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KCNQ2-Related Disorders

Francesco Miceli, PhD,[1] Maria Virginia Soldovieri, PhD,[2] Sarah Weckhuysen, MD, PhD,[3] Edward Cooper, MD, PhD,[4] and Maurizio Taglialatela, MD, PhD[1]

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Summary

Clinical characteristics

KCNQ2-related disorders represent a continuum of overlapping neonatal epileptic phenotypes ranging from self-limited familial neonatal epilepsy (SLFNE) at the mild end to neonatal-onset developmental and epileptic encephalopathy (NEO-DEE) at the severe end. Additional, less common phenotypes consisting of neonatal encephalopathy with non-epileptic myoclonus, infantile or childhood-onset developmental and epileptic encephalopathy (DEE), and isolated intellectual disability (ID) without epilepsy have also been described.

- ***KCNQ2*-SLFNE** is characterized by seizures that start in otherwise healthy infants between two and eight days after term birth and spontaneously disappear between the first and the sixth to 12th month of life. There is always a seizure-free interval between birth and the onset of seizures. Seizures are characterized by sudden onset with prominent motor involvement, often accompanied by apnea and cyanosis; video EEG identifies seizures as focal onset with tonic stiffening of limb(s) and some migration during each seizure's evolution. About 30% of individuals with *KCNQ2*-SLFNE develop epileptic seizures later in life.
- ***KCNQ2*-NEO-DEE** is characterized by multiple daily seizures beginning in the first week of life that are mostly tonic, with associated focal motor and autonomic features. Seizures generally cease between ages nine months and four years. At onset, EEG shows a burst-suppression pattern or multifocal epileptiform activity; early brain MRI can show basal ganglia hyperdensities and later MRIs may show white matter or general volume loss. Moderate-to-profound developmental impairment is present.

Diagnosis/testing

The diagnosis of a *KCNQ2*-related disorder is established in a proband with suggestive findings and a heterozygous pathogenic variant in *KCNQ2* identified by molecular genetic testing.

Author Affiliations: 1 Division of Pharmacology, Department of Neuroscience, University of Naples Federico II, Naples, Italy; Email: frmiceli@unina.it; Email: maurizio.taglialatela@unina.it. 2 Department of Medicine and Health Science, University of Molise, Campobasso, Italy; Email: mariavirginia.soldovieri@unimol.it. 3 Department of Neurology, University Hospital Antwerp; Applied and Translational Neurogenomics Group, VIB Center for Molecular Neurology, Antwerp, Belgium; Email: sarah.weckhuysen@uantwerpen.be. 4 Departments of Neurology, Neuroscience, and Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas; Email: ecc1@bcm.edu.

Management

Treatment of manifestations:

- ***KCNQ2*-SLFNE.** Seizures are generally controlled with conventional anti-seizure medication (ASM), although a significant number of individuals experience seizure freedom spontaneously.
- ***KCNQ2*-NEO-DEE.** Seizures may be resistant to multiple ASMs alone or in combination. Seizure freedom is more likely achieved when receiving sodium channel blockers. Individualized therapies are utilized for developmental delay and intellectual disability.

Surveillance:

- ***KCNQ2*-SLFNE.** EEG at age three, 12, and 24 months is appropriate. At 24 months EEG should be normal.
- ***KCNQ2*-NEO-DEE.** EEG monitoring as clinically indicated

Genetic counseling

KCNQ2-related disorders are inherited in an autosomal dominant manner. Most individuals diagnosed with *KCNQ2*-SLFNE are heterozygous for a pathogenic variant inherited from a parent. Most individuals diagnosed with *KCNQ2*-NEO-DEE have a *de novo* pathogenic variant. Each child of a heterozygous individual with *KCNQ2*-SLFNE has a 50% chance of inheriting the pathogenic variant. Given the severity of the disease course, individuals with *KCNQ2*-NEO-DEE rarely reproduce. Once a *KCNQ2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

GeneReview Scope

KCNQ2-Related Disorders: Included Phenotypes [1]	
More common presentations	• Self-limited familial neonatal epilepsy (SLFNE) • Neonatal-onset developmental and epileptic encephalopathy (NEO-DEE)
Less common presentations	• Neonatal encephalopathy with non-epileptic myoclonus • Non-neonatal-onset developmental and epileptic encephalopathy • Isolated intellectual disability

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

KCNQ2-related disorders represent a continuum of overlapping neonatal epileptic phenotypes ranging from self-limited familial neonatal epilepsy (SLFNE) at the mild end to neonatal-onset developmental and epileptic encephalopathy (NEO-DEE) at the severe end. Individuals with pathogenic variants in *KCNQ2* with other phenotypes including neonatal encephalopathy with non-epileptic myoclonus, epilepsy developing in infancy or childhood, and isolated intellectual disability (ID) without epilepsy have also been described.

Suggestive Findings

A *KCNQ2*-related disorder **should be considered** in individuals with the following presentations.

