, Institute for Communicative and Cognitive Neurosciences (ICCONS), Thiruvananthapuram, Kerala 695 033, India
[c] Department of Neurology, ICCONS, Shoranur, Kerala 679 523, India
[d] HINDLABS (SAT Hospital), Thiruvananthapuram, Kerala 695 011, India
[e] Department of Neurogenetics, ICCONS, Kavalappara, Shoranur, Palakkad, Kerala 679 523, India
[f] Department of Audiology and Speech Language Pathology, ICCONS, Shoranur, Kerala 679 523, India

ARTICLE INFO

Keywords:
Polymicrogyria
Peripheral blood lymphocytes
mRNA
Tubulins

ABSTRACT

Background: Polymicrogyria (PMG), a complex malformation of cortical development, has to date no genetic or biological mechanism attributed. Fine tuning of neuronal proliferation, differentiation, and migration are pivotal in the development and gyrification of cerebral cortex. Several genes are associated with cortical folding and PMG. We compared the peripheral blood gene expressions of a panel of 31 PMG/cortical folding-associated genes between children with PMG and healthy control subjects in an effort to identify any peripheral markers of PMG.
Methods: Twenty drug-naïve children with PMG and an equal number of age- and gender-matched healthy controls participated in the study. SYBR Green-based comparative Ct method was used to compare the expressions of 31 genes between the PMG and control groups. GAPDH was used as the reference gene.
Results: There was a significant difference in the expression of *TUBB2B* (p=0.005), *GPSM2* (p=0.029), *GMPPB* (p=0.019), *IBA57* (p=0.012), *NDE1* (p=0.005), and *RAB3GAP2* (p=0.034) among children with PMG when compared to the control subjects.
Discussion: These genes play crucial roles during neurogenesis and development of cerebral cortex. To the best of our knowledge this is the first study to examine the expressions of PMG-/cortical malformation-associated genes in the peripheral blood samples of children with PMG.

Introduction

Polymicrogyria (PMG) is a complex malformation of cortical development in which the surface of the brain has more than the normal number of gyri which are small, and separated by shallow sulci [1]. PMG accounts for approximately 16% of cortical malformations [2]. While unilateral PMG is generally sporadic, bilateral generalized PMG is inherited as an autosomal recessive trait [3]. PMG is sometimes dichotomized as unilayered or four-layered based on the histopathology, or as focal or diffuse [4]. Considering the lobar topography, frontal PMG is the most common type, followed by perisylvian region, and parietal lobe [2].

PMG is a malformation of the developing brain, where the insult and the resultant alteration of the gyral-sulcal architecture is postulated to occur late in the process of neuronal migration or early in the process of cortical organization [5]. Though often seen as the sole malformation, PMG may be seen associated with other brain malformations such as, corpus callosal agenesis, megalencephaly, nodular heterotopia or cerebellar hypoplasia [6]. Children with PMG, may present with seizures, developmental delay, hemiparesis, quadriparesis, intellectual disability or language delay [7].

In a population-based pediatric cohort, Kolbjer et al [2] reported a PMG prevalence of 2.3 per 10,000 children and an overall yearly incidence of 1.88. The factors reported to be leading to the development of PMG include, intrauterine cytomegalovirus infection [8], chromosomal aberrations [9], gene mutations [7], maternal drug ingestion [10], placental abruption [10], twin to twin transfusion [11], and intrauterine death of a twin [12].

* Corresponding author.
E-mail address: anitha.a72@gmail.com (A. Anitha).

https://doi.org/10.1016/j.nexres.2026.101540
Received 15 November 2024; Received in revised form 20 February 2026; Accepted 25 February 2026
Available online 26 February 2026

A genetic basis for PMG is supported by the occurrence of familial cases [13], and manifestation in patients with chromosomal aberrations/gene mutations [14], and genetically determined syndromes such as Walker-Warburg syndrome [15], Zellweger syndrome [16], and Aicardi syndrome [17]. In a genetic study of 109 patients with PMG, a confirmed genetic cause was present in one-third of the patients [2]. The biochemical, structural and endocrinological mechanisms that facilitate the gyral formation and folding of the human cerebral cortex has been the substrate of various neurobiological investigatory studies. The normal migration of neurons and their final organization into the six-layered cerebral cortex needs accurate regulation of neuronal proliferation, migration and synapse formation [18]. The process of cortical folding that occurs during embryonic development is crucial for the optimal functioning of the brain [19]. The highly patterned and safeguarded nature of cortical organization and folding indicate that it is genetically regulated.

Several genes have been reported to be associated with cortical folding and PMG [14]. Here, we compared the peripheral blood gene expression [messenger RNA (mRNA) levels] of a panel of 31 PMG/cortical folding-associated genes (Table 1) between children with PMG and healthy control subjects in an effort to identify any peripheral markers of PMG.

Materials and methods

Ethical statement

The study was approved by the Institutional Ethics Committees (IEC) of Government Medical College Thiruvananthapuram (GMCT; HEC No. 11/41/2019/MCT) and Institute for Communicative and Cognitive Neurosciences (ICCONS; IEC/IRB No. 001/IEC/2019/ICCONS-SRR), Shoranur. Written informed consent was obtained from the parents of all of the participants.

Subject recruitment

Twenty drug-naïve patients with PMG were recruited for the study (13 males and 7 females; mean age: 5.7 ± 0.8 years). The diagnosis of PMG in clinically suspected cases was confirmed by a neurologist and a radiologist based on 1.5T or 3T magnetic resonance imaging (MRI). There were 14 cases of bilateral PMG and 6 cases of unilateral PMG. PMG was observed in the perisylvian region (n=9), temporal region (n=5), parietal region (n=4), fronto-parietal region (n=3), and superior temporal gyrus (n=2). Agenesis of corpus callosum was observed in five children with PMG. MRI findings indicated the presence of heterotopia in five patients.

Global developmental delay, assessed on the basis of Trivandrum Developmental Screening Chart [51], was observed in 16 children with PMG. Intellectual disability was observed in seven PMG patients, while seizures were noted in six. A delay in speech or a slow progression of speech development was noted in 11 patients. Hemiparesis was identified in three patients, while hemiplegia was observed in four patients. Two patients exhibited microcephaly, and an increased head size was recorded in one patient.

