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Original Article

The clinical and imaging features of *FLNA* positive and negative periventricular nodular heterotopia

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ABSTRACT

Background: Periventricular nodular heterotopia (PVNH) is caused by abnormal neuronal migration, resulting in the neurons accumulate as nodules along the surface of the lateral ventricles. PVNH often cause epilepsy, psychomotor development or cognition problem. Mutations in *FLNA* (Filamin A) is the most common underlying genetic etiology. Our purpose is to delineate the clinical and imaging spectrum that differentiates *FLNA*-positive and *FLNA*-negative PVNH patients.

Methods: We included 21 patients with confirmed PVNH. The detailed clinical information, electroencephalography, and other clinical findings were recorded. Detailed brain MR imaging was assessed. Mutation analysis of the *FLNA* gene was used Sanger sequencing or a next generation sequencing based assay.

Results: *FLNA* mutations were identified in 9 patients (7 females and 2 males), including two nonsense, two splice site, three frameshift, and two missense mutations. In *FLNA*-positive group, 8 patients had anterior predominant bilateral symmetric presentation and only one had asymmetrical distribution and dilated ventricles. Extra-cerebral features were more often observed in *FLNA*-positive group than *FLNA*-negative group.

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Conclusion: Genetics of PVNH is heterogenous, and mutations in *FLNA* gene account for less than half of the patients in our cohort. Our finding between *FLNA*-positive and *FLNA*-negative patients could guide the clinicians to select relevant genetic testing.

At a glance commentary

Scientific background on the subject

Periventricular nodular heterotopia (PVNH) is a developmental brain anomaly caused by impaired neuronal migration. Pathogenic variants in *FLNA* (Filamin A) are the most common underlying genetic etiology of PVNH, which accounts for only 20–30% of PVNH cases in Western countries. The role of *FLNA* in Asian PVNH population is unexplored.

What this study adds to the field

The current study reported the percentage of *FLNA* mutations in Asian PVNH patients. It also delineated the clinical and imaging spectrum that differentiates the *FLNA*-positive and *FLNA*-negative PVNH patients, which could guide the clinicians to select relevant genetic testing.

Nodular heterotopia (NH) is one of the most common malformations of cortical development (MCD) related to epilepsy [1]. Periventricular nodular heterotopia (PVNH) is the most common type of NH [2]. The neuronal migration abnormality results in the neurons accumulate as nodules along the surface of the lateral ventricles. Patients with PVNH often had epilepsy with multiple epileptogenic zone and variable seizure severity, psychomotor development and/or cognition problem. PVNH is predominantly observed in women, due to an X-linked dominant mutation caused by *FLNA* (Filamin A) [2]. PVNH is often accompanied by other cerebral malformations such as cerebellar anomaly, ventricular abnormalities, mega cisterna magna and hypoplasia or agenesis of corpus callosum [2,3]. There are also several associated extra-cerebral findings, including cardiac valves disease [4], patent duct arteriosus [3,4], joint hyperextensibility [4], chronic constipation [3], chronic obstructive lung disease [3,5], or coagulopathy. Hitherto, mutations in *FLNA* genes account for only 20–30% of PVNH cases in Western countries [2,6]. Here, we report the percentage of *FLNA* mutations in Asian PVNH patients as well as to delineate the clinical and imaging spectrum that differentiates the *FLNA*-positive and *FLNA*-negative PVNH patients. By early detecting the *FLNA* mutations, we could provide genetic counseling to the family and offer medical surveillance for other organ systems to avoid complications.

Materials and methods

Subjects & clinico-imaging phenotyping

The study included 21 patients with radiologically confirmed PVNH, followed up at or referred by other neurologists to the Department of Neurology of Kaohsiung Chang Gung Memorial Hospital, Taiwan and Department of Neurology of Malaya Medical Center, University of Malaya. Most of the patients are Chinese ethnicity, except one Malay and one Indian. The detailed clinical information, electroencephalography (EEG), neurological examination and other associated manifestations were sourced from medical records. For those who were using antiseizure drugs (ASMs), types of ASMs and response to ASMs were detailed recorded. The study was approved by the local human research ethics committees and written consents were obtained from all subjects. In minors and those with intellectual disabilities, consents were obtained from their legal guardian.

