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Research Letter

Detection of a novel c.7106_7110delinsT heterozygous mutation in the *FLNA* gene in an asymptomatic mother with periventricular nodular heterotopia during prenatal genetic counseling

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Dear Editor,

A 31-year-old, gravida 5, para 1, pregnant woman was referred to the hospital at 16 weeks of gestation for genetic counseling of periventricular nodular heterotopia (PVNH). The woman and her husband were healthy. She had experienced three spontaneous abortions. The couple had a 2-year-old daughter who had suffered from seizures and symptomatic PVNH. The woman was incidentally found to have PVNH (Figure 1) confirmed by magnetic resonance imaging at the age of 27 years because of headache. During this pregnancy, prenatal ultrasound findings revealed a female fetus with no structural abnormality. Following genetic counseling of PVNH, cytogenetic analysis of the mother and the affected daughter revealed a normal karyotype of 46,XX. Array comparative genomic hybridization analysis of the DNA extracted from the peripheral blood of the affected 2-year-old daughter revealed no genomic imbalance. Mutational analysis of the *FLNA* gene using the genomic DNAs extracted from the peripheral blood of the mother and the affected daughter revealed a heterozygous deletion/insertion (delins) mutation in exon 43 of the *FLNA* gene or c.7106_7110delinsT mutation of which there is a 5-base (AGTGC) deletion and one nucleotide insertion (T), resulting in a frameshift and the introduction of a premature stop codon after adding 23 inappropriate amino acids (Figure 2). At 23 weeks of gestation, prenatal ultrasound revealed severe oligohydramnios, and, therefore, a planned amniocentesis was delayed. Intrauterine fetal death occurred at 24 weeks of gestation. A 316-g macerated female fetus was delivered. Molecular analysis of the placenta revealed the same mutation in the *FLNA* gene as the mother.

FLNA-related PVNH or PVNH1 (OMIM 300049) is an X-linked dominant disorder of neuronal migration caused by mutation of the filamin A (*FLNA*) gene (OMIM 300017) on Xq28 that encodes filamin A [1]. *FLNA*-related PVNH is characterized by uncalcified nodules of neurons situated ectopically along the surface of bilateral lateral ventricles because of a neuronal migration disorder that causes the neurons being unable to migrate appropriately from the ventricular zone to the cortex during development [1–3]. Most affected individuals with *FLNA*-related PVNH are females with heterozygous loss-of-function mutations of *FLNA*, whereas affected males are predominantly lethal in early life [1–3]. Affected females with *FLNA*-related PVNH usually present with epilepsy, but normal to borderline intelligence and psychomotor development, and have the risk of connective tissues abnormalities such as vascular, cardiac, cutaneous, and joint-related symptoms [1–4].

The peculiar aspect of this presentation is the identification of a loss-of-function heterozygous mutation in the *FLNA* gene in an asymptomatic mother and her affected daughter as well as a correct diagnosis of familial *FLNA*-related PVNH. PVNH is a genetically

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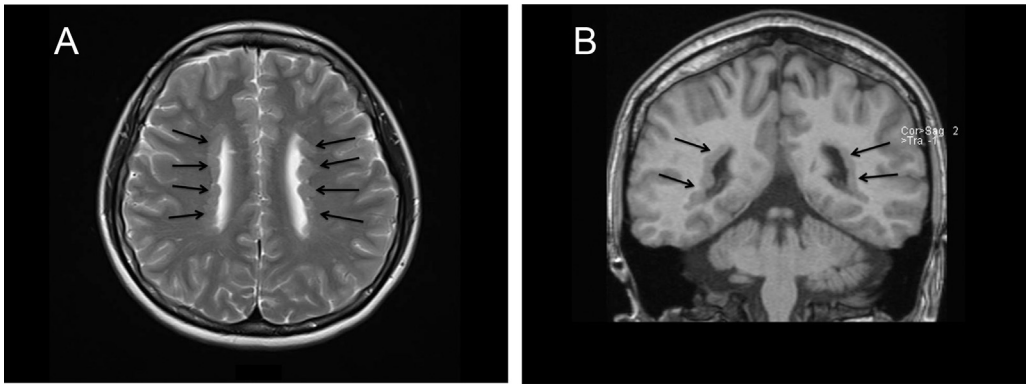

Figure 1. (A, B) Magnetic resonance imaging findings of periventricular nodular heterotopia (arrows) in the mother.