Sixteen patients reported no family history of neurological disorders, whereas three had family members with epilepsy, and one had a first cousin diagnosed with PMG. Among the 20 PMG patients, 17 were born to parents who were not biologically related, whereas third-degree consanguinity was noted in one set of parents, and distant consanguinity in two other sets of parents. The mother of one of the patients reported that she had experienced pregnancy-induced hypertension. There were no other notable prenatal or environmental insults, as reported by the parents, that could have influenced the development of the disease. Pre-term birth occurred in three patients. One of the patients

Table 1
Genes and primers.

Genes	Forward primer sequence	Reverse primer sequence	Product size (bp)	Reference†
ADGRG1	CGACATGCTGGGAGATTACA	GGTGACAGAAGTGGCTAACA	138	[20]
ASPM	TGTCTGAGCCAGCGAAATAG	GCCTCTCCATAATGCCTGAA	123	[21]
COL18A1	GGCTCGATTTCTCCAGGATTT	CTGCTAACAGGTCTGGGTTT	116	[22]
COL3A1	CTGGCATTCCTTCGACTTCT	AGCTTCAGGGCCTTCTTTAC	116	Jorgensen et al, 2014 [23]
CPT2	CGAGCTGACTGATGCCTTAAA	TTCTTTGCCTCCTCTCTGAAAC	112	[24]
DCHS1	CCCAATTCCAGAGGACTTTCTAC	GAATAGGAGAGGAGGCCAAATG	121	[25]
DOCK6	CGAGTTCTACGAGGAGTTCAAG	AGCAGTGGGATCCAAGTAAAG	147	[26]
DYNC1H1	GCTCTCTTCCCAAAGCCATTA	CGTTCCTCTTTCTCCCTCTTTATC	117	[27]
EML1	CGGGTCATTCCAGCTTCATTA	TCCACACTTACGACTTGCTTAC	127	[28]
FLNA	CCACCATGACAACACCTACA	GGAGATACTGCCACTGAGAAAG	120	[29]
GMPPB	GCCAGGGCTGTATGGAATAATA	CCTGCCTGTATCCTCATTGG	127	[30]
GPSM2	TGAGCAGCGTCTCCTTATTG	TGTAGTATTCCGAGGCAGTTTC	122	[31]
HSD17B4	GGAGTTGGTAAAGGCTCCTTAG	CACAACCTTCTCTCCTTCTTCC	111	[32]
IBA57	GCTGTGGTCAGAGAAGATCAAG	TCGGACTACTTGGAGACTGTAG	114	[33]
LAGE3	CAACTTTCTTGACCAGCTTTCC	CCTACAAGGAGACGCAAAGT	120	[34]
LAMB1	CTCTACAGACAGAAGCCGAAAG	GCCTCAAGAGACATCTGGAAATA	133	[35]
LAMC3	CTGTCCTGATTCCAGCTTCTC	CTCTGAACACCATCTCCCATTAG	135	[36]
NDE1	TCCTTCCTCACTCCTACTCTTT	CTAACAGCCTCAAAGGGACTTAT	134	[37]
PAX6	GTCCAACGGATGTGTGAGTAA	CCCGCTTATACTGGGCTATTT	134	[38]
PEX1	GGGTAATTGCACGAGAGAGTAG	TTGCAGCCTGTGCTCTAATAA	123	[39]
PEX26	GCAAGAGTTGGTGAGCAATAAG	CTGGGCGACGATACTACTAAAC	104	[40]
PI4KA	CTCCACTGCCTTTGACTACTT	GGCGGTCAGGTACTTCTTATC	133	[41]
PIK3CA	TCCTTCCTCACTCCTACTCTTT	CTAACAGCCTCAAAGGGACTTAT	134	[42]
PIK3R2	CGCGAGTATGACCAGCTTTA	CAGGTATTCCTTGCTGCATTTC	147	[43]
POMGNT1	AGGAGAGTACCTGGGAATCAT	GCCCTCAGGACAGTCAATAAA	125	[44]
POMT1	TCTCTGATGAGCACCTCCTT	CTACGCTGGCCTCTGAAATAC	112	[45]
RAB3GAP2	CCAGCTCTAGCTGTGGATTTAG	GAATGGCCTCTTCTCCTAAGTG	118	[46]
RELN	CTTGCTGGTGACAGGACTATAC	GGCTACCACACTGCACATAA	133	[47]
TUBB2B	AGAGTGGAGCCGGGAATAA	TCACAGCTCTCTGACTCCTT	103	[48]
USP18	CTAACTACCACTGGCAGGAAAC	CGTAGATCCAGGAACGGAAATG	125	[49]
WDR62	GTGGAGGTGTATCCTGAGTTTG	TCCAAGTTCCAGAAGCGAATG	101	[50]
GAPDH *	GACCACTTTGTCAAGCTCATTTC	CTCTCTTCCTCTTGTGCTCTTG	119	-

* Reference gene
† PMG/cortical malformation-related

was born with arthrogryposis multiplex congenita.

Twenty age-and-gender-matched healthy control subjects (14 males and 6 females; mean age: 6.8 ± 0.9 years) were also recruited for the study.

RNA extraction and cDNA synthesis

Two milliliters of peripheral blood samples were collected from the participants in EDTA vacutainer tubes. Total RNA was extracted from the whole blood samples using NucleoSpin RNA Blood, Midi kit (Macherey-Nagel, Duren, Germany) following the manufacturer's protocol. cDNA was synthesized from total RNA using PrimerScript RT Reagent Kit (Takara Bio, Shiga, Japan) following the manufacturer's protocol.

Quantitative PCR (qPCR) to examine gene expression (mRNA levels)

SYBR Green-based comparative Ct method ($2^{-\Delta\Delta Ct}$) was used to compare the expressions of 31 genes between the PMG and control groups. GAPDH was used as the reference gene. Table 1 gives the list of primers used in qPCR. The primers were designed using PrimerQuest Tool (https://www.idtdna.com/PrimerQuest/Home/Index).

