RESEARCH ARTICLE OPEN ACCESS

KCNQ2 Variants in Neonatal Epilepsy

Clinical Characteristics and Neurodevelopmental Outcomes in 30 Patients

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Neurol Genet 2026;12:e200380. doi:10.1212/NXG.0000000000200380

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Abstract

Background and Objectives

The aim of this study was to characterize clinical features, genetic architecture, treatment responses, and neurodevelopmental outcomes in neonatal epilepsy associated with *KCNQ2* variants and to delineate genotype-phenotype correlations.

Methods

We conducted a retrospective, two-center study of 30 neonates from 2019 to 2024. All patients underwent whole-exome sequencing with Sanger confirmation and, at last follow-up, were classified, according to International League Against Epilepsy criteria as having self-limited (familial) neonatal epilepsy (SeL[F]NE) or developmental and epileptic encephalopathy (DEE). Primary outcomes were seizure freedom by 6 months and milestone-based three-level neurodevelopment (normal/mild/severe). Clinical/EEG/MRI features and variant class/topology were compared across phenotypes.

Results

Most infants presented in the first week of life (median 3 days), typically with focal tonic seizures. EEG abnormalities were common (90%); burst-suppression/profound discontinuity consistently signaled adverse neurodevelopment. MRI was often normal (53%) or nonspecific. We identified 29 distinct variants (32 occurrences) across 30 patients. Twenty-eight carried a single heterozygous variant, and 2 carried 2 heterozygous variants (phase not determined); missense variants predominated (21/30, 70%). Clear topology-phenotype patterns emerged: transmembrane missense variants—especially S5-pore-S6—were enriched in DEE, whereas C-terminal/nontransmembrane variants were associated with SeL(F)NE and benign outcomes. At the last follow-up, SeL(F)NE accounted for 63% and DEE 37%. Seizure freedom reached 93%. Oxcarbazepine was often associated with seizure control after phenobarbital nonresponse, but this observational signal should not be interpreted as causal. Neurodevelopment was normal in 63%; delays occurred only within the DEE cohort. All 5 single-allele truncating/NMD lesions (CNV deletion, canonical splice-site, 2 nonsense, 1 frameshift) aligned with SeL(F)NE, whereas the 2 individuals with 2 heterozygous variants were classified as DEE with marked impairment; however, phase was not determined and 1 recurrent variant (p.E515D) was classified as likely benign, precluding inference of 2 pathogenic alleles.

Discussion

KCNQ2-related neonatal epilepsy shows robust, topology-dependent genotype-phenotype correlations with prognostic utility: early EEG patterns flag risk; transmembrane missense variants are associated with DEE, whereas single-allele truncating/NMD variants are associated with SeL(F)NE. Apparent benefits of oxcarbazepine reflect associations in an observational cohort and should not be interpreted as causal; prospective, phenotype-stratified studies are warranted. Long-term developmental surveillance remains essential, particularly for individuals with DEE and those with severe early EEG patterns or variants in transmembrane/pore regions.

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Glossary

ASM = antiseizure medication; **DEE** = developmental and epileptic encephalopathy; **DQ** = developmental quotient; **ILAE** = International League Against Epilepsy; **IM** = M-current; **PB** = phenobarbital; **WES** = whole-exome sequencing.

Introduction

Neonatal seizures are among the most common neurologic emergencies during the perinatal period, with an estimated incidence of 1–4 per 1,000 live births and even higher rates reported in preterm infants.[1,2] These seizures pose a significant threat to normal brain development and long-term neurologic outcomes.

The KCNQ (Kv7) gene family encodes subunits of voltage-gated potassium channels that regulate neuronal excitability by forming tetrameric channels.[3] In particular, *KCNQ2* (Kv7.2) and KCNQ3 (Kv7.3) co-assemble into heterotetramers that generate the M-current (IM), a non-inactivating current that stabilizes the resting membrane potential and suppresses repetitive firing.[4-6]

KCNQ2 is located on 20q13.33 and is highly expressed in the hippocampus and neocortex, with marked enrichment at the axon initial segment, where it modulates action-potential initiation and neuronal excitability.[3,7] *KCNQ2* variants are a major cause of neonatal-onset epilepsy. At the mechanistic level, *KCNQ2*-related disorders are autosomal-dominant; however, variant origin and intergenerational transmission are heterogeneous across the clinical spectrum: self-limited (familial) neonatal epilepsy [SeL(F)NE; formerly BFNS] often segregates in an autosomal-dominant fashion with variable penetrance, whereas most variants associated with developmental and epileptic encephalopathy (DEE) are de novo and not transmitted.[8] Accordingly, *KCNQ2*-related disorders span a clinical spectrum anchored by these 2 syndromes, ranging from SeL(F)NE to DEE.[9,10]

The widespread application of whole-exome sequencing (WES), a high-throughput next-generation sequencing technology, has significantly enhanced the ability to detect genetic variants in individuals with epilepsy, leading to the identification of numerous novel pathogenic variants and risk factors associated with epilepsy and encephalopathy.[11,12] However, despite these advancements, the complete genotypic and phenotypic spectrum of *KCNQ2*-related epilepsy remains incompletely understood, particularly concerning its long-term developmental outcomes and treatment response. Therefore, this study retrospectively analyzed 30 neonates with epilepsy associated with *KCNQ2* gene variants, systematically summarizing their clinical features, treatment responses, and developmental outcomes. The aim was to further explore potential genotype-phenotype correlations and deepen the current understanding of *KCNQ2*-associated epileptic disorders. The findings are expected to assist clinicians in achieving earlier diagnosis, optimizing therapeutic strategies, and improving prognostic evaluation.