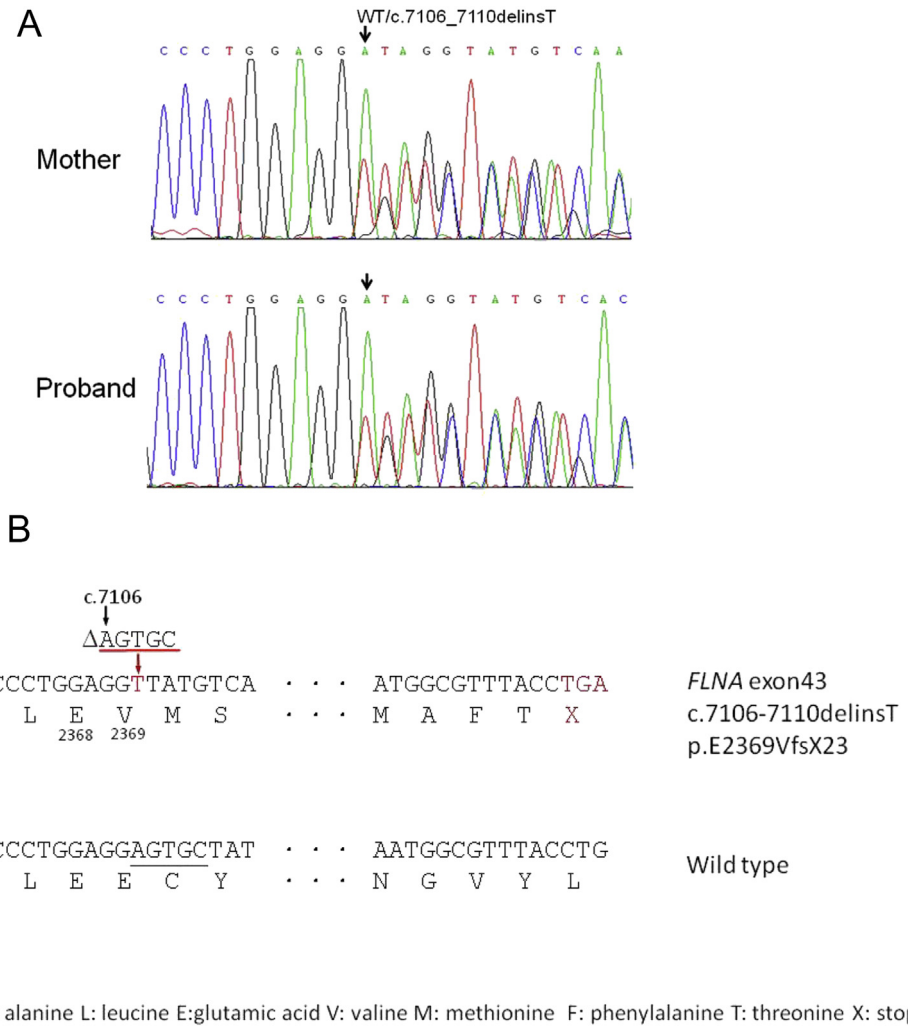

Figure 2. (A, B) The c.7106_7110delinsT heterozygous mutation in the *FLNA* gene in the asymptomatic mother and the affected daughter.

heterogeneous condition which has several types, such as PVNH1 or *FLNA*-related PVNH caused by mutation in the *FLNA* gene on Xq28 (X-linked dominant), PVNH2 (OMIM 608097) caused by mutation in the *ARFGEF2* gene (OMIM 605371) on 20q13.13 (autosomal recessive), PVNH3 (OMIM 608098) caused by 5p15.1 abnormality, PVNH5 (OMIM 612881) caused by deletion of distal 5q (5q14.3-q15), and PVNH6 (OMIM 615544) caused by mutation in the *ERMARD* gene (OMIM 615532) on 6q27 (autosomal dominant). Since the mother in this presentation is asymptomatic, the affected daughter suffers from seizures and both have a normal karyotype, an X-linked dominant inheritance in the family is likely. Therefore, we speculated *FLNA*-related PVNH and made a mutational analysis

of *FLNA* and successfully identified a novel *FLNA* mutation in this family.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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