Letter

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KCNB1 frameshift variant caused inherited intellectual disability, developmental delay, and seizure

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SUMMARY Potassium voltage-gated channel subfamily B member 1 (*KCNB1*) encodes Kv2.1 potassium channel. KCNB1 mutations are known to cause global developmental delay, behavioral disorders, and various epilepsies. Most variants occur de novo and are rarely inherited. Here, we report a 14-year-old male patient who was admitted to our clinic with seizures, developmental delay history, and intellectual disability. Brain magnetic resonance image (MRI) was normal and electroencephalogram (EEG) showed spike and sharp-wave complexes emerging in the left hemisphere parietooccipital areas, which were paroxysmally generalized. We performed whole exome sequence analysis (WES) and identified a heterozygous frameshift mutation c.522delA in exon 1 of *KCNB1* (NM_004975.4) predicting a premature stop codon p.Lys174Asnfs*20 in the proband. Sanger sequencing confirmed the heterozygous c.522delA mutation in the proband and his mother who also had epilepsy and learning difficulties. His 45 year old mother had used antiepileptic drugs for 9 years after a seizure episode at 12 years old. Also, his mother's uncle's son is nonverbal and has developmental delay and epilepsy. Our study shows that frameshift mutation cytoplasmic domain of *KCNB1* gene can cause intrafamilial phenotypic variability and relatively mild clinical findings in these patients.

Keywords *KCNB1*, epilepsy, intellectual disability, intrafamilial phenotypic variability

Developmental and epileptic encephalopathies (DEE) are a broad and genetically heterogeneous group of neurodevelopmental disorders, which are characterized by social, cognitive, motor, language, and behavioral problems with or without epileptic seizures (*1*). Recent studies with next-generation sequencing reveal the involvement of gene-encoding ion channels in the pathogenesis of DEE (*1*). Potassium voltage-gated channel subfamily B member 1 (*KCNB1*) encodes Kv2.1 potassium channel and is expressed in various neurons and organs (*2*). *KCNB1* mutations are known to cause global developmental delay, behavioral problems, and various epilepsies (Developmental and epileptic encephalopathy-26) (*3*). To date, 51 distinct *KCNB1* pathogenic variants have been reported in 74 unrelated patients with DEE. Most common findings in these patients are epilepsy, early developmental delay, autism spectrum disorder (ASD), and other psychiatric and behavioral disorders (*4*).

Here, we report a child and his 45 year old mother with a novel *KCNB1* mutation identified by whole-exome sequencing (WES). The child presented with seizures, developmental delay history and borderline intellectual functioning whereas the mother just presented with seizure history, and learning difficulties.

A 14-year-old male patient was admitted to our medical genetic outpatient clinic with seizures, developmental delay history and mild intellectual disability. He was born to non-consanguineous parents as a first child after a full-term pregnancy due to fetal macrosomia through cesarean section. At presentation, his height was 55 cm (> 97 percentile), weight was 4.6 kg (> 97 percentile) and head circumference was 38 cm (> 97 percentile). He was able to walk independently at 17 months. He could speak his first meaningful word's at 3 years. He was always ahead of his peers in terms of height and weight. Apart from these, he did not have any problems until 14 years old. He started primary school at the normal time and learned to read and write on time. At the age of 14, he had afebrile generalized tonic-clonic seizures and repeated twice after 10 days from the first seizure. At this time, electroencephalogram (EEG) showed spike and sharp-wave complexes emerging in the left hemisphere parietooccipital areas, which were paroxysmally generalized. He has started to use levetirasetam therapy after a second seizure attack. He

still continues to use levetirasetam and has had no other seizure attack until now. He caught up with his peers in terms of speaking and other developmental parameters later. The patient has no dysmorphic features or other noteworthy findings revealed at physical examination. Neurological examination was normal except for mild intellectual disability. Laboratory investigations including hemogram, biochemical and metabolic investigations, cranial MRI, echocardiogram, and EEG was reported normal at 15 years old.

His 45 year old mother had used an antiepileptic drug (Maliasin) for 9 years after a seizure episode at 12 years old. The mother of the proband had the first seizure attack at 12 years old and had used antiepileptic drug (Maliasin) for 9 years without a further epilepsy attack. The mother stated that she had experienced learning difficulties throughout the education process. Other growth and developmental parameters of the mother were normal for her age. We decided to perform a whole exome sequence analyses for the proband to elucidate underlying genetic etiology. The parents of the patient provided written informed consent for participation in this study. The study was performed according to the Declaration of Helsinki protocols.

