Genotype–Phenotype Analysis of Human Frontoparietal Polymicrogyria Syndromes

Xianhua Piao, MD, PhD,[1] Bernard S. Chang, MD,[2] Adria Bodell, MS,[2] Katelyn Woods, BS,[1] Bruria BenZeev, MD,[3] Meral Topcu, MD,[4] Renzo Guerrini, MD,[5] Hadassa Goldberg-Stern, MD,[6,7] Laszlo Sztriha, MD, PhD,[8] William B. Dobyns, MD,[9] A. James Barkovich, MD,[10] and Christopher A. Walsh, MD, PhD[2]

Human cerebral cortical polymicrogyria is a heterogeneous disorder, with only one known gene (*GPR56*) associated with an apparently distinctive phenotype, termed *bilateral frontoparietal polymicrogyria* (BFPP). To define the range of abnormalities that could be caused by human *GPR56* mutations and to establish diagnostic criteria for BFPP, we analyzed the *GPR56* gene in a cohort of 29 patients with typical BFPP. We identified homozygous *GPR56* mutations in all 29 patients with typical BFPP. The total of 11 *GPR56* mutations found represented a variety of distinct founder mutations in various populations throughout the world. In addition, we analyzed five patients with BFPP who did not show *GPR56* mutation and found that they define a clinically, radiographically, and genetically distinct syndrome that we termed BFPP2. Finally, we studied seven patients with a variety of other polymicrogyria syndromes including bilateral frontal polymicrogyria, bilateral perisylvian polymicrogyria, and bilateral generalized polymicrogyria. No *GPR56* mutation was found in these patients. This study provides a molecular confirmation of the BFPP phenotype and provides the wherewithal for diagnostic screening.

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Polymicrogyria is a cortical malformation characterized by supernumerary, small gyri with abnormal cortical lamination. Harbord and colleagues[1] first described bilateral frontoparietal polymicrogyria (BFPP; OMIM 606854), an autosomal recessively inherited condition, as an "autosomal recessive neuronal migration defect with nonprogressive cerebellar ataxia." Since this initial description, many cases of BFPP have been reported under five different diagnoses: "autosomal recessive syndrome of pachygyria," "neuronal migration abnormality," "cobblestone lissencephaly," "lissencephaly with cerebellar hypoplasia," and "bilateral frontoparietal polymicrogyria."[1–6] Using clinical and genetic approaches, we have defined the typical features of BFPP (see Discussion) and linked the BFPP locus to chromosome 16q12-21.[6,7]

Recently, mutations of the *GPR56* gene were reported in patients with BFPP, mostly in patients originating from the Middle East, except for one founder mutation shared by three families from India, Pakistan, and Afghanistan and another mutation in a nonconsanguineous French Canadian family.[8] This study summarizes the previously identified BFPP families and describes additional mutational analysis in six new BFPP families with more diverse ethnic backgrounds and in patients with a variety of other bilateral polymicrogyria syndromes.

Subjects and Methods

Patients

The newly identified BFPP families comprise four consanguineous families(Table 1; Pedigrees 14–17) and two nonconsanguineous families (see Table 1; Pedigrees 13 and 18). Informed consent was obtained from all patients according

From the [1]Division of Newborn Medicine, Department of Medicine, Children's Hospital Boston and Harvard Medical School; [2]Department of Neurology, Howard Hughes Medical Institute, Beth Israel Deaconess Medical Center, Children's Hospital Boston and Harvard Medical School, Boston, MA; [3]Pediatric Neurologist, Sheba Medical Center, Ramat-Gan, Israel; [4]Department of Pediatrics, Section of Child Neurology, Hacettepe University Faculty of Medicine, Ankara, Turkey; [5]Epilepsy, Neurophysiology & Neurogenetics Unit, Division of Child Neurology and Psychiatry, University of Pisa & Instituto di Ricovera e Cura a Carattere Scientifico Fondazione Stella Maris, Pisa, Italy; [6]Epilepsy Center, Schnieder Children's Medical Center, Petach-Tiqva; [7]Sackler School of Medicine, Tell Aviv University, Tel Aviv, Israel; [8]Department of Paediatrics, United Arab Emirates University, Al-Ain, United Arab Emirates; [9]Department of Human Genetics, University of Chicago, Chicago, IL; and [10]Pediatric Neuroradiology, Department of Radiology, University of California, San Francisco, San Francisco, CA.

