

# Case Report

## Two Cases of KCNQ2 Encephalopathy

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**Abstract** KCNQ2 encephalopathy is increasingly recognised as one of the causes of early infantile epileptic encephalopathy (EIEE). We report two cases of KCNQ2 encephalopathy, presenting as neonatal-onset seizures refractory to multiple anti-epileptic medications. The diagnosis was confirmed by epilepsy EIEE gene panel, which analyses hundreds of epilepsy-related genes. The EIEE gene panel is a useful diagnostic tool in patients with early-onset intractable epilepsy.

**Key words** *CHRNA4; Epilepsy; Epileptic encephalopathy; KCNQ2*

### Introduction

KCNQ2 encephalopathy is increasingly recognised as one of the causes of early infantile epileptic encephalopathy (EIEE). We describe two patients with KCNQ2 encephalopathy, presenting as neonatal-onset intractable epilepsy. With the aid of epilepsy gene panel, the diagnosis of KCNQ2 encephalopathy was confirmed.

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### Case 1

The first case was a female baby of a non-consanguineous Chinese couple. She was born at 38 weeks gestation by emergency Caesarean section due to failed induction. Her birth weight was 2.92 kg. Antenatal and perinatal history were otherwise unremarkable. Regarding her family history, the patient's paternal aunt had one episode of convulsion in her teenage. She did not have medical treatment or follow-up for her seizure, and there was no recurrence.

The baby first presented with unstable temperature and convulsion on Day 3 (71 hours) of life. The semiology was focal tonic and clonic seizures, presenting as rhythmic limb twitching, increased limb tone, eye deviation, versive head movements and cyanosis. These seizures lasted for less than a minute and occurred up to 5 times per day. Physical examination found a lethargic baby with generalised hypotonia and weak suckling reflex.

She was given intravenous phenobarbitone, which resulted in transient seizure control. Metabolic investigations, including plasma ammonia, plasma and cerebrospinal fluid lactate, plasma amino acids, acylcarnitine profile and urine organic acids were unremarkable. Cerebrospinal fluid culture and viral study did not reveal an infective aetiology. Cerebrospinal fluid neurotransmitter study did not point to a specific diagnosis. Electroencephalogram (EEG) on Day 4 of life (Figure 1)

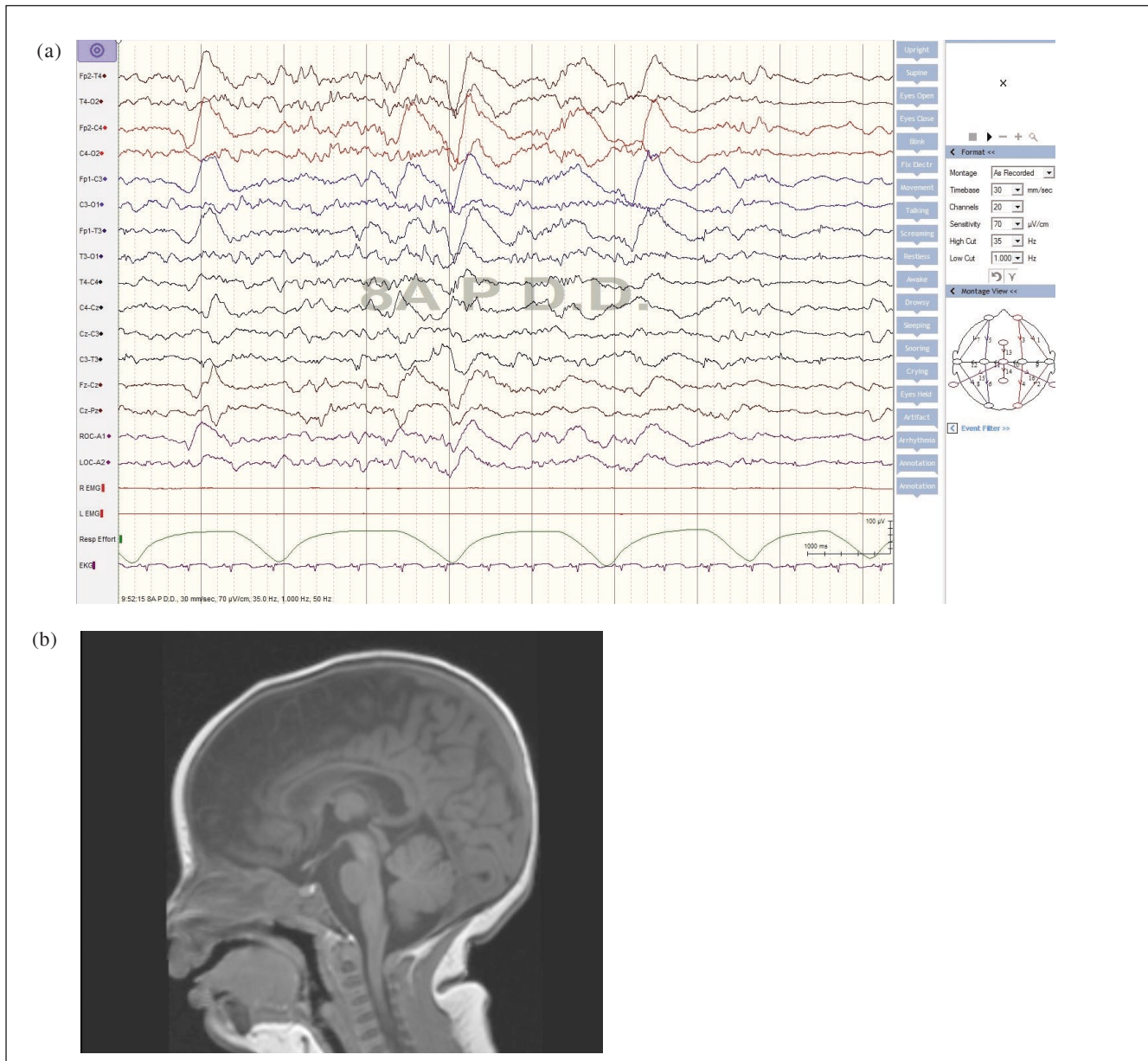
showed no evidence of electrographic seizures or burst-suppression pattern. The background was symmetrical and synchronous. The baby still had occasional seizures while she was put on phenobarbitone, hence the treatment was changed to levetiracetam and topiramate subsequently.