Methods

We retrospectively screened records and, after applying prespecified inclusion and exclusion criteria, enrolled 30 eligible neonates with epilepsy and *KCNQ2* variants identified by genetic testing who were admitted to Qilu Hospital of Shandong University and Children's Hospital Affiliated to Shandong University between January 2019 and December 2024. Given the retrospective design of the study and the use of deidentified patient data, the requirement for informed consent was waived by the ethics committee.

Inclusion criteria were as follows: (1) seizure onset within 28 days after birth or before a corrected gestational age of 44 weeks; (2) completion of cranial imaging, electroencephalography (EEG), and WES during hospitalization, with complete clinical data available; and (3) identification of *KCNQ2* variants by genetic testing. Exclusion criteria included the following: (1) seizures attributed to clearly identified causes such as hypoxic-ischemic encephalopathy, CNS infection, vascular events (e.g., intracranial hemorrhage or cerebral infarction), congenital brain malformations, or metabolic disorders and (2) follow-up duration less than 3 months or loss to follow-up.

Clinical data were extracted from medical records and supplemented through telephone interviews and/or written questionnaires. Clinical information (birth history, seizure semiology/frequency per International League Against Epilepsy (ILAE) criteria, physical examination findings, developmental milestones, family history, and results of clinical genetic and metabolic evaluations) was abstracted from standardized medical records using a uniform case-report form. When items were missing, caregivers were contacted via structured telephone interview or a written questionnaire. For individuals with inherited variants, epilepsy history in the carrier parent(s) was specifically reviewed from available medical records and/or structured caregiver interviews whenever possible. Follow-up information—including developmental status—was obtained from routine clinic revisit documentation or the same structured telephone contacts. As a retrospective study based on standardized medical records, recall bias was minimized. EEG and MRI were obtained at initial presentation after seizure onset and were performed within 10 days of the first seizure. For consistency, we analyzed only these baseline studies, because follow-up EEG/

MRI examinations were performed at nonstandardized ages, and follow-up brain MRI in clinically well children was particularly inconsistent because families frequently declined repeat sedated MRI. Baseline clinical features, early EEG/MRI findings, treatment, and outcomes are summarized in Table 1. All data were extracted by trained clinicians using a uniform data collection form to reduce information bias. EEG and MRI evaluations were completed and interpreted prior to the availability of genetic testing results, which typically required approximately 30 working days, thereby minimizing potential observer bias. Follow-up data were supplemented through structured telephone interviews to reduce loss to follow-up.

Genetic Testing and Variant Categorization

KCNQ2 variants were identified through WES in all patients. All detected variants were subsequently confirmed by orthogonal methods when applicable (e.g., Sanger sequencing for single-nucleotide variants and small indels) to confirm their authenticity and determine the mode of inheritance (i.e., parental origin or de novo). All *KCNQ2* variants were systematically interpreted using the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) standards.[13] Evidence codes incorporated (1) population frequency data from gnomAD v4.1.0 (GRCh38) to support rarity or frequency-based benign evidence (PM2/BS1); (2) confirmed de novo occurrence by parental testing (PS2); and (3) predicted loss of function for nonsense, frameshift, canonical ±1/±2 splice-site variants, and exon-level deletions/copy-number variants (PVS1). Each variant was assigned a final ACMG/AMP classification (pathogenic, likely pathogenic, VUS, likely benign, or benign), and the corresponding evidence codes and classifications are listed in Table 2. Variants outside canonical splice sites (e.g., splice-region variants) were classified conservatively without applying PVS1 in the absence of RNA or functional evidence. Familial segregation analysis was performed when parental samples were available. For descriptive purposes, variants were further grouped as truncating (predicted loss-of-function) vs nontruncating. In individuals carrying 2 *KCNQ2* variants, variants were reported as 2 heterozygous variants; phase (in cis vs in trans) was not assumed unless formally determined. For topology mapping, each variant was further assigned to transmembrane segments (S1–S6/pore) or to nontransmembrane N-/C-terminal regions.

At last follow-up, each patient was classified as SeL(F)NE or DEE, consistent with ILAE criteria. For this study, SeL(F)NE denoted neonatal-onset seizures with subsequent remission and age-appropriate development, whereas DEE denoted persistent, drug-resistant seizures accompanied by global developmental impairment. Neurodevelopmental outcomes were determined using a standardized milestone interview covering 4 domains (gross motor, fine motor, language/communication, and social-cognitive). When standardized instruments (e.g., Bayley and GDS) were available as part of routine care, composite/developmental quotient (DQ) thresholds took precedence (≥85 normal; 70–84 mild; <70 severe) and were used to calibrate milestone-based ratings. When standardized testing was unavailable, prespecified age-specific thresholds were applied as follows.

0–6 Months of Age

Mild: delay ≥1–2 months in any single domain.

Severe: any of the following—delay ≥2–3 months in ≥2 domains; delay ≥3 months in ≥3 domains; or functional dependence/skill regression.

6–24 Months of Age

Mild: delay ≥2–3 months in any single domain.

Severe: any of the following—delay ≥4–6 months in ≥2 domains; marked delay in ≥3 domains; or key milestones (e.g., independent sitting/walking or meaningful words) well beyond expected windows with functional impact.