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URLs and accession numbers for data are listed in the Appendix on page 686.

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Address correspondence to Dr Walsh, Department of Neurology, Howard Hughes Medical Institute, Beth Israel Deaconess Medical Center, Children's Hospital Boston and Harvard Medical School, 77 Avenue Louis Pasteur, Room 266, Boston, MA 02115.
E-mail: cwalsh@bidmc.harvard.edu

Table 1. Comparison of Brain Magnetic Resonance Imaging Findings in Patients with and without GPR56 Mutations

			Pedigree Comments			Brain MRI Findings		
Diagnosis	Pedigrees	*GPR56* Mutation	Consanguinity	Ethnicity	Affected (n)	PMG	WM	Brainstem and Cerebellum
BFPP	1	Yes	First cousin	Palestinian[a]	3	FP	Patchy signal change	Slightly small pons and superior vermis
	2	Yes	First cousin	Palestinian[a]	2	FP	Patchy signal change	Small pons and superior vermis
	3	Yes	NC	Pakistani	2	FP	Reduced volume, periventricular signal change	Small pons and superior vermis
	4	Yes	NC	Indian	2	FP	Reduced volume, patchy signal change	Slightly small pons and vermis
	5	Yes	First cousin	Arabic (Qatar)	2	FP	Patchy signal change	Small brainstem
	6	Yes	First cousin	Pakistani	1	FP	Patchy radiolucency	Small cerebellum
	7	Yes	First cousin	Afghani	1	FP	Reduced volume, patchy signal change	Small pons and superior vermis
	8	Yes	First cousin	Palestinian[b]	2	FP	Reduced volume, patchy signal change	Small pons and cerebellum
	9	Yes	First cousin	Palestinian[b]	1	FP	Reduced volume, frontal subcortical signal change	Small brainstem and cerebellum
	10	Yes	Consanguineous[c]	Arabic (Bedouin)[d]	3	FP	Reduced volume, patchy signal change	Small vermis
	11	Yes	First cousin	Saudi Arabian	1	FP	Reduced volume, patchy signal change	Small pons and vermis
	12	Yes	NC	French Canadian	2	FP	Reduced volume, patchy signal change	Small pons, small/dysplastic cerebellum
	13	Yes	NC	Israeli Jewish[e]	1	FP	Patchy signal change	Small vermis
	14	Yes	First cousin	Israeli Jewish[e]	2	FP	Patchy signal change	Small pons and vermis
	15	Yes	First cousin	Turkish	1	FP	Severely reduced volume, patchy signal change	Small pons and vermis
	16	Yes	Second cousin	Italian[d]	1	FP	Reduced volume, patchy signal change	Slightly small vermis
	17	Yes	First cousin	Arabic (UAE)	1	FP	Reduced volume, patchy signal change	Slightly small pons and vermis
	18	Yes	NC	Hispanic	1	FP	Mildly reduced volume, patchy signal change	Slightly small cerebellar hemispheres
BFPP2	A1	NO	First cousin	Arabic (UAE)	1	FP	Reduced volume	Normal
	A2	No	NC	American	1	FP	Markedly reduced volume	Small brainstem and vermis
	A3	No	NC	Australian	1	FP	Reduced volume	Repaired posterior encephalocele, normal size pons and cerebellum
	A4	No	NC	Bulgaria	1	FP	Slightly reduced volume, patchy signal change	Normal
	A5	No	NC	German	1	FP	Reduced volume, frontal signal change	Normal

Table 1. Continued

Diagnosis	Pedigrees	*GPR56* Mutation	Pedigree Comments			Brain MRI Findings		
			Consanguinity	Ethnicity	Affected (n)	PMG	WM	Brainstem and Cerebellum
BFP	B1	No	First cousin	Afghani	1	Frontal	Normal	Normal
	B2	No	NC	Turkish	1	Frontal	Reduced volume	Normal
BPP	C1	No	NC	Turkish	1	Perisylvian	Markedly reduced volume	Normal
BGP	D1	No	NC	Turkish	1	Diffuse	Mildly reduced volume	Normal
	D2	No	NC	Arabic (UAE)	1	Diffuse	Slightly reduced volume	Normal
	D3	No	NC	German	1	Diffuse	Reduced volume	Normal
	D4	No	NC	American	1	Diffuse	Diffuse signal change	Small pons and cerebellum

