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ORIGINAL COMMUNICATION

# *KCNQ2* related early-onset epileptic encephalopathies in Chinese children

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## Abstract

**Objective** To study the phenotype, genotype, treatment strategies, and short-term prognosis of Chinese children with *KCNQ2* (potassium voltage-gated channel subfamily Q member 2) related early-onset epileptic encephalopathies (*KCNQ2*-EOEEs) in Southwest China.

**Methods** We used targeted next-generation sequencing (NGS) to identify *KCNQ2* variants in Chinese patients with EOEEs. And patients with *KCNQ2*-EOEEs were confirmed after clinical and genetic analyses. We followed them in our cohort and analyzed their clinical data.

**Results** 122 patients with EOEEs were registered from August 2015 to October 2017, and 78 underwent targeted NGS. Seven among them were confirmed to be caused by pathogenic *KCNQ2* variants, 6 of that were de novo and 1 was inherited. The median seizure onset age of the 7 patients was 5 days. Tonic–clonic and tonic seizures were the major seizure types; the electroencephalograms of all patients showed multifocal sharp waves initially. When new seizure types appeared in infancy, the most common type was epileptic spasm. At the last follow-up, seizures persisted in only one patient, and another patient had seizure recurrence. The identified pathogenic *KCNQ2* variants introduced amino acid missense changes, or in one instance, frameshift variant, four of which have not been reported. Valproic acid (VPA) was effective as concomitant treatment in three patients, and all patients had intellectual/developmental disabilities (IDDs).

**Conclusions** The *KCNQ2* missense variant plays an important role in EOEE pathogenesis, and patients with *KCNQ2*-EOEEs mainly present with intractable seizures and IDDs. Moreover, VPA has potential as an effective therapeutic strategy.

**Keywords** *KCNQ2* · Early-onset epileptic encephalopathies · Phenotype · Genotype · China

## Introduction

Epileptic encephalopathies (EEs) are a group of heterogeneous brain disorders occurring at a critical period of brain development, where frequent abnormal ictal (seizure) and/or interictal electroencephalogram (EEG) epileptiform activity is mainly responsible (in idiopathic epilepsies) or contributes to (in cryptogenic/symptomatic epilepsies) behavioral, cognitive, and/or motor slowing or regression [1, 2]. With the development of gene sequencing technology, genetic causes, mainly heterogeneous and de novo variants, have been identified in many different EEs [3]. Furthermore, targeted next-generation sequencing (NGS) panels increase the genetic diagnostic yield from < 10 to > 25% in patients with EEs [4]. It has been indicated that the pathogenic *KCNQ2* (potassium voltage-gated channel subfamily Q member 2) variant plays an important role in the etiology of EEs with

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genetic causes at the age of 0–3 months [3]. In the present study, we aimed to determine the pathogenic *KCNQ2* variants in a selected cohort of patients with EEs whose age of onset was < 6 months, and collected detailed clinical features of seven patients with *KCNQ2* related early-onset epileptic encephalopathies (*KCNQ2*-EOEEs). We describe the clinical and genetic features of these patients, and discuss the genotype–phenotype correlations and possible treatment options.

## Materials and methods

### Patients

A total of 122 patients with EOEEs were registered at the Children's Hospital of Chongqing Medical University, the first pediatric medical center in Southwest China, from August 2015 to October 2017. Clinical features, neuroimaging, or blood/urinary metabolic diseases screening, and normal routine karyotyping showed that these patients had no history of perinatal hypoxia, intracranial infection, or cranial trauma, and no evidence of inherited metabolic disorder or neurodegenerative disorders. Of the 122 patients, 78 underwent targeted NGS (Table S1): 15 were identified as carriers of heterozygous *KCNQ2* variants. Clinical and genetic analysis confirmed that EOEEs in seven of the 15 were due to *KCNQ2* variants (Table 1). We obtained their detailed clinical and genetic information, and performed 6–24 months' follow-up, including episodes of seizures, developmental milestones, and therapeutic regimes.

