A KCNQ2 E515D mutation associated with benign familial neonatal seizures and continuous spike and waves during slow-wave sleep syndrome in Taiwan

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KEYWORDS
benign familial neonatal seizures; continuous spike and waves during slow-wave sleep; E515D mutation; KCNQ2

Background/Purpose: Pediatric epilepsy caused by a KCNQ2 gene mutation usually manifests as benign familial neonatal seizures (BFNS) during the 1st week of life. However, the exact mechanism, phenotype, and genotype of the KCNQ2 mutation are unclear.

Methods: We studied the KCNQ2 genotype from 75 nonconsanguineous patients with childhood epilepsy without an identified cause (age range: from 2 days to 18 years) and from 55 healthy adult controls without epilepsy. KCNQ2 mutation variants were transfected into HEK293 cells to investigate what functional changes they induced.

Results: Four (5%) of the patients had the E515D KCNQ2 mutation, which the computer-based PolyPhen algorithm predicted to be deleterious. Their seizure outcomes were favorable, but three had an intellectual disability. Two patients with E515D presented with continuous spikes and waves during slow-wave sleep (CSWS), and the other two presented with BFNS. We also analyzed 10 affected family members with the same KCNQ2 mutation: all had epilepsy (8 had BFNS and 2 had CSWS). A functional analysis showed that the recordings of the E515D currents were significantly different (p < 0.05), which suggested that channels with KCNQ2 E515D variants are less sensitive to voltage and require stronger depolarization to reach opening probabilities than those with the wild type or N780T (a benign polymorphism).

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Introduction

*KCNQ2*-associated childhood epilepsy is a rare, inherited, autosomal-dominant form of neonatal epileptic syndrome. Seizures usually occur during the 1st week after birth. Benign familial neonatal seizures (BFNS) (OMIM#121200), a central nervous system channelopathy (ion channel dysfunction), is an autosomal-dominant benign familial epilepsy syndrome.1,2 *KCNQ2* mutations can contribute to benign familial neonatal–infantile seizures and benign familial infantile seizures.1–4 Patients with BFNS usually have seizures in the neonatal period with a predicted benign course.1–5 Most BFNS spontaneously disappear during the infant’s first 12 months of life.6 Despite expectations of typical neurological development, on follow-up, some patients present with epilepsy, recurrent febrile seizures, or developmental delays. Moreover, some affected children have recurrent febrile seizures, benign childhood epilepsy with centrotemporal spikes, or rare photosensitive myoclonic epilepsy.7 However, at present, the outcomes in these patients cannot be predicted accurately. The diagnosis depends on family history, clinical features, and genetic study. The mutant gene is located at 20q13, a voltage-gated potassium channel gene (*KCNQ2*).

The *KCNQ2* gene is expressed predominantly in the brain and encoded for voltage-gated potassium channel subunits that underlie the M-current, a repolarizing current that limits repetitive firing during long-lasting depolarizing inputs.6,8,9 Each subunit of *KCNQ2* consists of heteromultimeric channels with six transmembrane domains (S1–S6), including a voltage sensor in S4, a loop between S5 and S6 that builds the ion channel pore, a cytoplasmic Nterminal, and a long C-terminal region of mostly unknown function.1,10 In the *KCNQ2* gene, mutations can cause a haploinsufficiency or a more severe dominant-negative effect.11–13 The precise genotype–phenotype correlation is not known, but the degree of functional disability caused by *KCNQ2* mutations is important.

A *KCNQ2* phenotype of neonatal epileptic encephalopathy has recently been reported.14–16 Most cases are *de novo* mutations, and patients present with severe seizures and grave neurological consequences. Some patients present with burst suppression or multiple focal spikes on neonatal electroencephalograms (EEGs). Seizures remit as the patients become older, but there are usually intellectual developmental delays. A loss of function via the dominant-negative effect of the *KCNQ2* gene is presumed to be the major mechanism for *KCNQ2* encephalopathy.17–19

Focal epilepsy with speech disorder with or without mental retardation (OMIM#245570) in children includes Landau–Kleffner syndrome and continuous spikes and waves during slow-wave sleep syndrome (CSWS). The diagnostic criteria of CSWS include at least one EEG compatible with the CSWS pattern (spike-wave index > 50%) clearly activated during sleep, compared with EEG tracings while awake. Cognitive outcomes vary. More than 50% have favorable outcomes. However, others show a slow disease progression or a poor cognitive prognosis.20 The etiology of CSWS is considered to be heterogeneous. Involvement of the *SRPX2* and *ELP4* genes with CSWS has been reported; however, the *KCNQ2* mutation has not been reported before.

