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NLM Citation: Miceli F, Soldovieri MV, Weckhuysen S, et al. *KCNQ3*-Related Disorders. 2014 May 22 [Updated 2023 Sep 28]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

KCNQ3-Related Disorders

Francesco Miceli, PhD,[1] Maria Virginia Soldovieri, PhD,[2] Sarah Weckhuysen, MD, PhD,[3] Edward C Cooper, MD, PhD,[4] and Maurizio Taglialatela, MD, PhD[5]

Created: May 22, 2014; Updated: September 28, 2023.

Summary

Clinical characteristics

KCNQ3-related disorders include self-limited familial neonatal epilepsy (SLFNE) and self-limited familial infantile epilepsy (SLFIE), seizure disorders that occur in children who typically have normal psychomotor development. An additional *KCNQ3*-related neurodevelopmental disorder (NDD) with and without epilepsy has also been described.

In *KCNQ3*-SLFNE, seizures begin in an otherwise healthy infant between age days two and eight of life and spontaneously disappear within the first year of life. Seizures are generally brief, lasting one to two minutes. Seizure types include tonic or apneic episodes and focal clonic activity, with or without autonomic changes. Motor activity may be confined to one body part, migrate to other regions, or generalize. Infants are normal between seizures and feed normally.

In *KCNQ3*-SLFIE, seizures start in the first year of life beyond the neonatal period and disappear after age one to two years. Seizures are generally brief, lasting two minutes; they appear as daily repeated clusters. Seizure types are usually focal, but can also include generalized, causing diffuse hypertonia with jerks of the limbs, head deviation, or motor arrest with unconsciousness and cyanosis. Infants are normal between seizures and psychomotor development is usually normal.

In *KCNQ3*-NDD, individuals present with intellectual disability with or without seizures and/or cortical visual impairment. As little clinical information on these individuals is available, the clinical presentation of *KCNQ3*-NDD remains to be defined.

Author Affiliations: 1 Division of Pharmacology, Department of Neuroscience, University of Naples Federico II, Naples, Italy; Email: frmiceli@unina.it. 2 Department of Health Science, University of Molise, Campobasso, Italy; Email: mariavirginia.soldovieri@unimol.it. 3 Applied & Translational Neurogenomics Group VIB Center for Molecular Neurology, University of Antwerp; Neurology Department, University Hospital, Antwerp, Belgium; Email: sarah.weckhuysen@uantwerpen.vib.be. 4 Departments of Neurology, Neuroscience, and Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas; Email: ecc1@bcm.edu. 5 Division of Pharmacology, Department of Neuroscience, University of Naples Federico II, Naples, Italy; Email: mtaglial@unina.it.

Diagnosis/testing

The diagnosis of a *KCNQ3*-related disorder is established in a proband with suggestive findings and at least one heterozygous pathogenic variant in *KCNQ3* identified by molecular genetic testing. Rarely, affected individuals have biallelic pathogenic variants in *KCNQ3*.

Management

Treatment of manifestations: The seizures of *KCNQ3*-SLFNE are generally controlled with anti-seizure medications (ASMs) including phenobarbital and phenytoin or carbamazepine, usually withdrawn at age three to six months. The seizures of *KCNQ3*-SLFIE are usually completely controlled with adequate doses of phenobarbital, carbamazepine, or valproate. In rare instances of seizure recurrence, the starting dose of ASM is often low. ASMs are usually withdrawn after one to three years. *KCNQ3*-NDD is managed using standard evaluations, therapies, and educational support tailored to the individual's needs.

Surveillance: In children with *KCNQ3*-SLFNE, EEGs at onset and age three, 12, and 24 months are recommended; the EEG at 24 months should be normal. In children with *KCNQ3*-SLFIE, EEGs at onset and age 12, 24, and 36 months are recommended; the EEG at 36 months should be normal.

