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KCNQ2 pathogenic variants in early-infantile developmental and epileptic encephalopathy in Indonesia

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Abstract: Early-infantile developmental and epileptic encephalopathies (EIDEE) are characterized by developmental delays and life-threatening seizures beginning in the early infantile period. The most frequent genetic cause of neonatal epilepsy is *KCNQ2*-associated genetic epilepsy. We determined the pathogenic variant in EIDEE cases using *KCNQ2* variant screening and whole-exome sequencing (WES) approaches. The subjects were children <18 years of age with EIDEE in our hospital. We performed the *KCNQ2* pathogenic variant screening using PCR on four exons and WES in our patients. We involved six patients: three males and three females, with the patient age range between 2 and 15 months old at the time of blood sampling. One pathogenic variant in exon 6 of the *KCNQ2* gene, c.868G>A (p.Gly290Ser), was found in one patient. In addition, two synonymous SNVs were also found in our patient. Our study identifies one pathogenic variant in the *KCNQ2* gene in one EIDEE patient. These findings led us to give the patient a sodium channel blocker, which led to improved outcomes. Our study also suggests the importance of the *KCNQ2* pathogenic variant screening for selected EIDEE patients.

Keywords: *KCNQ2*; Whole-exome sequencing; Single gene test; Indonesia; Early infantile developmental; Epileptic encephalopathies.

1.0 INTRODUCTION

Early-infantile developmental and epileptic encephalopathies (EIDEE) are characterized by developmental delays and life-threatening seizures beginning in the early infantile period (up to age 3 months). Several genes have been implicated in EIDEE, including Ohtahara Syndrome and Myoclonic Encephalopathy. EIDEE is thought to affect 10 per 100,000 live births, and at least 20–30% of epileptic encephalopathies are explained by a single gene variation (Olson et al., 2017; Zuberi et al., 2022).

The most frequent genetic cause of neonatal epilepsy is *KCNQ2*-associated genetic epilepsy. About 1 in 17,000 people are thought to have hereditary epilepsy related to *KCNQ2* (Lee et al., 2021). Clinical manifestations of *KCNQ2*-associated genetic epilepsy are divided into two groups: (1) self-limited (familial) neonatal epilepsy (SeLNE) and self-limited familial neonatal-infantile epilepsy (SeLFNIE), in which drug responsiveness and developmental milestones are typically normal; and (2) EIDEE, in which conditions of developmental impairment are caused by both an underlying cause and negative effects from uncontrolled epileptic activity. Patients with *KCNQ2*-related SeLNE and SeLFNIE frequently experience seizures as newborns that generally would end on their own during an infant's first year of life; also, their prognosis is good and expected to have benign outcomes (Berg et al., 2021; Kato et al., 2013; Lee et al., 2019; Lee et al., 2021; Zuberi et al., 2022).

Patients with *KCNQ2*-Developmental and Epileptic Encephalopathies (DEE) appear with intractable seizures, poor neurological outcomes, intellectual developmental delays, multifocal spikes or interictal burst suppression on electroencephalograms (EEGs) which may progress to hypsarrhythmia. Additionally, Magnetic Resonance Imaging (MRI) examinations during the newborn era can show basal ganglia or thalamic MRI signal abnormalities, while mild frontal lobe atrophy and a thin corpus callosum have also been recorded (Kato et al., 2013; Lee et al., 2019; Lee et al., 2021; Zuberi et al., 2022). After diagnosis, sodium channel blockers are the treatment of choice for *KCNQ2*-associated genetic epilepsy (Lee et al., 2021). First-line medications such as phenobarbital frequently fail to control *KCNQ2*-DEE seizures in newborns, but according to several studies, oxcarbazepine and phenytoin were found to be effective in treating *KCNQ2*-DEE. Oxcarbazepine, however, is infrequently prescribed by doctors as the first treatment for neonatal refractory seizures (Lee et al., 2021).

Early diagnosis and timely seizure therapy are associated with improved long-term neurodevelopmental outcomes (Lee et al., 2021). Clinical characteristics, typically EEG results, age at which seizures begin, family history, and genetic testing can all help to support the diagnosis (Lee et al., 2019). Next-generation sequencing (NGS) is now used as the first line for genetic testing in EIDEE. However, a *KCNQ2* pathogenic variant screening might be used for selected EIDEE patients (Lee et al., 2021). In Indonesia, no prior study has attempted to gain insight into the pathogenic variant of *KCNQ2* in epilepsy. We determined the pathogenic variant in EIDEE cases using *KCNQ2* variant screening and whole-exome sequencing (WES) approaches.