>24 Months of Age

Mild: limited tasks achievable with minimal assistance.

Severe: any of the following—ongoing need for structured rehabilitation/educational support; multidomain functional dependence; or a clinical diagnosis of global developmental delay/intellectual disability.

Statistical Analysis

A descriptive statistical analysis was conducted on the retrospectively collected clinical data. Continuous variables following a normal distribution were presented as mean ± SD, while non-normally distributed continuous variables were expressed as median (range). Categorical variables were summarized as frequencies and percentages.

In addition, we queried the ClinVar and OMIM databases to determine whether each *KCNQ2* variant had been previously reported in clinical settings and to retrieve the corresponding pathogenicity classifications and associated clinical phenotypes.[14,15]

Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective study was approved by the Institutional Review Board of Qilu Hospital of Shandong University (Approval No. KYLL-202503-024). Clinical data from Qilu Hospital and the Children's Hospital Affiliated to Shandong University were reviewed under this approval. Owing to the retrospective design and use of deidentified patient data, the requirement for written informed consent was waived by the ethics committee. No animal experiments were performed. No images or videos of recognizable individuals are included; therefore, consent to disclose identifiable information was not applicable. No images or videos of recognizable individuals are included, and all reported data were deidentified. This study was not a clinical trial and was not prospectively registered.

Table 1 Baseline Clinical Features, Early EEG/MRI, Treatment, and Seizure Control and Developmental Outcomes in 30 Neonates With *KCNQ2*-Related Epilepsy

Case	Onset ≤7 d of life	Initial seizure types	EEG	MRI	Initial ASM(s)	Final ASM(s)	Seizure outcome	Developmental outcome
1	N	FT	Multi	EAS widen	PB	PB/OXC	SF ≤ 3 mo	Normal
2	N	FT	Multi	EAS widen	PB	PB/OXC	SF ≤ 3 mo	Mild
3	N	FT	Multi	EAS widen	PB	LEV	SF ≤ 3 mo	Normal
4	N	FM	Multi	GP abn	PB/LEV	TPM/OXC	SF 3–6 mo	Normal
5	N	FMC	BS	EAS widen	PB/LEV	LEV/LCM	AS,2–3/mo	Severe
6	Y	FT	Multi	GP abn	PB	OXC	SF > 6 mo	Normal
7	Y	FT	Multi	GP abn	PB	OXC	SF ≤ 3 mo	Normal
8	Y	FMC	Multi	N	PB	TPM/LEV/VPA	SF > 6 mo	Severe
9	Y	FT	Multi	N	LEV	OXC	SF 3–6 mo	Mild
10	N	FMC	N	EAS widen	PB	LEV	SF 3–6 mo	Normal
11	Y	FMC	Multi	N	PB	LEV	SF ≤ 3 mo	Normal
12	N	FT	Multi	EAS widen	PB/LEV	OXC	SF ≤ 3 mo	Normal
13	Y	FT	Multi	N	PB/LEV	OXC	SF ≤ 3 mo	Normal
14	Y	FT	N	EAS widen	PB	OXC	SF ≤ 3 mo	Normal
15	Y	FMC	Multi	EAS widen	PB	LEV	SF ≤ 3 mo	Normal
16	Y	FT	Multi	EAS widen	PB/LEV	OXC	SF ≤ 3 mo	Normal
17	Y	FT	N	N	PB	OXC/TPM	SF ≤ 3 mo	Severe
18	Y	FT	Other	N	PB	TPM/OXC	SF ≤ 3 mo	Severe
19	Y	FT	Multi	N	PB/LEV	OXC	SF 3–6 mo	Normal
20	Y	FMC	Multi	N	PB/LEV	TPM/OXC	AS, wk	Severe
21	Y	FT	N	N	LEV	OXC	SF ≤ 3 mo	Normal
22	N	FT	Focal	N	PB/LEV	LEV/LCM	SF ≤ 3 mo	Normal
23	N	FT	Multi	N	PB	LEV/OXC	SF 3–6 mo	Normal
24	Y	FMC	Focal	N	PB	PB	SF ≤ 3 mo	Normal
25	Y	FT	Focal	SDH	PB	LEV	SF ≤ 3 mo	Mild
26	Y	FT	BS	GP abn	LEV	LEV/TPM/OXC	SF ≤ 3 mo	Severe
27	Y	FT	Focal	N	PB	LEV	SF ≤ 3 mo	Normal
28	Y	FMC	BS	N	PB/LEV	PB/LEV	SF ≤ 3 mo	Severe
29	N	FT	Focal	N	PB	OXC	SF ≤ 3 mo	Severe
30	Y	FT	Focal	N	PB	OXC	SF ≤ 3 mo	Normal

