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GPR56-Related Polymicrogyria: Clinicoradiologic Profile of 4 Patients

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Abstract

Bilateral frontoparietal polymicrogyria is an autosomal recessive cortical malformation associated with abnormalities of neuronal migration, white matter changes, and mild brainstem and cerebellar abnormalities. Affected patients present with delayed milestones, intellectual disability, epilepsy, ataxia, and eye movement abnormalities. The clinicoradiologic profile resembles congenital muscular dystrophy. However, no muscle disease or characteristic eye abnormalities of congenial muscular dystrophy are detected in these children. *GPR56* is the only confirmed gene associated with bilateral frontoparietal polymicrogyria. Antenatal diagnosis is possible if the index case is genetically confirmed. Four patients from different Indian families with a distinct clinicoradiologic profile resembling congenital muscular dystrophy with mutations in the *GPR56* gene are described.

Keywords

bilateral frontoparietal polymicrogyria, GPR56, congenital muscular dystrophy, epilepsy, cobblestone lissencephaly

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Polymicrogyria is a disorder of neuronal migration where normal gyri are replaced by multiple (poly) and small (micro) gyri.[1] Genetic as well as acquired causes have been implicated in polymicrogyria. Bilateral frontoparietal polymicrogyria is a radiological diagnosis with distinct MRI features consisting of bilateral frontoparietal polymicrogyria, white matter abnormalities, and cerebellar and brainstem hypoplasia.[2,3] All these features often resemble cobblestone lissencephaly associated with congenital muscular dystrophy but absence of muscle and eye abnormalities makes congenial muscular dystrophy unlikely. Mutations in the *GPR56* gene have been found to underlie this disorder.[4-12]

We describe the clinicoradiologic profile of 4 patients from different Indian families initially reminiscent of congenital muscular dystrophy who were later found to harbor the *GPR56* mutations.

Case Summary

All 4 unrelated children hailing from different parts of Indian subcontinent presented before 2 years of age to the child neurology clinic at a tertiary facility in a large metropolitan Indian city. Global developmental delay of varying severity was the uniform presentation. Antenatal and birth details were normal. Parental consanguinity was present in 2 of the 4 children. One patient had an elder brother with global developmental delay and epilepsy who had not been investigated and had died at 11 years of age. No dysmorphism was noted in any of these patients. Clinical characteristic of these patients are summarized in Table 1. Routine investigations for global delay including creatine kinase enzyme were normal. Cranial MRIs in all were distinct with little inter-individual variability. Bilateral symmetric diffuse polymicrogyria with frontoparietal predominance and subcortical and deep periventricular hyperintensities on T2-weighted / fluid-attenuated inversion recovery sequences were uniformly seen. A mild degree of brainstem and cerebellar vermian hypoplasia along with small cerebellar cortical cysts were noted (Figure 1). Interictal electroencephalograms (EEGs) in 3 of 4 patients showed bilateral frontocentral fast frequency activities.

Though the initial impression on imaging suggested congenial muscular dystrophy, the absence of clinical muscle disease, normal creatine kinase enzyme levels, and lack of the characteristic ocular findings of congenial muscular dystrophy made this diagnosis unlikely. A prior muscle biopsy in case 3 done elsewhere showed mild fiber-type disproportion without characteristic findings of congenial muscular dystrophy.

Gene sequencing revealed homozygous mutations of the *GPR56* gene in all the 4 children and corresponding heterozygous mutations in the parents, confirming a carrier state. Table 1 details the individual mutations in all 4 patients. One child

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Table 1. Characteristics of Patients Presenting with *GPR56*-Related Polymicrogyria.

