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A Rare Case of Polymicrogyria in an Elderly Individual With Unique Polygenic Underlining

Andrey Frolov [1], Stuart G. Atwood [1], Miguel A. Guzman [2], John R. Martin III [1]

1. Department of Surgery - Center for Anatomical Science and Education, Saint Louis University School of Medicine, St. Louis, USA 2. Department of Pathology, Saint Louis University School of Medicine, St. Louis, USA

Corresponding author: John R. Martin III, john.martin@health.slu.edu

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Abstract

Polymicrogyria (PMG) is the most common malformation of cortical development (MCD) and presents as an irregularly patterned cortical surface with numerous small gyri and shallow sulci leading to various neurological deficits including developmental delays, intellectual disability, epilepsy, and language and motor issues. The presentation of PMG varies and is often found in conjunction with other congenital anomalies. Histologically, PMG features an abnormal cortical structure and dyslamination, resulting in its classification as a defect of neuronal migration and organization. Due in part to a variety of etiologies, little is known about the molecular mechanism(s) underlining PMG. To address this gap in knowledge, a case study is presented where an elderly individual with a medical history of unspecified PMG was examined postmortem by using a combination of anatomical, magnetic resonance imaging (MRI), histopathological, and genetic techniques. The results of the study allowed the classification of this case as bifrontal PMG. The genetic screening by whole exome sequencing (WES) on the Illumina Next Generation Sequencing (NGS) platform yielded 83 rare (minor allele frequency, MAF ⩽ 0.01) pathological/deleterious variants where none of the respective genes has been previously linked to PMG. However, a subsequent analysis of those variants revealed that a significant number of affected genes were associated with most of the biological processes known to be impaired in PMG thereby pointing toward a polygenic nature in the present case. One of the notable features of the WES dataset was the presence of rare pathological/deleterious variants of genes (*ADGRA2*, *PCDHA1*, *PCDHA12*, *PTK7*, *TPGS1*, and *USP4*) involved in the regulation of Wnt signaling potentially highlighting the latter as an important PMG contributor in the present case. Notably, *ADGRA2* warrants a closer look as a candidate gene for PMG because it not only regulates cortical patterning but has also been recently linked to two cases of bifrontal PMG with multiple congenital anomalies through its compound heterozygous mutations.

Categories: Genetics, Pathology, Anatomy
Keywords: bifrontal, malformation of cortical development, next-generation sequencing, polymicrogyria, whole exome sequencing

Introduction

Polymicrogyria (PMG) is a malformation of cortical development (MCD) characterized primarily by overfolding of the cortical surface, producing an irregular pattern with numerous small gyri and shallow sulci [1]. With an incidence of 2.3 per 10,000 births [2], PMG is the most common form of MCD, accounting for 20% of all cases [1,3]. PMG has a remarkably heterogeneous phenotype [4] where common clinical presentations may include epilepsy, intellectual disabilities, and deficits in language and/or motor skills. To complicate this matter even further, these symptoms are often observed in conjunction with syndromes bearing multiple congenital anomalies, as well as symptoms specific to the affected cortical areas [1,4]. The phenotypical heterogeneity of PMG could be partially explained by its etiological diversity that in addition to variable genetic underpinnings [4-6] could also include environmental factors such as maternal infection during pregnancy, hypoxia/ischemia, and trauma [5]. Genetic PMG causes are diverse and could include chromosomal aberrations, copy number variations, or mutations involving a single or multiple genes [6]. The most common single-gene mutations target genes encoding cytoskeletal proteins *(TUBA1A, TUBB2B, TUBB3,* and *TUBA8),* genes regulating cell growth *(PIK3R2* and *FIG4)* and extracellular matrix *(COL18A1* and *LAMC3)*, as well as neuronal proliferation and migration *(WDR62)* [4,6]. Such remarkable phenotypical and etiological diversity makes the study of addressing molecular mechanism(s) of PMG in humans extremely difficult and could explain the paucity of the available respective information.

Therefore, the main objective of this study was to gain additional insights into the mechanism(s) governing PMG development through a postmortem study with a multifaceted approach including magnetic resonance imaging (MRI), gross anatomical examination and dissection, histopathological examination, as well as genetic screening by the whole exome sequencing (WES) on the next-generation sequencing (NGS) platform. A clearer understanding of the nature of the above pathology may further advance our understanding of the mechanism(s) regulating brain development in humans.