Original brain MR imaging was sourced. The morphology, location, and symmetry of PVNH were analyzed. We classified periventricular heterotopia according to the location of heterotopic nodules as previously described with modification [2]. Patients were classified into four groups: 1. The heterotopia located bilaterally symmetric along the frontal and the body of the lateral ventricles, (anterior predominant type); 2. The heterotopia located in bilateral temporo-occipital and trigones of the lateral ventricles (Inferior type); 3. Bilateral asymmetric periventricular nodules with or without subcortical heterotopia; 4. Unilateral focal periventricular nodule (presence of isolated or multiple nodule heterotopia in a restricted area adjacent to the ventricle) with or without subcortical heterotopias [2,7–9]. We also reviewed the presence of associated abnormalities, including corpus callosum malformation, mega cisterna magna, white matter lesion, abnormal cortical gyration/cortical thinning, posterior fossa abnormality (defined as posterior fossa cysts, brain stem or cerebellar malformation), dilated ventricle, or intracranial aneurysms.

Molecular analysis of FLNA

Genomic DNA was extracted from patients' peripheral blood leukocytes using QIAGEN DNA extraction kits (Qiagen, Germany). We designed an amplicon-based targeted resequencing technique covering all 48 coding exons of *FLNA* gene and their flanking (at least 10 base pairs) intronic regions. Multiplex polymerase chain reactions were used to amplify *FLNA* gene. The amplified libraries were sequenced using Illumina MiSeq platform. Standardized bioinformatics pipeline was used as previously described [10]. Four prediction programs, including SIFT (v1.03) [11], PolyPhen-2 (v2.2.2 build r394) [12], MutationTaster 2 [13], and Combined Annotation Dependent Depletion (CADD v1.2) [14] were used to prioritize variants. The cutoff value of CADD was set at 20. All identified pathogenic or likely pathogenic variants were confirmed by Sanger sequencing. The pathogenicity of the variants was classified according to the ACMG/AMP guideline [15].

Statistical analysis

Fisher exact or Chi-Squared test was used to compare the clinical and genetic features between the *FLNA* positive and negative groups.

Results

Patients

Among 21 patients with PVNH, *FLNA* mutations were identified in 9 (9/21, 42.9%) patients, including two nonsense mutations (case 1 & 2), two splice site mutations (case 3 & 4), three frameshift mutations (case 5, 6, & 7), and two missense mutations (case 8 & 9). The identified *FLNA* mutations were detailed in Table 1. Among the *FLNA* positive patients, seven were females and two were male. As for the remaining 12 patients without *FLNA* mutations, 6 were females and 6 were males. There was no gender difference between the two groups ($p = 0.367$).

The most common *FLNA* mutations were loss-of-function mutations (7/9, 77.8%), such as nonsense, frameshift and splicing, which were predictive to reduce the expression level of filamin A. Additionally, there were two missense mutations: p. Thr608Met and p.Glu1661Lys, which is located in the fourth and 15th repeat of Rod 1 domain, respectively. Both missense variants were predicted to deleterious by multiple in silico prediction algorithms. All of the variants were not presented in ExAc or gnomAD database and classified as pathogenic or likely pathogenic according to ACMG guideline. Interestingly, both missense mutations were identified in male patients in hemizygous status. In patient 8, the mutation was passed on to an affected daughter (heterozygous status) who has epilepsy but normal brain MRI.

The clinical spectrum, epileptic features and neuroimaging findings were summarized in Table 2 (*FLNA*-positive) and Table 3 (*FLNA*-negative). All patients in both groups had epilepsy. Among patients with *FLNA* positive, most (8/9, 88.9%) patients had anterior predominant bilateral PVNH (type 1) on MRI except one had bilateral asymmetric PVNH with adjacent subcortical heterotopia (type 3). None of *FLNA* positive had inferior type or unilateral PVNH (type 2 and 4). In the *FLNA* negative group, there were two patients had anterior predominant type (type 1), 4 patients had inferior PVNH (type 2), and 2 patients had type 3 (bilateral asymmetric). Four patients had type 4, including three with unilateral focal nodular PVNH without subcortical heterotopia and one patient had unilateral focal nodule PVNH combined with subcortical heterotopia.