	Case 1	Case 2	Case 3	Case 4
Age at presentation/gender	6 mo / male	16 mo / male	24 mo / male	14 mo / female
Family history	First child	Consanguinity, 1 of 3 elder siblings affected	First child	Consanguinity, 1 normal elder sibling
Community	Punjabi	Gujarati	Sindhi	Marathi
Motor delay	Severe	Severe	Severe	Moderate
Cognitive delay	Mild	Severe	Moderate	Moderate
Autistic traits	Mild on FU	Mild	Absent	Absent
Epilepsy	No (FU 24 mo)	Generalized seizures from 18 mo (FU 32 mo)	No (FU 36 mo)	Complex febrile seizures (FU 30 mo)
Head size	Normal	Large (>95th percentile)	Normal	Normal
Tone abnormalities	Hypotonia, dystonia	Normal	Hypotonia	Hypotonia
Ocular findings	Nystagmus, strabismus	Macular pigmentary changes	Strabismus, nystagmus	Strabismus
Cerebellar signs	Ataxia, tremors, dysmetria	Absent	Mild ataxia	Absent
Deep tendon reflexes	Normal	Normal	Increased	Normal
Brain MRI				
PMG distribution	Bilateral frontoparietal	Diffuse maxima frontoparietal	Diffuse maxima frontoparietal	Diffuse maxima frontoparietal
White matter abnormalities	Frontal and periventricular	Diffuse	Frontal and periventricular	Diffuse
Brain stem	Mild thinning	Mild thinning	Normal	Mild thinning
Cerebellum	Cerebellar cysts	Cerebellar cysts	Inferior vermian hypoplasia; cerebellar cyst	Cerebellar cysts
EEG findings	Faster frequencies over the frontocentral region	Faster frequencies over the frontocentral region	Not done	Faster frequencies over the frontocentral region
GPR56 mutation/ reference	Exon 4: c739_746, Known	Exon 12: c.1426C>T, Novel	Exon 4: c.739_746, Known	Exon 2: c.113G>A, Known

Abbreviations: EEG, electroencephalographic; FU, follow-up; PMG, polymicrogyria.

had a novel mutation that led to a stop codon resulting in a truncated protein and was hence considered pathogenic. Two of 4 unrelated children had a common mutation.

With intensive neurorehabilitation, slow but steady developmental gains were seen, with 3 of 4 patients achieving independent sitting and 2 of 4 able to speak a few meaningful words. One infant displayed few autistic traits at 15 months. Seizures were easily controlled, with sodium valproate in one and intermittent clobazam prophylaxis in the girl with complex febrile seizures. Prenatal *GPR56* gene sequencing was successful in identifying a normal fetus in 1 family.

Discussion

Bilateral frontoparietal polymicrogyria is an autosomal recessive polymicrogyria syndrome, which was not recognized until genetic testing and high-resolution neuroimaging became available.[2,3]

Harbord et al[2] in 1990 had first described an autosomal recessive disorder with extensive brain malformation along with cerebellar ataxia in 2 siblings. Similarly, Dobyns et al[3] in 1996 described 3 patients from 2 consanguineous families with cobblestone lissencephaly and normal eyes and muscles. The bilateral frontoparietal polymicrogyria locus was linked to chromosome 16q12.2–21 in 19 patients from 10 kindreds, and later mutations were identified in the *GPR56* gene in all these patients.[4-6]

GPR56 is a member of the adhesion G protein–coupled receptor (GPCR) family.[7] Experimental research in mice reveals that loss of GPR56 function disrupts the pial basement membrane, leading to abnormal migration of neurons in the developing brain, resulting in bilateral frontoparietal polymicrogyria.[8,9] All our 4 patients revealed homozygous mutations in the GPR56 protein with heterozygous status in the parents, confirming an autosomal recessive mode of inheritance. Until now, fewer than 60 patients worldwide have been described with bilateral frontoparietal polymicrogyria.[5,9-13]

The *GPR56* gene is composed of 14 exons with a coding region of 2,061 bp (GenBank accession number AF106858) from exons 2 to 14. So far, 26 independent mutations in the *GPR56* gene have been identified, 25 of which are homozygous germline mutations and a single case of compound heterozygous mutation.[14]

A novel mutation c.1426C>T of exon 12 altering amino acid sequence pARG476 was found in one of our patients, which resulted in a truncated protein and hence was the likely the cause of the disease. The remaining 3 patients harbored previously known mutations.[10] Two of 4 patients had homozygosity for a deletion of nucleotides 739 through 746 of the *GPR56* gene. This mutation has also described by Piao et al[6] in a