### Targeted NGS

Prior to performing the study, we obtained written informed consent from the participants, and approval from the Children's Hospital of Chongqing Medical University Ethics Committee. Genomic DNA was extracted from the peripheral blood leukocytes of the patients and 50 normal controls without epilepsy or any related history.

A custom-designed panel capturing the coding exons of 535 genes associated with epilepsy, including *KCNQ2*, was synthetized using the Agilent SureSelect Target Enrichment System (Table S2), which contains a total of 12,000 probes covering 1.285 Mbp. Targeted NGS was subsequently performed on an Illumina NextSeq 500 system (San Diego, CA, USA) with 101-bp paired-end reads to screen for variants. Multiple sequence alignments of the affected amino acids were performed using a sequence alignment program (Clustal W; The Biology Workbench, San Diego, CA, USA). Image analysis and base calling were performed using RTA (Real-Time Analysis) software (Illumina) and CASAVA software v1.8 (Illumina). Duplicate reads were marked using Picard (https://picard.sourceforge.net/index.shtml) and excluded from downstream analysis. Then, clean paired-end reads were aligned to GRCh37/hg19 (Genome Reference Consortium *Homo sapiens* [human] genome assembly GRCh37 [hg19]) with NovoAlign software (Novocraft Technologies, Selangor, Malaysia). Local realignments around small insertions or deletions (InDels) and base quality score recalibration were performed using the Genome Analysis Toolkit [5]. Single-nucleotide variants and small InDels were identified using the Genome Analysis Toolkit and were annotated using ANNOVAR (https://www.openbioinformatics.org/annovar/). The sequencing depth of these variants was more than 5 × (average, 223 ×).

After filtering the low-quality variations, clean reads were aligned to the reference hg19 through Short Oligonucleotide Analysis Package 2.21 (SOAP 2.21; soap.genomics.org.cn/soapsnp.html) to determine single-nucleotide polymorphisms (SNPs). Then, reads were realigned and InDels were detected. The identified SNPs and InDels were annotated and the candidate pathogenic variations were confirmed using the Exome-assistant tool (https://122.228.158.106/exomeassistant) and MagicViewer (https://bioinformatics.zj.cn/magicviewer/), respectively. Non-synonymous variants were evaluated using the algorithms PolyPhen-2 (https://genetics.bwh.harvard.edu/pph2/), Sorting Intolerant From Tolerant (SIFT; https://sift.jcvi.org/), Protein Analysis Through Evolutionary Relationships (PANTHER; www.pantherdb.org), VariantTaster (https://www.varianttaster.org/), and Pathogenic Variant Prediction (PMut; https://mmb.pcb.ub.es/PMut/) to determine the pathogenicity. Subsequently,

**Table 1** *KCNQ2* genotypes of patients with EOEEs

| Patient | Position | Exon | Variant | Protein | Novel/reported | Parental derivation |
|---|---|---|---|---|---|---|
| P1 | 62038584 | 15 | c.1948dupG | p.E650fs | Novel | De novo |
| P2 | 62076061 | 4 | c.641G>A | p.R214Q | Novel | De novo |
| P3 | 62070962 | 6 | c.916G>C | p.A306P | Reported | De novo |
| P4 | 62070003 | 7 | c.998G>A | p.R333Q | Reported | M |
| P5 | 62044888 | 15 | c.1678C>T | p.R560W | Reported | De novo |
| P6 | 62069982 | 7 | c.1019T>C | p.I340T | Novel | De novo |
| P7 | 62073809 | 5 | c.766G>A | p.G256R | Novel | De novo |

*EOEEs* early-onset epileptic encephalopathies, *M* mother

candidate probable pathogenic variations were confirmed after excluding variations detected in the healthy controls more than twice.

### Sanger sequencing

Sanger sequencing was performed to validate the probably pathogenic variations identified by the targeted NGS to determine the parental origin.