Self-limited familial neonatal epilepsy (SLFNE)

- Seizures in an otherwise healthy infant with onset between two and eight days after term birth and spontaneously disappearing between the first and the sixth to the 12th month of life

- The neonatal seizures may appear "convulsive" to some observers, as they share several features with generalized convulsions occurring in older children: sudden onset with prominent motor involvement, often accompanied by apnea and cyanosis. However, more careful electroclinical review using video EEG identifies the seizures as focal onset with tonic stiffening of limb(s) and some migration during each seizure's evolution.
- Normal physical examination and laboratory tests prior to onset of seizures, between seizure episodes, and following cessation of seizures
- No specific EEG criteria; EEG background is normal, or may show focal epileptiform discharges at neonatal onset but rapidly normalizes during early infancy.
- Normal brain imaging
- Family history of neonatal seizures is usually present; full family history may require interviewing older relatives (parent may be unaware).

Neonatal-onset developmental and epileptic encephalopathy (NEO-DEE)

- Seizure onset in the first week of life with EEGs showing a burst-suppression pattern or multifocal epileptiform activity
- Seizures are mostly tonic, with associated focal motor and autonomic features (similar to SLFNE).
- Multiple daily seizures occur at onset, with frequent seizures in the first few months to the first year of life, although this natural history is frequently ameliorated by treatment using appropriate anti-seizure medication.
- Cessation of seizures generally between age nine months and four years. Recurrence of (generally less frequent) seizures may occur later in life.
- Encephalopathy is present from birth and persists even after seizures are controlled. Subsequent developmental impairment ranges from moderate to profound.
- Neonatal brain MRI may be normal or may show transient hyperdensities in the basal ganglia, and later MRIs may show white matter or general volume loss.

The following additional phenotypes appear more rarely in hospital-based, multicenter, and registry-based series, but have become established as *KCNQ2*-related disorders.

Neonatal encephalopathy with non-epileptic myoclonus

- Profound encephalopathy at birth with hypotonia and poor respiratory effort
- Spontaneous episodes of jerking movements (myoclonus); may also be provoked by touch and/or attempted arousal
- Defining neonatal video EEG findings: invariant burst-suppression EEG background; body and limb jerks (myoclonus) without cortical accompaniment
- Epileptic spasms and other seizure types and profound encephalopathy emerging in early infancy
- Progressive volume loss and hypomyelination on brain MRI

Non-neonatal-onset developmental and epileptic encephalopathy (DEE)

- Infantile- or childhood-onset epilepsy, including West syndrome
- Neurodevelopment is usually impaired from birth, although normal early development with stagnation at onset of seizures has been described.
- Subsequent developmental impairment is moderate to severe, even if seizures are controlled.
- Brain MRI may show mild volume loss.

Isolated intellectual disability (ID)

- ID without epilepsy
- Motor and speech delay may be present.

- Brain MRI is normal or shows mild myelinization delay.

Establishing the Diagnosis

The diagnosis of a *KCNQ2*-related disorder is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *KCNQ2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *KCNQ2* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

No specific study has been carried out on the cost-effectiveness or diagnostic yield of specific genetic tests in individuals with *KCNQ2*-related disorders. Because the phenotype of a *KCNQ2*-related disorder may be indistinguishable from many other inherited disorders with or without epilepsy, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**. However, as *KCNQ2* is by far the most common genetic cause of neonatal seizures, **single-gene testing** of *KCNQ2* may still be warranted, especially in individuals with the less severe, familial disorder with characteristic phenotypic features of SLFNE [Symonds & McTague 2020].

- **An epilepsy or developmental and epileptic encephalopathy multigene panel** that includes *KCNQ2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

- **Single-gene testing.** Sequence analysis of *KCNQ2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Table 1. Molecular Genetic Testing Used in *KCNQ2*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
KCNQ2	Sequence analysis [4]	>90% [5]
	Gene-targeted deletion/duplication analysis [6]	<10% [5, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Thirteen additional individuals with large contiguous gene deletions (not included in these calculations) have been reported (see Genetically Related Disorders).
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Okumura et al [2015]) may not be detected by these methods.
7. Kurahashi et al [2009] and Okumura et al [2015] reported individuals with deletion of *KCNQ2* and the adjacent gene *CHRNA4*. The clinical course in these individuals was that of typical SLFNE, and neither had the phenotype of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), another focal epilepsy caused by pathogenic missense (but not deletion) variants in *CHRNA4*. Individuals with larger deletions involving additional genes have a different phenotype (see Genetically Related Disorders).

Clinical Characteristics

Clinical Description

KCNQ2-related disorders include a continuum of overlapping neonatal-onset epileptic phenotypes ranging from self-limited familial neonatal epilepsy (SLFNE) at the mild end to neonatal-onset developmental and epileptic encephalopathy (NEO-DEE) at the severe end. Less common phenotypes consist of neonatal encephalopathy with non-epileptic myoclonus, later-onset (infantile or childhood) developmental and epileptic encephalopathy (DEE), and isolated intellectual disability (ID) without epilepsy. *KCNQ2* variants have also been associated with peripheral nerve hyperexcitability (myokymia), self-limited familial infantile epilepsy (SLFIE), or self-limited familial neonatal-infantile epilepsy (SLFNIE) in a small number of families or individuals.