Abbreviations: AS = active seizures; AS, 2–3/mo = active seizures with a frequency of 2–3 per month; AS, wk = active seizures occurring approximately weekly; BS = burst-suppression; Drugs: PB = phenobarbital; EAS widen = widened extra-axial spaces; EEG: Multi = multifocal discharges; Final ASM(s) = antiseizure medication regimen at last follow-up; FM = focal myoclonic; FT = focal tonic; FMC = focal motor with tonic-clonic features; FM = focal myoclonic. EEG: Multi = multifocal discharges; Focal = focal-onset discharges; BS = burst-suppression; Other = nonspecific paroxysmal delta-theta activity with intermixed sharp waves. MRI: N = normal; EAS widen = widened extra-axial spaces; GP abn = globus pallidus signal abnormality; SDH = subdural hematoma. Outcomes: SF = seizure-free; AS = active seizures; AS, 2–3/mo = active seizures with a frequency of 2–3 per month; AS, wk = active seizures occurring approximately weekly; SF ≤ 3 mo = seizure freedom achieved by ≤3 months; SF 3–6 mo = seizure freedom achieved between 3 and 6 months; SF > 6 mo = seizure freedom achieved after >6 months; mo = months; wk = weekly. Drugs: Initial ASM(s) = antiseizure medication regimen initiated during the index admission; Final ASM(s) = antiseizure medication regimen at last follow-up; PB = phenobarbital; LEV = levetiracetam; OXC = oxcarbazepine; LCM = lacosamide; TPM = topiramate; VPA = valproate. Onset ≤7 days of life (Y/N) indicates whether clinical seizures began within the first postnatal week (Y = yes, onset ≤7 days; N = no, onset >7 and ≤28 days of life). Developmental outcome categories were defined as follows: normal (DQ ≥ 85 or age-appropriate milestones), mild delay (DQ 70–84 or mild delay per prespecified age-specific thresholds), and severe impairment (DQ < 70 or meeting severe criteria as detailed in Methods).

Table 2 *KCNQ2* Variants With ACMG/AMP Classification and Genotype-Phenotype Summary in 30 Neonates

Case	Nucleotide change	Amino acid change	Inheritance	ClinVar	ACMG/AMP codes	ACMG/AMP class	Phenotype
1	c.485A>G	p.K162R	M	Novel	PM2	VUS	SeL(F)NE
2	c.637C>G	p.R213G	DN	Novel	PS2; PM2	Likely pathogenic	DEE
3	20q13.33 del (100.2 kb)	—	UNK	Novel	PVS1 (CNV LoF)	Likely pathogenic	SeL(F)NE
4	c.365C>T	p.S122L	UNK	Reported	PM2	VUS	SeL(F)NE
5	c.902G>T	p.G301V	DN	Novel	PS2; PM2	Likely pathogenic	DEE
6	c.1687G>A	p.D563N	DN	Reported	PS2; PM2	Likely pathogenic	SeL(F)NE
7	c.587C>T	p.Q196*	UNK	Novel	PVS1; PM2	Likely pathogenic	SeL(F)NE
8	c.629G>A	p.R210H	DN	Reported	PS2; PM2	Likely pathogenic	DEE
9	c.247_249del AAC	p.N83del	UNK	Novel	PM2; PM4	VUS	DEE
10	c.1185G>T	p.R395S	P	Novel	PM2	VUS	SeL(F)NE
11	c.1058G>A	p.R353H	UNK	Reported	PM2	VUS	SeL(F)NE
12	c.1040A>G	p.Y347C	M	Novel	PM2	VUS	SeL(F)NE
13	c.1185G>T	p.R395S	P	Novel	PM2	VUS	SeL(F)NE
14	c.1024-2A>C	—	M	Reported	PVS1; PM2	Likely pathogenic	SeL(F)NE
15	c.1631G>A	p.C544Y	M	Reported	PM2	VUS	SeL(F)NE
16	c.1076C>G	p.T359M	M	Novel	PM2	VUS	SeL(F)NE
17	c.881C>T	p.A294V	DN	Novel	PS2; PM2	Likely pathogenic	DEE
18	c.679G>C	p.G227A	DN	Novel	PS2; PM2	Likely pathogenic	DEE
19	c.2228delC	p.P743Rfs*187	P	Novel	PVS1; PM2	Likely pathogenic	SeL(F)NE
20a	c.1058G>C	p.R353P	DN	Novel	PS2; PM2	Likely pathogenic	DEE
20b	c.1545G>C	p.E515D	P	Reported	BS1	Likely benign	DEE
21	c.1910T>C	p.L637P	UNK	Reported	PM2	VUS	SeL(F)NE
22	c.737C>G	p.A246V	P	Novel	PM2	VUS	SeL(F)NE
23	c.769G>A	p.E257K	M	Novel	PM2	VUS	SeL(F)NE
24	c.816 + 5G>A	—	P	Novel	PM2	VUS	SeL(F)NE
25	c.1639C>T	p.R547W	DN	Reported	PS2; PM2	Likely pathogenic	DEE
26	c.913_915delTTC	p.F305del	DN	Reported	PS2; PM2; PM4	Likely pathogenic	DEE
27	c.386T>C	p.L129P	DN	Novel	PS2; PM2	Likely pathogenic	SeL(F)NE
28	c.815T>G	p.L272R	DN	Novel	PS2; PM2	Likely pathogenic	DEE
29a	c.109del	p.D37Tfs*5	P	Novel	PVS1; PM2	Likely pathogenic	DEE
29b	c.1545G>C	p.E515D	M	Reported	BS1	Likely benign	DEE
30	c.961C>T	p.Q321*	M	Novel	PVS1; PM2	Likely pathogenic	SeL(F)NE