## Results

### Identification of pathogenic KCNQ2 variants

Seven patients with pathogenic *KCNQ2* heterozygous variants were identified: in 1 patient, the variant originated from the mother, and the other 6 were de novo. Based on the Human Gene Mutation Database (HGMD), four *KCNQ2* variants (p.E650fs, p.R214Q, p.I340T, p.G256R) were novel variants, and the other 3 were reported pathogenic variations. Four variants were located at the C-terminus proximal region, and one each in the voltage sensor S4, the extracellular loop following S5, and the S6 segment (Fig. 1). The 6 *KCNQ2* missense variants were located at the extremely conserved positions (Fig. 2), and PolyPhen-2, SIFT, and MutationTaster predicted that the novel missense variants would be damaging to protein function (Table 2). Other eight patients with EOEEs were identified as carriers of the same heterozygous *KCNQ2* variant c.A2264>G(p.Y755C), and all of them were inherited from one of the parents with normal phenotype. In addition, the clinical significance of this variation had been predicted to be benign or likely benign according to Clinvar Database (https://www.ncbi.nlm.nih.gov/clinvar/variation/129333/). This variant was consequently excluded.

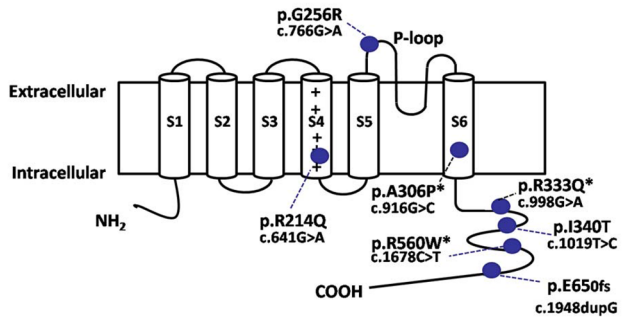


**Fig. 1** Topologic representation of a Kv7.2 subunit showing the seven transmembrane segments (S1–S6) and the intracellular N- and C-termini. Dotted line indicates the location of the variant investigated (asterisk: reported variants)

### Clinical findings

Pathogenic *KCNQ2* variants were confirmed in one patient with Ohtahara Syndrome (OS, patient 5) and six patients with unclassified EOEEs, two of whom showed transition to West Syndrome (WS, patient 1 and 6). We followed these patients from 3 months to 2 years after EOEE diagnosis, and obtained their detailed clinical information (Table 3). Five patients (patients 2, 3, 4, 6, and 7) had initial epileptic attacks within 1 week (the earliest onset was 4 h after birth). Hourly or daily tonic seizures (TS) were initially noted in five patients. Initial EEG studies showed a pattern of multifocal sharp waves in all patients, and one patient also showed burst suppression (BS) pattern EEG. Two patients had epileptic spasms (ES), and hypsarrhythmia on EEG was noted. The mother of one patient (patient 4) had epilepsy and intellectual disability. Three patients had perinatal period disorders, including fetal intrauterine distress (patient 1), meconium-stained amniotic fluid (patients 1 and 3), and premature rupture of fetal membrane (patient 6). Three showed hypermyotonia. Normal brain images were confirmed in all patients.

### Treatment and outcome

Six patients (86%) received levetiracetam (LEV) initially at the age of 10 days–4 months, at daily doses of 45–60 mg/kg/day. Five patients achieved seizure freedom with treatment with a particular antiepileptic drug (AED) (patient 4) or combinations thereof (patients 1, 2, 6, and 7). Valproic acid (VPA) was used most frequently as an add-on drug at daily doses of 30–35 mg/kg/day, and three patients achieved seizure freedom after receiving VPA (Fig. 2).