KCNQ2-Related Self-Limited Familial Neonatal Epilepsy (SLFNE)

Seizures in neonates with *KCNQ2*-SLFNE start between age two and eight days of life and spontaneously disappear between the first and the sixth to 12th month of life in otherwise healthy infants, in a context of normal neuropsychological development and EEG recordings. There is always a seizure-free interval between birth and the onset of seizures.

Approximately 30% of children with *KCNQ2*-SLFNE experience subsequent (i.e., post-infantile) focal or generalized seizures of the following types: simple febrile seizures (13%), seizures in childhood (10%), and seizures primarily in adolescence or adulthood (14%). In a few children with *KCNQ2*-SLFNE, EEG has shown centrotemporal spikes and sharp waves or self-limited epilepsy with centrotemporal spikes [Coppola et al 2003, Ishii et al 2012].

KCNQ2-Related Neonatal-Onset Developmental and Epileptic Encephalopathy (NEO-DEE)

KCNQ2 pathogenic variants have been observed in individuals with neonatal-onset developmental and epileptic encephalopathy, early-onset refractory seizures, and intellectual disability [Weckhuysen et al 2012, Allen et al 2013, Carvill et al 2013, Milh et al 2013, Weckhuysen et al 2013, Allen et al 2014, Dalen Meurs-van der Schoor et al 2014, Milh et al 2015, Pisano et al 2015].

In most affected individuals, developmental delay is associated with axial hypotonia and/or spastic quadriplegia. Most individuals are severely delayed in reaching developmental milestones and are nonverbal or only use a few words or short sentences. Some are unable to sit independently, have poor eye contact, and show little interest in their surroundings.

Seizures as well as early MRI brain abnormalities (mainly occurring in the basal ganglia and thalamus) are generally resolved by age three years. Seizures may, however, recur later in life.

At the most severe end of the spectrum, some affected individuals have findings that fall within the clinical description of Ohtahara syndrome [Saitsu et al 2012, Kato et al 2013, Martin et al 2014], an early-onset age-related epileptic encephalopathy characterized by typical burst-suppression EEG pattern within the first months of life and poor outcomes in psychomotor development and seizure control. About 10% (5/48) of individuals with early-onset (within 3 months after birth) epileptic encephalopathies with a burst-suppression pattern have pathogenic variants in *KCNQ2* [Lee et al 2020].

Other Rarer Phenotypes

***KCNQ2*-related neonatal encephalopathy with non-epileptic myoclonus.** Individuals in this group have encephalopathy with hypotonia from birth. They show prominent startle-like myoclonus triggered by sound or touch that does not have an EEG correlate and could be misdiagnosed as seizures. EEG performed in the neonatal period shows a burst-suppression pattern, evolving to a slow background and multifocal epileptiform discharges later in life. In early infancy, individuals may develop epileptic spasms and/or other seizure types. Other findings include respiratory dysfunction and profound developmental delay. MRI shows hypomyelination and brain volume loss [Mulkey et al 2017].

***KCNQ2*-related non-neonatal-onset developmental and epileptic encephalopathy (DEE).** Seven children with a *de novo KCNQ2* pathogenic variant who did not have neonatal seizures but who developed infantile spasms with (modified) hypsarrhythmia between ages four and six months have been reported. In these individuals, moderate-to-severe developmental impairment occurred subsequently, even when seizures were controlled. Brain MRI may show mild volume loss [Allen et al 2013, Carvill et al 2013, Weckhuysen et al 2013, Millichap et al 2017].

***KCNQ2*-related isolated intellectual disability (ID).** Isolated ID has been reported in association with pathogenic variants in *KCNQ2* in eight individuals [Hewson et al 2017, Bruno et al 2021, Mary et al 2021, Xiong et al 2022]. None of these individuals presented with seizures at any age, except for one who had episodes of febrile convulsions. Mild EEG background anomalies without any ictal activity were noted, and MRI was normal or showed transitory mild myelinization delay. ID ranged from mild (IQ = 50-70) to severe (IQ = 20-35); all presented with a developmental delay that predominately affected speech, sometimes associated with motor delay and hypotonia. Autistic features and agitation were often present.

Myokymia. In two families with a *KCNQ2* pathogenic variant, neonatal seizures were later followed by peripheral nerve hyperexcitability (myokymia) [Dedek et al 2001] or myoclonus-like dyskinesia [Blumkin et al 2012]. A different *KCNQ2* variant affecting the same amino acid has been found in individuals with myokymia

in the distal upper limb [Wuttke et al 2007] and/or facial [Camelo et al 2020] muscles, in the absence of neonatal seizures.

Self-limited familial infantile epilepsy (SLFIE) is characterized by later onset of seizures (age ~6 months). Although pathogenic variants in *PRRT2* account for the largest majority (>90%) of affected individuals, a *KCNQ2* pathogenic variant has been identified in a Chinese family with SLFIE [Zhou et al 2006]; in this family, the proband also developed paroxysmal myokymic episodes. Another family with SLFIE and a *KCNQ2* pathogenic variant has been described by Zara et al [2013].

Self-limited familial neonatal-infantile epilepsy (SLFNIE) is characterized by onset of seizures between the neonatal and the infantile period and presence of a pathogenic variant in *KCNQ2* [Zara et al 2013, Zeng et al 2018] – although *SCN2A* pathogenic variants account for a large fraction of individuals with this disorder [Berkovic et al 2004].