[a]These families are from the same village.
[b]These families are from the same village but distinct from that of Pedigrees 1 and 2.
[c]This pedigree consists of two nuclear families who are distantly related to one another. One family is a first-cousin marriage and has two affected individuals, and the other set of parents are consanguineous, though their exact relationship is unknown.
[d]These families have the same mutation, R565W. However, single-nucleotide polymorphism analysis suggested this was a coincidental occurring mutation in two different families.
[e]These families are Israeli Jewish. Pedigree 13 is a nonconsanguineous family, the father is Karaite descendent, and the mother has a Polish-Egyptian origin. Pedigree 14 is pure Karaite descent.

MRI = magnetic resonance imaging; PMG = polymicrogyria; WM = white matter; BFPP = bilateral frontoparietal polymicrogyria; FP = frontoparietal; NC = nonconsanguineous; UAE = United Arab Emirates; BFP = bilateral frontal polymicrogyria; BPP = bilateral perisylvian polymicrogyria; BGP = bilateral generalized polymicrogyria.

to the guidelines of the Children's Hospital Boston and Beth Israel Deaconess Medical Center. Patients were assessed clinically by at least one of the authors.

A second group of patients also showed similar cortical malformation to that seen in patients with BFPP, but they lacked many of the typical features for BFPP associated with *GPR56* mutations (Fig 1A), so we refer to this syndrome as BFPP2. Specifically, Family A1 was a previously reported case.[9] It is a consanguineous family from the United Arab Emirates with one affected individual (see Table 1). The parents of Families A2 through A5 are nonconsanguineous (see Table 1). To determine the spectrum of malformation caused by *GPR56* mutations, we also analyzed the *GPR56* gene in several other polymicrogyria syndromes. These patients included two with bilateral frontal polymicrogyria, one with bilateral perisylvian polymicrogyria, and four with bilateral generalized polymicrogyria (see Table 1 and Fig 1B).

Mutation Analysis

DNA was extracted from peripheral blood with the use of standard methods. The *GPR56* gene spans ~45kb at the genomic level and is composed of 14 exons with a coding region of 2,061bp (GenBank accession number AF106858) from exons 2 to 14 (Fig 2). Primer pairs for amplification of each of the 13 *GPR56* coding exons (exons 2–14) were generated from the genomic sequence of *GPR56* (University of California, Santa Cruz, Genome Bioinformatics, Santa Cruz, CA; *GPR56* [*Homo sapiens*] range = chr16: 56211459–56256445). Exons were sequenced directly by BigDye Terminator sequencing (Applied Biosystems, Foster City, CA). Primer sequences are listed in Table 2.

Results

Sequence alterations in *GPR56* were found in all 29 patients with typical BFPP. Combined with the previous study, a total of 11 different mutations were identified, including 8 missense mutations, 2 splicing mutations, and 1 deletion mutation resulting in a translational frameshift and premature protein termination (Table 3; see Fig 2). All mutations except one missense mutation shared an indistinguishable phenotype, suggesting all are probably null alleles. The C346S mutation found in Families 8 and 9 also causes microcephaly, presumably by affecting proper protein trafficking of GPR56 and possibly that of other proteins (Table 3).[6]

In each pedigree analyzed, the *GPR56* mutation always segregated with the disease in the respective families and was not seen in 260 chromosomes from control subjects (70 Europeans and 60 Middle Eastern Arabian individuals). All patients, including those from nonconsanguineous families, carried homozygous mutations. Interestingly, all missense mutations affect regions of the protein predicted to represent the extracellular part of GPR56 (see Fig 2).