Despite some case-series reports14–16 and functional studies7–9 that have shown a correlation between the phenotype and genotype, this correlation still requires investigation. Moreover, because the *in vitro* functional consequences of *KCNQ2* mutations are not fully understood, we investigated the mutation variants from patients with childhood epilepsy without an identified cause and surveyed the functional changes in HEK293 cells transfected with *KCNQ2* mutation variants.

Patients and methods

We enrolled 75 patients who met all the three criteria for “childhood epilepsy without an identified cause”:

1. first seizure at <18 years of age; (2) age at last visit <18 years; and (3) at least one magnetic resonance imaging study with no detectable seizure-related lesions. Seizure onset occurred before the patient was 2 months old in 34 (45%) cases; eight of these cases had neonatal-onset epileptic encephalopathy, and the onset occurred between the age of 2 months and 18 years in the other 41. Next-generation sequences were used in 55 patients and direct sequences in 20 patients to screen for *KCNQ2* mutation variants. If the mutation variants were detected using next-generation sequences, direct Sanger sequences were used for patients and their relatives, if the latter were available.

Fifty-five healthy adults (110 chromosomes) without seizures were enrolled as controls. Next-generation sequences were used to screen their genomes for *KCNQ2*. Mutation variants were compared between the patient and control groups. Functional changes in the mutation variants were analyzed.

Next-generation sequencing (ion torrent amplicon sequencing)

Ten nanograms of each genomic DNA were used for a multiplex polymerase chain reaction of a panel covering the exon regions of *KCNQ2* (Ion AmpliSeq Custom Panel; Life Technologies, Rockville, MD, USA). Library construction
of the amplicons, and subsequent preparation and enrichment of the sequencing beads were performed following the manufacturer’s instructions. Sequencing was done on the 318 chip using the Ion Torrent Personal Genome Machine (Life Technologies) according to the manufacturer’s instructions. Data analysis, including alignment to the hg19 human reference genome and base calling, was performed using built-in Torrent Suite software. Each patient’s sequencing data were checked against the published mRNA sequencing data of KCNQ2 genes (NM_172107.3) (primer: Supplementary Table 1).

**KCNQ2 expression in HEK293 cells and in whole-cell patch-clamp analysis**

HEK293 cells were maintained in Dulbecco’s modified Eagle’s medium (Biowhittaker, Walkersville, MD, USA) supplemented with 10% fetal bovine serum, penicillin (100 U/mL), streptomycin (100 U/mL), and 2mM l-glutamine (Lonza, Walkersville, MD, USA). KCNQ2 mutations were made using a kit (QuickChange; Stratagene, La Jolla, CA, USA) and verified using sequencing.22

For electrophysiological analysis, the cells were bathed in modified Tyrode’s solution that contained 125mM of NaCl, 5.4mM of KCl, 1.8mM of CaCl2, 1mM of MgCl2, 6mM of glucose, and 6mM of 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (pH 7.4). Patch pipettes had a resistance of 3–4 Ω when filled with pipette solution that contained 125mM of potassium gluconate, 10mM of KCl, 5mM of HEPES, 5mM of ethylene glycol tetra-acetic acid, 2mM of MgCl2, 0.6mM of CaCl2, and 4mM of adenosine 5’-triphosphate disodium salt hydrate (pH 7.2).