Pregnancy management: The management of a pregnant woman with a *KCNQ3* pathogenic variant is the same as that for any other pregnant woman with a seizure disorder or at increased risk for a seizure disorder: (1) no ASM is required if the woman has been seizure-free or if the woman has no history of seizures; and (2) ASM may be continued for epilepsy that is active during pregnancy.

Genetic counseling

KCNQ3-SLFNE and *KCNQ3*-SLFIE are inherited in an autosomal dominant manner; most individuals have an affected parent, or a parent known to have been symptomatic in infancy. *KCNQ3*-NDD typically occurs as an autosomal dominant disorder caused by a *de novo* pathogenic variant. Rarely, *KCNQ3*-NDD is caused by biallelic pathogenic variants and inherited in an autosomal recessive manner.

Autosomal dominant inheritance: Each child of an individual with *KCNQ3*-SLFNE, *KCNQ3*-SLFIE, or autosomal dominant *KCNQ3*-NDD has a 50% chance of inheriting the pathogenic variant.

Autosomal recessive inheritance: If both parents of a child with autosomal recessive *KCNQ3*-NDD are known to be heterozygous for a *KCNQ3* pathogenic variant, each sib of an affected individual has a 25% chance of being affected at conception, a 50% chance of being an asymptomatic carrier, and a 25% of being asymptomatic and not a carrier.

Once the *KCNQ3* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

KCNQ3-Related Disorders: Most Common Phenotypes [1]	Mode of Inheritance
Self-limited familial neonatal epilepsy (SLFNE)	Autosomal dominant (typically inherited)
Self-limited familial infantile epilepsy (SLFIE)	
Neurodevelopmental disorder (NDD) ± seizures	Autosomal dominant (*de novo*) or, rarely, autosomal recessive

For synonyms and outdated names see Nomenclature.

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

KCNQ3-related disorders include self-limited familial neonatal epilepsy (SLFNE) and self-limited familial infantile epilepsy (SLFIE), which are epilepsy syndromes associated with a structurally normal brain and mostly normal neurologic findings and psychomotor development. Pathogenic variants in *KCNQ3* have also been described in individuals with neurodevelopmental features including developmental delay or intellectual disability with or without seizures.

Suggestive Findings

KCNQ3-related disorders **should be suspected** in individuals with the following clinical and laboratory findings (by phenotype), imaging findings, and family history.

***KCNQ3*-related self-limited familial neonatal epilepsy (*KCNQ3*-SLFNE)**

- **Clinical findings**
  - Seizures in an otherwise healthy infant with age of onset between two and eight days of life, spontaneously disappearing within the first year of life. The occurrence of a seizure-free interval between birth and the onset of seizures is a relevant diagnostic and prognostic element.
  - Wide spectrum of seizure types, including tonic or apneic episodes, focal tonic or clonic episodes, or autonomic changes. Motor activity may be confined to one body part, migrate to other body regions, or generalize. Seizures are usually brief, lasting one to two minutes.
  - Normal physical examination and laboratory tests prior to the onset of seizures, between seizure episodes, and following cessation of seizures.
  - No specific EEG findings. Ictal EEG may show focal onset with possible secondary generalization. Interictal EEG and EEG background are usually normal.
- **Laboratory findings.** The diagnosis of *KCNQ3*-SLFNE is suspected in individuals with clinical findings consistent with SLFNE and normal results on molecular testing for *KCNQ2*, the main gene for SLFNE (see *KCNQ2*-Related Disorders).

***KCNQ3*-related self-limited familial infantile epilepsy (*KCNQ3*-SLFIE)**

- **Clinical findings**
  - Brief, repeated, focal, and secondarily generalized seizures in an otherwise healthy infant; seizures occur within the first year of life after the neonatal period.
  - Seizures spontaneously disappear after age one to two years without neurologic sequelae in adulthood.
- **Laboratory findings.** The diagnosis of *KCNQ3*-SLFIE is suspected in individuals with clinical findings consistent with SLFIE and normal results on molecular testing for *PRRT2*, the main gene for SLFIE (see *PRRT2*-Associated Paroxysmal Movement Disorders).