No *GPR56* mutations were found in 12 patients with a variety of other polymicrogyria syndromes (see Table 1). For example, although the cortical malformation in patients with BFPP2 (Families A1–A5) resembles BFPP (ie, bilateral polymicrogyria that is worst in the frontal and parietal regions with an anterior-to-posterior gradient), these pedigrees showed fewer of the diagnostic criteria for typical BFPP, and none of them harbored a mutation in the *GPR56* gene (see Table 4). Interestingly, none of them had both white matter abnormalities and hypoplasia of the pons or cerebellar vermis. We thus suggest use of the term BFPP2 to re-

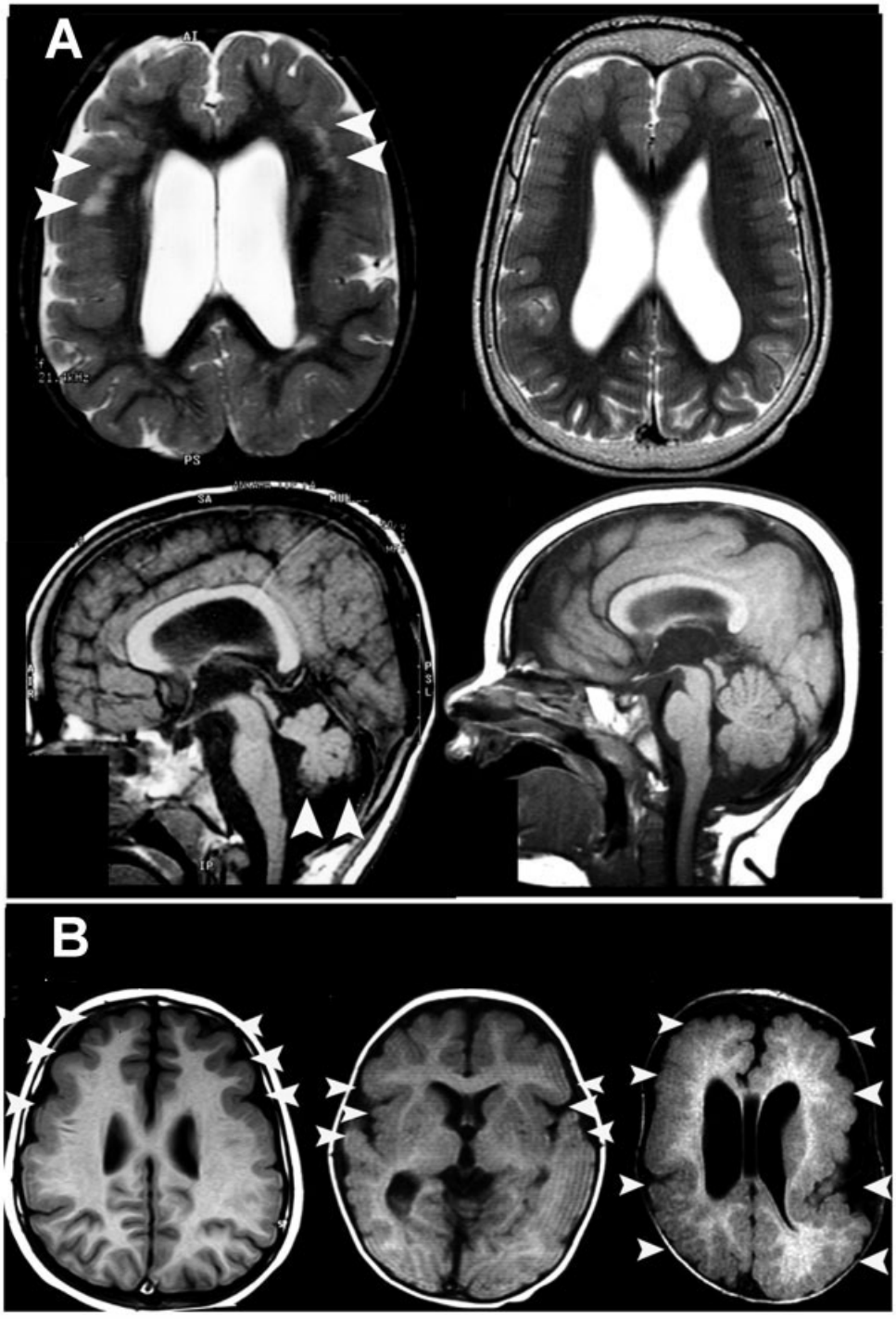

Fig 1. Representative brain magnetic resonance images (MRIs) for different bilateral polymicrogyria syndromes. (A) T2-weighted axial (a, b) and T1-weighted sagittal (c, d) brain MRI of a subject from Pedigree 15 (a, c), with bilateral frontoparietal polymicrogyria (BFPP) and a GPR56 *mutation, and subjects from Pedigrees A3 (b) and A5 (d), with BFPP cerebral cortex but no detectable mutation in* GPR56 *(BFPP2). The images from the subject with* GPR56 *mutation demonstrate polymicrogyria in the frontoparietal regions bilaterally, as well as patchy bilateral signal change in the white matter and hypoplasia of the cerebellar vermis and pons* (white arrowheads). *The images from the subjects with no* GPR56 *mutation (b, d) demonstrate similar cortical findings but no white matter abnormalities and a normal-size brainstem and cerebellum. (B) T1-weighted axial MRI of a subject from Pedigree B1 (a) with bilateral frontal polymicrogyria, an individual from Pedigree C1 (b) with bilateral perisylvian polymicrogyria, and an individual from Pedigree D3 (c) with bilateral generalized polymicrogyria.* White arrowheads *indicate regions of polymicrogyria.*

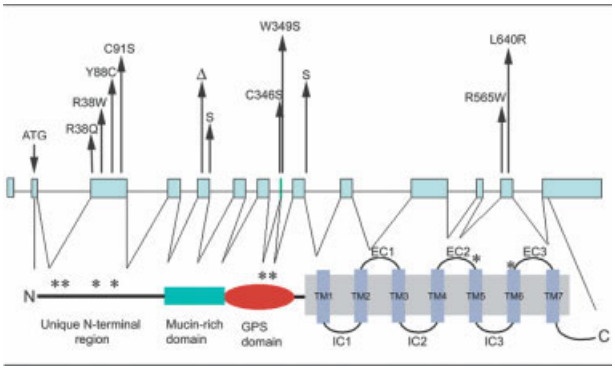

Fig 2. Schematic representation of the GPR56 *gene showing genomic structure, known protein domains, and mutations in bilateral frontoparietal polymicrogyria (BFPP) patients. The starting codon ATG is in the second exon.* Asterisks *indicate positions for the missense mutations: four at the tip of the N terminus (R38Q, R38W, Y88C, and C91S), two in the G protein–coupled receptor proteolytic site (GPS) domain (C346S and W349S), one in the second extracellular loop (R565W), and one in the third extracellular loop (L640R).* Open triangle *indicates the 7bp deletional mutation. EC = extracellular loop; IC = intracellular loop; S = splicing mutations; TM = transmembrane domain.*