We then compared the associated intracerebral malformation between *FLNA* positive and negative group. With regard to intracerebral malformations, corpus callosum abnormalities were seen in 3/9 (33.3%) *FLNA* positive versus 3/12 (25%) negative cases ($p = 1$); mega cisterna magna in 3/9 (33.3%) positive versus 3/12 (25%) negative cases ($p = 1$). Besides, posterior fossa abnormality was seen once in both groups (1/9, 11.1% versus 1/12, 8%). Dilated lateral ventricles tend to be more frequent in *FLNA* negative group (8/12, 66.7% versus 1/9, 11.1%) compared to *FLNA* positive group ($p = 0.0244$).

As for the systemic manifestations, the *FLNA* positive group frequently have variable systemic findings and connective tissue manifestations (7/9, 77.8%), including dysmorphic features, cardiovascular disease, skin and joint abnormality and intestinal dysfunction. On the contrary, there was no systemic, internal organ or connective tissue manifestations observed in *FLNA* negative group (0/12, $p = 0.0003$).

In terms of seizure outcome, the *FLNA* positive group had five (5/9) patients with medical refractory epilepsies, while the *FLNA* negative group had six (6/12) medical refractory patients ($p = 0.8$) [16].

Discussion

In our PVNH cohort, pathogenic variants in *FLNA* gene account for 43% of all cases. Most *FLNA* positive cases were female with loss-of-function variants; the neuroimaging showed anterior predominant bilateral PVNH. Patients with pathogenic *FLNA* variants were also more likely to have systemic manifestations, such as dysmorphism, cardiovascular disease, skin and joint abnormality, and intestinal dysfunction.

Among *FLNA* positive cases, there was an obvious female predominance (female-to-male ratio: 7:2), and loss of function variants. Female predominance was reported to be 93–100% in previous series [2,3,17], and only a few male patients were identified. In this study, both patients with missense variants were male, which is probably due to individuals with loss of function hemizygous *FLNA* variants are not viable. Previous reported male patients were all missense or distal truncating variants that have milder deleterious effect on Filamin A protein [18–21]. Interestingly, there was suggestion that male *FLNA* patients have higher incidence (69% compared to 33.3% in female and 50% in all *FLNA* mutations) of cardiac or aortic abnormality and may not presented with intellectual disability or epilepsy [3,17,21]. One of our male patients also had cardiac valve insufficiency. The reason for the prevalence of cardiac involvement in male patients remains uncertain. Both of our missense male patients still had seizures and mild intellectual disability.

Intriguingly, the missense variant in case 8 was inherited from the proband to his daughter, who does not have PVNH but had a few self-limited seizures without the need of antiepileptic drug. A previous study also reported a father-daughter pair with missense *FLNA* variant and milder phenotype [2]. For missense variant, the survival of male patients and mild phenotype in female patients is probably due to the presence of a normal allele as well as residual function of missense Filamin A compared to loss of function variants [18,20,21].

All *FLNA* positive patients in our cohort had anterior predominant PVNH except one who had subcortical heterotopia on the same side of PVNH (the father of hemizygous missense variant). A few patients with *FLNA* variants without anterior predominant PVNH have been reported [2,6,21]. On the

Table 1 Summary of the genetic and clinical data of *FLNA* positive patients.