***KCNQ3*-related neurodevelopmental disorder (*KCNQ3*-NDD)**, which can present as one or more of the following:

- Developmental delays or intellectual disability without epilepsy, with or without autism spectrum disorder
- Developmental delays or intellectual disability with epilepsy and cortical visual impairment, with or without autism spectrum disorder
- Developmental and epileptic encephalopathy (DEE), in which aggressive epileptogenic activity during brain maturation accompanies cognitive and neuropsychological stagnation or regression

Imaging findings. Brain MRI is usually normal.

Family history

- ***KCNQ3*-SLFNE and *KCNQ3*-SLFIE.** Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.
- ***KCNQ3*-NDD.** Because *KCNQ3*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of a *KCNQ3*-related disorder **is established** in a proband with suggestive findings and at least one heterozygous pathogenic (or likely pathogenic) variant in *KCNQ3* identified by molecular genetic testing (see Table 1). Rarely, some affected individuals have biallelic pathogenic (or likely pathogenic) variants in *KCNQ3*.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other epilepsy disorders are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of a *KCNQ3*-related disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *KCNQ3* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, 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; however, to date only one large intragenic deletion has been reported in one family with *KCNQ3*-SLFNE [Sands et al 2016]. Therefore, testing for intragenic deletions or duplications is unlikely to identify a disease-causing variant.

  Note: Single gene testing can be used for individuals who present with the SLFNE or SLFIE phenotype and have previously tested negative for pathogenic variants in *KCNQ2* or *PRRT2*, respectively.

- **A multigene panel** for disorders associated with epilepsy or developmental delay that includes *KCNQ3* 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. Notes: (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.

Note: For individuals who have had no previous molecular genetic testing, the authors recommend using a multigene panel or more comprehensive genomic testing whenever possible, given the lack of distinguishing features between the different genetic-related forms of SLFNE and SLFIE. For an individual with NDD, there are no features to distinguish *KCNQ3*-NDD from NDD caused by other genes; thus, single-gene testing is not recommended.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by epilepsy, **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. To date, the majority of *KCNQ3* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

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

Table 1. Molecular Genetic Testing Used in *KCNQ3*-Related Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
KCNQ3	Sequence analysis [3]	59/60 [4]
	Gene-targeted deletion/duplication analysis [5]	1/60 [4, 6]

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. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] and Charlier et al [1998], Hirose et al [2000], Singh et al [2003], Li et al [2006], Li et al [2008], Neubauer et al [2008], Rauch et al [2012], Allen et al [2013], Fister et al [2013], Zara et al [2013], Allen et al [2014], Soldovieri et al [2014], Fusco et al [2015], Grinton et al [2015], Grozeva et al [2015], Miceli et al [2015b], Bosch et al [2016], Maljevic et al [2016], Sands et al [2016], Deciphering Developmental Disorders Study [2017], Olson et al [2017], Ambrosino et al [2018], Kothur et al [2018], Piro et al [2019], Lauritano et al [2019], Sands et al [2019], Symonds et al [2019], Trinh et al [2019], Li et al [2020], Maghera et al [2020], Miceli et al [2020], Nardello et al [2020], Wang et al [2020], Miyake et al [2021], Arredondo et al [2022], Pijpers et al [2023]
5. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Sands et al [2016] reported an individual with SLFNE who had a deletion of exons 1-15 in *KCNQ3*.