2.0 MATERIALS AND METHODS

2.1 Sample requirements

The study subjects were children <18 years of age with the following inclusion criteria: (1) developmental epileptic encephalopathy; (2) onset of the first seizure in neonates diagnosed by a neuro-pediatrician; (3) the most common seizure type is tonic, myoclonic, and/or focal seizures; (4) seizures occur several times a day and increasingly frequent in the first year of life; and (5) EEG showed burst suppression or hypsarrhythmia.

Sample recruitment was conducted at Dr. Sardjito General Hospital from April until October 2022. Fourteen patients met the inclusion criteria. We collected detailed clinical symptoms, perinatal and family history, comorbidities, disease progression characteristics, developmental status, and relevant clinical testing such as EEG and MRI. Six patients with the typical symptoms associated with *KCNQ2*-associated genetic epilepsy were chosen for genetic testing by pediatric neurologists after reviewing all patients' clinical seizure semiology, EEG data, and brain imaging reports. All six patients underwent a *KCNQ2* variant screening, and three underwent a WES examination.

2.2 Genetic examination

2.2.1 Genomic DNA extraction, polymerase chain reaction (PCR), and direct sequencing

Genomic DNA was extracted from peripheral whole blood samples using a DNA extraction kit (Qiagen QiAmp DNA Mini Kit). All the extracted DNA was stored at -20°C until analysis. Four out of 19 exons of the *KCNQ2* gene were amplified using a PCR for each patient. We examined four exons that are the hotspot for pathogenic variants in the *KCNQ2* gene, i.e., exons 4, 5, 6, and 7 (Fang et al., 2019; Lee et al., 2019; Olson et

al., 2017). The primer sequences for the *KCNQ2* gene analysis were designed according to a previous study (Lee et al., 2017).

Direct sequencing was performed using a BigDye® Terminator V3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) and a genetic analyzer (ABI Prism 310; Applied Biosystems), with DNA Sequencing Analysis Software (Applied Biosystems).

2.2.2 Whole exome sequencing (WES)

The whole exome sequencing (WES) procedure was conducted on the three patients that met the *KCNQ2* criteria more suitably, as determined through the discussion among the researchers. WES was performed by 3Billion Inc. (Seoul, Korea) following the specified protocols (Richards et al., 2015; Seo et al., 2020). Exome capture was carried out using xGen Exome Research Panel v2 (Integrated DNA Technologies, Coralville, Iowa, USA), and sequencing was done using NovaSeq 6000 (Illumina, San Diego, CA, USA). The mitochondrial genome was sequenced. A total of 16,167,756,344 bases were generated and uniquely aligned to the Genome Reference Consortium Human Build 37 (GRCh37) and Revised Cambridge Reference Sequence (rCRS) of the mitochondrial genome.

The sequencing produced a mean depth-of-coverage of 224.15 within the captured region's 34,366,188 bases, equivalent to about 99.3% of the RefSeq protein coding region. The targeted bases were covered to a depth of 20x on about 99.10% of them. Information on the depth of coverage at the gene or exon level is available upon request. A total of 11,766 minor insertions and deletions (indel) and 68,232 single nucleotide variations (SNV) were found. These parameters are consistent with high-quality exome sequencing data and are deemed appropriate for analysis despite the poor coverage across 0.90% of the bases.

2.2.3 Variant interpretation

For the WES examination, variant interpretation was done using the 3Billion's developed software EVIDENCE (Seo et al., 2020), based on the guidelines recommended by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (Richards et al., 2015), in the context of the patient's phenotype, pertinent family history, and prior test results provided by the ordering physician.

2.2.4 Data analysis

The descriptive presentation of data compiled from samples included clinical data, genetic testing results, variants interpretation, and variant data. Everyone who participated in the investigation agreed on the final interpretation of the genetic variation finding.

2.3 Research ethics

Our research followed the criteria of medical ethics and was accepted by The Institutional Review Board of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital (KE/FK/1190/EC/2021). The authors confirm that the patient's parents, who had received medical care in our institution, gave their full informed consent. Authors reporting experiments on humans and/or using human tissue samples/human data must confirm that all experiments were performed per relevant guidelines and regulations.