fer to patients with BFPP, but who lack some of the diagnostic criteria for typical BFPP, show no mutation in *GPR56,* or both. However, patients with BFPP2 were not phenotypically homogeneous, which suggests that they are unlikely to represent a single clinical group. Although our coding sequence analysis alone cannot exclude regulatory mutations, the combination of genetic analyses and careful review of brain magnetic resonance images lend further support for a demarcation between classic BFPP and BFPP2. In addition, we performed linkage analysis on Family A1, the only consanguineous family from this group, and found no evidence for linkage to the *GPR56* locus (data not shown). Therefore, we conclude that there is a clear genetic separation between patients with classic BFPP and those with BFPP2.

Furthermore, no mutation in *GPR56* was found in any of the patients with bilateral frontal polymicrogyria, bilateral perisylvian polymicrogyria, and bilateral generalized polymicrogyria, suggesting the phenotype of *GPR56* mutation does not extend to other types of bilateral polymicrogyria syndromes.

Discussion

Here, we presented clinical phenotype of 29 BFPP patients harboring mutations in *GPR56* who share considerable clinical homogeneity with 5 common clinical features and 3 typical magnetic resonance imaging findings identified: (1) mental retardation of moderate to severe degree; (2) motor developmental delay; (3) seizures, most commonly symptomatic generalized epilepsy; (4) cerebellar signs, consisting of ataxia; (5) dysconjugate gaze, presenting variably as esotropia, nystagmus, exotropia, or strabismus; (6) bilateral polymicrogyria with anterior to posterior gradient; (7) bilateral patchy white matter signal changes without specific pattern; and (8) brainstem and cerebellar hypoplasia (see Fig 1A). Mental retardation and motor developmental delay were documented in all patients who had complete medical records available for review, whereas cerebellar signs, dysconjugate gaze, and seizures were presented in 94, 88, and 95% of BFPP cases, respectively (see Table 4).