Clinical Characteristics

Clinical Description

To date, about 140 individuals have been identified with a pathogenic variant in *KCNQ3* [Charlier et al 1998, Hirose et al 2000, Singh et al 2003, Li et al 2006, Li et al 2008, Neubauer et al 2008, Rauch et al 2012, Allen et al 2013, Fister et al 2013, Zara et al 2013, Allen et al 2014, Soldovieri et al 2014, Fusco et al 2015, Grinton et al 2015, Grozeva et al 2015, Miceli et al 2015b, Bosch et al 2016, Maljevic et al 2016, Sands et al 2016, Deciphering Developmental Disorders Study 2017, Ambrosino et al 2018, Kothur et al 2018, Lauritano et al 2019, Piro et al 2019, Sands et al 2019, Symonds et al 2019, Trinh et al 2019, Li et al 2020, Maghera et al 2020, Miceli et al 2020, Nardello et al 2020, Wang et al 2020, Miyake et al 2021, Arredondo et al 2022, Pijpers et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *KCNQ3*-Related Disorders: Frequency of Select Features [1]

Phenotype	Feature	% of Persons w/ Feature [2]	Comment
***KCNQ3*-SLFNE**	Epilepsy	>90%	• Age of onset of seizures is between 2-8 days of life; spontaneously disappear between age 1-12 mos in otherwise healthy infant. • Seizures are generally brief, lasting 1-2 minutes. • Seizure types incl tonic or apneic episodes, focal clonic activity, & autonomic changes.
	Normal psychomotor development	>90%	Rare reports of DD or ID
***KCNQ3*-SLFIE**	Epilepsy	100% (6/6)	• Age of onset of seizures is w/in 1st yr of life, beyond neonatal period, & seizures disappear in 1-2 years. • Seizures are generally brief, lasting ~2 minutes; they are usually focal but can be also generalized.
	Normal psychomotor development	100% (6/6)	
***KCNQ3*-NDD**	Developmental delays / intellectual disability	>90%	Moderate-to-severe ID
	Autism spectrum disorder	~20% (12/59)	Autistic features incl stereotypies, mouthing nonfood objects, & aggressive, impulsive, & self-injurious behaviors. [3] Given that ASD features (& other details about phenotype) in larger cohorts of ID/DD are not reported, this figure may be underestimated.
	Epilepsy	~20%	Even persons w/o clinical seizures often have abundant sleep-activated epileptic activity on EEG recordings.

ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual delay; NDD = neurodevelopmental disorder; SLFIE = self-limited familial infantile epilepsy; SLFNE = self-limited familial neonatal epilepsy

1. Soldovieri et al [2014], Miceli et al [2015b], Sands et al [2019], Maghera et al [2020]

2. Percentages are based on nearly 140 reported symptomatic individuals with heterozygous pathogenic variants only and do not include individuals with biallelic pathogenic variants in *KCNQ3*.

3. Sands et al [2019]

KCNQ3-related disorders include self-limited familial neonatal epilepsy (SLFNE) and self-limited familial infantile epilepsy (SLFIE), seizure disorders that occur in children who have structurally normal brains, normal interictal neurologic examinations, and normal psychomotor development. Pathogenic variants in *KCNQ3* have

also been reported in individuals with neurodevelopmental disorders with or without epilepsy, expanding the known phenotypes.

***KCNQ3*-related self-limited familial neonatal epilepsy (*KCNQ3*-SLFNE)** is characterized by seizures that start in an otherwise healthy infant between ages two and eight days of life and spontaneously disappear during the first year of life. Seizures are generally brief, lasting one to two minutes. Seizure types include tonic or apneic episodes, focal clonic activity, and autonomic changes. Motor activity may be confined to one body part, migrate to other regions, or generalize. Infants are well between seizures and feed normally.

Psychomotor development is usually normal. However, two individuals within a family with *KCNQ3*-SLFNE described by Soldovieri et al [2014] and three individuals in another family reported by Miceli et al [2015b] showed (in addition to seizures) intellectual disability. Notably, although intellectual and/or developmental delays have not been considered characteristic of SLFNE, recent reports highlight evidence for variable expressivity in individuals with *KCNQ2*-SLFNE [Millichap et al 2016, Al Yazidi et al 2017, Hewson et al 2017].