Patient 4 had daily TS (10–30 s/episode, 5–8 episodes/day) 4 h after birth, and that transformed to TSC with the same frequency at the age of 5 days. She received oral LEV (daily dose gradually increasing from 40 mg/kg to 60 mg/kg within 1 month), and seizure frequency began to reduce from the age of 5 months. Finally, she achieved seizure freedom at the age of 17 months.

Three patients (42.9%) with intractable seizures achieved seizure freedom after the addition of VPA. Patient 1 had TS (10–60 s/episode, 5–10 episodes/day) at the age of 2 months and failed to respond to LEV. Steroids were added to his treatment regimen (15 mg/kg methylprednisolone intravenously for 3 days and 4 mg/kg/day prednisone orally for 1 month) when seizure types transformed to spasms (5–10 episodes/cluster, 3–5 clusters/day) at the age of 4 months; however, the frequency of spasms did not reduce until oral VPA was administered (35 mg/kg/day) one month later. Patient 6 also had TS (15–30 s/episode, 10–20 episodes/day) 1 day after birth that did not respond to LEV. Subsequently, both steroid (15 mg/kg methylprednisolone intravenously

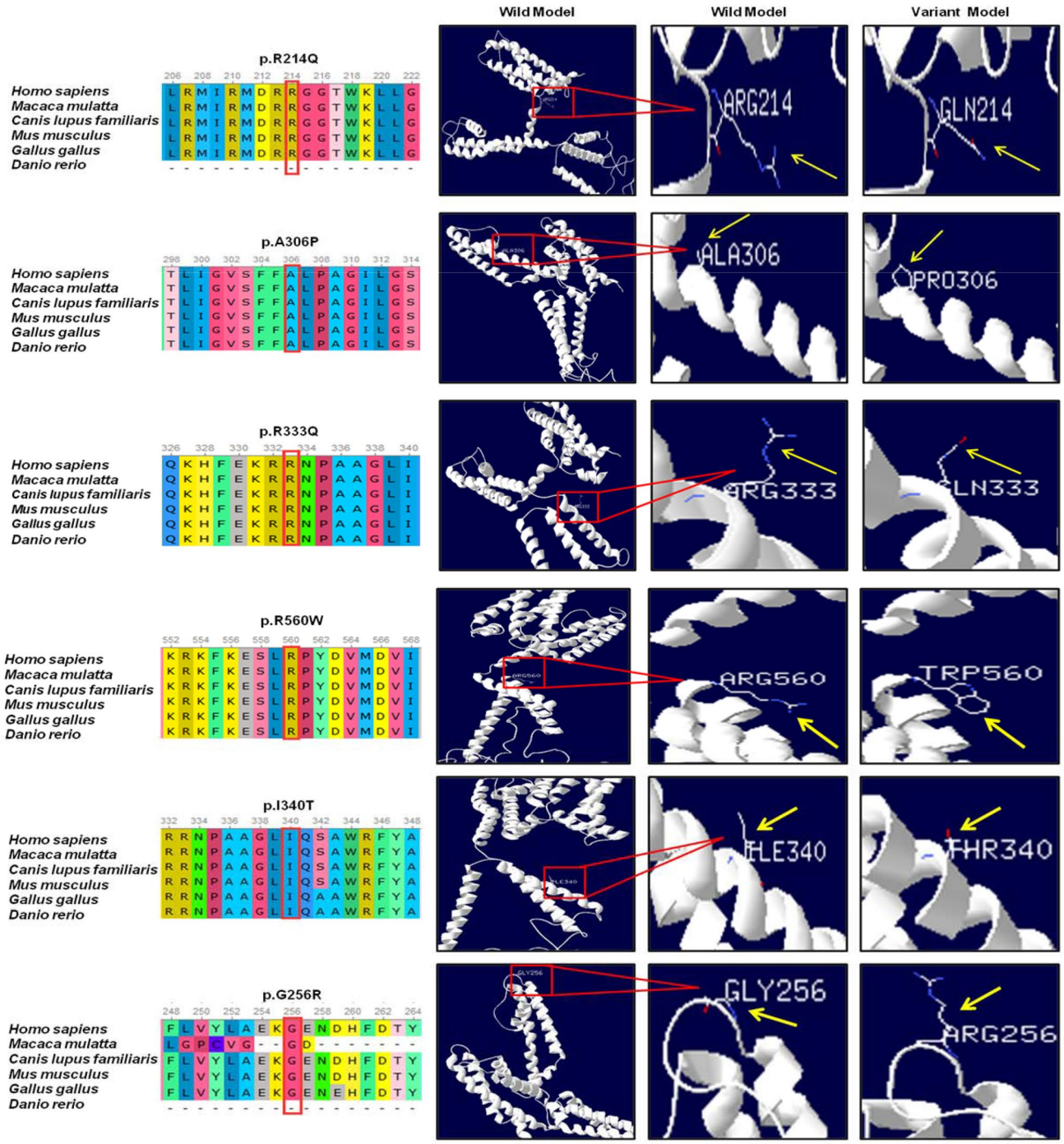


**Fig. 2** Molecular analysis of *KCNQ2* missense variants. Positions compared with the NCBI reference gene (NM_172106). Conservation of the altered amino acid was shown in the MUSCLE alignment, and Changes in protein structures were predicted in the SWISS-MODEL (arrows: the change site of the predicted protein structure)

for 3 days and 4 mg/kg/d prednisone orally for 1 month) and topiramate (TPM, gradually increased from 1 mg/kg/day to 7 mg/kg/day) were added, however, the seizure frequency did not reduce in the following 1 month until oral VPA was administered (30 mg/kg/day). Patient 2 had TS (5–10 s/episode, 3–10 episodes/day) initially and failed to respond to LEV and phenobarbital (PB, 5 mg/kg/day orally), and seizure frequency was reduced after oral VPA was administered (35 mg/kg/day) at the age of 5 months.

