To the Editor: Periventricular nodular heterotopias (PNHs) represent a malformation of cortical development caused by an improper neuronal migration during forebrain formation.[1,2] There is a wide spectrum of anatomical and clinical presentations of PNH, ranging from asymptomatic small unilateral or bilateral nodules to extensive agglomerates of heterotopia lining the lateral ventricles with epilepsy and intellectual disabilities. The mutations in X-linked gene, filamin A (FLNA) gene, were identified in approximately 100% of familial PNHs and 25% of sporadic cases.[3] Here, we reported a novel frameshift mutation of FLNA gene in a Chinese family with PNH.

The proband, a 27-year-old Chinese woman, was seen in the outpatient clinic of China Meitan General Hospital in October 2014 due to seizures for 2 years. After visiting our clinic, the patient has been seizure-free on valproate for one and a half years. She was born at term from healthy nonrelated parents after normal pregnancy and delivery. Her psychomotor and cognitive development appeared normal. Her general and neurological examination was unremarkable except for cyanosis in lips. Interictal electroencephalogram was moderately abnormal with spike waves. Brain magnetic resonance imaging (MRI) revealed bilateral gray matter nodules along the surface of lateral ventricles that defined as PNH [Figure 1a]. Echocardiography revealed partial anomalous pulmonary venous connection and mild bicuspid and tricuspid regurgitation. This patient’s mother was 50-year-old without epilepsy and mental retardation, and her brain MRI revealed bilateral gray matter nodules along the surface of lateral ventricles and enlarged cisterna magna [Figure 1b]. The proband’s elder sister (II 1) was a 28-year-old married woman who had four female children. Her second daughter had cleft lip. She had three spontaneous abortions that the fetus gender was unknown. The proband’s elder sister had no seizure history, mental retardation, and refused to do MRI. Pedigree of this PNH family is shown in Figure 1c.

Sanger sequencing of genomic DNA was performed in the proband, her family members, and 110 unrelated normal controls. Genetic sequencing analysis revealed a frameshift mutation (c.7539_7540insA) at exon 46 in FLNA gene, which was found in three patients (I 2, II 1, and II 3) of this family [Figure 1d], but was not found in her healthy family members and the 110 unrelated normal controls [Figure 1e]. The FLNA mutation (c.7539_7540insA) is predicted to truncate the FLNA protein by 91 amino acids, resulting in a variant FLNA protein that lacks one FLNA/ABP280 repeat. This mutation has not been recorded in the Human Gene Mutation Database, dsSNP database, and 1000 Genomes Project database, suggesting it was a novel mutation. Up to date, 105 other point mutations in FLNA gene have been reported in association with PNH.

The diagnosis of PNH mainly relies on brain MRI, which reveals bilateral, nearly contiguous PNH lining the lateral ventricles isolated or associated with thinning of the corpus callosum and malformations of the posterior fossa such as cerebellar hypoplasia and enlarged cisterna magna. Although PNH patients typically have seizures, subclinical patients without epilepsy were also reported previously. Family history consistent with X-linked inheritance.[4] In this family, brain MRI of the proband and her mother suggested as PNH. The proband’s elder sister (II 1) was thought to be a subclinical PNH patient due to positive family history, FLNA mutation, and multiple miscarriages.

PNH is commonly related to mutations of FLNA gene, which encodes a cytoskeleton protein FLNA.[5] FLNA, a protein bound to actin, has an important role in regulating cell migration and cell shape. This protein interacts with actin-mediated adhesion through interactions with integrins. FLNA seems to play a role in the vasculature development, and the mutations of FLNA gene have been associated with an increased frequency of stroke and heart defects.[6] The cytoskeletal cross-linking and scaffolding functions of FLNA are reflected in its structure, which is characterized by a conserved N-terminal actin binding domain followed by 24 β-pleated “filamin repeats” that exhibit significant structural...
This 280,000 protein has a N-terminal actin-binding domain comprised two calponin homology domains: CH1 and CH2. The molecule adds 24 immunoglobulin-like repeats interrupted by two hinge regions between repeats 15 and 16, and between repeats 23 and 24. Homodimerization is mediated by repeat 24 nearest to the C-terminal. Missing the 24th repeat due to this mutation (c.7539_7540insA) might affect the normal function of the FLNA protein, resulting in PNH in this family.

To the best of our knowledge, it was a de novo mutation (c.7539_7540insA) of FLNA gene found in this PNH family. This report could facilitate a better cardiovascular and genetic study for clinically obvious and subclinical PNH patients.

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Conflicts of interest
There are no conflicts of interest.

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