TB Green Premix Ex Taq II (Tli RNase H Plus) (Takara Bio) was used for SYBR Green-qPCR. Each 10 μl qPCR reaction consisted of 0.4 μM each of the forward and reverse primers, 0.2X ROX Reference Dye, 1X TB Green Premix, and cDNA template. All of the qPCR reactions were performed in duplicate. QuantStudio 5 Real-Time PCR system (Applied Biosystems by Thermo Fisher Scientific, Singapore) was used for carrying out qPCR. The shuttle PCR standard protocol for qPCR was as follows. A hold stage of 95°C for 30 s was followed by 40 cycles of 95°C for 3 s, 60°C for 30 s, and a Melt Curve Stage.

Comparison of gene expression between the PMG and control groups was done by the $2^{-\Delta\Delta Ct}$ method of relative quantification.

Statistical analysis

Kolmogorov-Smirnov test was used to assess the normality of data distribution. Any significant difference in the expression of various genes between the PMG and control groups was done by t-test for normally distributed data or by Mann-Whitney test for skewed data.

Results

There was no significant difference in age (t-test p=0.367) or gender distribution (Chi-square p=0.736) between the PMG and control groups.

Among the 31 genes studied (Table 1), the expressions of nine genes (*ADGRG1,DOCK6,EML1,LAMB1,LAMC3,PAX6,PEX26,PIK3R2,RELN*) were not found in detectable levels in the peripheral blood cDNA, and were omitted from further analyses.

There was a significant difference in the expression of *TUBB2B, GPSM2, GMPPB, IBA57, NDE1*, and *RAB3GAP2* among children with PMG compared to control subjects. While the expressions of *TUBB2B* (Mann-Whitney p=0.005), *GPSM2* (Mann-Whitney p=0.029), *GMPPB* (Mann-Whitney p=0.019), and *IBA57* (t-test p=0.012) were decreased in the blood samples of children with PMG, the expressions of *NDE1* (t-test p=0.005), and *RAB3GAP2* (t-test p=0.034) were increased in the PMG group compared with the healthy controls (Fig. 1). There was no significant difference in the expressions of the other genes between the PMG and control groups.

Discussion

To the best of our knowledge this is the first study to examine the gene expressions of PMG-/cortical malformation-associated genes in the peripheral blood samples of children with PMG. We observed decreased expressions of *TUBB2B, GPSM2, GMPPB* and *IBA57*, and increased expressions of *NDE1* and *RAB3GAP2* in the PMG group compared to healthy controls.

TUBB2B is a beta isoform of tubulin, and constitutes a major component of microtubules. The microtubules play a crucial role in neurogenesis, neuronal migration, neuronal differentiation, and cortical development [52]. Mutations in tubulin genes have been implicated in malformations of cortical development [53]. TUBB2B is mainly expressed in the developing neurons, and its expression undergoes a developmental transition [54]. Pathogenic variants in *TUBB2B* is associated with PMG, pachygyria, dysgyria, dysmorphic basal ganglia, corpus callosum dysgenesis, and cerebellar anomalies [55,56–57].

During early neurogenesis, GPSM2 (G Protein Signaling Modulator 2) plays a major role in cell-fate determination in the cerebral cortex [58]. *GPSM2* mutations cause brain malformations such as, frontal PMG, agenesis of corpus callosum, and grey matter heterotopia in

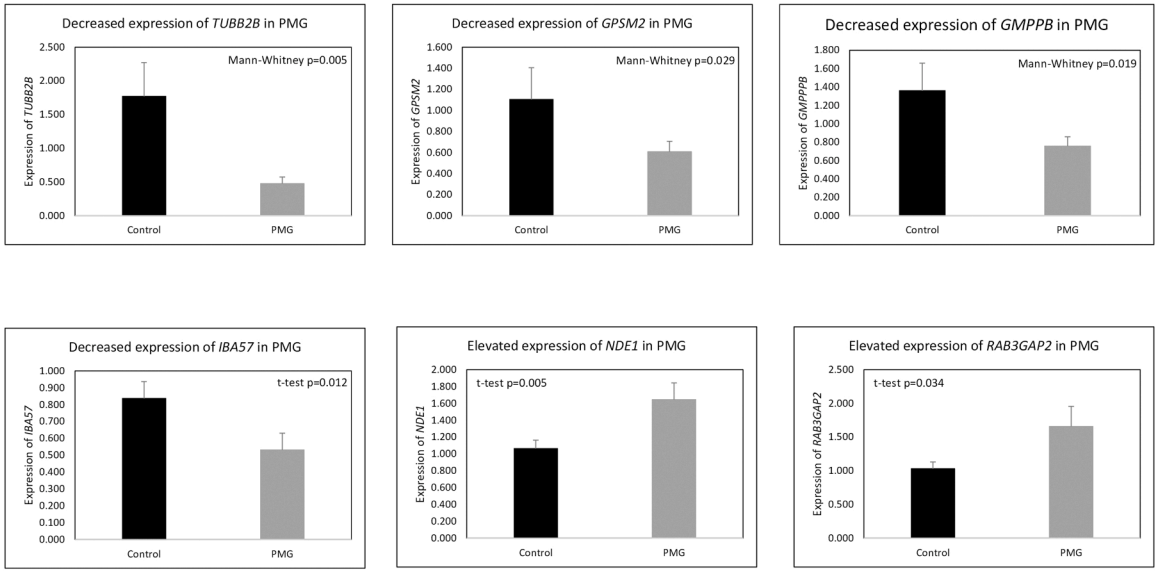

Fig. 1. Differential expression of *TUBB2B, GPSM2, GMPPB, IBA57, NDE1*, and *RAB3GAP2* in the polymicrogyria (PMG) group compared with healthy controls. SYBR Green-based comparative Ct method was used to compare the gene expressions between PMG and control groups. GAPDH was used as the reference gene for normalization. $2^{-\Delta\Delta Ct}$ values are shown along the Y-axis.

Chudley-McCullough syndrome [31,59].

