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A New Case With Cortical Malformation Caused by Biallelic Variants in *LAMC3*

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Abstract

Objective

In this study, we report the case of a 24-year-old man with intellectual disability and childhood-onset seizures. This patient had newly identified biallelic variants in the laminin subunit gamma 3 (*LAMC3*) gene with unreported cortical malformation.

Methods

Exome sequencing.

Results

Genetic analyses revealed new biallelic variants in the *LAMC3* gene. An MRI examination of the brain revealed cortical malformations predominantly in the temporal lobes and mildly in the occipital, frontal, and parietal lobes. In addition, our patient also exhibited mild midline malformation in the ventral pons, which is unique to *LAMC3* variants.

Discussion

Patients with *LAMC3* variants have been reported to exhibit cortical malformation predominantly in the occipital lobes, but this patient exhibited cortical malformation predominantly in the temporal lobes and mildly in the occipital, frontal, and parietal lobes. In addition, this patient also exhibited mild midline malformation in the ventral pons. These unique findings cast new light on the role of *LAMC3* in brain development.

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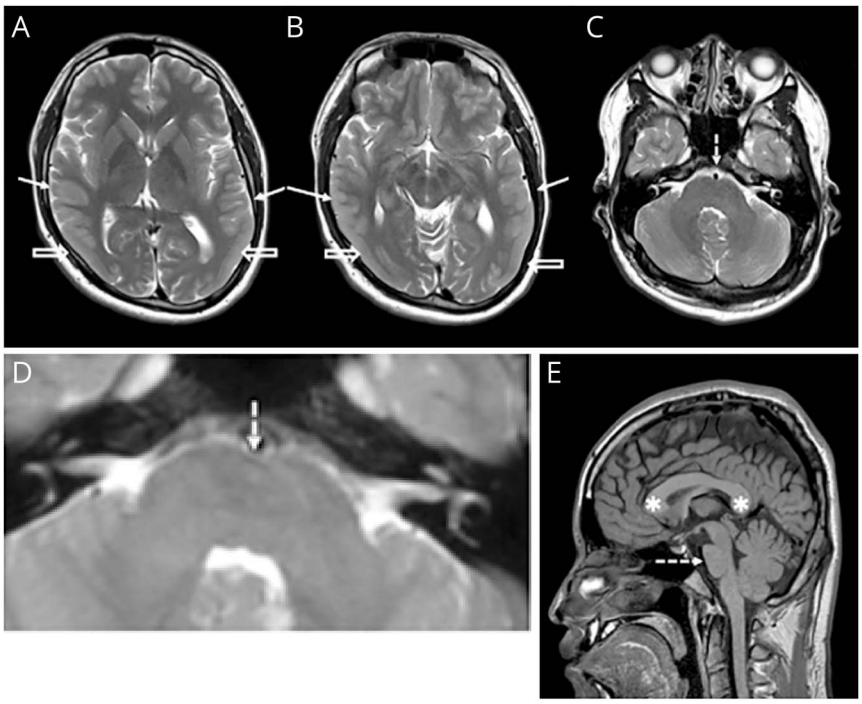
Figure 1 Magnetic Resonance Images



(A–D) Axial T2-weighted images of MRI, (E) sagittal T1-weighted image of MRI. (A, B) The image shows polymicrogyria with a thick cortex and abnormal gyration in the bilateral ventral temporal lobe. (→) The cobblestone brain malformation with thick cortex and agyria (⇒) with subcortical linear T2 hyperintensity (A⁎) in the dorsal temporal lobe were noted. (C, D) There is loss of pontine convexity owing to a midline depression. As a result, the vertical diameter of the bridge is shorter than the horizontal diameter (…→). (E) The midline image shows hypoplasia of the bulge of the ventral pons (…→). A thick corpus callosum was also noted (**).

Malformations of cortical development cause a group of disorders encompassing macroscopic and microscopic abnormalities of the cerebral cortex that arise in perinatal life (starting in the 7th week and peaking between 12 and 22 weeks). Clinical symptoms may arise later during infancy or even adulthood in milder cases.[1-5] Seizures, developmental delay, impaired visual function, and cognitive delays can also be observed in affected individuals. Variants in actin-associated or microtubule-associated genes have been associated with cortical malformation.[6] Barak previously showed that biallelic variants in the laminin subunit gamma 3 (*LAMC3*) gene affect the cortical development and lead to malformations.[7]

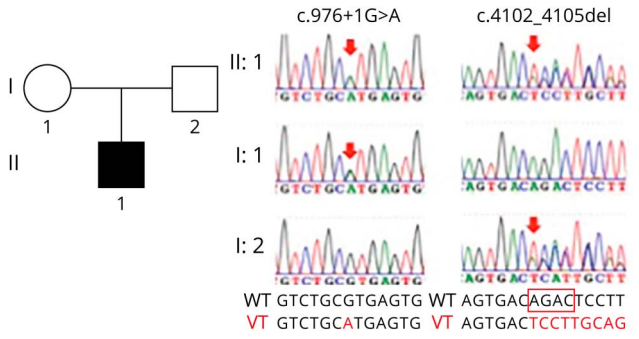
In this study, we report a 24-year-old man with intellectual disability and epileptic attacks. On imaging studies, he exhibited brain malformations comprising posterior predominant pachygyria and elongated brainstem. Genetic analyses revealed biallelic variants in the *LAMC3* genes as the cause of a distinctive and most likely pathognomonic brain malformation.

Case Presentation

A 24-year-old right-handed male patient, born to nonconsanguineous healthy parents with normal development, with a 16-year history of epilepsy was admitted to our clinic. He had no family history of neurologic disorders. He showed intellectual developmental delay since infancy. His total IQ was 80 at the age of 16 years. He had graduated from junior high school and had since been working at a place for disabled individuals.