Genotype-Phenotype Correlations

Pathogenic changes associated with ***KCNQ2*-SLFNE** are truncating variants (splice, nonsense, and frameshift), whole-gene deletions, or heterozygous missense variants resulting in haploinsufficiency with a 20%-30% reduction of the M-current density when mutated subunits are expressed together with wild type subunits in heterologous cell systems [Goto et al 2019, Dirkx et al 2020].

Pathogenic changes identified in ***KCNQ2*-NEO-DEE** are all *de novo* heterozygous missense variants or in-frame indels shown to exert more severe functional defects on potassium current function. Most cause a dominant-negative reduction of more than 50% of the M-current function [Miceli et al 2013, Orhan et al 2014]. Variants associated with *KCNQ2*-NEO-DEE are clustered in four high-risk zones: the S4 voltage-sensor, the pore, the C-terminal proximal segment, and near the C-terminal B helix; all these regions are critical determinants for channel function [Millichap et al 2016, Goto et al 2019].

More rarely, specific variants cause gain-of-function effects, with the M-current density being increased to >100% when mutated subunits are coexpressed with wild type subunits. Gain-of-function variants are typically associated with neurodevelopmental phenotypes **without neonatal seizures**, such as neonatal encephalopathy with non-epileptic myoclonus, non-neonatal-onset DEE, or isolated ID [Miceli et al 2015, Millichap et al 2017, Mulkey et al 2017, Dirkx et al 2020, Mary et al 2021].

Individuals harboring identical recurring pathogenic variants so far appear to have broadly similar seizure and developmental outcomes. However, there are a few reports in which the same *KCNQ2* pathogenic variant has been reported in several severely affected individuals and in a family with SLFNE [Sadewa et al 2008, Milh et al 2015].

A few children with *KCNQ2*-NEO-DEE had a mosaic parent (the pathogenic allele detected in blood, skin, and hair root samples ranging from 5% to 30% of cells). Neurologic development in the mosaic parents was normal, although several had neonatal seizures [Weckhuysen et al 2012, Milh et al 2015, Stosser et al 2018]; these findings suggest that in order to cause a persistent neurologic disease, *KCNQ2* pathogenic variants with a more severe functional effect must be present in a sufficient proportion of cells.

Penetrance

Penetrance is incomplete in *KCNQ2*-SLFNE, with about 77%-85% of individuals heterozygous for a pathogenic variant in *KCNQ2* showing neonatal or early-infantile seizures [Plouin & Neubauer 2012, Grinton et al 2015].

Penetrance is complete for germline variants leading to *KCNQ2*-related NEO-DEE or to rarer phenotypes such as neonatal encephalopathy with non-epileptic myoclonus, non-neonatal-onset DEE, or isolated ID.

No age- or sex-related differences have been reported.

Nomenclature

The familial occurrence of neonatal seizures was first reported by Rett & Teubel [1964], who described an epileptic syndrome in which children in three generations had neonatal seizures that mostly disappeared in girls after six to eight weeks but persisted in boys throughout adolescence. The neonatal seizures were not associated with perinatal complications, such as intracranial bleeding. The term "benign" was added to the designation "familial neonatal convulsions" by Bjerre & Corelius [1968], who described a five-generation family with neonatal convulsions but normal motor and mental development, highlighting the mostly favorable outcome of the syndrome.

Subsequently it was noted that in rare instances, *KCNQ2* pathogenic variants can be observed in children who develop a therapy-resistant epileptic encephalopathy shortly after birth and a variable degree of ID by age four to five years [Alfonso et al 1997, Dedek et al 2003, Borgatti et al 2004, Schmitt et al 2005] – calling into question the use of "benign" to describe this disorder [Steinlein et al 2007]. In the most recent International League Against Epilepsy (ILAE) classification, the term "benign" is replaced by "self-limited" as a descriptor for epilepsy, referring to the likely spontaneous resolution of the symptoms [Scheffer et al 2017]. Thus, the benign familial neonatal convulsion definition previously adopted has been replaced by self-limited familial neonatal epilepsy (SLFNE).

More recent reports of certain *KCNQ2* pathogenic variants leading to a distinct phenotype characterized by neonatal epileptic encephalopathy with early-onset refractory seizures and ID of unknown origin led to proposal of the name "*KCNQ2* encephalopathy" [Weckhuysen et al 2012]. However, given the uncertain role played by the ongoing seizure activity on the developmental slowing, arrest, or regression occurring in this and other conditions, the term "developmental and epileptic encephalopathy" (DEE) has been proposed as an alternative designation [Scheffer et al 2017].

Prevalence

KCNQ2-related disorders are rare. Nevertheless, in cohort studies on the yield of genetic testing in individuals with presumed genetic epilepsies, *KCNQ2* consistently ranks among the most frequently implicated genes [Truty et al 2019, Symonds & McTague 2020]. To date, about 200 families with *KCNQ2*-SLFNE, about 200 individuals with *KCNQ2*-NEO-DEE, and seven individuals with *KCNQ2*-related isolated ID from many different nationalities have been described in the literature.