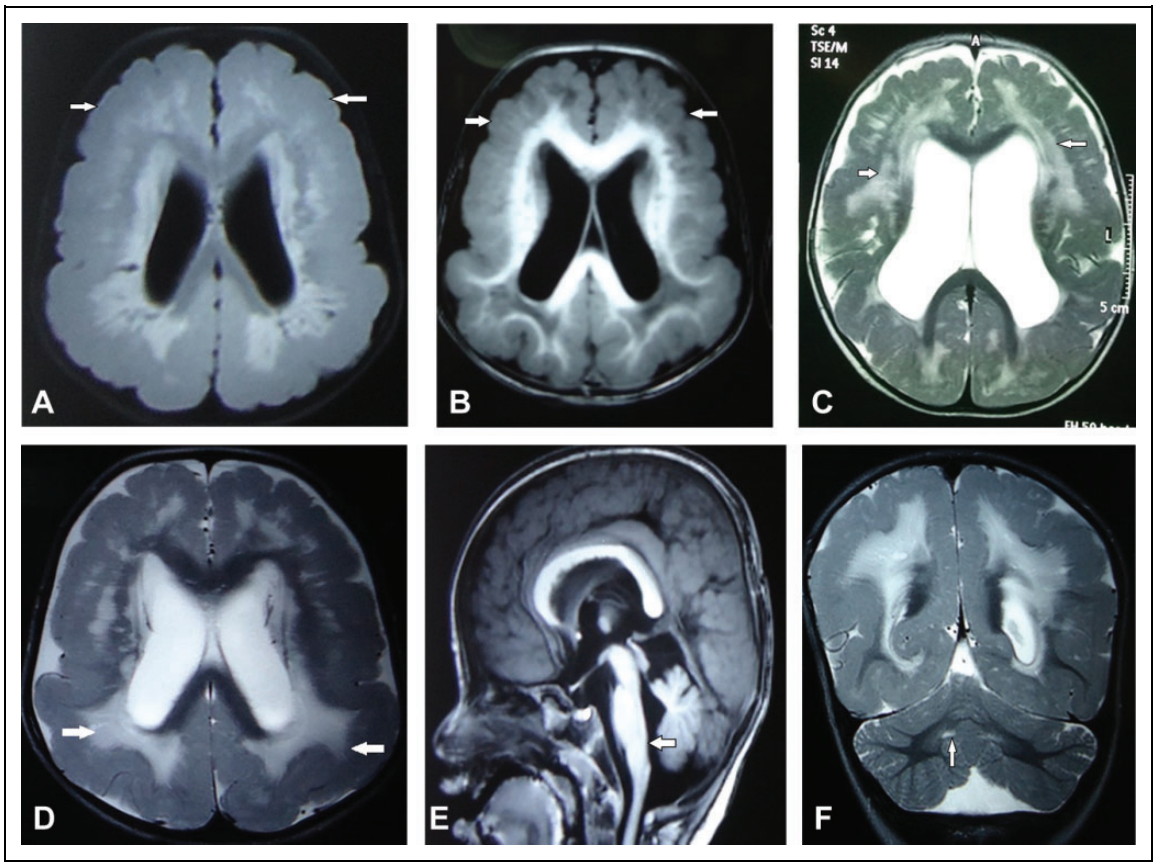

Figure 1. Representative brain magnetic resonance images (MRIs) of patients with *GPR56*-associated polymicrogyria. (A),(B) Showing PMG; (C),(D) Showing white matter changes; (E) Brainstem hypoplasia; and (F) Cerebellar cyst.

nonconsanguineous Indian family from Gujarat and 2 consanguineous families, 1 from Pakistan and 1 from Afghanistan each. As many tribes in Pakistan and Afghanistan originated from India, a founder mutation maintained through a substantial population is suggested.[10]

Though bilateral frontoparietal polymicrogyria is considered rare, 4 confirmed patients from a single center in India may indicate that this disorder may be more common than previously thought. The possibility that this may be due to referral bias, ours being a tertiary center, cannot be discounted, however. The clinical phenotype and natural history of bilateral frontoparietal polymicrogyria due to mutations in the *GRP56* gene is yet to be fully elucidated because of the rarity of this malformation. Based on 2 large series of 43 patients, initial presentation was uniform, with global developmental delay noticed before age 1 year.[10,12] Moderate to severe mental retardation and communication skills limited to a few words or phrases were universal. Cerebellar ataxia, epilepsy, and abnormal eye movements were also noted consistently as has been described in other reports.[2-5,10-14] Head size was normal or large in the initial stages, and a few had microcephaly.[12]

Most patients made motor progress over subsequent years and were able to walk independently with mild to moderate ataxia. Age of ambulation in one series of 14 patients varied from 1.5 to 5 years (median 2.5 years).[12]

Our patients conformed to this phenotype with global developmental delay (4/4), autistic traits (2/4), ataxia (2/4), and epilepsy (1/4). Head size was normal in 3 children, whereas 1 child had macrocephaly. Central hypotonia was seen in 3, with normal to brisk deep tendon reflexes in all. Nystagmus (2/4) and strabismus (3/4) was also seen.