GMPPB encodes a cytoplasmic protein that catalyzes the synthesis of GDP-mannose from GTP and mannose-1-phosphate. The expression of GMPPB protein increases during brain and skeletal muscle development, implicating its role during the development and differentiation of neuronal and myogenic cells [60]. GMPPB is associated with a wide spectrum of muscular/neuromuscular disorders [61]. PMG, microcephaly, and cortical hypoplasia are reported in patients harboring bi-allelic mutations of *GMPPB* [30].

IBA57 is a nuclear-encoded mitochondrial protein. The mitochondria play a vital role in the fine tuning of energy metabolism during neurogenesis [62]. *IBA57* mutations disrupt the iron-sulfur cluster assembly leading to cortical malformations including PMG, white matter abnormalities, hypoplasia of corpus callosum and medulla oblongata, cavitating leukoencephalopathy, microcephaly, cytotoxic edema of the cortex, and abnormal signal alterations in the brainstem and spinal cord [33,63].

NDE1, a key modulator of cytoplasmic dynein, is abundantly expressed in the neuroepithelial cells of the developing cerebral cortex, predominantly at the centrosome [64]. It protects the brain genome during the S phase of the initial differentiation of neural progenitor cells [65]. NDE1 has an essential role in neurogenesis and cortical gyrification [66]. NDE1 deficiency results in severe disruption of neurogenesis and defective cortical lamination [64]. Bi-allelic variations in *NDE1* cause extreme primary microcephaly with lissencephaly [67].

RAB3GAP2, which belongs to the RAB3 protein family, is the regulatory subunit of Rab3 GTPase-activating complex. Members of the RAB3 protein family are involved in the exocytosis of neurotransmitters [68]. Developmental expression studies in zebrafish have shown that Rab3gap2 expression was restricted to the central nervous system, implicating its role in neurodevelopment [69]. RAB3GAP variants lead to Warburg Micro syndrome, characterized by congenital cataracts, absence of visually evoked potentials, microphthalmia, microcephaly, PMG, hypoplasia of corpus callosum, and severe developmental delay [46,70]. *RAB3GAP2* variants have been identified in Martsolf syndrome as well, characterized by postnatal microcephaly, moderate mental retardation, axial hypotonia and PMG [71].

The PMG patients included in this study have previously undergone whole exome sequencing (WES) during which clinically relevant pathogenic variants were identified in *ROS1* and *PIK3R2* genes in one patient each. The *TUBB2B* gene harboured a variant, c.743C>T (p.Ala248Val), which was found in five PMG patients. This variant has conflicting classifications of pathogenicity (benign, likely pathogenic) with a CADD-PHRED score of 25. Despite the absence of clinically pathogenic predictions, variants exhibiting CADD-PHRED scores >20 were identified in several other genes; however, such variants were observed in only one or two patients each [72].

Studies on the expression of all the aforementioned genes have highlighted their crucial role in early neurogenesis. Additionally, TUBB2B, GMPPB, and NDE1 are abundantly expressed in the developing brain. BioGRID (https://thebiogrid.org/) has recognized GMPPB as a prominent interacting partner of TUBB2B, with a quantitative score (relative biotinylation score) of 1. Interestingly, we noted a significant positive correlation between the expressions of *TUBB2B* and *GMPPB* in our control subjects (Spearman's rho=0.468, p-value=0.04), but not in the PMG patients (Spearman's rho=-0.044, p-value=0.86). Although the precise onset time of PMG remains undetermined, it has been proposed to occur both early, due to abnormal proliferation and migration of neuroblasts, and late, due to impaired post-migrational maturation of the cortex. Given the available information, while it is challenging to provide a mechanistic explanation for the observed altered expression of *TUBB2B, GPSM2, GMPPB, IBA57, NDE1*, and *RAB3GAP2* in the peripheral blood of PMG patients, it can be inferred that the normal functions of these genes during neurodevelopment may be disrupted by their altered expression in PMG. Whether they operate within a shared molecular pathway is yet to be clarified.

Limitation

A limitation of this study is the small sample size. Further, the gene expression was analyzed in blood samples. PMG, being a neurodevelopmental abnormality, the results need to be replicated in brain tissues. Even though the blood samples are non-invasive, easily accessible alternatives to brain samples, there is always the issue of whether they can serve as direct correlates of intricate brain dysfunctions. Another limitation of the study is that a heterogeneous group of PMG patients were recruited for the study. Due to the high clinical and etiological heterogeneity associated with PMG, interpreting the results can become challenging.

Summary statement

We observed differential expression of neurogenesis-relevant genes (*TUBB2B, GPSM2, GMPPB, IBA57, NDE1, RAB3GAP2)* in the peripheral blood lymphocytes of children with PMG compared to healthy controls.

Funding

This work was funded by the Indian Council of Medical Research (ICMR) Task Force on Rare Diseases (Grant No.: 33/11/2019-TF/Rare/BMS to A.A.).

Data availability statement

The data from this study are confidential, but may be obtained with proper Data Use Agreements with Institute for Communicative and Cognitive Neurosciences (ICCONS). Researchers interested in this data may contact Dr. Ayyappan Anitha at anitha.a72@gmail.com. It may take a few months to negotiate data sharing agreements. The corresponding author may be approached for assistance in replication attempts for two years following publication.

CRediT authorship contribution statement

Mary Iype: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Conceptualization. **Mithran Omana Surendran:** Writing – review & editing, Writing – original draft, Software, Resources, Investigation, Formal analysis, Data curation. **Jesmy James:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Aadhira Raghu:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Smriti Menon:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Arya K. S:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Gokul Babu:** Writing – review & editing, Writing – original draft, Validation, Software, Investigation, Formal analysis, Data curation. **Rahul Kumminimana:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Ayyappan Anitha:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

No competing interests declared.

Acknowledgements

We thank the children and their families for having cooperated for the study by contributing their valuable time and enduring the process

of blood collection.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nexres.2026.101540.

References

[1] AJ. Barkovich, Current concepts of polymicrogyria, Neuroradiology 52 (6) (2010 Jun) 479–487, https://doi.org/10.1007/s00234-009-0644-2.