To measure the voltage dependence of activation, the cells were clamped using 3-second conditioning voltage pulses to potentials between 180 mV and 140 mV in 10-mV increments from a holding potential of 0 mV. Data

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of clinical phenotypes for four index patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient no. 1 2 3 4</td>
</tr>
<tr>
<td>Age at time of study</td>
<td>7 y 2 mo 13 y 1 y 13 y</td>
</tr>
<tr>
<td>KCNQ2 genotype</td>
<td>c.1545G&gt;C (E515D) c.1545G&gt;C (E515D) c.1545G&gt;C (E515D) c.1545G&gt;C (E515D)</td>
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<tr>
<td>Inheritance</td>
<td>Maternal Paternal Paternal Paternal</td>
</tr>
<tr>
<td>Other genetic study for diagnosis</td>
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</tr>
<tr>
<td>Gender</td>
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<tr>
<td>Family mutation</td>
<td>Mother Father NA Mother</td>
</tr>
<tr>
<td>Age at first visit</td>
<td>Day 2 6 y Day 5</td>
</tr>
<tr>
<td>Age at first seizure</td>
<td>Day 2 NA</td>
</tr>
<tr>
<td>Family history</td>
<td>Neonatal seizures in grandmother, mother, one brother, one sister Neonatal seizures in father Neonatal seizures in father NA</td>
</tr>
<tr>
<td>Family members with epilepsy</td>
<td>5 (BFNS) 2 (1 BFNS, 1 CSWS) 2 (BFNS) 1 (CSWS)</td>
</tr>
<tr>
<td>Seizure type</td>
<td>Generalized tonic Absence like Generalized tonic Generalized tonic, absence like</td>
</tr>
<tr>
<td>Seizure frequency before 1st week after birth</td>
<td>&gt; 50 (+++) NA +</td>
</tr>
<tr>
<td>Seizure frequency before drug control</td>
<td>++++ + +</td>
</tr>
<tr>
<td>Drug control</td>
<td>Intravenous PB, PHT, oral SAB, then oral PB, SAB VPA, CLN, then VPA. PB ineffective, then OXC Oral VPA, TOP, then VPA</td>
</tr>
<tr>
<td>Seizure frequency after drug control</td>
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<tr>
<td>Epileptic syndrome</td>
<td>BFNS CSWS BFNS CSWS</td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>NP NP</td>
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<tr>
<td>Developmental delay/ Intellectual disability</td>
<td>Mild (IQ: 70) Mild (IQ: 71)</td>
</tr>
<tr>
<td>Additional features</td>
<td>Emotional disorder</td>
</tr>
</tbody>
</table>

BFNS = benign familial neonatal seizures; CLN = clonazepam; CSWS = continuous spike and waves during slow-wave sleep syndrome; EEG = electroencephalography; IQ = intelligence quotient; MRI = magnetic resonance imaging; NA = not available or history cannot be traced; NP = nothing particular; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; SAB = vigabatrin; TOP = topiramate; VPA = valproic acid; ++++ = daily seizures; +++ = weekly seizures; ++ = monthly seizures; + = yearly seizures or less than yearly seizures.

BFSN = benign familial neonatal seizures; CLN = clonazepam; CSWS = continuous spike and waves during slow-wave sleep syndrome; EEG = electroencephalography; IQ = intelligence quotient; MRI = magnetic resonance imaging; NA = not available or history cannot be traced; NP = nothing particular; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; SAB = vigabatrin; TOP = topiramate; VPA = valproic acid; ++++ = daily seizures; +++ = weekly seizures; ++ = monthly seizures; + = yearly seizures or less than yearly seizures.
acquisition and analyses were performed using electrophysiological data acquisition and analysis software (Clampex 10.0; Molecular Devices, Sunnyvale, CA, USA). The KCNQ2 mutation and wild-type variants were transfected into HEK293 cells to investigate the functional changes that cause cell-current changes. We also performed functional analyses of the wild-type allele with a proven benign polymorphism of c.2339A>C (N780T) (rs1801475) that accounts for >40% of healthy controls in Taiwan,23 as a negative control, and the R213Q15 mutation, which causes neonatal epileptic encephalopathy, as a positive control.

Cytoplasmic and membranous protein separation

Three wells were covered with HEK293 cells (6 x 10⁶) in a 10-cm cell-culture dish. The cells were washed two or three times with phosphate buffered saline that contained 4 g of NaCl, 0.1 g of KCl, 0.72 g of Na₂HPO₄, and 0.13 g of KH₂PO₄, at an adjusted pH of 7.4. They were then added to the cells containing sucrose in a homogeneous solution [40mM of Tris-HCl (pH 7.4), 0.34M of sucrose, 10mM of EDTA, and 1mM of MgSO₄] before being used and subsequently added to 1 mL of 1mM phenylmethylsulfonyl fluoride. The cell mixture was placed on ice and sonicated three times for 2 minutes each time (intensity: 30), and then slowly added to a mixture of 50% sucrose in a centrifuge tube [40mM Tris-HCl (pH 7.4), 50% sucrose, 10mM of EDTA, 1mM of MgSO₄, and 2mM of NaCl], and completely heat-shocked cell homogenates. After the solution had been centrifuged in an ultra-high-speed rotor (55-Ti; Beckman Coulter Taiwan, Taipei, Taiwan) at 4°C and 26,200 rpm for 90 minutes, cellular proteins rose to the top.