Epilepsy is consistently seen in *GPR56*-related bilateral frontoparietal polymicrogyria, and evolution to epileptic encephalopathy including West syndrome and Lennox-Gastaut syndrome has also been reported.[10-14] The most common EEG pattern described is bursts of fast activity in the frontocentral regions or more diffuse notched theta sharp waves over bilateral frontal and temporal areas as was seen in our patients as well.[12]

Neuroimaging features in all 4 patients were consistent to that reported in the literature, with bilateral symmetrical polymicrogyria being most prominent in the frontoparietal regions and relatively spared perisylvian region or a generalized polymicrogyria with decreasing anteroposterior gradient of severity. Asymmetric patchy white matter signal changes with enlargement of lateral ventricles are distinctive and frequently seen in cobblestone lissencephalies but not seen in other polymicrogyria syndromes.[10-14] Pontine hypoplasia with flattening of the ventral portion at the level of the middle cerebellar peduncle is common. Cerebellar vermian dysplasia with cysts is often seen in cobblestone lissencephalies, and may be more

obvious than cortical polymicrogyria in infancy.[11,12] A recent autopsy study on a 35-week-old fetus with *GPR56* mutations (12) revealed several features of cobblestone lissencephalies, and the authors propose that cobblestone lissencephalies and polymicrogyria are a continuum, with the latter on the less severe end of the spectrum.

Piao et al[10] did not find the *GPR56* mutations in 5 patients with bilateral frontoparietal polymicrogyria who lacked the white matter or posterior fossa abnormalities and additional 7 patients with bilateral frontal, perisylvian, or generalized polymicrogyria.[10] This confirmed the high specificity of imaging changes in *GRP56*-related bilateral frontoparietal polymicrogyria. Some authors have labeled bilateral frontoparietal polymicrogyria without white matter and brainstem changes as bilateral frontoparietal polymicrogyria 2.[10]

Imaging features are fairly similar to what one gets in the cobblestone lissencephalies associated with the dystroglycanopathies (Fukuyama disease, muscle-eye-brain disease, Walker-Warburg syndrome) though some differentiating features have been highlighted.

The cerebellum is more hypoplastic, and a pontomedullary kink and hydrocephalus are characteristically seen in Walker-Warburg syndrome.[15] Eye findings of cataracts, glaucoma, optic atrophy, and retinal dysplasia found in cobblestone lissencephalies and congenial muscular dystrophy are absent in *GPR56*-related polymicrogyria. Clinically, lack of muscle disease and a normal CPK refutes the diagnosis of congenial muscular dystrophy.

Intrauterine cytomegalovirus infection can cause polymicrogyria with dysmyelination in a subset of patients. However, microcephaly rather than normo/macrocephaly is clinically distinguishing whereas the magnetic resonance imaging (MRI) lacks the frontoparietal gradient and brainstem/cerebellar changes.[16] Temporal pole cysts and periventricular calcifications described in some cases of intrauterine cytomegalovirus are not seen in GPR56 patients.[17]

Finally, similar MRI abnormalities have recently been described in polymicrogyria associated with homozygous deleterious mutations in the *LAMB1* gene, encoding protein laminin subunit beta-1 with a constellation of brain malformations, including cortical gyral and white matter signal abnormalities, severe cerebellar dysplasia, brainstem hypoplasia, and occipital encephalocele.[18]

Management is primarily supportive, with a focus on rehabilitation. Genetic counseling and prenatal diagnosis in subsequent pregnancies are integral to management in this autosomal recessive malformation syndrome. We could do this in one of the families in this study.