[2] S. Kolbjer, D.A. Martín Muñoz, A.K. Örtqvist, M. Pettersson, A. Hammarsjö, B. M. Anderlid, et al., Polymicrogyria: epidemiology, imaging, and clinical aspects in a population-based cohort, Brain Commun. 5 (4) (2023 Aug 11) fcad213, https://doi.org/10.1093/braincomms/fcad213.

[3] C.A. Stutterd, S. Brock, K. Stouffs, M. Fanjul-Fernandez, P.J. Lockhart, G. McGillivray, et al., Genetic heterogeneity of polymicrogyria: study of 123 patients using deep sequencing, Brain Commun. 3 (1) (2021 Jan 16) fcaa221, https://doi.org/10.1093/braincomms/fcaa221.

[4] A.R. Judkins, D. Martinez, P. Ferreira, W.B. Dobyns, JA. Golden, Polymicrogyria includes fusion of the molecular layer and decreased neuronal populations, but normal cortical laminar organization, J. Neuropathol. Exp. Neurol. 70 (6) (2011 Jun) 438–443, https://doi.org/10.1097/NEN.0b013e31821ccf1c.

[5] A.J. Barkovich, R.I. Kuzniecky, G.D. Jackson, R. Guerrini, WB. Dobyns, A developmental and genetic classification for malformations of cortical development, Neurology 65 (12) (2005 Dec 27) 1873–1887, https://doi.org/10.1212/01.wnl.0000183747.05269.2d.

[6] E. Parrini, V. Conti, W.B. Dobyns, R. Guerrini, Genetic basis of brain malformations, Mol. Syndromol. 7 (4) (2016 Sep) 220–233, https://doi.org/10.1159/000448639.

[7] A. Jansen, E. Andermann, Genetics of the polymicrogyria syndromes, J. Med. Genet. 42 (5) (2005 May) 369–378, https://doi.org/10.1136/jmg.2004.023952.

[8] V.M. Bosnjak, I. Daković, V. Duranović, L. Lujić, G. Krakar, B. Marn, Malformations of cortical development in children with congenital cytomegalovirus infection - A study of nine children with proven congenital cytomegalovirus infection, Coll. Antropol. 35 (Suppl 1) (2011 Jan) 229–234.

[9] W.B. Dobyns, G. Mirzaa, S.L. Christian, K. Petras, J. Roseberry, G.D. Clark, et al., Consistent chromosome abnormalities identify novel polymicrogyria loci in 1p36.3, 2p16.1-p23.1, 4q21.21-q22.1, 6q26-q27 and 21q2, Am. J. Med. Genet. A 146A (13) (2008 Jul 1) 1637–1654, https://doi.org/10.1002/ajmg.a.32293.

[10] A.J. Barkovich, H. Rowley, A. Bollen, Correlation of prenatal events with the development of polymicrogyria, AJNR Am. J. Neuroradiol. 16 (4 Suppl) (1995 Apr) 822–827.

[11] S. Sugama, K. Kusano, Monozygous twin with polymicrogyria and normal co-twin, Pediatr. Neurol. 11 (1) (1994 Jul) 62–63, https://doi.org/10.1016/0887-8994(94)90094-9.

[12] P. Van Bogaert, C. Donner, P. David, F. Rodesch, E.F. Avni, HB. Szliwowski, Congenital bilateral perisylvian syndrome in a monozygotic twin with intra-uterine death of the co-twin, Dev. Med. Child Neurol. 38 (2) (1996 Feb) 166–170, https://doi.org/10.1111/j.1469-8749.1996.tb12088.x.

[13] B.S. Chang, K.A. Apse, R. Caraballo, J.H. Cross, A. Mclellan, R.D. Jacobson, et al., A familial syndrome of unilateral polymicrogyria affecting the right hemisphere, Neurology 66 (1) (2006 Jan 10) 133–135, https://doi.org/10.1212/01.wnl.0000191393.06679.e9.

[14] J. James, M. Iype, M.O. Surendran, A. Anitha, S.V. Thomas, The genetic landscape of polymicrogyria, Ann. Indian Acad. Neurol. 25 (4) (2022) 616–626, https://doi.org/10.4103/aian.aian_97_22.

[15] AJ. Barkovich, Neuroimaging manifestations and classification of congenital muscular dystrophies, AJNR Am. J. Neuroradiol. 19 (8) (1998 Sep) 1389–1396.

[16] M.R. Mohebbi, E.T. Rush, W.B. Rizzo, RC. Banagale, Zellweger syndrome and associated brain malformations: Report of a novel peroxin1 (PEX1) mutation in a native American infant, J. Child Neurol. 27 (12) (2012 Dec 1) 1589–1592, https://doi.org/10.1177/0883073811435918.

[17] B. Hopkins, V.R. Sutton, R.A. Lewis, I. Van den Veyver, G. Clark, Neuroimaging aspects of Aicardi syndrome, Am. J. Med. Genet. A 146A (22) (2008 Nov 15) 2871–2878, https://doi.org/10.1002/ajmg.a.32537.

[18] A.N. Mallela, H. Deng, A. Bush, E. Goldschmidt, Different principles govern different scales of brain folding, Cereb. Cortex 30 (9) (2020 Jul 30) 4938–4948, https://doi.org/10.1093/cercor/bhaa086.

[19] V. Fernández, C. Llinares-Benadero, V. Borrell, Cerebral cortex expansion and folding: what have we learned? EMBO J. 35 (10) (2016 May 17) 1021–1044, https://doi.org/10.15252/embj.201593701.

[20] O.M. Schlüter, F. Schmitz, R. Jahn, C. Rosenmund, TC. Südhof, A complete genetic analysis of neuronal Rab3 function, J. Neurosci. 24 (29) (2004 Jul 21) 6629–6637, https://doi.org/10.1523/JNEUROSCI.1610-04.2004.

[21] F. Carneiro, J. Duarte, F. Laranjeira, S. Barbosa-Gouveia, M.L. Couce, MJ. Fonseca, Case report: Diffuse polymicrogyria associated with a novel ADGRG1 variant, Front. Pediatr. 9 (2021 Aug 27) 728077, https://doi.org/10.3389/fped.2021.728077.