At the age of 8 years, he had tonic-clonic and absence seizures. His mother, as an eyewitness, reported syncope-like falls associated with unusual movements initiated in the left upper limb. He was admitted to a hospital where he underwent EEG and cranial MRI, resulting in a diagnosis of focal motor onset epilepsy. He was treated with valproate (1,000 mg, twice daily), which reduced the seizure frequency to the point that it seldom occurred. At the age of 15 years, he stopped his medication. He worked as a cleaning staff after graduating senior high school. He had no relapse of seizures until the age of 24 years when he experienced a tonic-clonic seizure with absence after tremors in the left

Figure 2 Electropherograms of the Patient and His Parents



Familial pedigrees and Sanger sequencing confirmation of *LAMC3* variants. The c.976+1G>A and c.4102_4105 del variants were inherited from the mother and father, respectively.

Table 1 Predicted Pathogenicity of *LAMC3* Variants

Gene	Refseq	Variant	Origin	gnomAD	SpliceAI[a] (AG|AL|DG|DL)	ACMG classification
LAMC3	NM_06059.4	c.976+1G > A	Maternal	0.00002630	0.00|0.01|0.04|0.99	PVS1, PM2, PM3, PP3
LAMC3	NM_06059.4	c.4102_4105del, p.(Arg1368Serfs*48)	Paternal	—	0.02|0.01|0.00|0.00	PVS1, PM2, PM3

Abbreviations: ACMG = the American College of Medical Genetics and Genomics; AG = acceptor gain; AL = acceptor loss; DG = donor gain; DL = donor loss.
[a] Splice AI: Delta score >0.8 can be interpreted as the probability of the variant being splice-altering with high precision.

hand. After starting with 100 mg of lacosamide per day, he experienced no seizures.

He showed no abnormal findings on neurologic examination, except for a slightly ataxic gait. EEG revealed negative spikes in the right temporal lobe, accompanied by theta waves of 5–7 Hz. On imaging studies, he exhibited cortical malformation in the dorsal cerebrum, and mild midline malformation was noted. Imaging revealed cobblestone malformation predominantly on the dorsal side of the bilateral temporal lobe. The pons was wide with a shallow ventral cleft in the midline (Figure 1).

Genetic Analysis

We performed whole-exome sequencing and identified 2 candidate variants in the *LAMC3* gene (NM_06059.4), the c.976+1G>A and c.4102_4105del, p.(Arg1368Serfs*48). Sanger sequencing using the trio samples confirmed that the c.976+1G>A and c.4102_4105del variants were inherited from his mother and father, respectively (Figure 2). The c.976+1G>A variant had been previously found in a patient with cortical malformation, whereas the c.4102_4105del variant was novel. Analysis in SpliceAI predicted that the c.976+1G>A variant would cause donor site loss with high probability. Based on the American College of Medical Genetics and Genomics standards and guidelines, both variants were classified as pathogenic and considered to be causative in this case (Table 1). This study was approved by the Ethics committee of our institution, and we obtained written informed consent from the patient to perform this study.

Discussion

Barkovich et al. introduced a classification system of malformations of cortical development derived from the disruption of 3 major stages of cortical development as follows: malformations due to abnormal neuronal and glial proliferation or apoptosis such as focal cortical dysplasia, malformations due to abnormal neuronal migration, such as subependymal heterotopia and classic lissencephaly, and malformations due to abnormal postmigrational development, such as polymicrogyria and cobblestone brain malformation. Polymicrogyria and cobblestone brain malformation resulted from abnormal development of the pial limiting membrane of the brain with consequent overmigration of the neurons through gaps in the membrane and early abnormal folding of the cortex.[8,9]

Barak et al.[2] first described biallelic *LAMC3* variants in Turkish families with occipital polymicrogyria and epileptic patients. Until now, 7 unrelated families worldwide have been reported to exhibit cortical malformations due to *LAMC3* variants. All these patients with *LAMC3* variants exhibited cortical malformations involving the occipital lobe, except for the patient reported by Qian et al.,[4] while Kasper et al.[3] reported a patient with cortical malformation predominantly in the frontal lobe. In addition, a patient reported by Zamboni et al. also exhibited cortical malformation in the frontal, parietal, and temporal lobes. Our patient had an abnormal distribution of the cortical malformations in the occipital, frontal, parietal, and temporal lobes similar to that in the patient reported by Zamboni et al.[10] However, our patient also exhibited mild midline malformation in the ventral pons with findings that were unique for *LAMC3* variants and had not been reported previously. The clinical features of patients with *LAMC3* variants are summarized in eTable 1. There were 9 variants in the *LAMC3* gene. A seizure was the most common clinical feature of patients with cortical malformations due to *LAMC3* variants. These seizures seemed to be treatable by antiepileptic drugs. Developmental delay was typical of the clinical features of our patient but was not observed in the patient reported by Kasper. In addition, previously reported 8 patients were all women and born to consanguineous parents, but our patient was a man born to nonconsanguineous parents. Although further investigations are needed, these studies suggest that *LAMC3* plays a unique role in the nervous system.

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Disclosure

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Kazuo Abe, MD, PhD	Department of Neurology, Hyogo College of Medicine Hospital; Center of Neurology, Gratia Hospital	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Kumiko Ando, MD, PhD	Department of Diagnostic Radiology, Kobe City Medical Center General Hospital	Major role in the acquisition of data; analysis or interpretation of data
Mitsuhiro Kato, MD, PhD	Department of Pediatrics, Showa University School of Medicine	Major role in the acquisition of data; analysis or interpretation of data
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Shintaro Aoki, MS	Department of Biochemistry, Hamamatsu University School of Medicine	Major role in the acquisition of data; analysis or interpretation of data
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