Pt	Chr	Position	Ref	Alt	Type	Coding change (NM_001110556)	AA change	MAF in controls	Inheritance	Significance	Age of presentation	Sex	Seizure type	EEG	Neuroimaging	Epilepsy control
1	X	153594957	G	C	nonsense	c.1038C>G	P.Tyr346Ter	Not present	Inherited	Pathogenic	16	F	FAS, FIAS with BTCS	Bilateral temporal independent epileptiform discharge	Anterior predominant bilateral PVNH; mega cisterna magna	Drugs resistant LTG 500mg/day CBZ 600mg/day
2	X	153594957	G	C	nonsense	c.1038C>G	P.Tyr346Ter	Not present	Inherited	Pathogenic	11	F	FIAS	Frequent slow spike and wave complexes and multifocal sharp waves	Anterior predominant bilateral PVNH; mega cisterna magna	Drugs resistant LEV 1500mg/day VPA 750mg/day CBZ 400mg/day
3	X	153595756	C	T	Splice	c.868+9G>A	N/A	Not present	De novo	Pathogenic	23	F	FIAS	N/A	Anterior predominant bilateral PVNH	N/A
4	X	153579949	C	G	Splice	c.7023G>C	p.Gln2341His	Not present	N/A	Likely pathogenic	13	F	FIAS with BTCS	Frequent right fronto-temporal spike-wave complexes	Anterior predominant bilateral PVNH	Seizure free for 20 months with CBZ 600mg/day
5	X	153595820	T	-	Frameshift	c.813delA	p.Ala273Leufs*7	Not present	De novo	Pathogenic	29	F	BTCS	Right temporal epileptiform discharge	Anterior predominant bilateral PVNH	Seizure free for 1 year with LTG 150mg/day
6	X	153586850	-	TGCTGTG	Frameshift	c.4560-4561insCACAGCA	p.Ile1521Cysfs*10	Not present	De novo	Pathogenic	25	F	FIAS	Normal	Anterior predominant bilateral PVNH; mega cisterna magna	Seizure free for 4 years
7	X	153581806-153581809	CATA	-	Frameshift	c.5877-5880delTATG	p.Met1960Profs*3	Not present	De novo	Likely pathogenic	17	F	FIAS	Multifocal interictal epileptiform discharge over R't and L't F-T area	Anterior predominant bilateral PVNH; posterior fossa arachnoid cyst	Seizure free for 6 months with OXC 1200mg/day LTG 400mg/day LEV 2500mg/day
8	X	153593194	G	A	Missense	c.1823C>T	p.Thr608Met	Not present	Inherited	Likely pathogenic	47	M	FIAS	Lateralized periodic pattern over left pareito-central area	Unilateral asymmetric PVNH; enlarged ventricle; subcortical heterotopia	Seizure free for 1 year with LEV 2000mg/day VPA 1200mg/day
9	X	153583405	C	T	Missense	c.4981G>A	p.Glu1661Lys	Not present	N/A	Likely pathogenic /Novel	12	M	FIAS	normal	Anterior predominant bilateral PVNH; a cavernoma about 8 mm in size in left parieto-occipital junction	N/A

Abbreviations: BTCS: bilateral tonic-clonic seizures; CBZ: Carbamazepine; EEG: electroencephalography; FAS: focal aware seizures; FIAS: focal impaired awareness seizures; LEV: Levetiracetam; LTG: Lamotrigine; N/A: not applicable; OXC: oxcarbazepine; PVNH: periventricular nodular heterotopia; VPA: Valproic acid.

contrary, there were also two (2/10, 20%) of all anterior predominant PVNH patients were negative for *FLNA*. Previous studies also reported that 51–74% of anterior predominant PVNH were negative for *FLNA* variants [2,17,22].

As for other associated features, we found that *FLNA* positive cases are likely to have more systemic manifestations (~78%) while none of the *FLNA* negative patients had associated internal organ abnormality or cardiovascular abnormality [23–25]. The most common extracerebral features are cardiac abnormalities followed by gut dysfunction and joint hypermobility. *FLNA* encodes for Filamin A protein, which is highly expressed in the arteries, gastrointestinal (esophagus and colon) and urogenital system (uterus and bladder) based on GTEx data. FLNA is an actin-binding protein that links actins to membrane glycoproteins, which plays an important role in the remodeling the cytoskeleton and cell-cell adhesions. Therefore, it is possible that the systemic manifestations are due to the non-CNS expression and function of FLNA. Whereas the genetic cause of *FLNA* negative PVNH cases remain unknown, it is possible that the causative genes have a more limited expression and function in the brain. On the contrary, the intracerebral malformation was not significantly different in the two groups, except for the enlarged ventricle which is more prominent in *FLNA* negative group. This is informative in the clinics where bilateral anterior predominant PVNH associated with systemic features is more likely to be positive for *FLNA* gene screening.

There was no difference of seizure outcomes between the two groups, and nearly half patients had refractory seizure using multiple antiseizure medications (ASMs). This is in accordance with previous studies where near a third patients

Table 2 Clinical and brain MRI features of *FLNA* positive patients.