Abbreviations: DEE = developmental and epileptic encephalopathy; Inheritance: DN = de novo; M = maternal; P = paternal; UNK = unknown.
HGVS nomenclature is based on *KCNQ2* NM_172107.2 (NP_736633.2). Variants were classified according to ACMG/AMP standards (Richards et al., 2015); evidence codes and classifications are shown. De novo variants were confirmed by parental testing (PS2). Population frequency evidence was derived from gnomAD v4.1.0 (GRCh38). The intragenic deletion involving *KCNQ2* exons 2–17 was interpreted as a predicted loss-of-function event (population CNV frequency could not be queried).
Cases 20a/20b and 29a/29b represent 2 variants in the same individual (Case 20: p.R353P de novo, p.E515D paternal; Case 29: p.D37Tfs*5 paternal, p.E515D maternal). ClinVar: Reported, present in ClinVar/dbSNP and/or prior literature; Novel, no record at the time of analysis (accessed October 2025). Carrier parent epilepsy history was reviewed; only the mother of Case 23 reported epilepsy. Phenotype refers to the individual's clinical phenotype: SeL(F) NE, self-limited (familial) neonatal epilepsy.

Data Availability

Individual deidentified participant data underlying the results reported in this article—including case-level clinical variables, EEG/MRI annotations, and *KCNQ2* variant classifications—will be made available to qualified investigators on reasonable request to the corresponding author beginning on publication and for 36 months thereafter. The study protocol and a data dictionary/codebook will also be shared. Access will be provided under a data use agreement after approval by the institutional data access committee, for methodologically sound proposals that comply with ethical and legal requirements.

Results

Clinical Characteristics

A total of 30 neonates with neonatal-onset epilepsy harboring *KCNQ2* variants were included in this study, comprising 12 male infants and 18 female infants. The mean birth weight was 3179 ± 462 g. Seizure onset occurred at a median age of 3 days (range: 0–27 days), with most patients (20/30, 67%) presenting within the first week of life.

Seizure types were classified according to the ILAE guidelines.[9] The most common initial seizure type was focal tonic seizures, observed in 21 patients (21/30, 70%). Focal motor seizures with tonic-clonic features were reported in 8 patients (27%) and focal myoclonic seizures in 1 patient (3%). All seizures lasted less than 5 minutes and occurred in clusters. All patients underwent ≥4 hours of video-EEG monitoring, and both EEG and MRI were completed within 10 days of the first seizure in all cases. Interictal epileptiform discharges were multifocal in 17 of 30 (57%) and focal in 6 of 30 (20%). EEG background was normal in 3 of 30 (10%) and atypically abnormal in 2 of 30 (7%), with either frequent sharp spikes or paroxysmal delta/theta activity with intermixed sharp waves. A burst-suppression background was present in 3 of 30 (10%) overall. EEG features were not mutually exclusive. All 30 patients underwent brain MRI (MRI) shortly after seizure onset. Sixteen patients (16/30, 53%) had MRI findings consistent with normal neonatal brain imaging. Abnormal MRI findings were observed in 14 patients (47%), including partial widening of extra-axial spaces in 9 cases (30%), increased signal intensity in the globus pallidus in 4 cases (13%), and subdural hematoma in 1 case (3%). Details are provided in Table 1.

Based on ILAE-aligned criteria applied at last follow-up, phenotypes were assigned as self-limited (familial) neonatal epilepsy (SeL(F)NE) in 19 of 30 (63%) and DEE in 11 of 30 (37%). Severe neonatal EEG patterns (burst-suppression or profoundly discontinuous backgrounds) aligned with poor developmental prognosis and were classified within the DEE subset.

Genetic Findings

We identified *KCNQ2* variants (RefSeq: NM_172107.2) in 30 neonates. Overall, 32 variant occurrences were observed across the cohort, representing 29 distinct variants (recurrent variants included c.1185G > T [p.R395S] in siblings [Cases 10 and 13] and c.1545G > C [p.E515D] in 2 individuals [Cases 20 and 29]). At the patient level, 28 of 30 carried 1 heterozygous *KCNQ2* variant, whereas 2 of 30 (Cases 20 and 29) carried 2 heterozygous *KCNQ2* variants; phase (in cis vs in trans) was not determined and was not assumed. Grouped by predicted effect, the variants fell into nontruncating and truncating/NMD categories. At the patient level, patients carrying any truncating/NMD variant were assigned to the truncating/NMD group (e.g., Case 29, which carried a frameshift variant). The nontruncating set comprised 21 missense variants (21/30, 70%; including 1 patient [Case 20] with 2 concurrent missense variants, c.1058G > C [p.R353P, de novo] and c.1545G > C [p.E515D, paternally inherited; ACMG/AMP likely benign]), 2 in-frame deletions, and 1 splice-region variant (total 24/30, 80%). In addition, 1 patient (Case 29) carried a missense variant c.1545G > C (p.E515D, maternally inherited; ACMG/AMP likely benign) in the same individual as a truncating variant c.109delG (p.D37Tfs*5, paternally inherited). The truncating/NMD group (predicted loss of function) included 1 large copy-number deletion (>50 kb), 1 canonical splice-site variant, 2 nonsense variants (p.Q196*, p.Q321*), and 2 frameshift variants; Case 29 carried the frameshift (c.109delG) alongside the missense change.

Details are presented in Table 2. By ACMG/AMP classification, 17 of 32 variants were classified as likely pathogenic, 13 of 32 as VUS, and 2 of 32 as likely benign (Table 2). Of 32 variant occurrences, 11 had been previously reported and 21 were novel. Regarding inheritance (counted by patients), 14 were inherited (7 maternal, 5 paternal; Case 20 had 1 de novo missense variant and 1 paternal; Case 29 had variants inherited from each parent), 10 were confirmed de novo, and 6 were undetermined because of unavailable parental samples. Among carrier parents with available history, only the mother of Case 23 reported epilepsy; no epilepsy history was reported in other carrier parents when information was available.