3.0 RESULTS

3.1 Characteristics of the patients

A total of six patients with global developmental delays and the onset of the first seizure <1 month were analyzed for *KCNQ2* variants. Three males and three females were included in the study, with the range of the patient's age at the time of blood sampling between 2 and 15 months old. The phenotype and genotype data of the patients are summarized in **Table 1**. EEG was performed in all patients, and the majority of them had abnormal epileptiform discharge, and three of the six patients had burst suppression patterns (**Figure 1**).

3.2 Genetic testing results

3.2.1 KCNQ2 pathogenic variant screening

In the *KCNQ2* pathogenic variant screening, we found one patient (patient 6) with a pathogenic variant in exon 6, c.868G>A (p.Gly290Ser) (**Figure 2**). Besides that, we also found synonymous single-nucleotide variants (sSNVs); one patient (patient 1) in exon 5 (dbSNP: rs370174915) and all patients in exon 6 (dbSNP: rs2297385) (**Figure 2**).

3.2.2 WES findings

One patient (patient 6) with the WES examination showed a heterozygous variant in exon 6 of the *KCNQ2* gene, c.868G>A (p.Gly290Ser). The patient's genotypes and inheritance pattern were verified using Sanger sequencing (**Figure 3**). Subsequently, it was established that the patient had a *de novo* variant. This variant was previously reported as pathogenic (dbSNP: rs1057516098). Moreover, WES did not find any pathogenic variant in the other two patients.

Table 1. Genotype and phenotype of patients.

Patient Number	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Variant	c.912C>T c.754T>C	c.912C>T	c.912C>T	c.912C>T	c.912C>T	c.912C>T c.868G>A
Amino acid change	(p.Phe304=) (p.Leu252=)	(p.Phe304=)	(p.Phe304=)	(p.Phe304=)	(p.Phe304=)	(p.Phe304=) (p.Gly290Ser)
Type	Synonymous variant	Synonymous variant	Synonymous variant	Synonymous variant	Synonymous variant	Synonymous and missense variant
Family variant	NA	NA	NA	NA	NA	*de novo*
Sex	Male	Female	Female	Male	Female	Male
Genetic study	*KCNQ2* screening	*KCNQ2* screening	*KCNQ2* screening	*KCNQ2* screening and WES	*KCNQ2* screening and WES	*KCNQ2* screening and WES
Age at first seizure	Day 5	Week 3	Day 2	Day 2	Month 1	Day 1
Seizure type	General tonic, spasm	Focal, spasm	General tonic clonic, spasm	General tonic, absence, focal	General tonic clonic, focal, spasm	General tonic
EEG finding	Diffuse slowing and low amplitude	Epileptiform discharges	Burst suppression pattern	Generalized epileptiform discharges	Hypsarrhythmia pattern	Asymmetrical, abnormal epileptiform
Drug	Phenobarbital, clonazepam	Phenobarbital	Valproic acid, phenobarbital	Valproic acid	Valproic acid, Phenobarbital, carbamazepine	Valproic acid, Phenobarbital, carbamazepine, levetiracetam
MRI/CT	Hyperintense in basal ganglia	Cerebral atrophy	Cerebral atrophy	Cerebral atrophy	NA	Cerebral atrophy

