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

Kazuo Abe, MD, PhD, Kumiko Ando, MD, PhD, Mitsuhiro Kato, MD, PhD, Hirotomo Saitsu, MD, PhD, Mitsuko Nakashima, MD, PhD, Shintaro Aoki, MS, and Takashi Kimura, MD, PhD

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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.
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. 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. Barak previously showed that biallelic variants in the laminin subunit gamma 3 (LAMC3) gene affect the cortical development and lead to malformations.

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 non-consanguineous 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...
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**

Barakovich et al. 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., while Kasper et al. 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. 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 non-consanguineous parents. Although further investigations are needed, these studies suggest that LAMC3 plays a unique role in the nervous system.

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**Disclosure**

None. Go to Neurology.org/NG for full disclosures.
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### Appendix Authors

| Name                  | Location                                                                 | Contribution                                                                 |
|-----------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Kazuo Abe, MD, PhD    | Department of Neurology, Hyogo College of Medicine Hospital; Center of  | 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     | Major role in the acquisition of data; analysis or interpretation of data    |
|                       | Hospital                  |                                                                               |
| Mitsuhiro Kato, MD,   | Department of Pediatrics, Showa University School of Medicine            | Major role in the acquisition of data; analysis or interpretation of data    |
| PhD                   |                           |                                                                               |
| Hirotomo Saitsu, MD,  | Department of Biochemistry, Hamamatsu University School of Medicine      | Major role in the acquisition of data; analysis or interpretation of data    |
| PhD                   |                           |                                                                               |
| Mitsuko Nakashima,    | Department of Biochemistry, Hamamatsu University School of Medicine      | Major role in the acquisition of data; analysis or interpretation of data    |
| MD, PhD               |                           |                                                                               |
| Shintaro Aoki, MS     | Department of Biochemistry, Hamamatsu University School of Medicine      | Major role in the acquisition of data; analysis or interpretation of data    |
|                       |                           |                                                                               |
| Takashi Kimura, MD,   | Department of Neurology, Hyogo College of Medicine Hospital              | Major role in the acquisition of data; analysis or interpretation of data    |
| PhD                   |                           |                                                                               |

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