Statistical analysis

Data are represented as means ± standard deviation. Significant differences were evaluated using an independent t test or an analysis of variance test. Significance was set at p < 0.05.

Results

The c.1545G>C (E515D) KCNQ2 mutation was detected in four (5%) of the 75 patients with epilepsy without an identified cause. We also scanned for and analyzed the mutations in 55 healthy controls (adults without a history of epileptic seizures).

Four (3 boys and 1 girl) of the 75 patients (5%) had the c.1545G>G>C (E515D) KCNQ2 mutation, a variant not found in the control group. The computer-based PolyPhen algorithm predicted that this mutation was deleterious and would cause functional damage (score = 1.0), and classified it as a pathogenic mutation (http://www.ncbi.nlm.nih.gov/clinvar/RCV000020972/). All the patients with the E515D mutation had epilepsy, and their seizures were controlled by medication. One had normal intelligence and three had a mild intellectual disability (Table 1).

Ten family members of the four index patients had the same E515D KCNQ2 mutation (Table 1). Eight had BFNS and two had CSWS.

Of the four patients with the c.1545G>C (E515D) mutation, three had generalized tonic seizures and two had absence-like seizures. The ages of the patients at their first visit to our clinic varied: two patients (Patients 1 and 3) had BFNS, and two (Patients 2 and 4) who began to have seizures at 6 years of age presented with CSWS. Patient 1, who was described in a prior study,24 last visited our clinic at the age of 7 years and 2 months. This patient’s neonatal seizures were initially poorly controlled despite treatment with two antiepileptic drugs. After 2 weeks, however, the seizure control was good. Patient 1 later developed epilepsy and an intellectual disability. Five family members had epilepsy with BFNS and had the E515D mutation (Figure 1 and Table 1).

Patients 2 and 4 took valproate as a first-line drug. Owing to Patient 4’s frequent spikes, topiramate was added to the antiepileptic drug regimen, which reduced the number of seizures to about one per year. All four instances of the E515D mutation were hereditary: one of the parents had the KCNQ2 mutation in each instance (Table S1). All magnetic resonance imaging studies were normal. However, in Patients 2 and 4, EEGs showed CSWS, but without obvious clinical seizures (Figure 2). The common presentation in three patients with the E515D mutation was well-controlled seizures and an intellectual disability. Patients 2 and 4 had an intellectual disability, CSWS, and inattention.

Functional analysis

To investigate the functional consequences of the N780T, E515D, and R213Q mutations, macroscopic currents were...
recorded with the whole-cell configuration of the patch-clamp technique in HEK293 cells transfected with cDNAs encoded for the wild type or one of the following mutants: c.1545G>C (E515D), c.2339A>C (N780T), and c.638G>A (R213Q).

The electrophysiological properties of the human wild-type mutant in KCNQ2 homomeric and heteromeric (wild type and mutant Z1:1) channels transiently expressed in HEK293 cells were analyzed. The cells were clamped between /C080 mV and +40 mV in 10-mV increments from a holding potential of /C080 mV [wild type (n = 18), E515D (n = 20), N780T (n = 13), and R213Q (n = 3)] (Figures 3A–D). The membrane potential currents were induced with conditioning voltage pulses to potentials between −80 mV and +40 mV using whole-cell patch-clamp analysis. The data were then fit to a Boltzmann distribution of the following form:

\[ \frac{G}{G_{\text{max}}} = \frac{1}{1 + \exp\left(\frac{V - V_{1/2}}{dx}\right)} \]

where V is the test potential, \( V_{1/2} \) the half-activation potential, \( dx \) the slope, and \( G_{\text{max}} \) the maximal amplitude of the Boltzmann distribution. The E515D substitution in KCNQ2 affected both \( V_{1/2} \) and \( dx \) of the conductance–voltage curve in the homomeric configuration, which suggested that channels carrying KCNQ2 E515D subunits are less sensitive to voltage and thus require stronger depolarization to reach opening probabilities than the homomeric channels formed by wild-type KCNQ2 subunits (Figure 4 and Table S2).