Patient 5 was diagnosed with OS, and did not respond to LEV and PB (5 mg/kg/day); seizure frequency was reduced from 15–20 episodes/day to 3–5 episodes/day in

**Table 2** Protein function prediction of missense variants

| Variant | Protein function | | |
|---|---|---|---|
| | SIFT | PolyPhen-2 | Mutation-Taster |
| c.641G>A, p.R214Q | D | D | D |
| c.916G>C, p.A306P[a] | D | D | D |
| c.998G>A, p.R333Q[a] | D | D | A |
| c.1678C>T, p.R560W[a] | D | D | D |
| c.1019T>C, p.I340T | D | B | D |
| c.766G>A, p.G256R | D | B | D |

SIFT: D, damaging; PolyPhen-2: B, benign; D, probable damaging; MutationTaster: A, disease-causing automatic; D, disease-causing

[a]Reported variation

the following 1 month after oral TPM was administered (6 mg/kg/day), and the patient finally achieved seizure freedom at the age of 3 months, but the seizures recurred after 5 months. Patient 7 did not respond to LEV initially and gradually achieved seizure freedom after oral PB was administered (5 mg/kg/day) at the age of one month. Only one patient (patient 3) presenting tonic–clonic seizures (TCS, 10–15 s/episode, 5–10 episodes/day) received PB (5 mg/kg/day) and LEV (60 mg/kg/day) successively in the neonatal period, and the seizure frequency was reduced to 3–5 episodes/day, but did not stop.

Six patients showed intellectual disability from moderate to profound developmental delay; one patient could walk without support (patient 4); five patients were bedridden (patients 1, 2, 5, 6, and 7). Only patient 3 showed mild developmental delay with follow-up to the age of 10 months (Fig. 3).