She was admitted to the paediatric intensive care unit of another hospital at 2 months of age for status epilepticus. EEG at that admission showed multifocal discharges and an episode of electrographic seizure originating from the left temporal region. Phenobarbitone

was reintroduced, and the dosage of levetiracetam was increased. Her seizure control had improved since.

Magnetic Resonance Imaging (MRI) scan of the brain performed at 2 months of age showed mild thinning of corpus callosum and benign enlargement of subarachnoid space.

EIEE gene panel identified a heterozygous mutation of KCNQ2. A novel missense variant of KCNQ2 gene NM\_172107.3:c.1691T>G p.(Val564Gly) was detected in the patient. The nucleotide substitution from thymine to



**Figure 1** (a) EEG of Case 1 performed on Day 4 of life (sensitivity 70 µV/cm); (b) MRI brain (T1W coronal cut) of Case 1, showing mild thinning of the genu and body of corpus callosum, which measures about 1.8 mm in thickness.

guanine resulted in a change in the amino acid sequence of the *KCNQ2* gene. Sanger sequencing did not identify the mutation in either parent, suggesting that it was a *de novo* variant. Multiple *in silico* prediction tools (including PolyPhen-2) suggested that this mutation was damaging and affected normal protein function. The variant was absent from population control exomes and genomes. Hence this missense mutation was determined to be likely pathogenic. To our knowledge, this missense mutation has not been reported in the literature.

This patient was last seen in the outpatient clinic at 12 months of age. She had a mild degree of developmental delay, in terms of her gross motor and fine motor aspects. She was able to walk with support, reach out for objects and make monosyllabic babble. She still had occasional brief seizures, often triggered by febrile illnesses, while she was receiving phenobarbitone, levetiracetam and topiramate.

## Case 2

The second case was a female baby of a non-consanguineous Chinese couple. She was born at 39 weeks gestation by vacuum extraction due to prolonged second stage of labour. Her birth weight was 3.1 kg. Her antenatal and perinatal history were otherwise unremarkable. She was referred to our unit as she presented with multifocal clonic seizures on Day 2 (46 hours) of life. These seizures manifested as twitching of four limbs, followed by apnoea and oxygen desaturation. Her seizures were controlled with intravenous phenobarbitone. Physical examination showed normal limb tone with no sign of encephalopathy or focal deficits. Cerebrospinal fluid study did not show evidence of central nervous system infection. Metabolic investigations, including serum lactate, ammonia, biotinidase, plasma amino acid and urine organic acids were unremarkable. Cerebrospinal fluid lactate was normal. EEG performed on Day 10 of life was unremarkable, with a continuous and symmetrical background. No electrographic seizure or burst-suppression pattern were captured.

