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LETTER TO THE EDITOR

A Frameshift Variant in the *SEMA6B* Gene Causes Global Developmental Delay and Febrile Seizures

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Dear Editor,

Hamanaka *et al.* first reported semaphorin 6B (*SEMA6B*) (MIM 608873) as a causative gene for progressive myoclonic epilepsy (PME) in 2020 [1]. They reported that four variants occurred in the last exon of *SEMA6B* in five unrelated individuals with PME. The clinical presentations of these patients harboring truncated *SEMA6B de novo* variants (DNVs) were characterized by progressive neurological decline (age of onset: about 2 years old) and myoclonic epilepsy (age of onset: 1 year 5 months to 6 years old). These DNVs are located in the last exon closer to the C-terminus [termed the NMD(−) region] of the *SEMA6B* gene and could escape from nonsense-mediated mRNA decay (NMD). These DNVs were postulated to cause severe neurodevelopmental defects by a dominant-negative or gain-of-function effect [1].

Semaphorins are a large family of transmembrane axon-guidance molecules characterized by N-terminal SEMA domain. *SEMA6B* is one of the vertebrate semaphorins and plays a role in neuronal development, transcription regulation, and cancer [2]. Since human *SEMA6B* was first identified in a cDNA pool of breast cancer donors in 2001 [3], so far, the *SEMA6B* gene has been commonly associated with cancers such as breast cancer [4], thyroid carcinoma [5], and gastric cancer [6]. Although *SEMA6B* plays a vital role in diverse functions in brain development including axon guidance, neuronal migration, and cerebellar development [7], it was not until 2020 that *SEMA6B* was been first ascertained as a causative gene for a neurodevelopmental disease – PME.

In our study, we performed whole-exome-sequencing on a patient with global developmental delay and identified a frameshift DNV (chr19:4544346-4544346; NM_032108.3: c.1934delG: p.G645fs) in the *SEMA6B* gene. Sanger sequencing was used to confirm the variant (Fig. 1). Different from the clinical phenotype-PME reported by Hamanaka *et al.*, our patient showed global developmental delay and febrile seizures. All participants signed informed consent forms, and the study was approved by the Ethics Committee of the Maternal and Child Health Hospital of Hunan Province (2020-S003).

The patient was born at full term following an uneventful pregnancy. He developed symptoms at the age of six months. He could lift his head briefly but could not roll over or follow moving objects. Upward twitching of the eyes and a stiff body followed by extending and shaking

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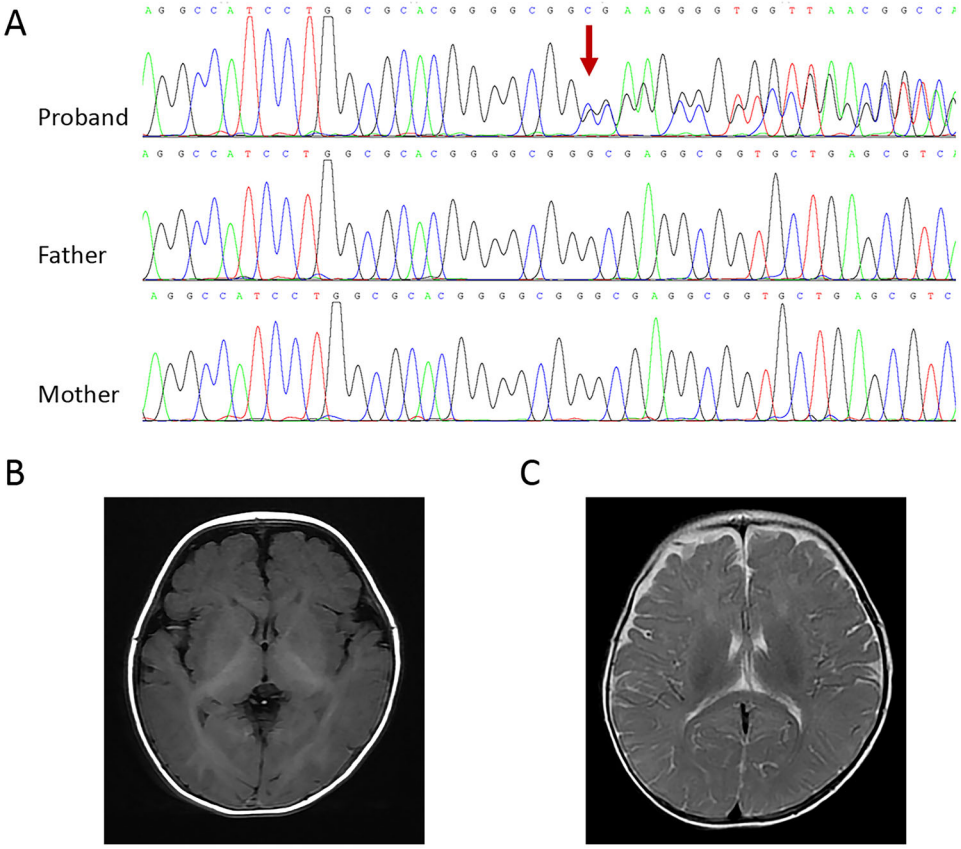