***KCNQ3*-related self-limited familial infantile epilepsy (*KCNQ3*-SLFIE)** is characterized by seizures that start in the first year of life, beyond the neonatal period, and disappear after age one to two years. Seizures are generally brief, lasting about two minutes; they appear as daily repeated clusters. Seizure type is usually focal, but can also be generalized, with jerking of the limbs, head deviation, and/or motor arrest with unconsciousness and cyanosis.

Infants are typically well between seizures and psychomotor development is usually normal.

***KCNQ3*-related neurodevelopmental disorder (*KCNQ3*-NDD).** A small number of individuals with *de novo* pathogenic missense variants in *KCNQ3* have been identified with neurodevelopmental disorder. *De novo* pathogenic variants in *KCNQ3* have been described in a few children with intellectual disability and autism spectrum disorder with or without epilepsy [Rauch et al 2012, Allen et al 2013, Grozeva et al 2015, Miceli et al 2015b, Deciphering Developmental Disorders Study 2017, Sands et al 2019, Wang et al 2020, Miyake et al 2021] and cortical visual impairment [Bosch et al 2016]. Several of these children were reported to show sleep-activated epileptic activity on EEG, even in the absence of clinical seizures. Little clinical information on these individuals is provided in most of these reports; thus, the clinical presentation of *KCNQ3*-NDD remains to be defined in more detail. Biallelic pathogenic variants have been identified in three families with developmental and epileptic encephalopathy with neonatal-onset seizures and global developmental delay [Ambrosino et al 2018, Kothur et al 2018, Lauritano et al 2019].

Genotype-Phenotype Correlations

Pathogenic variants in *KCNQ3* reported in typical familial forms of self-limited epilepsies (SLFNE and SLFIE) are commonly missense alterations located within the pore region (S5, S6, and intervening loop) and resulting in loss of function (LOF) of channel activity. Similar but more dramatic functional LOF effects have also been found in *KCNQ3* channels carrying autosomal dominantly transmitted pathogenic variants responsible for more severe phenotypes, leading to the hypothesis that the degree of *KCNQ3* functional impairment may contribute to clinical disease severity [Miceli et al 2015b]. Given the low number of pathogenic *KCNQ3* variants described to date, definitive genotype-phenotype correlations are not very clear.

De novo missense alterations affecting the first two positively charged residues within the S4 transmembrane segment of the voltage-sensing domain (p.Arg227Gln, p.Arg230Cys/Ser/His) have been reported in individuals with developmental delay, autism spectrum disorder, and sleep-activated epileptiform discharges on EEG. Functional analysis using voltage clamp recordings revealed that these pathogenic variants stabilized the activated state of the channel and result in gain-of-function (GOF) effects on channel activity. In contrast to individuals with LOF pathogenic variants in *KCNQ3*, neonatal and infantile seizures were not a common finding in individuals with GOF pathogenic variants [Sands et al 2019]. More recent evidence confirms that these S4

variants in *KCNQ3* are among the most recurrent in individuals with neurodevelopmental disorders [Wang et al 2020]. Additional *KCNQ3* pathogenic variants are described in individuals with neurodevelopmental disorders; however, these variants have not been functionally assessed for whether they cause LOF or GOF [Wang et al 2020]. Biallelic LOF pathogenic variants have been described in three families and lead to a more severe phenotype of neonatal-onset epilepsy and global developmental delay [Ambrosino et al 2018, Kothur et al 2018, Lauritano et al 2019].

Penetrance

In *KCNQ3*-SLFNE, penetrance is incomplete (0.8-0.85): SLFNE is found in 72/80 (90%) of individuals with a *KCNQ3* pathogenic variant [Charlier et al 1998, Hirose et al 2000, Singh et al 2003, Li et al 2006, Li et al 2008, Neubauer et al 2008, Fister et al 2013, Allen et al 2014, Soldovieri et al 2014, Grinton et al 2015, Miceli et al 2015b, Maljevic et al 2016, Sands et al 2016, Piro et al 2019, Symonds et al 2019, Maghera et al 2020, Miceli et al 2020, Pijpers et al 2023].