She developed frequent focal-onset seizures at 3 months of life. The semiology differed from initial presentation, and the seizures manifested as eye deviation, increased upper limb tone, focal limb twitching with variable laterality, as well as altered consciousness. These seizures were frequent and occurred up to 10 times per day. Phenobarbitone was replaced with levetiracetam. Sodium valproate and oxcarbazepine were subsequently added over the following months in hope of better seizure control.

MRI scan of the brain at 4 months of age was unremarkable apart from benign enlargement of subarachnoid space in infancy.

Genetic workup of this patient showed a *de novo* gross deletion of the genomic region over chromosome 20 q13.33 by an epilepsy gene panel testing using next generation sequencing of DNA sample extracted from blood. The finding was confirmed by array comparative genomic hybridisation analysis. Using postnatal DNA Chip (v1.0), a copy number loss of 20 q13.33 with 317 kb in size was detected. This *de novo* deletion of this genomic region encompassed 6 genes including partial *KCNQ2* gene (exons 8-17) and the entire *CHRNA4* gene, which was implicated in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). This deletion was expected to create a truncated protein or disrupt mRNA translation. The same variant was not reported in the literature. However, sub-genic deletions of exons 9-17 and 13-17 were reported as pathogenic. The variant of our case had encompassed the whole reported pathogenic variant, and therefore it was expected to be pathogenic.

In addition to this, a copy number gain of Xp22.31 of approximately 1.2 Mb in size was also detected, and this duplication was inherited from her asymptomatic mother. Since her mother was unaffected clinically, this variant was analysed as unknown clinical significance.

Our patient achieved seizure freedom at 8 months of age with oxcarbazepine and sodium valproate. EEG performed at 23 months of age showed occasional sharp waves arising from the right frontal and central regions (Figure 2). Nevertheless, she was able to wean off oxcarbazepine at 2 years of age, and she remained seizure-free on sodium valproate monotherapy for more than 2 years. She did not exhibit features suggestive of nocturnal frontal lobe epilepsy.

She was assessed to have mild developmental delay by the Child Assessment Centre at the age of 22 months, and she made good progress with the multi-disciplinary support from Early Education and Training Centre.

## Discussion

*KCNQ2* encodes the voltage-gated potassium channel subunit Kv7.2. Its mutations are known to be associated with benign familial neonatal seizures and EIEE. Benign familial neonatal seizures typically present in the first week of life. The median age of seizure onset is 3 days.<sup>1</sup> A family history of seizure is often obtained, as the disease is inherited in an autosomal dominant manner. It carries a

good prognosis as seizures spontaneously remit in the first year of life. The risk of subsequent epilepsy was reported to be 16%, and the chance of neurocognitive impairment did not appear to be increased.<sup>2</sup>

Recently, there are increasing reports of KCNQ2 mutations associated with neonatal onset EIEE.<sup>3,4</sup> EIEE is characterised by frequent intractable seizures, presence of encephalopathy and delayed development.