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Case Presentation

Anatomical characterization

An 81-year-old female body was received through the Saint Louis University (SLU) Gift Body Program with signed informed consent. Reported medical history included PMG, intellectual disability, static encephalopathy, moderately oral pharyngeal dysphagia, osteoporosis, cerebral palsy, irritable bowel syndrome, deafness, aphasia, ptyalism, and edentia. The cause of death for this individual was acute respiratory failure from acquired pneumonia, leading to hypoxia and severe sepsis. External examination of the donor revealed no external deformities as the extremities were normal with 10 fingers and toes. Body measurements revealed a height of 155 cm or (5’1”) and a head circumference of 50.15 cm. The distinct external characteristic of the donor was a protruding tongue. MRI revealed bifrontal PMG limited to the frontal lobes with small gyri, abnormal gyral patterns, and an irregular gray-white interface (Figure *1*). The subcortical areas, brainstem, and cerebellum appeared normally formed with no notable absences or hypoplasia.

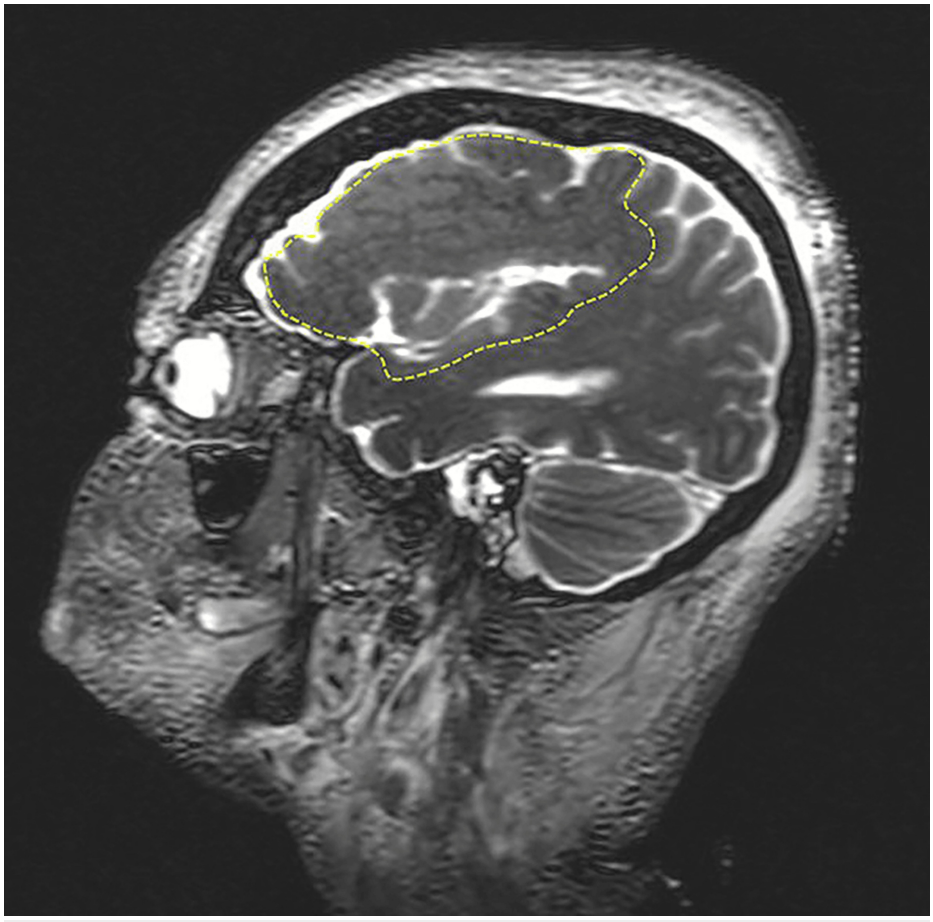

FIGURE 1: Magnetic resonance imaging of the donor head demonstrating the presence of polymicrogyria (PMG).

Parasagittal image of a T2-weighted MRI is shown. Note the aberrant boundary of the polymicrogyric cortex (depicted by stippled yellow lines) compared to the smooth gray-white boundary in normal cortical areas.