A recent prospective national epidemiologic cohort study from Scotland determined the incidence of the more common single-gene epilepsies of early childhood, and estimated that in infants under age six months *KCNQ2* was the most commonly associated gene, with an estimated incidence of 5.9:100,000 live births. Among the ten individuals included in this cohort, seven had self-limited neonatal or infantile-onset seizures and normal cognitive development at the most recent follow up, consistent with a *KCNQ2*-SLFNE diagnosis; two individuals had *KCNQ2*-NEO-DEE, and one had an unclassified drug-resistant focal epilepsy of onset at age three months and developed mild cognitive impairment [Symonds et al 2019].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with intragenic germline *KCNQ2* pathogenic variants.

Contiguous gene deletions. Deletions encompassing *KCNQ2* and adjacent genes have been identified in individuals with epilepsy phenotypes similar to SLFNE. Deletions restricted to *CHRNA4*, *KCNQ2*, and *COL20A1* were associated with a good developmental outcome, whereas delay in developmental milestones and behavioral

problems were observed in individuals with 20q13.33 deletions encompassing a greater number of genes [Traylor et al 2010, Pascual et al 2013, Okumura et al 2015].

Differential Diagnosis

Genetic disorders in the differential diagnosis of *KCNQ2*-related epilepsy. No specific EEG trait characterizes a *KCNQ2*-related disorder. The genetic differential diagnosis of *KCNQ2*-related epilepsy includes the differential diagnoses for:

- Self-limited familial neonatal epilepsy (SLFNE);
- Self-limited familial infantile epilepsy (SLFIE);
- Self-limited familial neonatal-infantile epilepsy (SLFNIE); and
- Developmental and epileptic encephalopathy (DEE).

Table 2. Selected Genes To Consider in the Differential Diagnosis of *KCNQ2*-Related Epilepsy

Gene(s)	Epilepsy Phenotype	MOI	Clinical Features of DiffDx Disorder
KCNQ3	Self-limited familial neonatal epilepsy (SLFNE)	AD	*KCNQ2*-SLFNE & *KCNQ3*-SLFNE are clinically indistinguishable; thus, molecular genetic testing of both genes is commonly performed when SLFNE is suspected.
PRRT2 *SCN2A* *SCN8A*	Self-limited familial infantile epilepsy (SLFIE) & self-limited familial neonatal-infantile epilepsy (SLFNIE) (OMIM PS601764)	AD	SLFIE & SLFNIE can closely resemble SLFNE in rare instances. In SLFIE, seizure onset is nearly always by age ~6 mos. In SLFNIE, age of seizure onset can vary w/in a family & incl both neonatal & infantile onset. [1]
>100 genes; more commonly involved genes: *ARX* *SCN2A* *SCN8A* *STXBP1*	Neonatal-onset developmental & epileptic encephalopathy (NEO-DEE) (OMIM PS308350)	XL AD [2]	When seizure onset is w/in the 1st few days of term birth, *KCNQ2* is the most commonly involved gene; when seizures begin later in the neonatal period, the chance that another gene is involved ↑. [3] No other clinical features or EEG findings discriminating among these candidates are known.

AD = autosomal dominant; DiffDx = differential diagnosis; MOI = mode of inheritance; XL = X-linked

1. Berkovic et al [2004]

2. ARX-related NEO-DEE is inherited in an X-linked manner. *SCN2A*-, *SCN8A*-, and *STXBP1*-related NEO-DEE are inherited in an autosomal dominant manner.

3. McTague et al [2016]

Genetic disorders in the differential diagnosis of *KCNQ2*-related isolated intellectual disability (ID). All genetic disorders with ID without other distinctive findings should be considered in the differential diagnosis of *KCNQ2*-related isolated ID. See OMIM Autosomal Dominant, Autosomal Recessive, and Nonsyndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

No clinical practice guidelines for *KCNQ2*-related disorders have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *KCNQ2*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with a *KCNQ2*-Related Disorder

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI & EEG • Video EEG monitoring incl sleep phase to obtain information on presence of seizures. A burst-suppression EEG pattern might only be seen during sleep.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in persons w/dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	• To assess for ↓ vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus • More complex findings may require subspecialty referral.
Hearing	Audiologic eval	To assess for hearing loss
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of a *KCNQ2*-related disorder to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with a *KCNQ2*-Related Disorder

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Education of parents/caregivers [1] • Seizures in persons w/SLFNE are generally controlled w/conventional ASM treatment, while seizures in persons w/NEO-DEE may be resistant to multiple ASMs alone or in combination. • Per a recent systematic review on ASM treatment in *KCNQ2*-related disorders, [2] 40/133 persons (~30%) w/the SLFNE phenotype experienced seizure freedom spontaneously; phenobarbital & sodium channel blockers (CBZ, OXC, LTG, & PHT) most often → seizure freedom in the remainder. [3] • In persons w/*KCNQ2*-NEO-DEE, seizure freedom was more likely to be achieved when on sodium channel blockers. [4]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Spasticity	• Orthopedics / physical medicine & rehab / PT & OT • Incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Poor weight gain / Slow growth	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Gastrointestinal dysfunction	Monitor for reflux or constipation.	Treatment as needed
Ophthalmologic involvement	By ophthalmologist	Treatment of refractive errors &/or strabismus
Central visual impairment	No specific treatment	Early intervention program to stimulate visual development
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Family/ Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CBZ = carbamazepine; DD/ID = developmental delay / intellectual disability; LTG = lamotrigine; NEO-DEE = neonatal-onset developmental and epileptic encephalopathy; OT = occupational therapy; OXC = oxacarbazepine; PHT = phenytoin; PT = physical therapy; SLFNE = self-limited familial neonatal epilepsy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