[22] H. Bolat, S.G. Sağer, A. Türkyılmaz, A.H. Çebi, Y. Akın, H. Onay, et al., Autosomal recessive primary microcephaly (MCPH) and novel pathogenic variants in ASPM and WDR62 genes, Mol. Syndromol. 13 (5) (2022 Dec) 363–369, https://doi.org/10.1159/000524391.

[23] B.A. Charsar, EM. Goldberg, Polymicrogyria and intractable epilepsy in siblings with Knobloch syndrome and homozygous mutation of COL18A1, Pediatr. Neurol. 76 (2017 Nov) 91–92, https://doi.org/10.1016/j.pediatrneurol.2017.08.003.

[24] I. Shelihan, E. Rossignol, J.C. Décarie, J.P. Bonnefont, M. Brivet, C. Brunel-Guitton, et al., Infantile onset carnitine palmitoyltransferase 2 deficiency: cortical polymicrogyria, schizencephaly, and gray matter heterotopias in an adolescent with normal development, JIMD Rep. 63 (1) (2022 Jan) 3–10, https://doi.org/10.1002/jmd2.12243.

[25] A. Pratic, F. Sullo, M. Ruggieri, A patient with Aicardi syndrome phenotype and DCHS1 gene variants. A new step in the pursuit of the genetic cause of the disease or an incidental finding? Advance (May 06, 2020) https://doi.org/10.22541/au.158880114.49311668.

[26] K.M. Jones, A. Silfvast-Kaiser, D.R. Leake, L.Z. Diaz, ML. Levy, Adams-Oliver syndrome type 2 in association with compound heterozygous DOCK6 mutations, Pediatr. Dermatol. 34 (5) (2017 Sep) e249–e253, https://doi.org/10.1111/pde.13239.

[27] W.R. Ge, P.P. Fu, W.N. Zhang, B. Zhang, Y.X. Ding, G. Yang, Case report: genotype and phenotype of DYNC1H1-related malformations of cortical development: a case report and literature review, Front Neurol. 14 (2023 Apr 25) 1163803, https://doi.org/10.3389/fneur.2023.1163803.

[28] R. Oegema, G. McGillivray, R. Leventer, A. Le Moing, N. Bahi-Buisson, A. Barnicoat, et al., EML1-associated brain overgrowth syndrome with ribbon-like heterotopia, Am. J. Med. Genet. C Semin. Med. Genet. 181 (4) (2019 Dec) 627–637, https://doi.org/10.1002/ajmg.c.31751.

[29] N. Fennell, N. Foulds, D.S. Johnson, L.C. Wilson, M. Wyatt, S.P. Robertson, et al., Association of mutations in FLNA with craniosynostosis, Eur. J. Hum. Genet. 23 (12) (2015 Dec) 1684–1688, https://doi.org/10.1038/ejhg.2015.31.

[30] G. Astrea, A. Romano, C. Angelini, C.G. Antozzi, R. Barresi, R. Battini, et al., Broad phenotypic spectrum and genotype-phenotype correlations in GMPPB-related dystroglycanopathies: an Italian cross-sectional study, Orphanet. J. Rare Dis. 13 (2018 Sep 26) 170, https://doi.org/10.1186/s13023-018-0863-x.

[31] D. Doherty, A.E. Chudley, G. Coghlan, G.E. Ishak, A.M. Innes, E.G. Lemire, et al., GPSM2 mutations cause the brain malformations and hearing loss in Chudley-McCullough syndrome, Am. J. Hum. Genet. 90 (6) (2012 Jun 8) 1088–1093, https://doi.org/10.1016/j.ajhg.2012.04.008.

[32] E.Y. Bae, Y. Yi, H.H. Lim, J.M. Lee, B. Lee, S.Y. Kim, et al., First Case of Peroxisomal D-bifunctional protein deficiency with novel HSD17B4 mutations and progressive neuropathy in Korea, J. Korean Med. Sci. 35 (39) (2020 Sep 28) e357, https://doi.org/10.3346/jkms.2020.35.e357.

[33] A. Ishiyama, C. Sakai, Y. Matsushima, S. Noguchi, S. Mitsuhashi, Y. Endo, et al., IBA57 mutations abrogate iron-sulfur cluster assembly leading to cavitating leukoencephalopathy, Neurol. Genet. 3 (5) (2017 Sep 8) e184, https://doi.org/10.1212/NXG.0000000000000184.

[34] L. Huang, X. Zhang, Y. Zhang, Y. Wang, J. Mao, Novel LAGE3 pathogenic variants combined with TRPC6 and NUP160 variants in Galloway-Mowat syndrome: a case report, Case Rep. Nephrol. Dial. 13 (1) (2023 Sep 25) 148–155, https://doi.org/10.1159/000533580.

[35] F. Radmanesh, A.O. Caglayan, J.L. Silhavy, C. Yilmaz, V. Cantagrel, T. Omar, et al., Mutations in *LAMB1* cause cobblestone brain malformation without muscular or ocular abnormalities, Am. J. Hum. Genet. 92 (3) (2013 Mar 7) 468–474, https://doi.org/10.1016/j.ajhg.2013.02.005.

[36] B.S. Kasper, C. Kraus, M. Schwarz, J. Rösch, C.T. Thiel, A. Reis, et al., A novel splice variant expands the LAMC3-associated cortical phenotype to frontal only polymicrogyria and adult-onset epilepsy, Am. J. Med. Genet. A 182 (11) (2020 Nov) 2761–2764, https://doi.org/10.1002/ajmg.a.61846.

[37] A.R. Paciorkowski, K. Keppler-Noreuil, L. Robinson, C. Sullivan, S. Sajan, S. L. Christian, et al., Deletion 16p13.11 uncovers NDE1 mutations on the non-deleted homolog and extends the spectrum of severe microcephaly to include fetal brain disruption, Am. J. Med. Genet. A 161 (7) (2013) 1523–1530, https://doi.org/10.1002/ajmg.a.35969. Jul.

[38] T.N. Mitchell, S.L. Free, K.A. Williamson, J.M. Stevens, A.J. Churchill, I.M. Hanson, et al., Polymicrogyria and absence of pineal gland due to PAX6 mutation, Ann. Neurol. 53 (5) (2003 May) 658–663, https://doi.org/10.1002/ana.10576.