Incomplete penetrance in *KCNQ3*-SLFNE and *KCNQ3*-SLFIE may be due to failure to recognize the seizures (which can be brief and disappear spontaneously very soon after onset) in some individuals.

Penetrance in *KCNQ3*-NDD is little studied given the small number of reported individuals, but pathogenic variants with a proven functional effect are fully penetrant.

Nomenclature

Rett & Teubel [1964] were the first to report familial occurrence of neonatal seizures of presumed genetic (rather than acquired) origin. To highlight the mostly favorable outcome of the syndrome in contrast to other causes of recurrent neonatal seizures, the term "benign" was later added to "familial neonatal convulsions" by Bjerre & Corelius [1968]. Terminology was further revised to benign familial neonatal epilepsy (BFNE) to reflect the fact that the seizures were often focal and for consistency of naming with other epilepsy syndromes [Berg et al 2010].

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 resolution of the seizures during early infancy as well as good developmental outcome [Scheffer et al 2017]. Thus, the benign "familial" neonatal convulsion definitions previously adopted have been replaced by self-limited familial neonatal epilepsy (SLFNE) and self-limited familial infantile epilepsy (SLFIE).

Prevalence

About 20 families (72 individuals) with SLFNE with a heterozygous *KCNQ3* pathogenic variant have been reported to date [Charlier et al 1998, Hirose et al 2000, Singh et al 2003, Li et al 2006, Li et al 2008, Neubauer et al 2008, Fister et al 2013, Allen et al 2014, Soldovieri et al 2014, Grinton et al 2015, Miceli et al 2015b, Maljevic et al 2016, Sands et al 2016, Piro et al 2019, Symonds et al 2019, Maghera et al 2020, Miceli et al 2020, Pijpers et al 2023]. The percentage of families with SLFNE who have pathogenic variants in *KCNQ3* is likely less than 5%, as *KCNQ2* is the main locus for SLFNE, accounting for more than 70% of cases (see *KCNQ2*-Related Disorders).

Only four families (8 individuals) with SLFIE and a heterozygous *KCNQ3* pathogenic variant have been reported to date [Singh et al 2003, Zara et al 2013, Fusco et al 2015, Nardello et al 2020]. No data on the prevalence of *KCNQ3* pathogenic variants in SLFIE are available; nevertheless, this figure is likely to be small given that *PRRT2* is the main gene for SLFIE.

The prevalence of *KCNQ3*-NDD is unknown but the disorder seems to be rare. Pathogenic *de novo* variants in *KCNQ3* are much less frequently identified than in its paralogue gene *KCNQ2*.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *KCNQ3*.

Differential Diagnosis

The genetic differential diagnosis of *KCNQ3*-related epilepsy (see Table 3) includes the differential diagnoses for:

- Self-limited familial neonatal epilepsy (SLFNE);
- Self-limited familial infantile epilepsy (SLFIE); and
- Self-limited familial neonatal-infantile epilepsy (SLFNIE).

Self-limited familial neonatal epilepsy (SLFNE). Pathogenic variants in *KCNQ3* represent an infrequent cause of SLFNE, as most families with SLFNE segregate pathogenic variants in *KCNQ2*. The diagnosis of SLFNE requires the absence of any other explanation for the seizures. No specific EEG patterns characterize SLFNE during neonatal seizures and interictal EEG is most commonly normal (50%-70% of infants).

Of note, laboratory tests and imaging studies are important to exclude other possible causes for seizures including non-genetic etiologies. It is important not to miss a diagnosis of a treatable meningoencephalitis in the early stages or of intracranial hemorrhage – as neonates may not exhibit the typical findings observed in older infants and children, and seizures may be the only early manifestation.

Self-limited familial infantile epilepsy (SLFIE). SLFIE is genetically distinct from SLFNE, with at least three genes involved in addition to *KCNQ3*.