2. Kuersten et al [2020]

3. Sands et al [2016]

4. Pisano et al [2015]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with a *KCNQ2*-Related Disorder

System/Concern	Evaluation	Frequency
Neurologic	Monitor w/EEG.	*KCNQ2*-SLFNE: • At age 3, 12, & 24 mos • EEG at 24 mos should be normal.
		KCNQ2-NEO-DEE & less common phenotypes: as clinically indicated
	Assess for new manifestations such as changes in seizure types, changes in tone, movement disorders.	At each visit
	Video EEG monitoring	When new or different seizure types are suspected

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress, communication skills, & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Gastrointestinal	Monitor for reflux & constipation.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

NEO-DEE = neonatal-onset developmental and epileptic encephalopathy; OT = occupational therapy; PT = physical therapy; SLFNE = self-limited familial neonatal epilepsy

Agents/Circumstances to Avoid

In individuals with known gain-of-function pathogenic variants in *KCNQ2*, the use of the potassium channel opener retigabine/ezogabine may be contraindicated.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

The pregnancy management of a woman with a *KCNQ2* pathogenic variant and epilepsy does not differ from that of any other pregnant woman with a seizure disorder.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Ezogabine (US approved name; also known as retigabine [trade name Trobalt in Europe or Potiga in US]) is a KCNQ activator that was approved in 2011 for clinical use as an adjunctive treatment of focal-onset seizures in individuals who respond inadequately to alternative treatments. Commercialization of retigabine was discontinued after June 2017, mainly due to its tendency to cause retinal and muco-cutaneous blue-gray discoloration after prolonged (>5 years) treatment. Treatment with ezogabine has been suggested as a form of targeted therapy in severe forms of *KCNQ2*-related epilepsies due to loss-of-function variants [Millichap et al 2016, Nissenkorn et al 2021], and a randomized, double-blind, placebo-controlled trial for young individuals diagnosed with neonatal-onset developmental and epileptic encephalopathy has recently been initiated (ClinicalTrials.gov Identifier: NCT04639310).

Search Clinical Trials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

KCNQ2-related disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *KCNQ2*-related self-limited familial neonatal epilepsy (*KCNQ2*-SLFNE) are heterozygous for a pathogenic variant inherited from a parent. Some individuals with *KCNQ2*-SLFNE have the disorder as the result of a *de novo* pathogenic variant.
- Most individuals diagnosed with *KCNQ2*-related neonatal-onset developmental and epileptic encephalopathy (*KCNQ2* NEO-DEE), or less common phenotypes such as neonatal encephalopathy with non-epileptic myoclonus, non-neonatal-onset developmental and epileptic encephalopathy (DEE), or isolated intellectual disability (ID), have a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with a *KCNQ2*-related disorder to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline mosaicism [Sadewa et al 2008]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism* and will not detect a pathogenic variant that is present in the germ cells only.

    * Because parental mosaicism (with leukocyte DNA allele frequencies ranging from 1% to 30%) has been reported in the parents of several individuals with *KCNQ2*-NEO-DEE, as in other DEEs [Weckhuysen et al 2012, Kato et al 2013, Milh et al 2015, Myers et al 2018], parental testing using a method with sufficient read depth to assess for low-level mosaicism is recommended. (Note: The neurologic development of the mosaic parents may be normal and they may or may not have a history of neonatal seizures [Weckhuysen et al 2012, Milh et al 2015].)

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is heterozygous for a *KCNQ2* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *KCNQ2* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is still slightly greater than that of the general population because of the possibility of parental germline (or somatic and germline) mosaicism [Sadewa et al 2008, Weckhuysen et al 2012, Kato et al 2013, Milh et al 2015, Myers et al 2018].
- If the parents have not been tested for the *KCNQ2* pathogenic variant but are clinically unaffected, the sibs are still at increased risk for a *KCNQ2*-related disorder. A parent without a known history of epilepsy may have the *KCNQ2* pathogenic variant identified in the proband – and the concomitant risk of transmitting the pathogenic variant in each conception – due to a combination of factors: (1) in *KCNQ2*-SLFNE, penetrance is high but incomplete; (2) an affected parent may be unaware of their history of infantile-period seizures; and (3) a parent with postzygotic mosaicism for a *KCNQ2* pathogenic variant associated with a severe phenotype may be unaffected or only mildly affected.

