



# KCNQ2-Associated Epilepsy: A Review of Variable Phenotypes and Neurodevelopmental Outcomes

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## Abstract

*KCNQ2* mutations can cause benign familial neonatal convulsions (BFNC), benign familial infantile convulsions (BFIC), and neonatal epileptic encephalopathy. *KCNQ2*-associated seizures usually manifest during the first week of life. Some affected children will have recurrent febrile seizures, benign childhood epilepsy with centrotemporal spikes (BCECTS), or idiopathic generalized epilepsy on follow-up. However, the outcomes in these patients cannot be accurately predicted. We reviewed the phenotypes, and genotypes of the *KCNQ2* mutation, pathophysiological mechanisms and drug treatments for *KCNQ2*-associated epilepsy. We conclude that *KCNQ2* mutations can cause various epileptic phenotypes and different neurodevelopmental outcomes in children.

## Keywords

Phenotype, Genotype, Neonatal, Seizure, Neurodevelopmental, Outcome

## Introduction

*KCNQ2* encodes for voltage-gated potassium channel subunits that underlie the M-current, a repolarizing current that limits repetitive firing during long-lasting depolarizing inputs [1-3]. *KCNQ2* mutations can contribute to benign familial neonatal convulsions (BFNC), benign familial infantile convulsions (BFIC) and to neonatal epileptic encephalopathy [4-9]. *KCNQ2*-associated childhood epilepsy can be inherited, autosomal-dominant form of neonatal epileptic syndrome. Seizures usually occur during the first 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 [4,6]. Patients with BFNS usually have seizures in the neonatal period with a predicted benign course [4,6,7,10,11]. Most BFNS spontaneously disappear during the

infant's first year of life [2,10,11]. Outcomes vary in patients with *KCNQ2*-associated epilepsy. Even in the most benign cases, in which neurodevelopmental outcomes are good, and most develop normal intelligence [2,12-14], 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 (BCECTS), idiopathic general epilepsies or rare photosensitive myoclonic epilepsy [15,16]. However, at present, the outcomes in these patients cannot be accurately predicted. The diagnosis depends on family history, clinical features, and genetic study. The mutations can be quickly detected based on next-generation sequencing (NGS). The mutant gene is located at 20q13, a voltage-gated potassium channel gene (*KCNQ2*).

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A *KCNQ2* phenotype of neonatal epileptic encephalopathy has been frequently reported [8,9,17,18]. Some patients present with burst-suppression or multiple focal spikes on neonatal electroencephalograms (EEGs). Seizures remit as the patients become older, but the patients usually have intellectual developmental delays. Magnetic resonance imaging (MRI) of the brain can show unremarkable findings or hyperintensities in the basal ganglia and thalamus [8,9,17]. Most cases are de novo mutations, and patients present with severe seizures and grave neurological consequences. Loss of function via the dominant-negative effect of the *KCNQ2* gene or gain of function are presumed to be the major mechanism for *KCNQ2* encephalopathy [19-22].

This article reviews current research on *KCNQ2*-associated epilepsy, the relationship between genotype and phenotype, pathophysiological mechanisms, and drug treatments.

### Known *KCNQ2* Mutations that Contribute to Epilepsy

#### ■ The phenotype of *KCNQ2*-associated epilepsy: variation of clinical phenotype (Supplementary Table 1)

*KCNQ2* mutations contribute to childhood epilepsy with variations of phenotype from BFNC, BFIC, neonatal epileptic encephalopathy, idiopathic generalized epilepsies and late childhood epileptic encephalopathy [2,8,9,14,17,23]. *KCNQ2*-associated epilepsy account for about 8% of childhood non-lesional epilepsy [8,9,17]. More than 80 different *KCNQ2* genotypes have been described thus far. Most are missense mutations 53(69%) (Table 1). The next two most common are indel 16 (21%) and splice-site mutations 8 (10%), similar to the The Human Gene Mutation Database (HGMD) database for *KCNQ2* mutations (<http://www.hgmd.cf.ac.uk>). Some *KCNQ2* mutations are in the S4 and S5 segments and in the pore region of voltage-gated potassium (K<sup>+</sup>) channels; they have a more severe dominant-negative effect and lead to early-onset epileptic encephalopathy. Mutations in the C-terminal region, particularly in the calmodulin domain, are reported [9,17] (Supplementary Table 1) to have more severe phenotypes (Supplementary Table 1). There are more case reports from Asia than from other parts of the world, which suggests that the *KCNQ2* mutation is global and pan-ethnic. Grinton [16] reported a series

of families with *KCNQ2* mutations: they had different phenotypes but the same genotype. The mechanism was not identified, but the study hypothesized interplay of pathogenic mutations, modifier genes, and other environmental factors.