Table 3. Selected Genes to Consider in the Differential Diagnosis of *KCNQ3*-SLFNE and *KCNQ3*-SLFIE

Gene(s)	Phenotype	MOI	Clinical Features
KCNQ2	Self-limited familial neonatal epilepsy (SLFNE) (See *KCNQ2*-Related Disorders.)	AD	The frequency of *KCNQ2* pathogenic variants as a cause of SLFNE is more than tenfold that of *KCNQ3* pathogenic variants. *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) (See *PRRT2*-Associated Paroxysmal Movement Disorders, *SCN8A*-Related Epilepsy and/or Neurodevelopmental Disorders, & OMIM PS601764.)	AD	*PRRT2* is the most commonly involved gene for SLFIE. While some persons w/*PRRT2* pathogenic variants develop paroxysmal kinesigenic dyskinesia later in life, clinical characteristics early in life do not differ from *KCNQ3*-SLFIE. 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]

AD = autosomal dominant; MOI = mode of inheritance

1. Berkovic et al [2004]

***KCNQ3*-related neurodevelopmental delay (NDD).** The phenotypic features associated with *KCNQ3*-NDD are not sufficiently specific to diagnose this condition clinically. All disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series for genes associated with the following:

- Autosomal dominant intellectual developmental disorders
- Autosomal recessive intellectual developmental disorders
- Nonsyndromic X-linked intellectual developmental disorders
- Syndromic X-linked intellectual developmental disorders

Management

No clinical practice guidelines for *KCNQ3*-related disorders have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *KCNQ3*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *KCNQ3*-Related Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist for eval of suspected seizures, as indicated	To incl EEG & high-resolution brain MRI if not performed as part of eval prior to diagnosis
Developmental evaluation	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings 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 gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings that 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 *KCNQ3*-related disorders 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.	

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

Epilepsy in *KCNQ3*-related disorders – notably self-limited familial neonatal epilepsy (SLFNE) and self-limited familial infantile epilepsy (SLFIE) – are usually treatable using standard anti-seizure medication (ASM).

Targeted therapy. Most individuals with SLFNE or SLFIE caused by *KCNQ3* pathogenic variants do not require therapy after seizure cessation. No targeted therapy is available for the most severe clinical phenotypes of *KCNQ3*-related disorders.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *KCNQ3*-Related Disorders: Treatment of Manifestations

Manifestation/Concern		Treatment	Considerations/Other
Epilepsy	**SLFNE**	Standard treatment w/ASM by experienced neurologist	• Seizures are generally well-controlled using standard ASM. Due to the limited nature of the epilepsy, most ASMs are discontinued between age 3-6 mos in *KCNQ2*-related disorders. [1] A significant number of persons w/SLFNE may experience seizure freedom spontaneously (40/133, ~30%), and phenobarbital & sodium channel blockers (carbamazepine [CBZ], oxcarbazepine [OXC], lamotrigine, & phenytoin) most often lead to seizure freedom in the remainder of persons. [2] • Neonates w/more severe or intractable seizures may benefit from other ASM (e.g., levetiracetam & topiramate) despite limited data & off-label use. [3] However, refractory seizures are uncommon in *KCNQ3*-SLFNE. • One study has shown that early initiation of CBZ or OXC in SLFNE was assoc w/shorter hospitalization. No side effects of CBZ were reported, suggesting that CBZ is safe & rapidly effective in neonates w/SLFNE, even in status epilepticus, & that CBZ should be the drug of choice in SLFNE. [2] • Education of parents/caregivers [4]
	SLFIE		• Seizures are generally well-controlled using standard ASM. Due to the limited nature of the epilepsy, most ASMs are discontinued between age 1-3 yrs w/no relapses. • Phenobarbital, carbamazepine, or valproate have been shown to control seizures.
Developmental delay / Intellectual disability		Standard treatment, which may incl supportive developmental therapies (OT, PT, ST) to address specific delayed areas	• Consultation w/neurodevelopmental specialist may be considered. • It is currently unclear whether behavior or cognition are improved by suppressing the abundant EEG abnormalities seen in some children during sleep.
Autism spectrum disorder		Standard treatment, which may incl ABA therapy	
Family/Community		Ensure appropriate social work involvement to connect families w/local resources & support.	