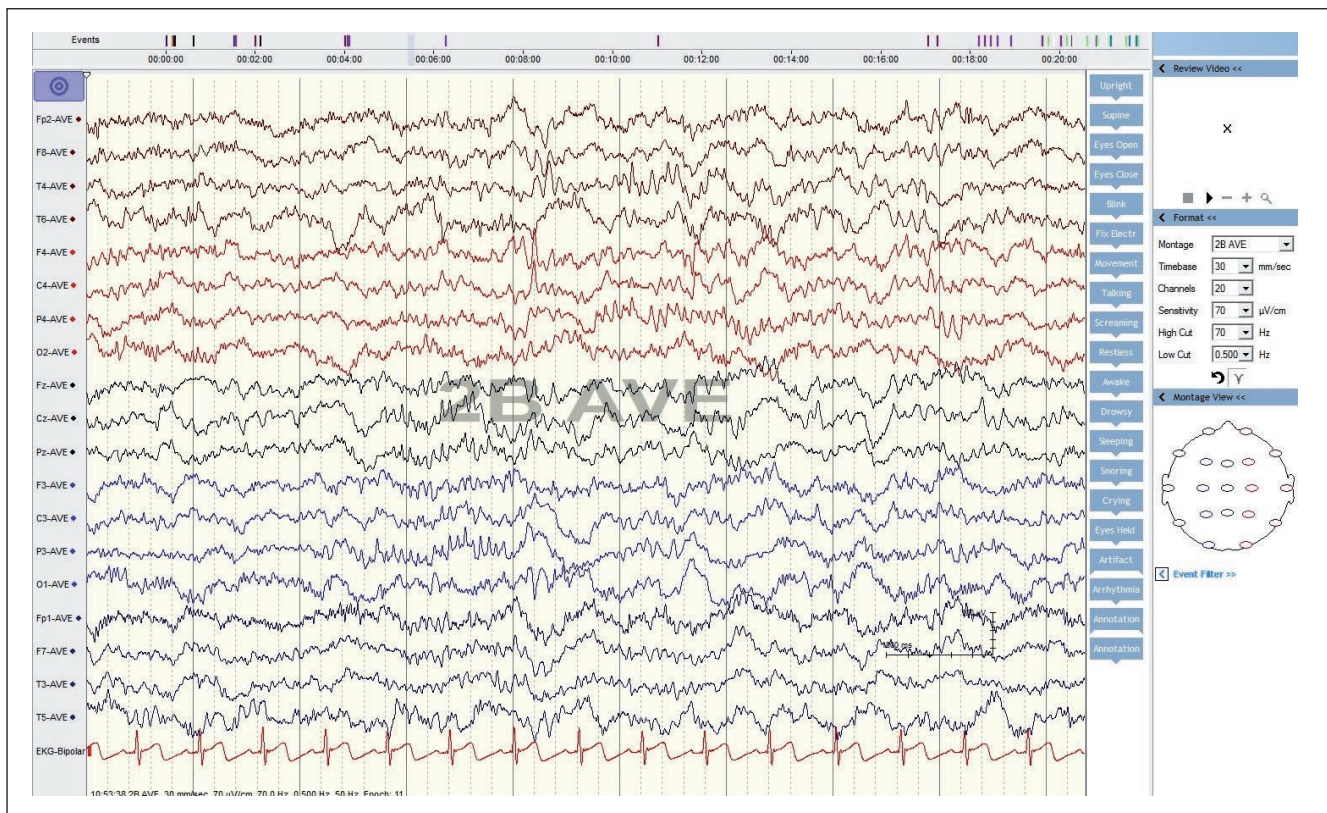
The genetic characteristics of benign familial neonatal seizures and early infantile epileptic encephalopathy were analysed in a study involving 259 patients with KCNQ2 variants.<sup>5</sup> It showed that most of the patients with benign familial neonatal seizures had truncating mutations (such as frameshift or nonsense mutations), whereas most of the patients with epileptic encephalopathy had missense mutations. Also, the majority of KCNQ2 variants in benign familial neonatal seizures were inherited, whereas the majority of KCNQ2 variants in KCNQ2 epileptic encephalopathy were *de novo* mutations.<sup>3,5</sup>

KCNQ2 epileptic encephalopathy presents as neonatal-onset seizures, usually within the first three days of life.<sup>4</sup>

Reported cases are usually term infants with no particular gender predilection. Family history of seizures may be present. Tonic seizures are most often reported, and other seizure types reported include focal seizures, myoclonic seizures and epileptic spasms.<sup>3</sup> These seizures are invariably frequent in the neonatal period and early infancy. They occur multiple times daily, and are refractory to anti-epileptic treatment.<sup>4</sup>

EEG of patients with KCNQ2 encephalopathy performed in the first week of life may show burst-suppression, dysmaturity, or no abnormal findings.<sup>3,4</sup> Follow-up EEGs at older age may show multifocal epileptiform discharges, background slowing or disorganisation, or hypsarrhythmia.<sup>4</sup> Our first patient did not have significant EEG abnormality, and the EEG of the second patient showed infrequent focal sharp waves, which are not specific to KCNQ2 encephalopathy.

MRI scans may show diffuse cerebral atrophy, thin corpus callosum, periventricular increased white matter signal, or hyperintensities at globus pallidus or thalamus.<sup>3,4,6</sup> In fact, thinning of the corpus callosum was



**Figure 2** EEG of Case 2 (sensitivity 70  $\mu$ V/cm) showing sharp wave arising from right frontal and central regions.

noted in our first patient.

KCNQ2 encephalopathy is associated with variable degrees of developmental impairment. In a group of 17 patients with KCNQ2 encephalopathy, the percentages of patients with mild to moderate intellectual disability and severe intellectual disability were 29% and 59% respectively.<sup>7</sup> KCNQ2 encephalopathy patients often experience comorbidities such as spastic quadriplegia, dystonia and oro-motor dysfunction.<sup>4</sup> For the two cases we described, a mild degree of developmental delay was observed.