The gross brain examination confirmed the presence of bifrontal PMG (Figure *2A*). Aberrant patterning of the small gyri of the frontal lobes was well defined, in addition to some asymmetrical aberrant patterning in the left parietal and right perisylvian regions, with the apparent absence of the central sulcus of Rolando and precentral gyrus. Coronal sections showed small cortical folds and shallow sulci over the frontal lobes (Figure *2B*). Subcortical structures were normally present, and the lateral ventricles showed mild to moderate enlargement, indicative of age-related hydrocephalus ex-vacuo. The cortex of the right frontal lobe showed a stippled grey-white matter boundary in the anterior cingulate gyrus, extending posteriorly in the superior and inferior frontal gyri (Figure *2B*).

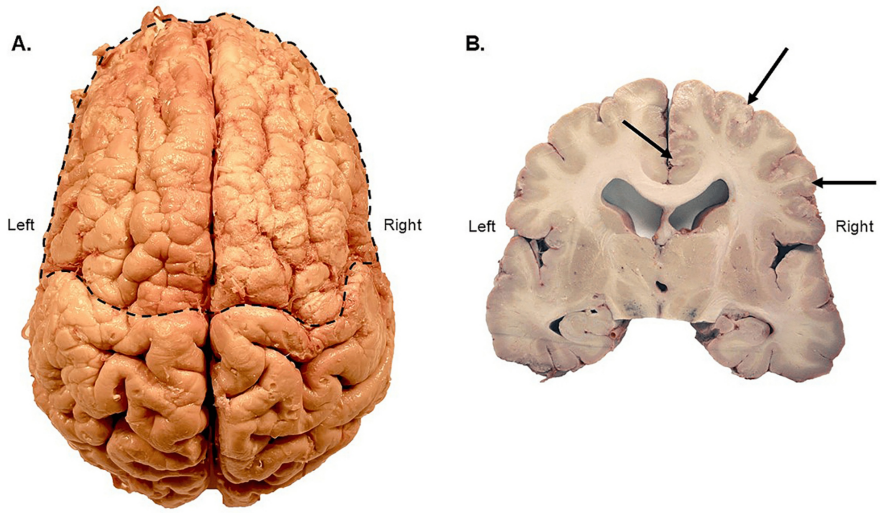

FIGURE 2: Superior and coronal views of the polymicrogyria (PMG) brain.

A. Superior view of the removed brain. Polymicrogyria (PMG) is evident in the outlined area when compared to the typical gyration of the more posterior brain. B. Coronal brain section at the level of the substantia nigra. The intact and fully developed corpus callosum is evident in this section; also of note is the stippled gray matter of the right hemisphere, as indicated by the arrows. Mild to moderate enlargement of the lateral ventricles was observed.

Examination of the histological images detailed multiple areas of true gyral fusion between adjacent molecular layers, with evidence of entrapped but otherwise normal, leptomeningeal blood vessels (Figure *3*). Additionally, a mild decrease in cortical thickness, with focal neuronal loss in the superficial layers and neuronal dyslamination of the neocortex, was noted. No neuronal heterotopias or dysplastic neurons were noted, and pial surfaces demonstrated no specific abnormalities.

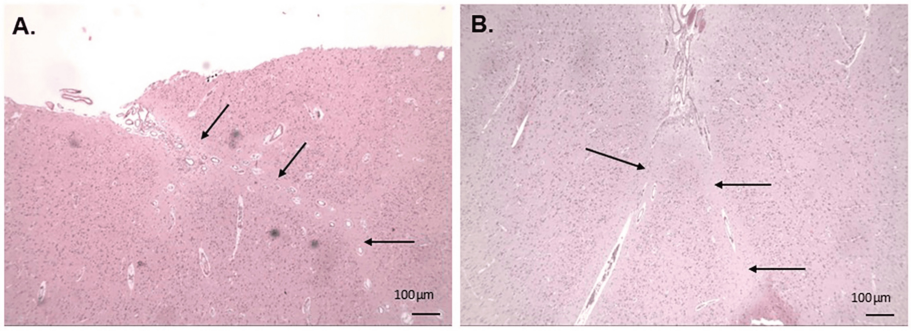

FIGURE 3: Hematoxylin and eosin (H&E)-stained sections of the right frontal lobe.