[39] S.Y. Cho, Y.P. Chang, J.Y. Park, H.D. Park, Y.B. Sohn, S.W. Park, et al., Two novel PEX1 mutations in a patient with Zellweger syndrome: The first Korean case confirmed by biochemical, and molecular evidence, Ann. Clin. Lab. Sci. 41 (2) (2011 Mar 20) 182–187.

[40] Y. He, S.B. Lin, W.X. Li, L. Yang, R. Zhang, C. Chen, et al., PEX26 gene genotype-phenotype correlation in neonates with Zellweger syndrome, Transl. Pediatr. 10 (7) (2021 Jul) 1825–1833, https://doi.org/10.21037/tp-21-103.

[41] A.T. Pagnamenta, M.F. Howard, E. Wisniewski, N. Popitsch, S.J.L. Knight, D. A. Keays, et al., Germline recessive mutations in PI4KA are associated with perisylvian polymicrogyria, cerebellar hypoplasia and arthrogryposis, Hum. Mol. Genet. 24 (13) (2015 Jul 1) 3732–3741, https://doi.org/10.1093/hmg/ddv117.

[42] H.J. Park, C.H. Shin, W.J. Yoo, T.J. Cho, M.J. Kim, M.W. Seong, et al., Detailed analysis of phenotypes and genotypes in megalencephaly-capillary malformation-polymicrogyria syndrome caused by somatic mosaicism of PIK3CA mutations, Orphanet. J. Rare Dis. 15 (1) (2020 Aug 10) 205, https://doi.org/10.1186/s13023-020-01480-y.

[43] G. Terrone, N. Voisin, A. Abdullah Alfaiz, G. Cappuccio, G. Vitiello, N. Guex, et al., De novo PIK3R2 variant causes polymicrogyria, corpus callosum hyperplasia and focal cortical dysplasia, Eur. J. Hum. Genet. 24 (9) (2016 Aug) 1359–1362, https://doi.org/10.1038/ejhg.2016.7.

[44] V.S. Vervoort, K.R. Holden, K.C. Ukadike, J.S. Collins, R.A. Saul, AK. Srivastava, POMGnT1 gene alterations in a family with neurological abnormalities, Ann. Neurol. 56 (1) (2004 Jul) 143–148, https://doi.org/10.1002/ana.20172.