## Discussion

In recent years, the identification of *KCNQ2* variants has been increasingly reported [6], and the seven patients reported herein share the typical electroclinical features of *KCNQ2*-EOEEs. The hallmark of this disorder is onset of refractory seizures within the first few days of life. Seizure types are mainly TS and TCS, and often asymmetric. At onset, EEG shows multifocal epileptiform activity or a BS pattern. Here, brain imaging revealed no abnormality, as with other reports [6, 7]. Motor and cognitive deficits are evident from birth and continue with different degrees of severity in all patients.

In our study, most patients described had seizure onset in the first week of life and failed to respond to several AEDs. As the patients had been treated at different centers and had variable ages at the time of study, initial AED treatment was heterogeneous. We observed that three of the seven patients were seizure-free on VPA. In two of these patients, steroids were added when ES onset was noted at the age of 3 months, which was apparently not efficacious in the following 1 or 2 months. The remaining patient was switched to VPA following PB administration. Two patients with TS and TCS responded to TPM and LEV, and one of them received 1-month PB treatment, which failed to control the seizures. The other patient achieved seizure freedom with 17-month single LEV treatment. Moreover, only one patient had recurrent seizures during follow-up. A few reports have focused on AED treatment in *KCNQ2*-EOEEs, and carbamazepine (CBZ) and phenytoin (PHT) are considered effective [6, 8-10]. However, there is strong relationship between HLA-B alleles and CBZ-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Han-Chinese [11, 12] and the HLA-B screening method is unavailable in some medical centers. Additionally, PTH also has high risk to induce SJS and TEN as an aromatic AED [13], and small increases in dose can produce large plasma concentrations and cause clinical toxicity because of its non-linear elimination kinetics [14]. CBZ and PTH were failed to be used in this cohort. And VPA also appeared effective in our study, especially in patients who showed transition to WS, which indicates that VPA may be a potential candidate for treating *KCNQ2*-EOEEs. VPA is one of the most widely prescribed AEDs with many mechanisms of action, including enhancing inhibitory γ-aminobutyric acid-ergic (GABAergic) transmission [15], reducing neuronal depolarization by blocking calcium channels and decreasing glutaminergic transmission [16, 17], and inhibiting both tetrodotoxin (TTX)-sensitive and TTX-resistant sodium currents [18, 19]. Recently, it was reported that VPA can reduce hyperexcitability in neurons by disrupting muscarinic acetylcholine receptor-induced M-current suppression [20]. This preservation of the M-current may provide more evidence for the effectiveness of VPA for treating EOEEs caused by pathological *KCNQ2* variations. PB was added for three patients with TS or TCS, and only one patient achieved seizure freedom at the age of 2 months; furthermore, PB was once reported to respond limitedly to *KCNQ2*-EOEEs [8], suggesting the uncertainty of its effect. LEV was effective for a few cases within a multi-AEDs treatment strategy [8]. However, in the present study, five patients who initially received LEV had to take another AED to achieve seizure freedom by the median age of 6 months, and only one patient achieved seizure freedom at the age of 17 months with single LEV administration. Moreover, most patients with *KCNQ2*-EOEEs become seizure-free at a certain age independent of AED treatment [8, 21]. Therefore, the effectiveness of LEV is uncertain, and it may not be the first-line choice for *KCNQ2*-EOEEs.

Vitamin B6 (pyridoxine) was recently described as having a positive effect on seizures in a few patients with