A. Right cingulate gyrus. The black arrows indicate areas of fused molecular layers between adjacent gyri. Leptomeningeal tissue and intracortical vessels are also evident in the upper part of this image. B. Right middle frontal gyrus. The microscopic image shows the cortical surface with fusion of the molecular layers (black arrows) which appears to extend into the underlying sulcus and includes entrapped leptomeningeal vessels.

Genetic screening

The post-mortem genetic screening by WES on the Illumina NGS platform and the respective bioinformatics analysis were performed as previously described [7]. The genetic screening revealed rare pathological/deleterious variants in 83 genes (Table *1*) with none of the genes listed in the table being previously linked to PMG [6]. Interestingly, among the genes listed in Table *1*, there was a group of five pleiotropic genes known to be involved in both neurogenesis and angiogenesis: *ADGRA2* [8,9], *JAG2* [10,11], *LAMA1* [12,13], *SEMA3D* [14,15], and *SYNM* [16]. These data were consistent with a recent hypothesis linking an aberrant hypersprouting angiogenesis to PMG development [17]. To test this hypothesis in the current setting, the histopathological examination of cerebral vasculature was performed but the outcomes were

unremarkable (data not shown).

Gene	Protein function
A1BG	Alpha-1-B glycoprotein
ABCA3	ATP binding cassette subfamily A member 3; brain development [18]; progenitor cell regulation; neurogenesis [19]; vesicle transport [20]
ABHD5	Abhydrolase domain containing 5, lysophosphatidic acid acyltransferase; skin barrier defect [21]
ACSS1	Acyl-CoA synthetase short chain family member 1
ADGRA2	Adhesion G protein-coupled receptor A2; brain development [8]; cerebral angiogenesis [9]; Wnt signaling [22,23]; bifrontal PMG with multiple congenital anomalies [24]
ADPRHL1	ADP-ribosylhydrolase-like 1 ROCK signaling [25]
BIRC7	Baculoviral IAP repeat containing 7
C19orf57	Break repair meiotic recombinase recruitment factor 1
CAPN12	Calpain 12; angiogenesis [26]; intellectual disability [27]
CARMIL3	Capping protein regulator and myosin 1 linker 3; brain ischemia [28]; cell migration [29]
CCDC198	Coiled-coil domain containing 198. Neurogenesis; progenitor cell regulation; cell migration [30]
CHAF1A	Chromatin assembly factor 1 subunit A. Neurogenesis [31,32]
CHRND	Cholinergic receptor nicotinic delta subunit. Neuromuscular junction formation [33]
CMPK2	Cytidine/uridine monophosphate kinase 2
CYP17A1	Cytochrome P450 family 17 subfamily A member 1; angiogenesis [34]
DENND1B	DENN domain containing 1B; vesicle transport [35]
DHRS2	Dehydrogenase/reductase 2
DNAH3	Dynein axonemal heavy chain 3; motile cilia regulation [36]
FLG2	Filaggrin 2; brain development [37]; skin disease [38]
GCC2	GRIP and coiled-coil domain containing 2
GLYATL3	Glycine-N-acyltransferase like 3
GUSB	Glucuronidase beta
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1
HLA-DRB5	Major histocompatibility complex, class II, DR beta 5
HLTF	Helicase-like transcription factor; neurogenesis/brain development [39]; neuronal cell death [40]
IFI30	IFI30 lysosomal thiol reductase; angiogenesis [41]; neuronal cells death [42]
JAG2	Jagged canonical notch ligand 2; progenitor cell regulation [11]; angiogenesis [10]
KMT2C	Lysine methyltransferase 2C; neurogenesis/brain development [43,44]
KRT19	Keratin 19
KRT86	Keratin 86
KRTAP3-2	Keratin associated protein 3-2
LAMA1	Laminin subunit alpha 1. Neurogenesis/brain development [12]; angiogenesis [13]
LONP1	Lon Peptidase 1, mitochondrial. Mitochondrial encephalopathy [45]; neuronal cell death [46]
LRGUK	Leucine-rich repeats and guanylate kinase domain containing. Motile cilia regulation [47]