Currents were significantly (p < 0.05) lower in homomeric and heteromeric E515D when the conditioning voltage potential ranged from −30 to −50 mV (Figure 4 and Table S2). The conductance–voltage curves showed that the wild-type variant significantly differed from the E515D and R213Q variants (p < 0.05; Figure 5), but was almost equal to N780T (Figure 5). An analysis of the half-maximal activation voltage (\( V_{1/2} \)) showed that \( V_{1/2} \) was significantly (p < 0.005) different between the wild-type (−20.635 ± 1.618) and R213Q (30.080 ± 2.789) variants (Table S2), and between the wild type and the wild-type + E515D mutant (1:1) (−16.075 ± 0.466) (p < 0.05). The current in the cells transfected with the KCNQ2 wild type, E515D, and wild-type KCNQ3 (1:1:0.5) was significantly lower at −50 to −30 conditioning voltage than it was in cells transfected with the wild-type KCNQ2 and wild-type KCNQ3 (1:1). A proven benign single-nucleotide polymorphism (SNP) transfected with N780T was not significantly different in functional degree when compared with the transfected homomeric cells (Figure 5).
Discussion

We found that the electrophysiological properties of HEK293 cells transfected with E515D were significantly different from those of the N780T mutant, which we showed to be a benign polymorphism, and the wild-type KCNQ2. The E515D mutation variant caused functional changes in the homomeric and heteromeric channels transiently expressed in HEK293 cells, and cells that had been transfected with the wild-type KCNQ2, KCNQ3, and E515D mutations showed currents that were different from those in HEK293 cells with wild type. Family histories and functional studies predict that the E515D mutation is highly likely to cause seizures. KCNQ2 mutations contribute to childhood epilepsy with a variety of phenotypes: from neonatal epileptic encephalopathy to generalized epilepsies without an identified cause and CSWS.

Although HEK293 homomeric and heteromeric cells transfected with the E515D variant had significantly different electrical functional properties than cells with the wild-type and N780T mutations, cells transfected with the wild-type KCNQ2, KCNQ3, and E515D mutations in a 1:2:1 ratio showed only current differences at a conditioning voltage of −50 mV from the HEK293 cells with wild type. In the first 3 postnatal months, hippocampal KCNQ3 protein expression is relatively lower than the KCNQ2 protein expression. KCNQ2 persists in the hippocampus and temporal lobe until adulthood, and KCNQ2 expression falls in older children. KCNQ3 expression persists longer than KCNQ2 expression. Functional changes in E515D KCNQ2 mutation-expressing homomeric and heteromeric transfected cells are a probable cause of seizures because of the relatively low expression of KCNQ3 protein in newborns.

The etiology of CSWS is considered heterogeneous. It might be associated with the evolution of atypical rolandic epilepsy, the evolution of focal epilepsy with a specific structural etiology (thalamic lesions, cerebral infarct, polymicrogyria, and hydrocephalus), a prior developmental delay of unknown etiology (possibly genetic), or, less likely, a chromosomal or monogenic condition. Subclinical EEG discharges contribute to CSWS-induced cognitive decline; thus, long-term EEG monitoring and nocturnal recording are critical for detecting changes. For CSWS, prolonged video-EEG monitoring is a useful diagnostic tool because it allows for accurate recognition of electroclinical syndromes. The evolution of epilepsy is well documented: seizures spontaneously disappear, as do the adolescence and preadolescence CSWS patterns, which is consistent with our cases. Our findings also support the notion that the etiology of CSWS in children includes the KCNQ2 mutation, which is first reported here, and that some patients develop CSWS, but in others it might not appear for years.