Among the 25 patients with a single *KCNQ2* variant and a single variant type (missense, nonsense, frameshift, or in-frame deletion), 16 had normal intellectual and motor development (64%), 3 had mild delay (12%), and 6 had significant impairment (24%). Topology-aware mapping showed that variants associated with normal neurodevelopment were predominantly located in the C-terminal, nontransmembrane region (mostly nontruncating), whereas variants linked to developmental delay clustered within transmembrane segments—particularly the S5-pore-S6 corridor—dominated by nontruncating missense changes (Figure 1). Consistent with phenotype assignment, missense variants within transmembrane regions were enriched in DEE, whereas variants outside transmembrane domains (notably C-terminal) predominated in SeL(F)NE.

Notable cases aligned with this grouping: the patient with a large 20q13.33 deletion (100.2 kb) (truncating/NMD) discontinued medication by 1 year and had normal development

at 2.5 years (SeL(F)NE course). Two patients with splice-affecting variants (Cases 14 and 24; 1 canonical splice-site [truncating/NMD] and 1 splice-region [nontruncating]) likewise showed normal development at last follow-up (2.5 and 3.5 years). By contrast, the 2 individuals carrying 2 heterozygous variants fell within the DEE group with marked impairment: Case 20 (2 missense, nontruncating) remained ASM-dependent at 4.5 years with significant delay; Case 29 (missense + frameshift) required ongoing medication at 5 years and had significant delays. In both Cases 20 and 29, phase was not determined (Table 2).

Treatment and Follow-Up Outcomes

At last follow-up (range, 6 months to 5.5 years), seizures were controlled in 28 of 30 patients (93%); 2 (Cases 5 and 20) had persistent seizures (≈2–3/month and weekly, respectively). Among those with seizure control, 18 of 28 (64%) were seizure-free on monotherapy (oxcarbazepine n = 11, levetiracetam n = 6, phenobarbital [PB] n = 1), while 8 of 28 (29%) required 2 agents and 2 of 28 (7%) required 3. Most controlled patients achieved remission within the first 6 months of life.

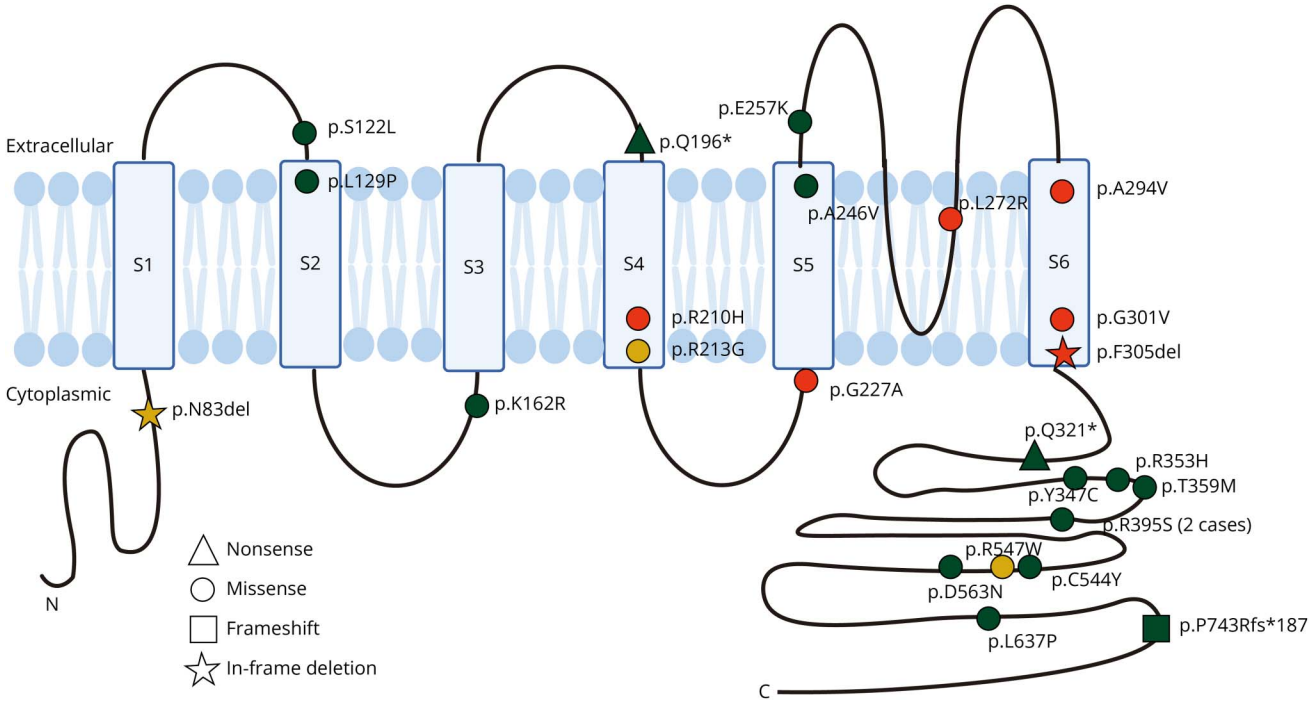
Neurodevelopmentally, according to the three-level classification summarized in Table 1, 19 of 30 (63%) had normal outcomes, 3 of 30 (10%) had mild delay, and 8 of 30 (27%) had severe impairment. Both patients with ongoing seizures and all cases with developmental delay (11/30, 37%) belonged to the DEE subset, whereas all patients with SeL(F)NE (19/30, 63%) had normal development. Genotype-outcome patterns are presented in Genetic Findings and the Figurefig1 and are not repeated here.