#### ■ Relationship of genotype and phenotype in *KCNQ2*-mutated patients

The different phenotypes of *KCNQ2* mutations—BFNC, BFIC, and neonatal epileptic encephalopathy—might be determined by the degree of functional disability. Functional studies on in vitro *KCNQ2* mutations show that genotype is involved in determining clinical phenotype, including the seizure frequency and outcome [10]. The phenotype and genotype correlation is complex. The same mutation could also manifest different phenotype [16]. Single mutations might manifest different clinical phenotypes in different family members. Borgatti et al. [24] reported that one novel mutation of *KCNQ2*, c.G1620A (p.K526N), rendered different phenotypes—BFNC-only, or BFNC plus early-onset epileptic encephalopathy or focal seizures and mental retardation—in different members of the same family. Genotype is critical to its phenotype in *KCNQ2*-associated epilepsy [10,25,26]. The more severe dominant negative effect probable caused by the mutation of critical region of S4, S5, and pore region. The other important functional region is the calmodulin region of C-terminal, which cause more severe phenotype, including mutations of p.M518V, p.R525Q, p.R532W, p.R553L, p.R553W and p.R560W (Supplementary Table 1).

The mutant channels of *KCNQ2* are on the cell surface. Some of the C-terminal mutations have been reported [20,24] to impair surface expression by, for example, reducing protein stability or by binding to calmodulin and thereby affecting transport to the surface membrane. However, the S4 domain in *KCNQ2* protein can affect channel gating and increase the threshold for channel activation [20,24]. When potassium channels that have mutant subunits homomerically or heteromerically bound to wild-type *KCNQ2* and *KCNQ3* subunits are expressed in Chinese hamster ovary (CHO) cells, the voltage-dependence of activation is altered in these channels, regardless of whether they change intracellular trafficking and plasma membrane expression [24]. The precise genotype-phenotype correlation is not known, but the degree of functional disability caused by *KCNQ2* mutations is important.

### ■ Mutation variants of *KCNQ2*-associated epileptic encephalopathy

Patients with *KCNQ2*-associated neonatal epileptic encephalopathy (most were *de novo*) have associated developmental delay or cognitive disability [8,9,12,27]. Patients with neonatal epileptic encephalopathy usually have *de novo* mutations because of the dominant-negative effect that contributes to the severe phenotype, which usually cannot pass on the mutations to the next sibling. Patients' seizures went into remission when they turned 1 year old. Patients with neonatal EEG burst-suppression have worse outcomes. The *KCNQ2*-associated burst-suppression pattern in newborns is different from other burst-suppression patterns with other etiologies, such as brain malformation, mutations of the *ARX* or *STXBP1* genes [17,27], and early myoclonic epileptic encephalopathy. *KCNQ2*-associated neonatal EEG burst-suppression usually induces general tonic seizures and, rarely, myoclonic seizures [8,17]. There are three *KCNQ2*-associated neonatal EEG burst-suppression phenotype differences. The first is an evolution to West syndrome, which is characterized by epileptic spasms, but this is infrequent. Second, medical control of seizures is relatively good. Third, the seizures will disappear or be otherwise mitigated after the patient turns 1 year old.

### ■ Late childhood epileptic encephalopathy and *KCNQ2* mutations

Late childhood epileptic encephalopathy syndromes include focal epilepsy with a speech disorder (FESD) with or without mental retardation (OMIM#245570). Landau-Kleffner syndrome (LKS) and continuous spikes and waves during slow-wave sleep syndrome (CSWS) are both recognized by the International League Against Epilepsy (ILAE). Both can cause abnormal behavior and apraxia, hyperactivity, attention deficit disorder, and cognitive decline [28,29]. 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 slow disease progression or a poor cognitive prognosis [28,29]. This late childhood epileptic encephalopathy (CSWS) is rarely reported to be correlated with *KCNQ2* mutations [23].

### ■ Etiologies of continuous spikes and waves during slow-wave sleep (CSWS)

The etiologies of LKS and CSWS are considered heterogeneous. The *SRPX2* and *ELP4* genes have been reported [30] to be involved with CSWS. This involvement 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, hydrocephalus), a prior developmental delay of unknown etiology (possibly genetic), or, less likely, a chromosomal or monogenic condition [28,29]. 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 [30]. The evolution of epilepsy is well documented: seizures spontaneously disappear, as do the adolescent and pre-adolescent CSWS patterns. Lee [23] supported the notion that the etiology of CSWS in children includes the *KCNQ2* mutation, and that some patients develop CSWS. Three of our 4 patients with *KCNQ2* mutations developed a mild intellectual disability and 2 had EEGs that showed CSWS in a case-series that included patients with *KCNQ2* mutations of E515D [23]. Despite the favorable outcomes of their seizures, these patients developed cognition and inattention problems. In electrophysiological *in vitro* functional studies using whole-cell patch-clamp analysis [23,31], the E515D *KCNQ2* mutation caused electrical current changes in the homomeric and heteromeric channels transiently expressed in HEK293 cells, and impaired the surface expression of *KCNQ2* protein. Segregation data and functional studies [23,31] predict that the E515D *KCNQ2* mutation is highly likely to cause seizures.