[45] S.E. Wallace, J.H. Conta, T.L. Winder, T. Willer, J.M. Eskuri, R. Haas, et al., A novel missense mutation in POMT1 modulates the severe congenital muscular dystrophy phenotype associated with POMT1 nonsense mutations, Neuromuscul. Disord. 24 (4) (2014 Apr) 312–320, https://doi.org/10.1016/j.nmd.2014.01.001.
[46] E. Imagawa, R. Fukai, M. Behnam, M. Goyal, N. Nouri, M. Nakashima, et al., Two novel homozygous RAB3GAP1 mutations cause Warburg micro syndrome, Hum. Genome Var. 2 (1) (2015 Sep 17) 1–3, https://doi.org/10.1038/hgv.2015.34.
[47] S.H. Eriksson, M. Thom, J. Heffernan, W.R. Lin, B.N. Harding, M.V. Squier, et al., Persistent reelin-expressing Cajal-Retzius cells in polymicrogyria, Brain 124 (Pt 7) (2001 Jul) 1350–1361, https://doi.org/10.1093/brain/124.7.1350.
[48] R. Guerrini, D. Mei, D.M. Cordelli, D. Pucatti, E. Franzoni, E. Parrini, Symmetric polymicrogyria and pachygyria associated with TUBB2B gene mutations, Eur. J. Hum. Genet. 20 (9) (2012 Sep) 995–998, https://doi.org/10.1038/ejhg.2012.21.
[49] M.E.C. Meuwissen, R. Schot, S. Buta, G. Oudesluijs, S. Tinschert, S.D. Speer, et al., Human USP18 deficiency underlies type 1 interferonopathy leading to severe pseudo-TORCH syndrome, J. Exp. Med. 213 (7) (2016 Jun 27) 1163–1174, https://doi.org/10.1084/jem.20151529.
[50] D.R. Murdock, G.D. Clark, M.N. Bainbridge, I. Newsham, Y.Q. Wu, D.M. Muzny, et al., Whole-exome sequencing identifies compound heterozygous mutations in WDR62 in siblings with recurrent polymicrogyria, Am. J. Med. Genet. A 155A (9) (2011 Sep) 2071–2077, https://doi.org/10.1002/ajmg.a.34165.
[51] M.K.C. Nair, G.S.H. Nair, B. George, N. Suma, C. Neethu, M.L. Leena, et al., Development and validation of Trivandrum Development Screening Chart for children aged 0-6 years [TDSC (0-6)], Indian J. Pediatr. 80 (Suppl 2) (2013 Nov) S248–S255, https://doi.org/10.1007/s12098-013-1144-2.
[52] M.W. Breuss, I. Leca, T. Gstrein, A.H. Hansen, DA. Keays, Tubulins and brain development – The origins of functional specification, Mol. Cell Neurosci. 84 (2017 Oct 1) 58–67, https://doi.org/10.1016/j.mcn.2017.03.002.
[53] R. Romaniello, F. Arrigoni, A.E. Fry, M.T. Bassi, M.I. Rees, R. Borgatti, et al., Tubulin genes and malformations of cortical development, Eur. J. Med. Genet. 61 (12) (2018 Dec) 744–754, https://doi.org/10.1016/j.ejmg.2018.07.012.
[54] M. Breuss, J. Morandell, S. Nimpf, T. Gstrein, M. Lauwers, T. Hochstoeger, et al., The expression of Tubb2b undergoes a developmental transition in murine cortical neurons, J. Comp. Neurol. 523 (15) (2015 Oct 15) 2161–2186, https://doi.org/10.1002/cne.23836.
[55] J. Dekker, K.E.M. Diderich, R. Schot, S.C. Husen, M.H.G. Dremmen, ATJI Go, et al., A novel family illustrating the mild phenotypic spectrum of TUBB2B variants, Eur. J. Paediatr. Neurol. 35 (2021 Nov) 35–39, https://doi.org/10.1016/j.ejpn.2021.09.007.
[56] X.H. Jaglin, K. Poirier, Y. Saillour, E. Buhler, G. Tian, N. Bahi-Buisson, et al., Mutations in the β-tubulin gene TUBB2B result in asymmetrical polymicrogyria, Nat. Genet. 41 (6) (2009 Jun) 746–752, https://doi.org/10.1038/ng.380.
[57] H. Wang, S. Li, S. Li, N. Jiang, J. Guo, W. Zhang, et al., De novo mutated TUBB2B associated pachygyria diagnosed by medical exome sequencing and long-range PCR, Fetal. Pediatr. Pathol. 38 (1) (2019 Feb) 63–71, https://doi.org/10.1080/15513815.2018.1538273.
[58] D. Konno, G. Shioi, A. Shitamukai, A. Mori, H. Kiyonari, T. Miyata, et al., Neuroepithelial progenitors undergo LGN-dependent planar divisions to maintain self-renewability during mammalian neurogenesis, Nat. Cell Biol. 10 (1) (2008 Jan) 93–101, https://doi.org/10.1038/ncb1673.
[59] A.R. Hamzeh, P. Nair, M. Mohamed, F. Saif, N. Tawfiq, Al-Ali MT, et al., A novel nonsense *GPSM2* mutation in a Yemeni family underlying Chudley-McCullough syndrome, Eur. J. Med. Genet. 59 (6) (2016 Jun 1) 337–341, https://doi.org/10.1016/j.ejmg.2016.05.006.
[60] M.K. Schurig, O. Umeh, H. Henze, M.J. Jung, L. Gresing, V. Blanchard, et al., Consequences of GMPPB deficiency for neuromuscular development and maintenance, Front. Mol. Neurosci. 17 (2024 Feb 14) 1356326, https://doi.org/10.3389/fnmol.2024.1356326.
[61] L. Sun, D. Shen, T. Xiong, Z. Zhou, X. Lu, F. Cui, Limb-girdle muscular dystrophy due to GMPPB mutations: A case report and comprehensive literature review, Bosn. J. Basic Med. Sci. 20 (2) (2020 May) 275–280, https://doi.org/10.17305/bjbms.2019.3992.
[62] D. Brunetti, W. Dykstra, S. Le, A. Zink, A. Prigione, Mitochondria in neurogenesis: Implications for mitochondrial diseases, Stem Cells 39 (10) (2021 Oct 1) 1289–1297, https://doi.org/10.1002/stem.3425.
[63] N. Ajit Bolar, A.V. Vanlander, C. Wilbrecht, N. Van der Aa, J. Smet, B. De Paepe, et al., Mutation of the iron-sulfur cluster assembly gene IBA57 causes severe myopathy and encephalopathy, Hum. Mol. Genet. 22 (13) (2013 Jul 1) 2590–2602, https://doi.org/10.1093/hmg/ddt107.
[64] M. Bakircioglu, O.P. Carvalho, M. Khurshid, J.J. Cox, B. Tuysuz, T. Barak, et al., The essential role of centrosomal NDE1 in human cerebral cortex neurogenesis, Am. J. Hum. Genet. 88 (5) (2011 May 13) 523–535, https://doi.org/10.1016/j.ajhg.2011.03.019.
[65] S.L. Houlihan, Y. Feng, The scaffold protein Nde1 safeguards the brain genome during S phase of early neural progenitor differentiation, Elife 3 (2014 Sep 23) e03297, https://doi.org/10.7554/eLife.03297.
[66] J. Soto-Perez, M. Baumgartner, RN. Kanadia, Role of NDE1 in the development and evolution of the gyrified cortex, Front. Neurosci. 14 (2020 Dec 18) 617513, https://doi.org/10.3389/fnins.2020.617513.
[67] F.S. Alkuraya, X. Cai, C. Emery, G.H. Mochida, Al-Dosari MS, J.M. Felie, et al., Human mutations in NDE1 cause extreme microcephaly with lissencephaly, Am. J. Hum. Genet. 88 (5) (2011 May 13) 536–547, https://doi.org/10.1016/j.ajhg.2011.04.003.
[68] I.A. Aligianis, N.V. Morgan, M. Mione, C.A. Johnson, E. Rosser, R.C. Hennekam, et al., Mutation in Rab3 GTPase-activating protein (RAB3GAP) noncatalytic subunit in a kindred with Martsolf syndrome, Am. J. Hum. Genet. 78 (4) (2006 Apr) 702–707, https://doi.org/10.1086/502681.
[69] G. Borck, H. Wunram, A. Steiert, A.E. Volk, F. Körber, S. Roters, et al., A homozygous RAB3GAP2 mutation causes Warburg Micro syndrome, Hum. Genet. 129 (1) (2011 Jan) 45–50, https://doi.org/10.1007/s00439-010-0896-2.
[70] M.S. Abdel-Hamid, S.F. Abdel-Ghafar, S.R. Ismail, L.M. Desouky, M.Y. Issa, L. K. Effat, et al., Micro and Martsolf syndromes in 34 new patients: Refining the phenotypic spectrum and further molecular insights, Clin. Genet. 98 (5) (2020 Nov) 445–456, https://doi.org/10.1111/cge.13825.
[71] M. Iype, J. James, M.O. Surendran, A. Anitha, Genetic profiling of polymicrogyria in a south Indian Cohort, Ann. Indian Acad. Neurol. 28 (3) (2025 May 1) 422–425, https://doi.org/10.4103/aian.aian_1096_24.
[72] A. Jørgensen, T. Fagerheim, S. Rand-Hendriksen, P.I. Lunde, T.O. Vorren, M. G. Pepin, et al., Vascular Ehlers–Danlos Syndrome in siblings with biallelic COL3A1 sequence variants and marked clinical variability in the extended family, Eur. J. Hum. Genet. 23 (6) (2015 Jun) 796–802, https://doi.org/10.1038/ejhg.2014.181.