NA = Not Available

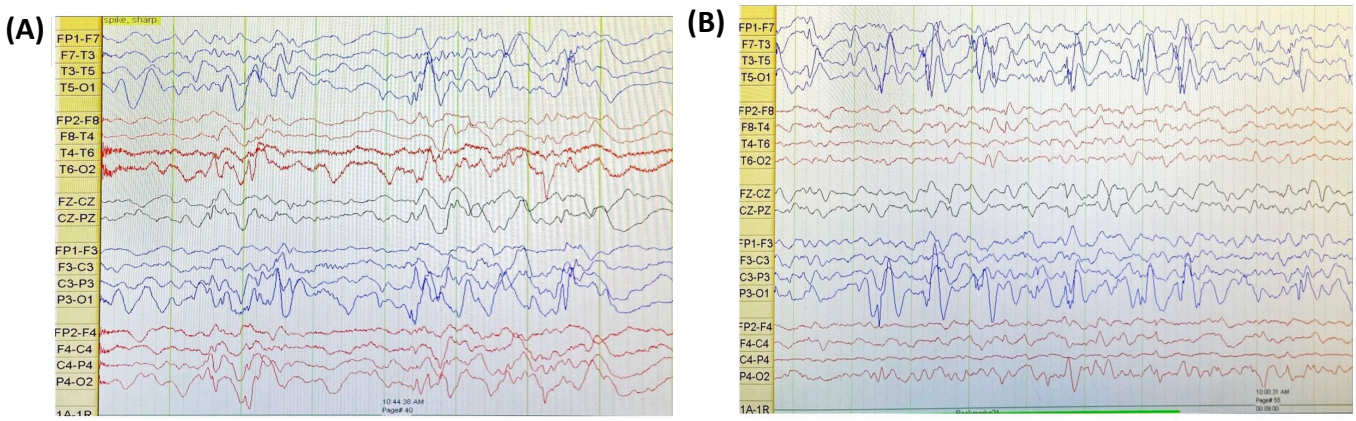

Figure 1. EEG showed a pattern of (A) generalized epileptiform discharges (patient 4); and (B) focal epileptiform discharges at the left temporoparietal region (patient 6).

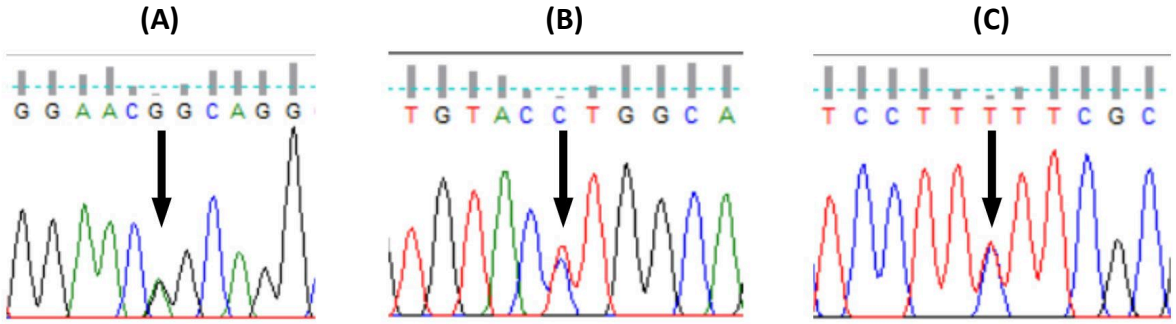

Figure 2. Sanger sequencing from *KCNQ2* variant screening: (A) pathogenic variant in patient 6; and (B) sSNVs at exon 5 in patient 1; and (C) exon 6 in patients 1 – 6.

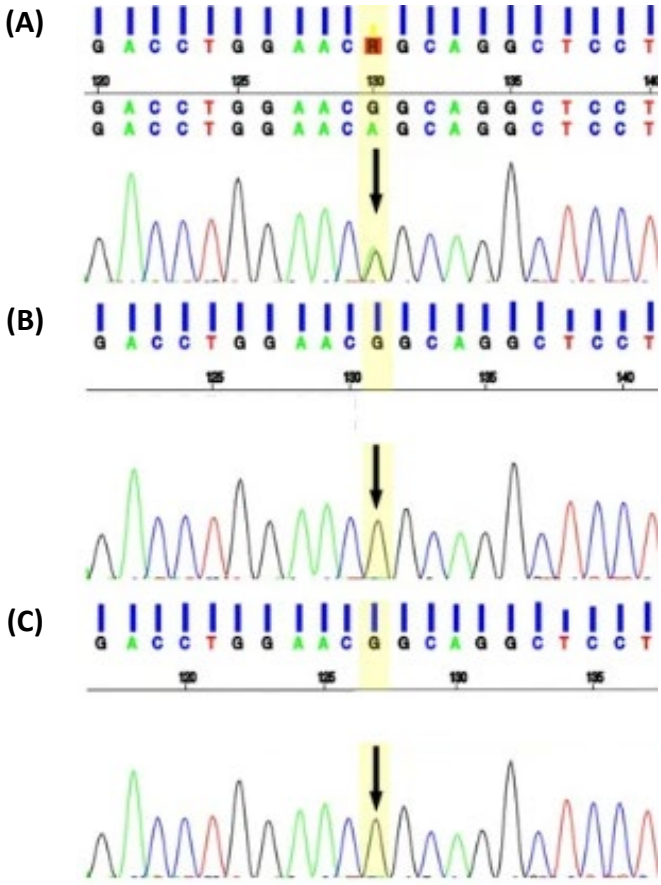

Figure 3. The genotypes and inheritance pattern of patient 6 were verified using Sanger sequencing. (A) Patient's Sanger sequencing. (B) Patient's mother's Sanger sequencing. (C) Patient's father's Sanger sequencing.