Pt	Associated clinical internal abnormalities	Cardiovascular anomalies	Cardiac echo	Joint hypermobility	Skin hyperextensible	Other musculoskeletal finding	Gastrointestinal dysfunction	Brain MRI associated imaging finding	Mega cisterna magna	Other abnormal finding	Corpus callosum abnormality
1		N	Normal	N	N	N	N		+		Hypoplasia
2		Atrial septal defect	Atrial septal defect post device closure without residual shunt	N	N	N	N		+		Hypoplasia
3		N	Normal	N	N	N	Dysmotility disorder of bowel		-		-
4		N/A	N/A	N	N	N	N		-		-
5		Patent ductus arteriosus	Patent ductus arteriosus s/p coil closure without residual shunt. Adequate LV and RV performance; Mild TR	Joint hypermobility;	Skin hyperextensible	N	Constipation in childhood		-		-
6		N	Normal	Mild finger hypermobility,	N	N	N		+		Generalized thinning
7		N	N/A	N	N	N	N		-	Posterior fossa arachnoid cyst	-
8		Dilated LA; trivial MR and TR	Dilated LA; thick IVS; trivial MR, trivial TR with TRPG(pressure gradient) 10mmHg	N	N	Ankle varus and hindfoot varus	N		-	Enlarged ventricle; subcortical heterotopia	-
9		N/A	N/A	N	N	N	N		-	A cavernoma about 8 mm in left parieto-occipital junction	-

Abbreviations: IVS: interventricular septum; LA: left atrial; LV: left ventricle; MR: mitral regurgitation; N: normal; N/A: not applicable; PVNH: periventricular nodular heterotopia; TR: tricuspid regurgitation; +: present; -: absent.

with *FLNA* mutations were unable to reach seizure free despite multiple ASMs [3].

Our *FLNA* mutation positive rate is higher than previous reports in Western countries ranged from 21 to 33% [2,6]. This is probably because the referral bias. More than half cases were unsolved and may have hitherto unidentified genetic causes, which indicates the genetic heterogeneity of PVNH. Several genes, such as *MAP1B*, *TMTC3*, *MEN1*, *NEDD4L*, *ACTG1*, and *ARFGEF2* have been recently associated with *FLNA* negative PVNH [26–31]. Our study has some limitations: first, the patient number is limited due to the rare occurrence of PVNH. Due to small number in each group, the statistics may not have the power to show minor differences. Lastly, we only captured and sequenced the *FLNA* gene, deletion or copy number variations of *FLNA* gene may be missed. Further studies using advanced techniques, such as multiplex ligation-dependent probe amplification (MLPA) or whole genome/whole exome sequencing (WGS/WES), may be required to identify the underlying genetic cause of unsolved cases.

Table 3 Summary of imaging finding of *FLNA* negative patients.

Pt	Case	Sex	Associated imaging finding	Heterotopia Symmetric	Heterotopia Diffuse	Mega cisterna magna	Posterior horns of lateral ventricle involved	Corpus callosum abnormality	Posterior fossa abnormality	Secondary imaging finding	Dilated ventricle	Type
10	K191	F		x	+	x	x	x	x		x	3
11	K619	F		x	+	+	+	x	x		+	3
12	K597	M		+	+	+	+	x	x		+	2
13	K63	M		x	+	+	+	x	Cerebellar vermial hypoplasia		+	2
14	K171	M		+	+	x	+	Hypoplasia; absence of septum pellucidum	x		+	2
15	S3	F		x	x	N/A	N/A	N/A	N/A		N/A	4
16	S163	F		x	x	N/A	x	x	x		x	4
17	S171	M		+	+	x	x	N/A	N/A		+	1
18	S239	M		+	+	x	N/A	x	N/A		+	4
19	K709	F		+	+	x	x	Hypoplasia of rostrum	x		+	2
20	K2241	F		x	+	x	+	x	x		x	4+5
21	bA599	M		+	x	x	x	Thinning corpus callosum	x		+	1

Abbreviations: N/A: not applicable; +: present; x: absent.

Conflicts of interest

There is no conflict of interest regarding the publication of this study.

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