Conclusion

The clinical profile of patients with *GPR56*-related bilateral frontoparietal polymicrogyria is homogenous, with intellectual disability of moderate to severe degree, motor developmental delay, dysconjugate gaze, epilepsy, and cerebellar signs like ataxia. Imaging features are distinct with bilateral diffuse frontoparietal predominant polymicrogyria with anterior to posterior gradient, white matter abnormalities, and cerebellar and brainstem hypoplasia. All these features resemble congenital muscular dystrophy, but lack of eye and muscle disease would recommend testing for the *GPR56* mutation. Awareness and diagnosis of this rare entity helps primarily in prevention in subsequent pregnancies in affected families.

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Author Contributions

VU and ND managed the children. ND drafted the manuscript and reviewed the literature. VU supervised the drafting of the manuscript.

Declaration of Conflicting Interests

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Ethical Approval

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References

1. Barkovich AJ, Kuzniecky RI, Jackson GD, et al. A developmental and genetic classification for malformations of cortical development. *Neurology*. 2005;65:1873-1887.
2. Harbord MG, Boyd S, Hall-Craggs MA, et al. Ataxia, developmental delay and an extensive neuronal migration abnormality in 2 siblings. *Neuropediatrics*. 1990;21:218-221.
3. Dobyns WB, Patton MA, Stratton RF, et al. Cobblestone lissencephaly with normal eyes and muscle. *Neuropediatrics*. 1996;27:70-75.
4. Piao X, Basel-Vanagaite L, Straussberg R, et al. An autosomal recessive form of bilateral frontoparietal polymicrogyria maps to chromosome 16q12.2-21. *Am J Hum Genet*. 2002;70:1028-1033.
5. Chang BS, Piao X, Bodell A, et al. Bilateral frontoparietal polymicrogyria: clinical and radiological features in 10 families with linkage to chromosome 16. *Ann Neurol*. 2003;53:596-606.
6. Piao X, Hill RS, Bodell A, Chang BS, et al. G protein-coupled receptor-dependent development of human frontal cortex. *Science*. 2004;303:2033-2036.
7. Bjarnadóttir TK, Fredriksson R, Höglund PJ, et al. The human and mouse repertoire of the adhesion family of G-protein-coupled receptors. *Genomics*. 2004;84:23-33.
8. Jeong SJ, Luo R, Li S, et al. Characterization of G protein-coupled receptor 56 protein expression in the mouse developing neocortex. *J Comp Neurol*. 2012;520:2930-2940.

9. Chiang NY, Hsiao CC, Huang YS, et al. Disease-associated GPR56 mutations cause bilateral frontoparietal polymicrogyria via multiple mechanisms. *J Biol Chem*. 2011;286:14215-14225.
10. Piao X, Chang BS, Bodell A, et al. Genotype-phenotype analysis of human frontoparietal polymicrogyria syndromes. *Ann Neurol*. 2005;58:680-687.
11. Parrini E, Ferrari AR, Dorn T, et al. Bilateral frontoparietal polymicrogyria, Lennox-Gastaut syndrome, and GPR56 gene mutations. *Epilepsia*. 2009;50:1344-1353.
12. Bahi-Buisson N, Poirier K, Boddaert N, et al. GPR56-related bilateral frontoparietal polymicrogyria: further evidence for an overlap with the cobblestone complex. *Brain*. 2010:133;3194-3209.
13. Nakayama T, Oguni H, Funatsuka M, et al. Three patients with severe bilateral frontoparietal polymicrogyria. *Pediatr Neurol*. 2008;38:353-356.
14. Fujii Y, Ishikawa N, Kobayashi Y, et al. Compound heterozygosity in GPR56 with bilateral frontoparietal polymicrogyria. *Brain Dev*. 2014;36:528-531.
15. Barkovich AJ. Neuroimaging manifestations and classification of congenital muscular dystrophies. *Am J Neuroradio*. 1998;19: 1389-1396.
16. Fink KR, Thapa MM, Ishak GE, Pruthi S. Neuroimaging of pediatric central nervous system cytomegalovirus infection. *Radiographics*. 2010;30:1779-1796.
17. O'Rourke D, Bradley L, King MD, Ryan S. Leukoencephalopathy with anterior temporal cysts due to congenital CMV infection diagnosed retrospectively. *J Neuroimaging*. 2010;20:292-293.
18. Radmanesh F, Caglayan AO, Silhavy JL, et al. Mutations in *LAMB1* cause cobblestone brain malformation without muscular or ocular abnormalities. *Am J Hum Genet*. 2013;92:468-474.