4.0 DISCUSSION

KCNQ2-associated genetic epilepsy is the most frequent genetic epilepsy in neonates (Lee et al., 2021). We identified 1 of 6 patients with the *KCNQ2* pathogenic variant. To our knowledge, this is the first documented case of the *KCNQ2* pathogenic variant from Indonesia. The pathogenic variant was a missense variant of the *KCNQ2* gene with a single substitution in exon 6, leading to the change of glycine into serine at position 290 (p.Gly290Ser). The KCNQ2 variant is associated with autosomal dominant, and in most cases, it is de novo, as in our patient. Missense variants are the most common of the *KCNQ2* variants reported in EIDEE; meanwhile, frameshift or nonsense variants are more frequently found in patients with benign outcomes (Kato et al., 2013).

In the *KCNQ2* variant screening, we examined four exons, i.e., exons 4, 5, 6, and 7. We found a pathogenic variant in one patient on exon 6, but no pathogenic variants were found in exons 4, 5, and 7. Our findings should be cautiously interpreted since we cannot exclude other variants in the *KCNQ2* gene because there is still the possibility of pathogenic variants in the other 15 exons.

Subsequently, we performed a WES on three patients. We found the same pathogenic variant in the *KCNQ2* gene in patient 6; however, we failed to identify any pathogenic variant in the other two patients.

In addition, we found two sSNVs in our patients. Although these variants were previously reported as benign/likely benign, previous studies have revealed that sSNVs are connected to 1% of human disorders or can be as harmful as non-synonymous variants (Zeng & Bromberg, 2019; National Center for Biotechnology Information, n.d.-a, n.d.-b). A variant may appear synonymous, but it might fundamentally impact the DNA, RNA, and/or protein level. sSNVs can interfere with essential functions, including transcription,

splicing, co-translational folding, and mRNA stability (Zeng & Bromberg, 2019).

Furthermore, sSNVs can lead to incorrect exon-intron boundary identification and change the pre-affinity mRNAs for spliceosomes, which can produce aberrant mRNAs and defective proteins. However, there are relatively few reports of sSNVs' impact in the literature (Zeng & Bromberg, 2019). A functional study is necessary to prove the impact of sSNVs on our patient's phenotype.

In more than 60% of *KCNQ2*-DEE, the EEG shows a burst suppression pattern, which can occasionally be asymmetrical. It may be possible to notice multifocal anomalies, including spikes, sharp waves, and hemispheric suppression (Zuberi et al., 2022). Three patients in our study showed a burst suppression pattern. Missense variants in the *KCNQ2* gene might cause a burst suppression in patient 6 (Olson et al., 2017).

The drug of choice for *KCNQ2*-associated genetic epilepsy includes sodium channel blockers for both benign and EIDEE groups. In the benign group, one-third of patients may achieve spontaneous seizure remission (without medication), and phenobarbital may be considered. *KCNQ2*-DEE approaches with phenobarbital as monotherapy did not reduce seizure frequency and seemed ineffective (Kuersten et al., 2020). Sodium channel blockers (e.g., carbamazepine, phenytoin, and levetiracetam) are the first-line therapy in *KCNQ2*-DEE. These drugs that target sodium channels stop the sodium ions from passing through the channels during the propagation of the action potential, preventing the onset of seizures. Voltage-gated sodium channels and KCNQ potassium channels, which appear to be unrelated, co-localize and are bound in crucial regions of the neuronal membrane (Pisano et al., 2015). Patient 6 previously received phenobarbital and valproic acid as antiepileptic drugs (AED). However, the seizures were still not resolved. After the *KCNQ2* pathogenic variant was found in this patient, we changed the treatment to carbamazepine. Subsequently, the frequency of seizures in this patient declined.

Several weaknesses of our study were noted, including 1) small sample size, 2) sampling based on physicians' decisions, 3) a *KCNQ2* variant screening was only on four of 17 exons, and 4) WES was performed in only three patients.

5.0 CONCLUSIONS

Our study identifies one pathogenic variant in the *KCNQ2* gene in one EIDEE patient. These findings led us to give the patient a sodium channel blocker, and the patient outcomes were improved. Our study also suggests the usefulness of the *KCNQ2* pathogenic variant screening for selected EIDEE patients.

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Conflicts of Interest: The authors declare no conflict of interest.

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