LRRC58	Leucine-rich repeat containing 58. Neuroinflammation [48,49]
MDH1	Malate dehydrogenase 1. Energy metabolism [50]; neuronal cell death [51]
MGST2	Microsomal glutathione S-transferase 2. Neuronal cell death [52]; angiogenesis [53]
MLXIP	MLX interacting protein. Brain development/neurogenesis; progenitor cell regulation; energy metabolism [54]
MPEG1	Macrophage expressed 1
MRPL57	Mitochondrial ribosomal protein L57. Energy metabolism [55]
MS4A15	Membrane spanning 4-domains A15. Brain development/neurogenesis [56]
MTUS1	Microtubule-associated scaffold protein 1. Rac signaling [57]
MYO7B	Myosin VIIB. Vesicle transport [58]. Possibly linked to brain development/neurogenesis [59]
NGLY1	N-glycanase 1. Brain development/neurogenesis [60,61]; neuronal cell death [62]
NMU	Neuromedin U
OBSCN	Obscurin, cytoskeletal calmodulin, and titin-interacting. Brain development/neurogenesis [63]
OPN3	Opsin 3
OR2S2	Olfactory receptor family 2 subfamily S member 2. BBB** regulation [64]
PAH	Phenylalanine hydroxylase
PCDHA1	Protocadherin alpha 1. Brain development/neurogenesis [65,66]; Wnt signaling [67]
PCDHA12	Protocadherin alpha 12. Brain development/neurogenesis [68]; Wnt signaling [69,70]
PGK2	Phosphoglycerate kinase 2
PHKB	Phosphorylase kinase regulatory subunit beta
PI15	Peptidase inhibitor 15
PLEKHG3	Pleckstrin homology and RhoGEF domain containing G3. Brain development/neurogenesis [71,72]; Rho signaling [72]; linked to mild intellectual disability [73]
PSG6	Pregnancy-specific beta-1-glycoprotein 6. Brain development/neurogenesis [74]
PTK7	Protein tyrosine kinase 7 (Inactive). Brain development/neurogenesis [75,76]; Wnt signaling [75,77]; cell migration [77]
PTPRN2	Protein tyrosine phosphatase receptor type N2. TGFβ signaling [78]; cerebral vasculature remodeling [79]
RGR	Retinal G protein coupled receptor
RIT2	Ras like without CAAX 2. Brain development/neurogenesis; Ras signaling [80]
RSL1D1	Ribosomal L1 domain containing 1 (cellular senescence-inhibited gene protein, CSIG). Cell proliferation and senescence [81]; linked to child cognitive development [82]
SEMA3D	Semaphorin 3D. Signaling [83]; linked to cognitive impairment [14]; angiogenesis [15]
SKIV2L	SKI2 subunit of superkiller complex
SLC26A1	Solute carrier family 26 member 1
SLC9C1	Solute carrier family 9 member C1. Sperm-specific component of motile cilia [84]
SYNM	Synemin. Neurogenesis; progenitor cell regulation; cell migration [16]
TIAM2	TIAM Rac1 associated GEF 2. Brain development/neurogenesis; Rho signaling [85]
TLN2	Talin 2
TMEM43	Transmembrane protein 43
TPGS1	Tubulin polyglutamylase complex Subunit 1. Cilia regulation [86]
TTN	Titin
TUT1	Terminal uridylyl transferase 1, U6 SnRNA-specific. Brain development/neurogenesis [87]; neuronal cell death [88]

TYK2	Tyrosine kinase 2. Brain development/neurogenesis [89]. Jak/Stat signaling; neuronal cell death [90]
UBE4B	Ubiquitination factor E4B. Brain development/neurogenesis; progenitor cell regulation; mTOR signaling [91]; neuronal cell death [92]
UGT1A7	UDP glucuronosyltransferase family 1 member A7; BBB regulation [93]
UNKL	Unk like zinc finger. Neurogenesis [94]
UPK1A	Uroplakin 1A
USP4	Ubiquitin specific peptidase 4. Brain development/neurogenesis [95,96]; neuronal cell death [97]; Wnt signaling [98,99]
ZBED9	SCAN domain containing 3 (SCAND3). Potential biomarker for mild cognitive impairment [100]
ZC3H3	Zinc finger CCCH-type containing 3
ZNF227	Zinc finger protein 227
ZNF540	Zinc finger protein 540
ZYX	Zyxin. Brain development/neurogenesis [101]; tight junction/BBB regulation [102]; Shh signaling [103]; cell migration [104]

TABLE 1: Complete list of genes with rare pathological/deleterious variants associated with the present case*.