The families analyzed here are from different ethnic groups with a wide geographic distribution, including Arabic-speaking Middle Eastern, Pakistani, Indian, Afghani, Canadian, Turkish, Italian, Israeli, and Hispanic American families. However, clinically, they have a homogeneous disease with typical clinical and radiographic features. The identification of mutations in *GPR56* in an ethnically diverse group of patients demonstrates the extensive geographic distribution of BFPP.

Table 2. Primer Sequen

Exons	Forward	Reverse
2	TCCACACTTGCTTCCCCAC	TGCCAGAAGGAAGGAGTG
3	TAGGTCCTGTCCCCTTCCAT	CCCAGTCCACTTTGCATTTT
4	GTCATGTCAGGGTGGTAGGG	CCCCAGGTGCCAAACTTAC
5	CACCATCACCACCGCTTTC	GCGACGGCACTGAGCTTCAG
6	GGATGGGTGTGTGTGTGTGT	TGCCTTCTTTCCACCTCTGT
7	TGTGCTGGGAGAGGGTTATC	GAGTCTGGAGGGAGGGAGAG
8	TCTGCCTGGCCTGTAAAGTT	GCCATCGCTCTCTCTTCAAA
9	CTTTTGGGGGTGGACACAGT	ATGAAAAGTGCTTGCACAGA
10	ACCAGGGACCCCAGGTTAG	CCATGACCGGAGATGTGTG
11	AGGATAGGGGCCATGTATGA	TAGGTGGAGAGGCAGAACCA
12	GTCCAAACTTGGGGGAACTT	GGAGACTGGAACCCAGGTGT
13	CAAGCGCACTTGCTGTAAAC	AGGTTCCCTGGGTGATCTCT
14	CAGACCCGAGTCACAATGG	GTTGGGCTTTCCAAAGTCTG

Table 3. Mutations in GPR56 Associated with Bilateral Frontoparietal Polymicrogyria

Pedigrees	Nucleotide Change[a]	Exon/Intron	Predicted Protein	Reference
1	IVS9 + 3G>C	Intron 9	Splicing mutation	Piao and colleagues[8]
2	IVS9 + 3G>C	Intron 9	Splicing mutation	Piao and colleagues[8]
3	E5 − 1G>C	5	Splicing mutation	Piao and colleagues[8]
4	739–746 delCAGGACC	5	Frameshift[b]	Piao and colleagues[8]
5	112C>T	3	R38W	Piao and colleagues[8]
6	739–746 delCAGGACC	5	Frameshift[b]	Piao and colleagues[8]
7	739–746 delCAGGACC	5	Frameshift[b]	Piao and colleagues[8]
8	1036T>A	8	C346S	Piao and colleagues[8]
9	1036T>A	8	C346S	Piao and colleagues[8]
10	1693C>T	13	R565W	Piao and colleagues[8]
11	272G>C	3	C91S	Piao and colleagues[8]
12	263A>G	3	Y88C	Piao and colleagues[8]
13	1046G>C	8	W349S	This report
14	1046G>C	8	W349S	This report
15	113G>A	3	R38Q	This report
16	1693C>T	13	R565W	This report
17	112C>T	3	R38W	This report
18	1919T>G	13	L640R	This report

All mutations are homozygous, even in nonconsanguineous families.

[a]Base pair counted from starting codon ATG. IVS represents intron; E represents exon; *plus sign* denotes intronic position 3′ of splice junction in donor; and *minus sign* denotes exonic position 5′ of splice junction in donor. For example, IVS9 + 3 means three bases of 3′ of the splice donor junction of intron 9.

[b]Deletion of 7bp that alters the translational reading frame, resulting in truncated protein with premature protein termination.