Offspring of a proband

- Each child of a heterozygous individual with *KCNQ2*-SLFNE has a 50% chance of inheriting the pathogenic variant.
  - Note: The possibility of somatic mosaicism should be evaluated in probands with *KCNQ2*-SLFNE who have a *de novo KCNQ2* missense variant not previously described in association with a self-limited phenotype. This is important because individuals with somatic mosaicism for a *KCNQ2* pathogenic variant may have SLFNE, while their offspring are at risk for *KCNQ2*-NEO-DEE [Weckhuysen et al 2012, Milh et al 2015].
  - The level of mosaicism in blood or other tissues may not reflect the level of mosaicism in the germline.
- Given the severity of the disease course, individuals with *KCNQ2*-related NEO-DEE (or with less common phenotypes such as neonatal encephalopathy with non-epileptic myoclonus, non-neonatal-onset DEE, or isolated ID) rarely reproduce.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *KCNQ2* pathogenic variant, members of the parent's family may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals and young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once a *KCNQ2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **European KCNQ2 Association**
  Email: europeankcnq2association@gmail.com
  www.europeankcnq2association.com
- **KCNQ2 Cure Alliance**
  Phone: 303-887-9532
  Email: info@KCNQ2Cure.org
  www.kcnq2cure.org
- **The Jack Pribaz Foundation**
  60187

Phone: 708-308-1440
Email: info@kcnq2.org
www.kcnq2.org

- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **The RIKEE Project (Rational Intervention for KCNQ2/3 Epileptic Encephalopathy) Patient Registry**
  Phone: 713-798-3464
  Fax: 713-798-3455
  www.rikee.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. KCNQ2-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KCNQ2	20q13.33	Potassium voltage-gated channel subfamily KQT member 2	KCNQ2 database RIKEE KCNQ2-5-related illness database	KCNQ2	KCNQ2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for KCNQ2-Related Disorders (View All in OMIM)

121200	SEIZURES, BENIGN FAMILIAL NEONATAL, 1; BFNS1
602235	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 2; KCNQ2
613720	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 7; DEE7

Molecular Pathogenesis

KCNQ2 encodes for voltage-gated potassium channel subunits. Four subunit polypeptides assemble to form a transmembrane ion pore whose opening allows potassium ions to leave the neuron. This outward flow tends to reduce neuronal firing, especially repetitive firing. *KCNQ2*-encoded subunits (called KCNQ2 or Kv7.2) form tetramers, by themselves or in combination with subunits encoded by other homologous *KCNQ* members expressed in the brain. Heterotetrameric channels formed by Kv7.2 and Kv7.3 subunits (the latter encoded by *KCNQ3*) are a common subtype in the brain, and this likely explains the overlapping phenotypic spectra associated with pathogenic variants in *KCNQ2* and *KCNQ3*. Kv7.2-containing channels contribute to neuronal

plasticity dependent on G-protein-coupled receptors, including muscarinic acetylcholine receptors. Suppression of KCNQ channels by I_M activation of G-protein-coupled receptors (including muscarinic receptors, hence the term "M-current," or I_M) increases neuronal excitability.

In vitro studies revealed a correlation between changes in KCNQ2 molecular properties and the associated phenotypes. Variants predicted to cause *KCNQ2* haploinsufficiency are nearly always associated with self-limited familial neonatal epilepsy (SLFNE). Missense variants identified in pedigrees with SLFNE lead to a mild (25%-50%) reduction of the potassium current [Schroeder et al 1998, Singh et al 2003, Soldovieri et al 2006], whereas more severe suppression of channel function and/or prevention of axonal subcellular localization is associated with pathogenic variants causing the neonatal-onset developmental and epileptic encephalopathy (NEO-DEE) phenotype [Miceli et al 2013, Orhan et al 2014, Abidi et al 2015, Soldovieri et al 2016, Tran et al 2020].

Various molecular mechanisms appear responsible for the pathogenic variant-induced current decrease, including a reduced number of functional channels in the plasma membrane, changes in the subcellular targeting of the channels [Abidi et al 2015], an altered regulation of their function by associated proteins (e.g., calmodulin, ankyrin-G, syntaxin-1A) or critical membrane components (phosphatidylinositol 4,5-bisphosphate, PIP_2), and a reduced sensitivity to changes in membrane potential by correctly assembled channels [Dedek et al 2001, Castaldo et al 2002, Miceli et al 2013, Ambrosino et al 2015].

By contrast, *KCNQ2* pathogenic variants whose associated phenotypes **lack** neonatal-onset seizures but include developmental impairment frequently exhibit increased channel function (gain of function) when expressed in vitro [Miceli et al 2015]. For example, the *KCNQ2* p.Arg201Cys or p.Arg201His variants found in babies with neonatal encephalopathy with non-epileptic myoclonus and infantile-onset epilepsy cause strongly increased currents [Mulkey et al 2017]. Some variants found in individuals with West syndrome (infantile-onset seizures) and intellectual disability (ID), and in individuals with isolated ID, also exhibit gain-of-function effects in vitro [Millichap et al 2017].

Many questions remain as to how the functional changes observed at the molecular level result in changes at the neuronal, circuit, and behavioral level during development. Efforts to standardize variant characterization and thereby improve comparability among studies are currently under way.

