



## KCNQ2-Related Benign Infantile Epilepsy in Preterm Dizygotic Twins

Chang Mi Kwon, MD, Kye Hyang Lee, MD

Department of Pediatrics, Daegu Catholic University School of Medicine, Daegu, Korea

Received: July 14, 2021

Accepted: July 30, 2021

### Corresponding author:

Kye Hyang Lee, MD

Department of Pediatrics, Daegu  
Catholic University School of  
Medicine, 33 Duryugongwon-ro  
17-gil, Nam-gu, Daegu 42472,  
Korea

Tel: +82-53-650-4242

Fax: +82-53-650-4243

E-mail: [rosalia@cu.ac.kr](mailto:rosalia@cu.ac.kr)

Potassium voltage-gated channel subfamily Q member 2 (*KCNQ2*)-related disorders represent a spectrum of overlapping neonatal epileptic phenotypes caused by heterozygous pathogenic variants (PVs) in *KCNQ2*. The clinical features of *KCNQ2*-related disorders range from a mild form of benign familial neonatal epilepsy (BFNE) to a severe form with neonatal epileptic encephalopathy. BFNE is an age-dependent familial epilepsy syndrome characterized by a wide spectrum of seizures that begin in otherwise healthy infants between the 2nd and 8th days of life and typically cease spontaneously. A family history of neonatal seizure is crucial for the diagnosis [1]. *KCNQ2*-related non-familial benign neonatal epilepsy has been previously reported [2]. However, *KCNQ2*-related benign infantile epilepsy in dizygotic twins with no family history of seizures has not been reported to date. Herein, we report the same PV of the *KCNQ2* gene in preterm dizygotic twins who presented with multiple seizures at a corrected age (CA) of 40 weeks. This study was approved by the Institutional Review Board of Daegu Catholic University Medical Center (CR-21-033). The requirement for publication consent was waived because personally identifiable protected health information was not disclosed in this report.

Case 1: Dizygotic twins were born by a moth-

er with gestational diabetes at 31 weeks and 5 days of gestational age. The family history was negative for seizures, intellectual disability, and other neurological disorders. The first twin was male and developed multifocal clonic seizures with apnea and cyanosis at a CA of 40 weeks. He did not have significant perinatal morbidity and was developing normally. Physical examination, routine laboratory testing, and electroencephalography (EEG) were normal. Brain magnetic resonance imaging (MRI) showed no significant abnormalities. The targeted gene panel for epilepsy performed at GC Genome (Yongin, Korea) detected a heterozygous nonsense variant in *KCNQ2* (NM\_172107.2: c.1741C > T; p.Arg581Ter), which was classified as pathogenic. The parents refused genetic testing for the identified PV. Based on the clinical and genetic testing results, the patient was diagnosed with *KCNQ2* gene-related non-familial benign infantile epilepsy. He remained seizure-free on phenobarbital (PB) until breakthrough seizures occurred at a CA of 4 months. PB was then switched to oxcarbazepine (OXZ). At a CA of 12 months, OXZ was tapered off successfully. Motor, language, and social development were normal over 2 years of follow-up without seizure episodes.

Case 2: The second twin was female and also presented with multiple seizures with cyanosis at

the same age. Her development and physical examination were normal. Routine blood testing, EEG, and brain MRI were also normal. Genetic testing revealed the same PV in the *KCNQ2* gene as her twin brother. She was free of seizures for 7 weeks on PB, but they recurred at a CA of 2 months. PB was then switched to OXZ. As with her brother, OXZ was also successfully tapered off at the CA of 12 months. Three months after discontinuing OXZ, she experienced a single generalized tonic-clonic seizure, which was triggered by fever (body temperature, 39.5°C). During subsequent follow-up, she developed normally without seizure occurrence.

Mutations in *KCNQ2* and *KCNQ3*, which encode two different KCNQ channel subunits, have been identified as causes of BFNE [1,2]. However, the exact pathogenic mechanisms underlying the age-dependent development and spontaneous remission of BFNE have not been elucidated. The KCNQ channel is a heteromeric tetramer consisting of *KCNQ2* and *KCNQ3* subunits that function as a voltage-dependent potassium channel and function as the predominant inhibitory system during the first week of life. Afterward, GABAergic transmission serves as the main inhibitory system. *KCNQ2* and *KCNQ3* are widely expressed, but mainly in the hippocampus, neocortex, and cerebellar cortex, where they are co-expressed and co-assembled. They are thought to fully function when they are assembled as a heterotetramer because these heteromeric channels generate a 15-fold larger current than homomeric channels [3]. Kanaumi et al. [3] examined developmental changes in *KCNQ2* and *KCNQ3* expression and found high expression of *KCNQ2* in fetal life that decreased after birth. The expression of *KCNQ3* increased in late fetal life to infancy. Simultaneous expression of *KCNQ2* and *KCNQ3* was significant mainly in the neonatal period: in the cerebellum from late neonatal life to infancy, in the hippocampal pyramidal cells from a gestational age of 36 weeks to 3 months of age, and in the temporal lobe in neonatal life. The developmental expression pattern of *KCNQ2* and *KCNQ3* may contribute to the age-dependent pathogenesis of BFNE [3]. Our patients were born premature, almost 2 months earlier than the expected date, and developed typical BFNE seizures at a CA of 40 weeks, which was full-term. The timing of their seizure presentation may be attributable to the temporal characteristics of expression of the mutated *KCNQ2* gene.

Two families with BFNE that had the same *KCNQ2* PV as our patients have been previously reported [4,5]. As the parents of our patients refused genetic testing, it is uncertain whether this PV is familial or *de novo*. Although non-familial benign neonatal epilepsy is a *KCNQ2*-related disorder phenotype, this variant may have been inherited from one of the parents. Since our patients were dizygotic twins, the variant is relatively unlikely to have occurred *de novo*. Carriers of mosaicism may be asymptomatic or present with

various disease symptoms, depending on factors such as the gene involved and/or the degree of mosaicism. This may explain certain diseases that show variable expressivity among different family members. Mosaic parents vary in the degree to which they are affected, from unaffected to severely affected according to the level of mosaicism [6]. Several cases of *KCNQ2* encephalopathy with parental mosaicism have been reported in patients who inherited the PVs from apparently healthy parents [7]. We hypothesize that the parents of our patients might be mosaic for the *KCNQ2* mutation. Alternatively, they may have had unrecognized seizures in the neonatal period. The dizygotic preterm twins reported here first developed seizures at a CA of 40 weeks and had no family history of seizures, which suggests the importance of age of onset in genetic epilepsy syndromes.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

## ORCID

Chang Mi Kwon, <https://orcid.org/0000-0003-1735-0130>

Kye Hyang Lee, <https://orcid.org/0000-0001-6646-8982>

## Author contribution

Conceptualization: KHL. Data curation: CMK and KHL. Formal analysis: CMK and KHL. Methodology: CMK and KHL. Project administration: CMK and KHL. Visualization: CMK and KHL. Writing - original draft: CMK. Writing - review & editing: KHL.

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