GPR56 encodes a member of the Family B G protein–coupled receptors, which have long N termini characterized by an extracellular "cysteine box" and hydrophilic, potentially mucin-rich domains.[10–12] The cysteine box contains four conserved cysteines and two tryptophans arranged in a specific fashion (C-x_2-W-$x_{6\text{-}16}$-W-x_4-C-$x_{10\text{-}22}$-C-x-C) just before the first transmembrane domain and serves as a cleavage site in some members of this group of G protein–coupled receptors.[13] Therefore, the cysteine box was also named the *G* protein–coupled receptor *p*roteolytic *s*ite (GPS) domain. We have shown previously that substitution of one of the four conserved cysteines in GPS domain, C346S, also causes microcephaly.[8] Here, we show one new mutation in GPR56 that occurs in the GPS domain, which results in the substitution of one of the two conserved tryptophans for serine (W349S) in two Israeli Jewish families. The affected individuals, however, have normal head circumference. Further biochemical analysis of these two mutations may shed light on the function of the GPS domain in this subclass of G protein–coupled receptors.

Mutation W349S was shared by two Israeli Jewish families with no known relationship, but who also shared alleles at flanking single-nucleotide polymorphisms, suggesting that the mutation represents a founder mutation. Pedigree 14 is a Karaite family with consanguineous parents who reside in Israel. The parents in Pedigree 13 are nonconsanguineous, with both parents sharing Karaite ancestry. Karaites represent a small Jewish minority who follows tenets of the original form of Judaism.

Mutation R565W occurs in an Italian family (Pedigree 15) and was seen previously in Pedigree 10, an extended Bedouin family.[8] However, single-nucleotide polymorphism analysis suggested this was a coincidental mutation in two different families without evidence of common haplotype. This mutation is a C→T transition at a CpG dinucleotide position. CpG dinucleotides mutate approximately 10 times faster than other dinucleotides due to cytosine methylation and the subsequent deamination and conversion of C→T, which may explain this recurrent mutation.[14]

In summary, BFPP is an autosomal recessive polymicrogyria syndrome, which was frequently misdiagnosed before the availability of genetic testing and high-resolution neuroimaging. Here, we have presented molecular analysis in a cohort of 29 classic BFPP patients from 18 ethnically diverse families and 12 patients with a variety of other polymicrogyria syndromes. We demonstrated that all predicted pathogenic *GPR56* sequence alterations were only found in patients with typical BFPP. *GPR56* mutations do not extend to cases of bilateral polymicrogyria that do not adhere to the BFPP cortical distribution, nor to cases with only the cortical

Table 4. Comparison of Clinical Features and Brain Magnetic Resonance Imaging Findings in Patients with BFPP and BFPP2 Syndromes