* Gene-to-protein name conversion was performed using the GeneCards database; **BBB: blood brain barrier.

Discussion

The current report provides additional insights into the molecular mechanism(s) underlining PMG development. The examination of the individual's brain by anatomical, MRI, and histological techniques allowed the classification of the observed MCD as bifrontal PMG with an absence of visible musculoskeletal defects often associated with PMG [1]. The performed genetic analysis provided several important insights into its development.

First, there was a plethora of genes linked to the biological processes that could be perturbed in PMG (Table *1*) [1,105] thereby being consistent with the polygenic underlining of the present case. *Second,* there were several genes involved in the regulation of cilia function including both of its types, primary and motile (Table *1*). Given the crucial role of motile cilia in neurodevelopment through regulation of cerebrospinal fluid (CSF) fluid flow [106,107] and ventricular development [108,109], as well as the absence of non-age related hydrocephalus pathology in the donor's brain (Figure *2*), one may conclude that PMG in the present case was not mediated by motile cilia but was rather associated with an input from the aberrant primary cilia-mediated signaling [110,111]. Such signaling aberration could be explained, at least in part, by the abnormal primary cilia formation driven by the mutated *TPGS1* (Table *1*) [86] and by impaired Wnt signaling, due to mutations in *ADGRA2, PCDHA1, PCDHA12, PTK7,* and *USP4* (Table *1*), which use primary cilia as a signaling platform [112].

Third, *ADGRA2,* also known as *GPR124,* was a very interesting gene because it not only positively regulates canonical Wnt signaling by increasing Wnt7 availability for Frizzled [22, 23], but by virtue of its compound heterozygous mutations, it has also been recently linked to two bifrontal PMG cases with multiple congenital anomalies [24]. It should also be noted that the other member of the same gene family, *ADGRG1 (GPR56)* with an autosomal recessive variant, was reported to be associated with bilateral frontoparietal PMG [113, 114]. Therefore, the results of the current report and the data presented in [24] merit a closer look at *AGDRA2* as a potentially causative gene in bifrontal PMG.

Fourth, the other notable feature of the genetic screening dataset was the presence of the biallelic *FLG2* variant (NM_001014342:exon3:c.C2606T:p.S869F; MAF = 4.21x10-6). *FLG2* is known for its association with skin diseases including atopic dermatitis [38], as well as for its link to neurodevelopmental aberrations, leading to autism spectrum disorder (ASD) with a prenatal excessive cortical expansion frequently seen in ASD children [37]. Such a link between neuro- and ectodermal development supports a hypothesis regarding the existence of the skin-brain axis, which could interdependently regulate both processes [37]. Unfortunately, due to the condition of cadaveric tissue subjected to the embalming solution, it was impossible to correctly assess the putative epidermal pathology in the donor and, therefore, evaluate the involvement of the skin-brain axis in the current case of bifrontal PMG. However, probing similar PMG cases for the autosomal recessive *FLG2* mutations and atopic syndromes antemortem would be worth pursuing.

Conclusions

The current rare case of bifrontal PMG in an elderly individual provided a unique opportunity to gain additional insights into the molecular mechanism(s) of PMG. Our results highlight the polygenic nature of PMG and the potential involvement of impaired Wnt signaling with the involvement of primary cilia deregulation and a direct Wnt signaling disruption. Our results also warrant additional studies on the *ADGRA2* gene as well as probing the skin-brain axis for their participation in the development of the cerebral cortex in humans.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: John R. Martin III, Andrey Frolov

Acquisition, analysis, or interpretation of data: John R. Martin III, Andrey Frolov, Miguel A. Guzman, Stuart G. Atwood

Drafting of the manuscript: John R. Martin III, Andrey Frolov

Supervision: John R. Martin III

Critical review of the manuscript for important intellectual content: Miguel A. Guzman, Stuart G. Atwood

Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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