**Table 3** Clinical features of patients with EOEEs caused by pathogenic *KCNQ2* variants

| | Sex | Age at onset | Seizure type | Age at treatment | Initial AEDs | Added AEDs | Effective AEDs | Current seizures | EEG features | Brain MRI | Development milestones | Perinatal history | Physical examination | FH |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P1 | M | 2 months | TS (2 months) | 3 months | LEV | Steroid | VPA | SF (14 months) | Multifocal sharp waves (2 months) | – (4 months) | Hold head steady/Babbles (2 years) | FIUD | Hypermyotonia (1 years) | – |
| | | | ES (4 months) | | | VPA | | | Hypsarrhythmia (4 months) | | Laugh at simple things(2 years) | MSAF | | |
| P2 | F | 7 days | TS (7 days) | 3 months | LEV | PB, | VPA | SF (7 months) | Multifocal sharp waves(3 months) | – (2 months) | Sit unsupported (16 months) | – | Hypermyotonia (1 months) | – |
| | | | | | | VPA | | | | | Babbles (16 months) | | | |
| P3 | M | 2 days | TCS (2 days) | 20 days | PB | LEV | LEV | TCS (5 months) | Multifocal sharp waves (12 days) | – (10 days) | Sit unsupported (10 months) | MSAF | – | – |
| | | | | | | | | | | – (3 months) | Babbles (9 months) | | | |
| P4 | F | 4 h | TS (4 h) | 10 days | LEV | – | LEV | SF (17 months) | Multifocal sharp waves (8 days) | – (9 days) | Stand alone/Babbles (1 years) | – | – | + |
| | | | TCS (5 days) | | | | | | | | Walk alone (17 months) | | | |
| P5 | F | 15 days | TS (15 days) | 1 months | LEV | PB | TPM | SF(3 months) | Multifocal sharp waves and | – (1 months) | Make vowel noises (14 months) | – | – | – |
| | | | TCS (20 days) | | | TPM | | TCS (8 months) | burst-suppression (1 months) | | Cannot hold head (14 months) | | | |
| P6 | F | 1 day | TCS (1 day) | 1 months | LEV | TPM | VPA | SF (6 months) | Multifocal sharp waves (15 days) | – (7 days) | Hold head steady (7 months) | PROM | Hypermyotonia (3 months) | – |
| | | | ES (3 months) | | | Steroid | | | Multifocal sharp waves (1 months) | – (3 months) | Smile at parents (4 months) | | | |
| | | | | | | VPA | | | Hypsarrhythmia (3 months) | | Focus on parents (4 months) | | | |
| P7 | M | 5 days | TS (5 days) | 20 days | LEV | PB | PB | SF (2 months) | Multifocal sharp waves (1 months) | – (1 months) | Cannot hold head (4 months) | – | – | – |
| | | | | | | | | | | | Smile at parents (4 months) | | | |
| | | | | | | | | | | | Make vowel noises (4 months) | | | |

The number in the parentheses represents the age at examination or clinical evaluation

*EOEEs* early-onset epileptic encephalopathies, *AEDs* anti-epilepsy drugs, *FH* family history, *EEG* electroencephalogram, *MRI* magnetic resonance imaging, *TCS* tonic–clonic seizures, *TS* tonic seizures, *ES* epileptic spasms, *LEV* levetiracetam, *PB* phenobarbital, *VPA* valproic acid, *TPM* topiramate, *SF* seizure-free, *FIUD* fetal intrauterine distress, *MSAF* meconium-stained amniotic fluid, *PROM* premature rupture of fetal membrane, *F* female, *M* male