After karyotype analyses with normal results, we decided to perform a WES analyses on this patient. After variant prioritization in the WES data, we identified a heterozygous frameshift mutation c.522delA in exon 1 of *KCNB1* (NM_004975.4) predicting a premature stop codon p.Lys174Asnfs*20 in the proband. Sanger sequencing confirmed the heterozygous c.522delA mutation in the proband and his mother who also had epilepsy and learning difficulties (Figure 1). KCNB1 mutation in this study was not annotated in databases of human variation [Exome Variant Server (*http://evs.gs.washington.edu/EVS/*), 1000 genomes (*http://www.1000genomes.org/*), dbSNP (*http://www.ncbi.nlm.nih.gov/projects/SNP/*)]. Additionally, the mutation was not seen in the Acıbadem Labgen in-house exome database.

The variant in our cases p.Lys174Asnfs*20 is located in the cytoplasmic domain of the *KCNB1* gene. In the literature, there is only a case who carried a de novo missense *KCNB1* variant at cytoplasmic N-terminal region (p.Glu43Gly). In contrast to our current case, the case by Bar *et al*. was nonverbal and had early-onset epilepsy, and developmental delay. But this patient also carried a de novo variant in *GABRA5* gene (p.Thr301Met), which causes developmental and epileptic encephalopathy-79 (DEE79). So, both variants were considered to be contributing to the patient's phenotype and we do not know the exact effect of the *KCNB1* (p.Glu43Gly) variant in this case. It is postulated that truncating variants in the C-terminal domain correlate with less severe epilepsy outcomes (*5,6*). Similar to this finding, truncating variants in the N-terminal domain may correlate with less severe

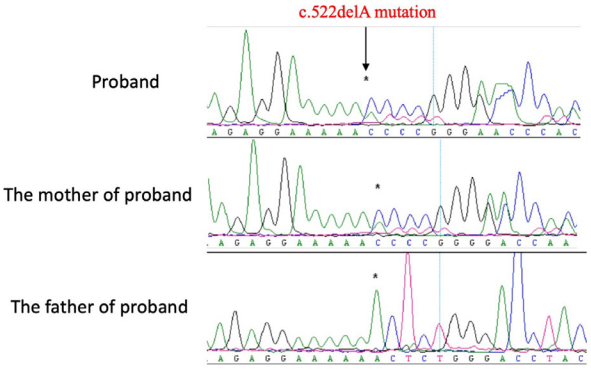

Figure 1. Electropherogram of the *KCNB1* mutation identified in the proband and his mother with his father's electropherogram.

epilepsy and milder developmental problems.

All the *KCNB1* variants identified occurred de novo, except for one maternally inherited variant (p.Arg583*) reported in 2019 (*6*).Our case is the second report that a *KCNB1* mutation in a patient was maternally inherited. In the case by Bare *et al*., the mother of the patient presented with a milder phenotype like intellectual disability with delayed language skills without epilepsy compared to his daughter who had a severe neurodevelopmental disorder with no language acquisition, autism spectrum disorder and behavioral disorders (*6*). This study emphasized that patients carrying a *KCNB1* variant with a relatively mild phenotype can transmit a severe disease to their offspring. Similar to this case, the mother in our study transmitted a relatively severe disease to his son supporting the view that inherited a *KCNB1* variant can be associated with intrafamilial variable expressivity.

Most of the reported cases with a *KCNB1* variant were relatively younger patients. Therefore, knowledge regarding its long-term outcome is limited. According to our current knowledge, this is the oldest patient with a *KCNB1* pathogenic variant. She had seizure history at 12 years old and learning difficulty history during her education period. No other difficulties have been experienced until now. Also no regression of verbal skills was noted during her life time in contrast to the case in the previous report by Lu *et al*. (*7*). We consider that type of variant and affected domain has a major impact on the patients' phenotype for patients with *KCNB1* variants. Truncating variants at the N terminal of the *KCNB1* gene may be more correlated with a milder disease phenotype. Further *KCNB1* cases with genotype-phenotype correlation are needed to prove this view. Also, the patient and his mother in our study had late age seizure onset supporting the view that late age seizure onset might correlate with a more benign disease course for patients with *KCNB1* variants (*7*).

To conclude, we report a proband and his 45 year old mother carrying a c.522delA variant in the *KCNB1*gene. Our study shows that frameshift mutation cytoplasmic domains of *KCNB1* gene can cause intrafamilial

phenotypic variability and relatively mild clinical findings in these patients. Further studies are needed to elucidate the effect of the *KCNB1* variants in different domains and to understand the course of the disease in elderly patients with *KCNB*1 variants.

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