Outcomes vary in patients with KCNQ2-associated epilepsy. Even in the most benign cases, in which neurodevelopmental outcomes are good, seizure remission usually occurs after the age of 3 years, and most develop normal intelligence. Three of our four patients with the E515D mutation developed a mild intellectual disability and two had CSWS, as shown by EEGs. This is interesting because, despite the favorable outcomes of their seizures, these patients developed cognition and inattention problems. To the best of our knowledge, these are the first patients with the KCNQ2 mutation and epileptic syndrome comorbid with CSWS. Involvement of the SRPX2 and ELP4 genes with CSWS has been reported. Thus, screening patients with CSWS without an identified cause for KCNQ2 is reasonable. The first case of a patient with the
E515D variant and BFNS was reported in 2009.24 In this case series, the E515D variant caused a mild phenotype of BFNS: benign rolandic epilepsy or CSWS, which implies that the KCNQ2 mutation also causes cognitive damage and, therefore, is not always benign. The exact mechanism for the difference in phenotypes is unknown, but some researchers30 have hypothesized that it is an interplay of pathogenic mutations, modifier genes, and other environmental factors.

Most cases of BFNS can be controlled with oxcarbazepine, vigabatrin, and valproate.14 16 Although BFNS is believed to be benign, patients with BFNS might have cluster seizures, which inevitably require drug control. In some patients, the seizures call for second-line drugs such as valproic acid and clonazepam. More second-line drugs, e.g., topiramate, are being developed. Vigabatrin is considered more effective for KCNQ2-associated seizures, which is similar to our findings in the current case series.

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Figure 4 Membrane potential currents induced with conditioning voltage pulses to potentials between −80 mV and +40 mV using whole-cell patch-clamp analysis. The solid lines indicate the fits of the experimental data to a single Boltzmann distribution. Each point is the mean ± SE of the data recorded. (A) The current in the cells with the E515D variant (homomeric: −10 mV to −50 mV; heteromeric: −10 mV to −50 mV) was significantly (p < 0.05) lower than that in the cells with the wild-type variant. (B) Current at a conditioning voltage of −50 mV was significantly (p < 0.05) lower in cells transfected with the KCNQ2 wild-type, E515D, and wild-type KCNQ3 (1:1:2) mutants. (C) Current at a conditioning voltage of −50 mV to −30 mV was significantly (p < 0.05) lower in cells transfected with the KCNQ2 wild-type, E515D, and wild-type KCNQ3 (1:1:0.5) mutants than in cells transfected with the wild-type KCNQ2 and wild-type KCNQ3 (1:1) mutants. (D) Western blot experiments on total lysates for plasma membrane proteins, from HEK293 cells transfected with the wild-type control and KCNQ2 E515D variant. The arrows show the membranous protein expression in wild type and E515D, as indicated. *KCNQ2 mutation variants compared with wild type.4 Wild-type + KCNQ2 mutation variants (1:1) compared with wild type. WT = wild type; WT + E515D = wild type + 515D (1:1).

Additional studies of effective drug therapy using retigabine (a.k.a., ezogabine) are necessary. Retigabine, which selectively opens the Kv7 potassium channel, has not yet been approved in Taiwan, but has been reported as effective in in vitro and in vivo studies.16 The mutation variants R213Q and R213W are in the same codon, but each contains a different amino acid substitution.4 Each yields distinct outcomes: R213W causes BFNS and R213Q causes a burst-suppression EEG. However, the functional change is significantly less in the R213Q carrier than in the R213W carrier.22 One functional study22 of the V589X, T359K, and P410fs12X variants reported that P410fs12X caused the most functional damage because of cell electrophysiology. The P410fs12X mutation results in a more severe phenotype that includes hemiplegic migraine and neonatal convulsions.22 The T359K variant caused a moderate developmental delay in a 4-year-old patient. In this study, the functional change...
in R213Q was a positive control, and the results of our conductance–voltage study were similar. The different phenotypes of KCNQ2 mutations, including BFNS, neonatal epileptic encephalopathy, and benign infantile familial convulsions, might be determined by the degree of functional disability. Parental germline mosaicism, genetic modifiers, and environmental factors are also possible explanations.

Conclusions

We hypothesize that patients with the KCNQ2 E515D mutation are susceptible to seizures. KCNQ2 should be a candidate gene when diagnosing childhood epilepsy without an identified cause. Newborns or older children with the KCNQ2 mutation might present with BFNS or CSWS, and they require long-term follow-up to assess the development of their intellectual function.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2016.11.009.

References