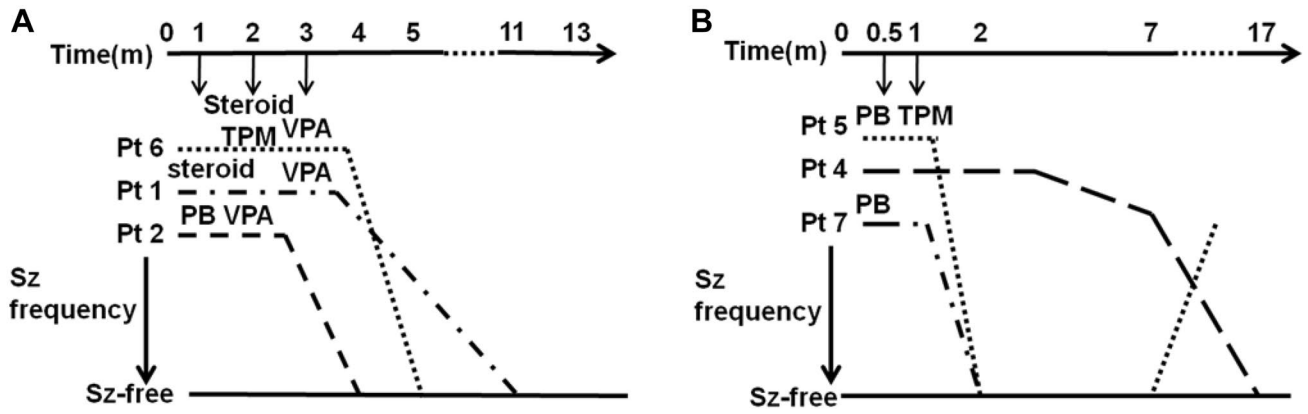


**Fig. 3** AED regimens of seizure-free patients. All patients received LEV initially. **a** Patients 1, 2, and 6 became seizure-free in the following 8, 2, and 2 months, respectively, after the addition of VPA. **b** Patient 4 became seizure-free in the following 17 months after taking LEV initially; patient 5 became seizure-free after the addition of TPM in the following 1 month, and was seizure-recurrent after 5 months; patient 7 became seizure-free in the following 1.5 months after the addition of PB (*Pt* patient, *Sz* seizure, *m* month)

*KCNQ2*-EOEEs [22]; however, the patients in our cohort had not been treated with vitamin B6. Moreover, further studies are needed to explore its antiepileptic effect. Acting as a neuronal KCNQ channel opener, retigabine has potential as an effective therapeutic strategy for *KCNQ2*-EOEEs [6, 23, 24], but has not been approved for use in pediatric patients based on the adverse effect of blue discoloration of the digits and the retina. Additionally, a recent study reported that three pathogenic *KCNQ2* variations that caused EOEEs prolonged potassium channel activation and increased the M-current, which indicates that retigabine could aggravate seizures in such patients [25].

Many studies have been focused on the genotype–phenotype correlation of *KCNQ2*-EOEEs. It has been reported that the degree of M-current inhibition may be positively correlated with the severity of the clinical phenotype [26, 27]. Even different variations of the same site can lead to different clinical phenotypes from benign epilepsy to EOEEs due to different degrees of M-current reduction [24]. It has been demonstrated that a prominent reduction of the M-current by dominant-negative mutational effects is the leading mechanism of *KCNQ2*-EOEEs [28]. However, a recent study reported that some *KCNQ2*-EOEEs could also be caused by prolonged potassium channel activation and enhanced M-current [25], that is opposite to previous reports [24, 26-28] and needs further researches. And additional mechanisms include insufficient expression of Kv7.2 subunits [29], and reduction of Kv7.2 subunits distributed in the axon initial segment [30]. Recently, it has been indicated that de novo pathogenic *KCNQ2* variations, especially those located in the voltage sensor, the pore, the C-terminus proximal region, and the calmodulin-binding B helix region, may lead to profound functional damage to the potassium ion channels and consequently result in EOEEs [24, 28]. And the variant sites we report here are concordant with those of previous reports [28, 31]. Further studies on the M-current density, expression and distribution of Kv7.2 subunits are necessary for the identification of genotype–phenotype correlation.

Our retrospective study reports seven patients with *KCNQ2*-EOEEs. We note the limitations of different treatment strategies in the series, and we report the clinical features of *KCNQ2*-EOEEs and novel pathogenic variations of *KCNQ2* in the Chinese population. Besides CBZ and PHT as the first-line choices for treating *KCNQ2*-EOEEs, VPA could be also considered, especially in patients with potential of transition to WS. Prospective clinical studies with appropriate design and further studies on genotype–phenotype correlations are warranted to aid the formulation of management strategies.

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## Compliance with ethical standards

**Conflicts of interest** None of the authors report any disclosures.

**Ethical approval** This study was approved by the Children's Hospital of Chongqing Medical University Ethics Committee.

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