Mechanism of disease causation. Functional studies of missense variants in *KCNQ2* identified in association with the SLFNE phenotype slightly reduce (by 25%-50%) channel function, suggesting haploinsufficiency as the primary pathogenic mechanism for *KCNQ2*-SLFNE. By contrast, missense pathogenic variants found in individuals with *KCNQ2*-NEO-DEE exert more severe functional defects on K^+ current function (by >50%), because incorporation of even a single altered subunit would severely "poison" the function of the entire tetrameric channel, suggesting that a dominant-negative effect could be responsible for the severe epileptic phenotype [Miceli et al 2013, Orhan et al 2014]. Thus, together with additional genetic and epigenetic factors, the extent of derangement of KCNQ2/3 (I_{KM}) channel function associated with a *KCNQ2* pathogenic variant appears as an important predictor of disease severity.

The molecular mechanisms responsible for the decrease in channel function caused by these variants appear heterogeneous, and include: (1) reduced K^+ ion permeation when the variant affects residues located in the pore domain; (2) decreased opening probability and faster closing kinetics at each membrane voltage for variants affecting critical gating residues in the voltage-sensing domain; (3) changes in the affinity and/or functional regulation of cytoplasmic regulators such as syntaxin-1A, calmodulin, or phosphatydilinositol-4,5-bisphosphate, and others; (4) mRNA instability and precocious subunit degradation by nonsense-mediated RNA decay when the variant affects transcript splicing sites or introduces large deletions in the protein; and (5) altered subcellular distribution when the interaction with axon-targeting signals or partners is disrupted [Nappi et al 2020]. In all

these cases, a reduced KCNQ2/3 (I_{KM}) channel function in excitatory neurons would increase their excitability and lower seizure threshold, thereby predisposing to epilepsy.

De novo missense variants in *KCNQ2* that cause gain-of-function effects on channel activity increase maximal current density and cause a marked hyperpolarizing shift in the voltage dependence of activation and an acceleration of activation kinetics, suggestive of an increased sensitivity of the opening process to voltage. Several hypotheses have been put forward to explain the paradoxic increase in neuronal excitability associated with an enhanced Kv7.2/IKM function in vitro, and possibly in vivo. These include: (1) preferential suppression of inhibitory interneuron function (the "interneuronopathy" hypothesis) [Catterall 2018]; (2) activation of a recurrent neuron-astrocyte-neuron excitatory loop; (3) faster action potential repolarization and sodium channel repriming; and (4) overactivation of the hyperpolarization-activated nonselective cation current resulting in secondary depolarizations [Niday & Tzingounis 2018].

Table 6. Notable *KCNQ2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_172107.4 NP_742105.1	c.593G>A	p.Arg198Gln	Assoc w/unique phenotype: no neonatal seizures, infantile spasms w/hypsarrhythmia on EEG at age 4-6 mos; subsequent DD & moderate-to-severe ID [Millichap et al 2017, Yang et al 2019, Liu et al 2021]
	c.601C>T	p.Arg201Cys	Assoc w/neonatal onset of profound encephalopathy, apparent weak respiratory drive, myoclonic-appearing mvmts w/o ictal EEG changes, & severe-to-profound DD [Mulkey et al 2017, Olson et al 2017, Kojima et al 2018]
	c.602G>A	p.Arg201His	
	c.821C>T	p.Thr274Met	Assoc w/*KCNQ2*-NEO-DEE. Among most frequently reported in literature [Weckhuysen et al 2012, Milh et al 2013, Orhan et al 2014, Milh et al 2015, Millichap et al 2016, Hortigüela et al 2017, Olson et al 2017, Zhang et al 2017, Borlot et al 2019, Maghera et al 2020] & in gene-specific databases (RIKEE)
	c.881C>T	p.Ala294Val	Assoc w/*KCNQ2*-NEO-DEE; milder phenotype is noted if variant is assoc w/mosaicism [Milh et al 2015]. Among most frequently reported in literature [Steinlein et al 2007, Kato et al 2013, Milh et al 2013, Allen et al 2014, Abidi et al 2015, Milh et al 2015, Pisano et al 2015, Millichap et al 2016, Hortigüela et al 2017, Olson et al 2017, Parrini et al 2017, Chen et al 2018, Kothur et al 2018] & gene-specific databases (RIKEE)
	c.916G>A	p.Ala306Thr	Assoc w/*KCNQ2*-SLFNE [Ronen et al 1993, Singh et al 1998, Soldovieri et al 2014], incl in the largest 6-generation family reported, w/69 affected persons

DD = developmental delay; ID = intellectual disability; NEO-DEE = neonatal-onset developmental and epileptic encephalopathy; SLFNE = self-limited familial neonatal epilepsy

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Author History

Giulia Bellini, PhD; Second University of Naples (2009-2016)
Edward Cooper, MD, PhD (2016-present)
Giangennaro Coppola, MD; University of Salerno (2013-2016)
Nishtha Joshi, BDS, MPH; Baylor College of Medicine (2016-2022)
Francesco Miceli, PhD (2009-present)
Emanuele Miraglia del Giudice, MD; Second University of Naples (2009-2016)
Antonio Pascotto, MD; Second University of Naples (2009-2013)
Maria Virginia Soldovieri, PhD (2009-present)
Maurizio Taglialatela, MD, PhD (2005-present)
Sarah Weckhuysen, MD, PhD (2016-present)

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