Contiguous deletion of KCNQ2 and CHRNA4, which is the case in our second patient, has been reported to follow a similar clinical course as KCNQ2 encephalopathy caused by missense mutations.<sup>8</sup> These patients presented with neonatal seizures and subsequent developmental delay. Family history of neonatal seizures was sometimes present. These patients did not develop ADFLE phenotype associated with CHRNA4 mutation.<sup>8</sup>

It was reported that up to 65% of KCNQ2 encephalopathy patients became seizure-free between the age of 1 month and early adolescence.<sup>7</sup> Nevertheless, seizures in this group of patients could be difficult to control despite multiple antiepileptic drugs. There are reports showing that carbamazepine and phenytoin, both sodium channel blockers, are effective in achieving seizure reduction or even freedom in KCNQ2 encephalopathy.<sup>6,9</sup> Since the voltage-gated sodium channels and KCNQ2 potassium channels are located in proximity at the neuronal membrane, it is postulated that the modulation of sodium channel may affect the function of the potassium channel as well.<sup>6</sup> For our two cases, sodium valproate, oxcarbazepine, levetiracetam and topiramate appeared to be effective in achieving seizure control.

We report two cases of KCNQ2-related EIEE, presenting as neonatal-onset intractable epilepsy, encephalopathy, and developmental delay. The clinical presentation and EEG changes represented the milder end of the spectrum of KCNQ2 encephalopathy. Further studies are needed to determine the genotype-phenotype correlation.

The EIEE gene panel employs Next Generation Sequencing, and targets at hundreds of genes implicated in EIEE, various genetic epilepsy syndromes, as well as neurometabolic disorders commonly causing intractable epilepsy. When applied to patients with EIEE, the

diagnostic yield was reported to be about 34%.<sup>10</sup> It is crucial to establish a genetic diagnosis early, as it guides clinicians on the selection of antiepileptic medications. In the case of KCNQ2 encephalopathy, sodium channel blockers are reported to be more effective in seizure control.<sup>6,9</sup> Making a genetic diagnosis can also better inform the clinicians and caregivers of the anticipated clinical course and prognosis of individual patients.

For patients presenting with drug-resistant epilepsy in the neonatal period, especially if their cranial imaging and metabolic investigations do not reveal a cause, clinicians should consider EIEE gene panel in obtaining a genetic diagnosis.

## Conflict of Interest

The authors have no conflicts of interest to disclose.

## References

1. Grinton BE, Heron SE, Pelekanos JT, et al. Familial neonatal seizures in 36 families: Clinical and genetic features correlate with outcome. *Epilepsia* 2015;56:1071-80.
2. Ronen GM, Rosales TO, Connolly M, Anderson VE, Leppert M. Seizure characteristics in chromosome 20 benign familial neonatal convulsions. *Neurology* 1993;43:1355-60.
3. Kato M, Yamagata T, Kubota M, et al. Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. *Epilepsia* 2013;54:1282-7.
4. Millichap JJ, Park KL, Tsuchida T, et al. KCNQ2 encephalopathy. *Neurol Genet* 2016;2:e96.
5. Goto A, Ishii A, Shibata M, Ihara Y, Cooper EC, Hirose S. Characteristics of KCNQ2 variants causing either benign neonatal epilepsy or developmental and epileptic encephalopathy. *Epilepsia*. 2019;60:1870-80.
6. Pisano T, Numis AL, Heavin SB, et al. Early and effective treatment of KCNQ2 encephalopathy. *Epilepsia* 2015;56:685-91.
7. Weckhuysen S, Ivanovic V, Hendrickx R, et al. Extending the KCNQ2 encephalopathy spectrum: Clinical and neuroimaging findings in 17 patients. *Neurology* 2013;81:1697-703.
8. Pascual FT, Wierenga KJ, Ng YT. Contiguous deletion of KCNQ2 and CHRNA4 may cause a different disorder from benign familial neonatal seizures. *Epilepsy Behav Case Reports* 2013;1:35-8.
9. Numis AL, Angriman M, Sullivan JE, et al. KCNQ2 encephalopathy: Delineation of the electroclinical phenotype and treatment response. *Neurology* 2014;82:368-70.
10. Na JH, Shin S, Yang D, et al. Targeted gene panel sequencing in early infantile onset developmental and epileptic encephalopathy. *Brain Dev* 2020;42:438-48.