			Clinical Features						Brain MRI Findings		
Family/ Patient	Age[a]/Sex	*GPR56* Mutation	Cognitive Delay	Motor Delay	Cerebellar Signs	Dysconjugate Gaze	Seizures	Head Circumference	PMG	WM Signal Changes	Brainstem/ Cerebellum Hypoplasia
1/IV-2	14 yr/F	Yes	Moderate	Yes	Yes	Esotropia	GTC, AS	Normal	FP	Yes	Yes
1/IV-3	9 yr/F	Yes	Yes	Yes	Yes	Esotropia	FS, atonic-drop	Normal	FP	Yes	Yes
1/IV-4	7 yr/M	Yes	Severe	Severe	Yes	Esotropia	FS, GTC	Normal	FP	Yes	Yes
2/IV-1	13 yr/F	Yes	Severe	Yes	Yes	Esotropia	GTC, atonic	Normal	FP	Yes	Yes
2/IV-4	4 yr/M	Yes	Severe	Yes	Yes	Esotropia	No	Normal	FP	Yes	Yes
3/II-1	4 yr/M	Yes	Yes	Yes	NA	Strabismus	Episodes of startles	Normal	FP	Yes	Yes
3/II-2	13 mo/F	Yes	Yes	Yes	NA	Strabismus	Episodes of startles	Normal	FP	Yes	Yes
4/II-1	24 yr/F	Yes	Yes	Yes	Yes	Exotropia	Blank episodes	Normal	FP	Yes	NA
4/II-2	20 yr/F	Yes	Yes	Yes	Yes	No	AS	Normal	FP	Yes	Yes
5/IV-1	13 yr/M	Yes	Moderate	Yes	Yes	Esotropia	GTC, myoclonic	Normal	FP	Yes	Yes
5/IV-3	6 yr/F	Yes	NA	Yes	Yes	Esotropia	Yes	Normal	FP	Yes	Yes
6/IV-1	5 yr/M	Yes	Severe	Severe	Yes	Esotropia	Generalized	>98th percentile	FP	Yes	Yes
7/V-1	8 yr/M	Yes	Moderate	Yes	NA	Esotropia	NA	NA	FP	Yes	Yes
8/IV-1	11 yr/F	Yes	Yes	Yes	NA	NA	NA	<2nd percentile	FP	Yes	Yes
8/IV-4	2 yr/F	Yes	NA	Yes	NA	NA	NA	<2nd percentile	FP	Yes	Yes
9/V-1	20 mo/M	Yes	Severe	Yes	Yes	Esotropia	Yes	<3rd percentile	FP	Yes	Yes
10/V-2	29 yr/F	Yes	Severe	Yes	NA	No	GTC, myoclonic	Normal	FP	Yes	Yes
10/V-5	22 yr/M	Yes	Severe	Yes	NA	Exotropia	GTC, myoclonic	Normal	FP	Yes	Yes
10/IV-3	21 yr/F	Yes	Severe	Yes	No	Yes	GTC, myoclonic	Normal	FP	Yes	Yes
11/II-1	7 yr/F	Yes	NA	NA	NA	NA	NA	NA	FP	Yes	Yes
12/II-1	10 yr/F	Yes	Yes	Yes	Yes	NA	NA	Normal	FP	Yes	Yes
12/II-2	2 yr/M	Yes	Yes	Yes	Yes	Nystagmus	NA	Normal	FP	Yes	Yes
13/II-1	28 mo/M	Yes	Severe	Yes	Yes	Yes	Yes	Normal	FP	Yes	Yes
14/II-1	21 yr/M	Yes	Yes	Yes	Yes	Nystagmus	Myoclonic	Normal	FP	Yes	Yes
14/II-2	12 yr/M	Yes	Yes	Yes	Yes	Nystagmus	GTC	Normal	FP	Yes	Yes
15/II-1	6 yr/M	Yes	Yes	Yes	NA	NA	Yes	NA	FP	Yes	Yes
16/II-1	9 yr/M	Yes	Yes	Yes	Yes	Strabismus	Yes	Normal	FP	Yes	Yes
17/II-1	1 yr/M	Yes	Yes	Yes	NA	Convergent squint	NA	3rd percentile	FP	Yes	Yes
18/II-1	3 yr/M	Yes	Yes	Yes	NA	No	Yes	Normal	FP	Yes	Yes
A1	8 yr/M	No	Yes	Yes	No	No	myoclonic	3rd percentile	FP	No	No
A2	14 mo/M	No	Yes	Yes	NA	No	Infantile spasm	Normal	FP	No	Yes
A3	11 yr/M	No	Yes	Yes	NA	Nystagmus	GTC	Normal	FP	No	No
A4	30 mo/M	No	Yes	Yes	No	No	No	<2nd percentile	FP	Yes	No
A5	2 yr/M	No	Yes	Yes	No	No	No	<2nd percentile	FP	Yes	No

[a]Age at most recent follow-up.

MRI = magnetic resonance imaging; PMG = polymicrogyria; WM = white matter; F = female; GTC = general tonic-clonic seizures; AS = absence seizure; FP = frontoparietal; FS = febrile seizure; M = male; NA, information not available.

abnormality but without both white matter and posterior fossa changes, and so we suggest the term BFPP2 to refer to these patients. This study has validated the precise criteria necessary for the accurate diagnosis of BFPP and provides a basis for genetic screening as part of a diagnostic workup.

Appendix

URLs and accession numbers for data presented herein are as follows: GenBank: http://www.ncbi.nlm.nih.gov/genbank (for *GPR56* [*H. sapiens*] messenger RNA [accession number NM_005682] and *GPR56* [*H. sapiens*] spliced variant [accession number NM_201524]); University of California, Santa

Cruz (UCSC), Genome Bioinformatics: http://genome.ucsc.edu (for *GPR56* [*H. sapiens*] genomic sequence [accession number NM_005682]); and Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/omim.

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