Fig. 1 **A** Sanger sequencing results of the *SEMA6B* variant in family members. The arrow points to the variant location. **B** Normal brain MRI (axial T1-weighted image) of the proband at six months old. **C** Normal brain MRI (axial T2-weighted image) of the proband at six months old.

limbs were observed once and the seizures lasted less than 2 min. The patient had a temperature of 40.5°C. The patient had no medical history of neurological disease or family history of seizures. Routine blood test, C-reactive protein test, procalcitonin test, blood culture test, and cerebrospinal fluid testing were normal. Brain magnetic resonance imaging (MRI) was normal (Fig. 1B, C). An EEG showed sporadic low-amplitude spike and slow-waves in the central parietal and midline regions during sleep (Fig. 2A). A febrile seizure was suspected. By two years, he could crawl and sit with support. The patient was again admitted to hospital for similar seizure patterns. Generalized tonic-clonic seizures occurred once and the patient had a temperature of 39°C. A recurrent febrile seizure was considered.

After we read the article published in 2020 by Hamanaka *et al.*, we performed EEG and electromyography (EMG) on our six-year-old patient who was seizure-free for four years. Neither sudden, rapid, and forceful twitches of the limbs nor sudden nodding, bending, or leaning back was noticed. No anti-seizure medications were administrated. An EEG revealed multiple slow waves in the frontal temporal region while asleep (Fig. 2B). No abnormality was found in synchronous EMG (Fig. 2B). Therefore, no evidence for myoclonic epilepsy was found in our patient. As a six-year-old child, he could not stand or walk and had no language skills that he could only babble "Yi", "Ah".

In our study, we first reported a patient carrying an *SEMA4B* variant who showed clinical features different from the patients reported by Hamanaka *et al.* (2020). Hamanaka *et al.* showed the *SEMA6B* gene to be the genetic cause of PME by presenting five patients with consistent clinical features. The major clinical features of the five reported patients were myoclonic epilepsy and childhood-to-juvenile-onset progressive neurological decline. However, our patient showed a different group of clinical manifestations: global developmental delay and febrile seizures. Our study may contribute to expanding the clinical phenotype and spectrum of *SEMA6B* variants and providing support for accurate genetic counseling.

The four reported *SEMA6B* truncated DNVs were located in the last exon of the *SEMA6B* gene and could escape from NMD. The pathogenesis of these *SEMA6B* NMD(−) region DNVs was likely to be a dominant-negative or gain-of-function effect by truncation the intracellular domain (ICD) close to the C-terminus, which was demonstrated by real-time PCR results. Functional study based on a zebrafish model also showed that the truncation of *sema6ba* and *sema6bb* in the last coding exon

