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.
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 hydropsplasia or agenesis of corpus callosum [2,3]. There are also several associated extra-cerebral findings, including cardiac valvus 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, which could guide the clinicians to select relevant genetic testing.

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.
**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 (0/9, 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 [2,17], 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 anti-epileptic 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
contrary, there were also two (2/10, 20%) of all anterior pre-
dominant 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 manifesta-
tions (~78%) while none of the FLNA negative patients had
associated internal organ abnormality or cardiovascular
abnormality [23–25]. The most common extracerebral fea-
tures are cardiac abnormalities followed by gut dysfunction
and joint hypermobility. FLNA encodes for Filamin A pro-
tein, which is highly expressed in the arteries, gastrointes-
tinal (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 un-
known, it is possible that the causative genes have a more
limited expression and function in the brain. On the con-
trary, 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 predom-
inant 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

| No. | Chr | Position | Ref | Alt | Type | Coding change (NM_00115566) | AA change | Mutation status | Inheritance | Significance | Age of presentation | Sex | Seizure type | EGS | Neuroimaging | Epilepsy control |
|-----|-----|----------|-----|-----|------|-----------------------------|-----------|-----------------|-------------|-------------|-----------------|-----|-------------|-----|-------------|----------------|---|
| 1   | X   | 153954857 | G   | C   | nonsense | c.1098C>G | P74X | Not present | Inherited | Pathogenic | 16 F | FAS, FIAS with RTCS | Bilateral temporal independent epileptiform discharge | Anterior predominant bilateral PVNH; mega cisterna magna | Drugs resistant | LTC 500mg/day | CBE 600mg/day |
| 2   | X   | 153954857 | G   | C   | nonsense | c.1098C>G | P74X | Not present | Inherited | Pathogenic | 11 F | FAS | Frequent spike and wave complexes and multifocal sharp waves | Anterior predominant bilateral PVNH; mega cisterna magna | Drugs resistant | LVE 1500mg/day | VPA 750mg/day | CBE 400mg/day |
| 3   | X   | 153955756 | C   | T   | Splice | c.884+4G>A | N/A | Not present | De novo | Pathogenic | 23 F | FAS | N/A | Anterior predominant bilateral PVNH | N/A |
| 4   | X   | 153775963 | C   | G   | Splice | c.702G>C | p.G127R | Not present | N/A | Likely pathogenic | 13 F | FAS with RTCS | Frequent right fronto-temporal spike-wave complexes | Anterior predominant bilateral PVNH | Seizure free for 20 months with CBZ 600mg/day |
| 5   | X   | 153955870 | T   | -   | Frameshift | c.813delA | p.A709X | Not present | De novo | Pathogenic | 29 F | RTCS | Right temporal epileptiform discharge | Anterior predominant bilateral PVNH | Seizure free for 1 year with LUG 150mg/day |
| 6   | X   | 153581808 | CA TA | - | Frameshift | c.8277→8280delTA | p.Met2760P→fs*10 | Not present | De novo | Pathogenic | 25 F | FAS | Normal | Anterior predominant bilateral PVNH; mega cisterna magna | Seizure free for 6 years |
| 7   | X   | 153581308 | CA TA | - | Frameshift | c.8777→8800delTA | p.Met2925P→fs*3 | Not present | De novo | Likely pathogenic | 17 F | FAS | Multifocal interictal epileptiform discharge over P4 and (17)F-T area | Anterior predominant bilateral PVNH; posterior fossa arachnoid cyst | Seizure free for 6 months with OXC 1200mg/day | LTG 400mg/day | LVE 3500mg/day |
| 8   | X   | 153933194 | G   | A   | Missense | c.1823C>T | p.Thr608Met | Not present | Inherited | Likely pathogenic | 47 M | FIAS | Lateralized periodic discharges over left parieto-central area | Bilateral asymmetric PVNM; enlarged ventricle; subcortical heterotopia | Seizure free for 1 year with LVE 2000mg/day | VPA 1200mg/day |
| 9   | X   | 153585402 | C   | T   | Missense | c.1981G>A | p.Glu661Lys | Not present | N/A | Likely pathogenic | 32 M | FIAS | Normal | Anterior predominant bilateral PVNH; a cavernous 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; LVE: Levetiracetam; LTG: Lamotrigine; N/A: not applicable; OXC: oxcarbazepine; PVNH: periventricular nodular heterotopia; VPA: Valproic acid.
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 2 Clinical and brain MRI features of FLNA positive patients.

| PI  | Cardiovascular anomalies | Cardiac echo | Joint hyporeactivity | Skin hyporeactivity | Other musculoskeletal finding | Gastrointestinal dysfunction | Mega cisterna magna | Other abnormal finding | Corpus callosum abnormality |
|-----|--------------------------|--------------|----------------------|---------------------|-------------------------------|---------------------------|---------------------|-----------------------|--------------------------|
| 1   | N                        | N            | N                    | N                   | N                             | N                         | +                  | -                     | Hypoplasia               |
| 2   | Atrial septal defect     | N            | N                    | N                   | N                             | N                         | N                   | -                     | Hypoplasia               |
| 3   | N                        | N            | N                    | N                   | N                             | N                         | N                   | -                     | N                        |
| 4   | N/A                      | N/A          | N                    | N                   | N                             | N                         | N                   | -                     | N                        |
| 5   | Patent ductus arteriosus | N/A          | N                    | N                   | N                             | N                         | N                   | -                     | N                        |
| 6   | N                        | N/A          | N                    | N                   | N                             | N                         | N                   | -                     | N                        |
| 7   | Dilated LA; tricuspid MR | N/A          | N                    | N                   | N                             | N                         | N                   | -                     | N                        |
| 8   | Dilated LA; tricuspid MR | N/A          | N                    | N                   | N                             | N                         | N                   | -                     | N                        |

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.

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

| PI  | Case | Sex | Heart topology finding | Heart topology | Mega cisterna magna | Posterior horn of lateral ventricle thickened | Corpus callosum abnormality | Posterior fossa abnormality | Dilated ventricle | Type |
|-----|------|-----|------------------------|---------------|---------------------|---------------------------------------------|-----------------------------|-----------------------------|-----------------|------|
| 10  | 619  | F   | x                      | x             | x                   | x                                          | x                           | -                           | -               | 3    |
| 11  | 619  | F   | x                      | x             | x                   | x                                          | x                           | -                           | -               | 3    |
| 12  | 625  | M   | x                      | x             | x                   | x                                          | x                           | -                           | -               | 2    |
| 13  | 633  | M   | +                      | +             | +                   | +                                          | +                           | -                           | -               | 2    |
| 14  | 671  | M   | +                      | +             | +                   | +                                          | +                           | -                           | -               | 2    |
| 15  | 53   | F   | +                      | x             | N/A                 | N/A                                        | N/A                         | N/A                         | N/A             | 4    |
| 16  | 516  | F   | +                      | x             | N/A                 | x                                          | x                           | x                           | x               | 4    |
| 17  | 521  | M   | +                      | +             | x                   | N/A                                        | N/A                         | N/A                         | N/A             | 3    |
| 18  | 5239 | M   | x                      | x             | x                   | x                                          | x                           | x                           | x               | 3    |
| 19  | 8709 | F   | x                      | x             | x                   | x                                          | x                           | x                           | x               | 1    |
| 20  | 62241| F   | x                      | x             | x                   | x                                          | x                           | x                           | 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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