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### Pathophysiological Mechanism between *KCNQ2* mutations and Epilepsy

#### ■ Functional analysis of *KCNQ2* mutation variants

The *KCNQ2* protein consists of heteromultimeric channels with six transmembrane domains (S1-S6), including a voltage sensor in S4, a loop between S5-S6 that builds the ion channel pore, a cytoplasmic N-terminal, and a long C-terminal region of mostly unknown function [4,31].

KCNQ2 protein is diffusely expressed in the brain in neurons, axons, and dendrites. In the *KCNQ2* gene, mutations can cause a haploinsufficiency, a more severe dominant-negative effect by a loss-of-function or a gain-of-function [12,14,22,32-34]. *KCNQ2* and *KCNQ3* genes are encoded together for potassium channels subunits underlying the M-current [2]. Only rare *KCNQ3* mutations have been detected in BFNC families [14], but more than 80 *KCNQ2* mutations have been identified.

One functional study [35] on the p.V589X, p.T359K, and p.P410fs12X variants showed that p.P410fs12X caused the most functional damage because of cell electrophysiology. The p.P410fs12X mutation caused a more severe phenotype that included hemiplegic migraine and neonatal convulsions. The p.T359K variant caused moderate developmental delay in a 4-year-old patient. Other examples are the mutation variants p.R213Q and p.R213W. Both are in the same codon, but each contains a different amino acid substitution: one in a Japanese family [36] and one in a western European family [8]. Each yielded distinct outcomes: p.R213W caused benign familial neonatal convulsions and p.R213Q caused burst-suppression EEGs. One reason might be that the p.R213Q mutation leads to significantly greater functional change than does the p.R213W mutation [25]. Other possibilities are parental germline mosaicism, genetic modifiers, and environmental factors.

Evidence [20,25,26,31] suggests that the mutations which contribute to *KCNQ2* encephalopathy have a dominant-negative effect on the electrical current amplitude of homomeric wild-type and mutant *KCNQ2* constructs, which correlates with clinical seizure frequencies and neurodevelopmental outcomes. However, there is a need for more studies on phenotype-genotype correlations in *KCNQ2*-related disorders. Additional studies on genotypes and phenotypes are needed to clarify the pathogenesis of two different phenotypes: *KCNQ2* epileptic encephalopathy and BFNC.

The different phenotypes of *KCNQ2* mutations, including BFNS, neonatal epileptic encephalopathy, and benign infantile familial convulsions (BFIC), might be determined by the degree of functional disability. Parental germline mosaicism, genetic modifiers, and environmental factors are also possible explanations.

### Treatment in *KCNQ*-Associated Seizures

Most cases of BFNC can be controlled with phenobarbital, oxcarbazepine, vigabatrin, and valproate [8,9,33]. Although BFNC is believed to be benign, patients with BFNC might have cluster seizures, which inevitably require drugs to control. In *KCNQ2*-associated encephalopathy, seizures call for other drugs like valproic acid and clonazepam. More second-line drugs are being developed, e.g., topiramate. Effective antiepileptic drugs (AEDs) for early-onset *KCNQ2*-associated epileptic encephalopathy are not unique [17,37].

Additional *in vitro* studies of effective AEDs showed that retigabine (a.k.a., ezogabine) therapy reversed the functional electrical current changes of transfected cells. Retigabine, which selectively opens the Kv7 potassium channel, has not yet been approved, but it has been reported as effective in *in vitro* and *in vivo* studies [17,35]. Long-term neurodevelopmental outcomes are grave in patients with *KCNQ2*-associated neonatal epileptic encephalopathy. Additional studies to develop treatments that are more effective are required.

### Future Works

Despite some case-series reports [8,9,17] and functional studies [19-21,34-38] that have shown a correlation between the phenotype and genotype, this correlation still requires investigation because the *in vitro* functional consequences of *KCNQ2* mutations are not fully understood. The genotype and phenotype relationship is complex. We believe that it is necessary to investigate how much membranous *KCNQ2* protein is expressed, and how it is associated with the phenotype. Additional studies to understand the pathogenesis of the potassium channel to epilepsy, particular mutations in the calmodulin domain of C-terminal, voltage sensor domains (S1-S4), and the pore region (S5, S6) are important.

### Conclusions

*KCNQ2* should be candidate gene when diagnosing neonatal or childhood epilepsy without an identified cause. Depending on NGS techniques, the mutations can be fast detected. Newborns with the *KCNQ2* mutation can have *KCNQ2*-associated epileptic encephalopathy. The *in vitro* functional study of the mutations

suggest that the genotype is involved with the phenotype. However, additional studies on the association of genotype and phenotype are still required.

## Disclosures

The authors declare that they have no conflicts of interest to disclose.

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