Discussion

In this two-center retrospective study of 30 neonates with epilepsy harboring *KCNQ2* variants, we systematically analyzed clinical features, genetic findings, treatment responses, and developmental outcomes. Most patients experienced seizure onset within the first week of life, with a median onset age of 3 days. This early-onset pattern is consistent with previous studies that identify *KCNQ2* as a leading genetic cause of neonatal epilepsy presenting within the first days after birth.[16-18] The most common initial seizure type in our cohort was focal tonic seizures (70%), followed by focal motor seizures with tonic-clonic features (27%); this distribution aligns with earlier reports showing that *KCNQ2*-related epilepsy often begins with focal tonic or motor seizures and, in more severe cases, may progress to multifocal or generalized seizures.[17,19-21]

Three patients (10%) exhibited markedly abnormal neonatal EEG patterns indicative of severe encephalopathy—one with

Figure *KCNQ2* Transmembrane Topology and Distribution of Variants With Developmental Outcomes



The schematic shows the intracellular amino (N) and carboxyl (C) termini, 6 transmembrane segments (S1–S6), and the S5-S6-pore loop. *KCNQ2* variants are mapped at approximate residue positions (not to scale). Only single-variant-type, single-allele cases are displayed (n = 25: missense, nonsense, frameshift, or in-frame deletion); cases carrying 2 heterozygous variants (Cases 20 and 29; phase not determined), copy-number deletion (Case 3), and splice-site/region variants (Cases 14, 24) are not depicted. Cases 10 and 13 are siblings with the same variant (p.R395S) and are indicated as "(2 cases)". Symbols: triangle = nonsense, circle = missense, square = frameshift, star = in-frame deletion. Colors: green = normal development, yellow = mild delay, red = significant delay (status at last follow-up).

multifocal discharges and a burst-suppression tendency and 2 with profoundly disorganized backgrounds with typical burst suppression—and all 3 had significant developmental delay. These observations support the value of early EEG—particularly burst suppression or severely disorganized backgrounds—as a prognostic marker of adverse neurodevelopment in *KCNQ2*-related epilepsies. Brain MRI obtained shortly after seizure onset was normal in 53%; among abnormal scans (47%), the most frequent findings were mild prominence of extra-axial CSF spaces and increased signal in the globus pallidus. Major structural anomalies are generally uncommon in *KCNQ2* disease,[17] and, although corpus callosum thinning has been described,[18,22] we did not observe callosal abnormalities. Because all MRI scans were performed in the early neonatal stage, evolving or delayed-onset structural changes cannot be excluded; longitudinal neuroimaging is warranted to clarify trajectories and their relevance to disease severity and long-term outcomes.

Across the cohort, we observed 32 variant occurrences representing 29 distinct *KCNQ2* variants, including missense variants, nonsense variants, in-frame deletions, large CNV deletions, splice-site/region variants, and frameshift changes (Table 2). Two individuals (Cases 20 and 29) each carried 2 heterozygous *KCNQ2* variants; phase (in cis vs in trans) was not determined and was not assumed. Missense variants were most common (21 patients), consistent with prior reports.[18,23,24] Of the 24 patients with determined inheritance, 14 carried familial variants and 10 had de novo variants; in 6 patients, parental origin could not be confirmed, given unavailable samples. These data highlight that *KCNQ2* variants arise both de novo and within families (autosomal-dominant segregation).

Previous studies suggest that specific variant locations within Kv7.2 relate to clinical severity.[23] Notably, many DEE-associated *KCNQ2* variants cluster between S5 and S6 (the pore-forming corridor), and perturbations of S6, a key gate, are predicted to impair channel function and exacerbate excitability.[16,25] Our cohort echoes these gradients: 5 infants with missense variants in or near S6 presented with DEE, while 1 variant between S2 and S3 was associated with a benign course. We also observed that variants carried by patients with normal neurodevelopment were predominantly located in C-terminal, nontransmembrane regions, consistent with prior findings.[26,27] Together, these patterns reinforce the clinical utility of variant topology for risk stratification. The Kv7.2/Kv7.3 heterotetramer provides a unifying framework across the SeL(F)NE-DEE spectrum. In KCNQ3, as in *KCNQ2*, transmembrane/pore missense variants (S4-S6, especially S5-pore-S6) often exert dominant-negative effects and are enriched in DEE, whereas truncating/NMD variants (nonsense, frameshift, canonical splice-site changes, and exon-level deletions) tend toward haploinsufficiency with residual assembly and more frequently align with SeL(F)NE and favorable development. Rare individuals carrying 2 KCNQ3 variants have been reported in DEE with substantial impairment.[28] These observations are concordant with our *KCNQ2* data (Table 2)—including that all 5 single-allele truncating/NMD cases were SeL(F)NE—and support mechanism-informed counseling across Kv7 channelopathies.