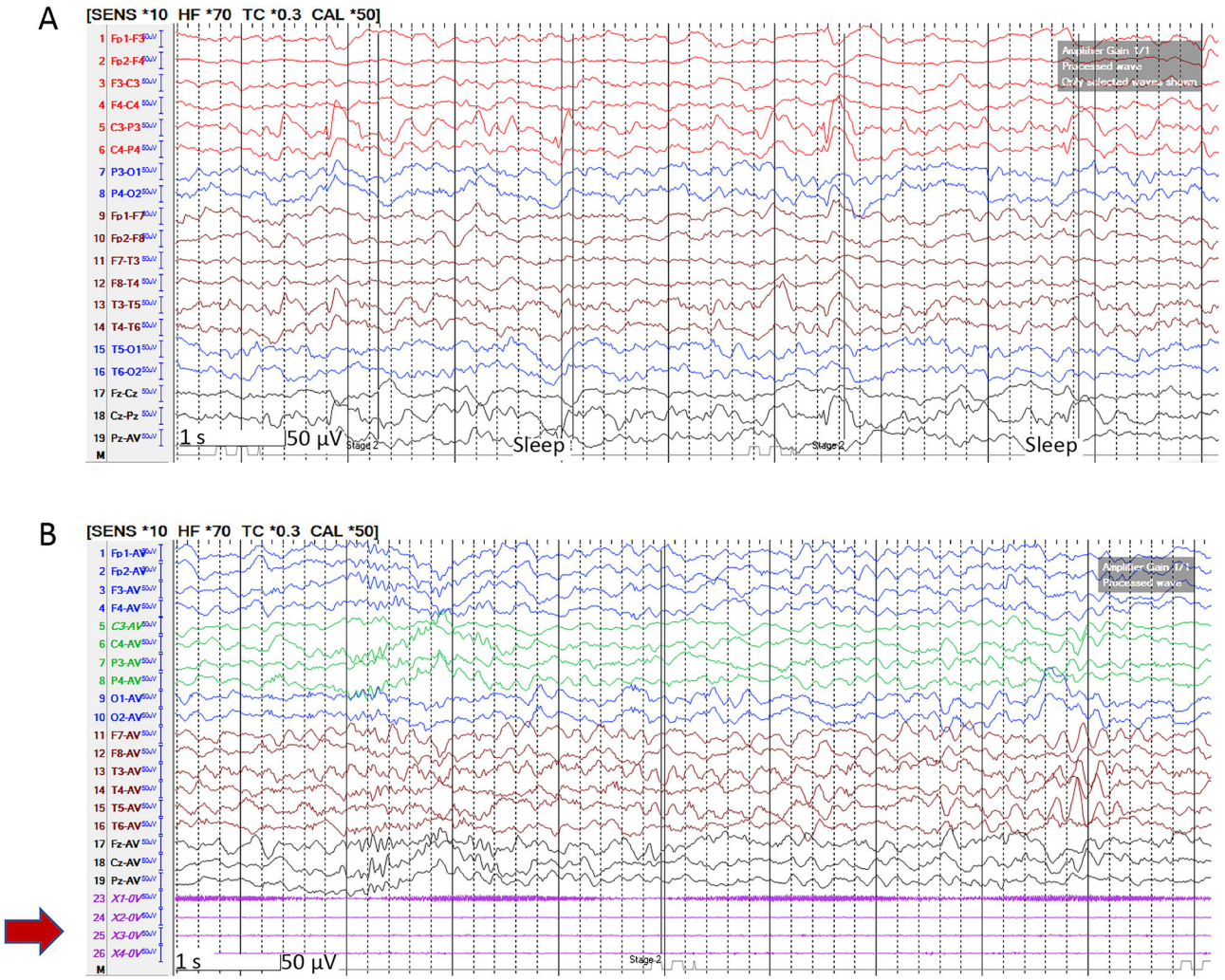

Fig. 2 **A** EEG showing sporadic low-amplitude spike and slow-waves in central parietal and midline regions during sleep at the age of six months. **B** EEG revealing multiple slow waves in the frontal temporal region while asleep at the age of six years. No abnormality was found in synchronous EMG. The arrows point to synchronous EMG.

could lead to severe neurodevelopmental phenotypes in zebrafish including a small head, epilepsy, and others [1]. Chick model also showed that a *SEMA6B* homolog lacking the ICD was unable to rescue neural development caused by absence of SEMA6B protein [7]. The following Sema6B-PlexA4 signaling pathway may be interrupted thus affecting the axon-repulsive activity [8–10]. Our variant was located in a region similar to those reported and our patient also showed severe neurodevelopmental defects indicating that the DNV in our patient might share mechanisms similar to those reported. However, our patient manifested different clinical phenotypes which contributed to understanding the clinical heterogeneities of *SEMA6B* variants.

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Conflict of interest All authors claim that there are no conflicts of interest.

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