Two patients carried 2 heterozygous *KCNQ2* variants (Cases 20 and 29). Case 20 had significant developmental delay and persistent seizures despite treatment. Case 29 achieved neonatal seizure control with oxcarbazepine yet showed marked developmental delay during follow-up. These observations are directionally consistent with prior reports describing individuals with 2 *KCNQ2* variants (e.g., a missense variant plus a 20q12.33 microdeletion) associated with seizure control but profound impairment,[29] as well as KCNQ3 evidence of additive, PIP_2-dependent loss of function reversible by retigabine in vitro.[28] However, in our two-variant cases, phase was not determined and p.E515D was classified as likely benign by ACMG/AMP (Table 2); therefore, we cannot conclude that 2 pathogenic alleles contributed to the phenotype. Collectively, they support a dosage/topology framework whereby pore-region missense in association with more severe genotypes associates with DEE and developmental impairment, while truncating/NMD changes more often align with self-limited phenotypes—underscoring the need for long-term, comprehensive follow-up.

In this study, 93% of patients achieved seizure control, most often with monotherapy. Among seizure-free patients on monotherapy (18/28, 64%), the most commonly used drug was oxcarbazepine (OXC), a sodium-channel blocker (11/18, 61%), followed by levetiracetam (LEV) (6/18, 33%) and PB (1/18, 6%). Among the 10 patients who required 2 or more antiseizure medications (ASMs), 6 (60%) achieved seizure control after the addition of OXC. These findings are consistent with Chinese series demonstrating OXC efficacy in *KCNQ2*-related epilepsy[26,27] and with international data noting substantial exposure to sodium-channel blockers—albeit with important caveats about parent-reported effectiveness and uncontrolled cotreatments.[30]

Seizure control was concentrated in the SeL(F)NE subset, whereas ongoing seizures occurred exclusively in DEE (2 patients). Most controlled patients entered remission within the first 6 months of life, a hallmark of SeL(F)NE, suggesting that natural history accounts for a substantial fraction of early seizure cessation in this subgroup. By contrast, DEE more often required polytherapy and encompassed the 2 patients with persistent seizures. Accordingly, drug-specific observations—particularly regarding OXC—should be understood as associations rather than causal effects. While carbamazepine is more frequently cited internationally for neonatal-onset *KCNQ2* epilepsy,[17,18,21] OXC—its structural analog with similar sodium-channel blockade—is widely used in Chinese practice and showed promising seizure control in our cohort. For neonates with *KCNQ2* variants who respond poorly to PB, early consideration of OXC may be warranted; however, neonatal OXC use is off-label, and, in our cohort, most initiations occurred after the neonatal period. Prospective, standardized studies are needed to define optimal

timing, dosing, and comparative effectiveness vs other first-line options.

KCNQ2 loss of function impairs IM, indirectly supporting the rationale for sodium-channel blockers that reduce repetitive firing. A direct, mechanism-targeted approach is retigabine, a Kv7 opener that stabilizes channels (Kv7.2–Kv7.5) in the open state and reduces excitability.[31-33] Despite early promise for *KCNQ2*-related epilepsy, retigabine (ezogabine/Potiga in the US; Trobalt in the EU) was voluntarily withdrawn from US and EU markets by the manufacturer in 2017 because of concerns about skin and retinal discoloration in regions regulated by the US Food and Drug Administration and the European Medicines Agency.[34,35] Thus, Kv7-directed therapy remains a mechanistic ideal rather than a current standard, underscoring the need for safer next-generation openers.

In our setting, OXC and LEV emerged as practical, effective options for seizure control, while DEE frequently required combination therapy and carried a higher risk of persistent seizures and developmental impairment. Given the observational design and potential confounding by indication, treatment findings should be interpreted cautiously and validated in prospective, phenotype-stratified studies that incorporate standardized outcome measures and, ideally, pharmacogenetic context.

The study has several limitations. This retrospective two-center study has a modest sample size; standardized developmental testing was often unavailable in real-world practice (particularly among children with more pronounced delays), so outcome assignment relied primarily on structured milestone assessments from clinic revisits and/or structured telephone interviews. This approach risks information bias and nonrandom missingness. We mitigated this with prespecified age-banded thresholds and cross-calibration against Bayley/GDS scores when available, but ratings were not masked dual reviews. EEG and MRI were obtained in the neonatal period only; follow-up studies were performed opportunistically at nonstandardized ages, and clinically well children often did not undergo repeat sedated MRI, precluding systematic assessment of evolving structural changes. Genetic characterization was constrained by incomplete parental samples for some cases and CNV analyses performed only when clinically indicated; no in vitro functional assays were undertaken, so links between variant topology and channel dysfunction are inferred rather than directly demonstrated. Finally, nonrandomized treatment exposure limits causal inference about ASM responsiveness (e.g., oxcarbazepine), which should be confirmed prospectively.

KCNQ2-related neonatal epilepsy shows high early seizure controllability but divergent developmental trajectories that are associated with variant topology. Incorporating rapid genetic testing and topology-aware variant interpretation into neonatal care pathways may refine prognostication, guide counseling, and inform individualized therapy, while longitudinal imaging and functional studies are needed to strengthen mechanistic links and optimize outcomes.

Author Contributions

Y. Li: major role in the acquisition of data. J. Li: analysis or interpretation of data. L. Li: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. H. Zhang: major role in the acquisition of data; study concept or design. X. Sun: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology® Genetics* July 31, 2025. Accepted in final form February 6, 2026. Submitted and externally peer-reviewed. The handling editor was Editor Peter B. Kang, MD, FAAN.

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