ABA = applied behavioral therapy; ASM = anti-seizure medication; CBZ = carbamazepine; OT = occupational therapy; OXC = oxcarbazepine; PT = physical therapy; ST = speech therapy

1. Kuersten et al [2020]

2. Sands et al [2016]

3. Tulloch et al [2012]

4. 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.

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.

Prevention of Primary Manifestations

No specific primary prevention measure is available before symptom appearance.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *KCNQ3*-Related Disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Monitor w/EEG	*KCNQ3*-SLFNE: • EEG at onset & age 3, 12, & 24 mos is recommended. • EEG at 24 mos should be normal.
		KCNQ3-SLFIE: • EEG at onset & age 12, 24, & 36 mos is recommended. • The EEG at 36 mos should be normal.
		KCNQ3-NDD: sleep EEG at diagnosis is recommended to evaluate presence of sleep-activated epileptic activity.
	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
Development	Monitor developmental progress, communication skills, & educational needs.	At each visit
Neurobehavioral/ Psychiatric	Assessment for anxiety, ADHD, ASD, aggression, & self-injury	
Family/Community	Assess family need for social work support & care coordination.	

Agents/Circumstances to Avoid

In individuals with known gain-of-function pathogenic variants in *KCNQ3*, the use of the potassium channel opener retigabine/ezogabine may be contraindicated.

Pregnancy Management

The management of a pregnant woman with a *KCNQ3* pathogenic variant is the same as that of any other pregnant woman with a history of (or at risk for) epilepsy.

- No medication is indicated if (1) the woman has been seizure free and is not taking medications or (2) the woman has no history of seizures.
- Treatment with anti-seizure medication (ASM) may be continued for active epilepsy during pregnancy.
- In general, women with epilepsy or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of ASM during pregnancy reduces this risk. However, exposure to ASM may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASM to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.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. Note: There may not be clinical trials for this disorder.

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

KCNQ3-related self-limited familial neonatal epilepsy (SLFNE) and *KCNQ3*-related self-limited familial infantile epilepsy (SLFIE) are inherited in an autosomal dominant manner.

In most individuals reported to date, *KCNQ3*-related neurodevelopmental disorder (NDD) occurs as an autosomal dominant disorder caused by a *de novo* pathogenic variant. Rarely, *KCNQ3*-NDD is caused by biallelic pathogenic variants and inherited in an autosomal recessive manner [Ambrosino et al 2018, Kothur et al 2018, Lauritano et al 2019].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *KCNQ3*-SLFNE and *KCNQ3*-SLFIE have an affected parent or a parent who is known to have been symptomatic in infancy. Of note, parents can be heterozygous for a *KCNQ3* pathogenic variant but have never been symptomatic, given that penetrance is incomplete; or neonatal seizures may have been unrecognized (or forgotten) as they are typically brief and disappear spontaneously soon after onset.
- In contrast, most individuals with autosomal dominant *KCNQ3*-NDD have the disorder as a result of a heterozygous *de novo KCNQ3* pathogenic variant. (See Autosomal Recessive Inheritance – Risk to Family Members for discussion of *KCNQ3*-NDD caused by biallelic pathogenic variants.)
- Molecular genetic testing is recommended for the parents of the proband 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 (or somatic and germline) mosaicism. 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.
- The family history of some individuals diagnosed with *KCNQ3*-SLFNE and *KCNQ3*-SLFIE may appear to be negative because of failure to recognize the disorder in family members and/or reduced penetrance. An initial, apparently negative family history may be regarded as uncertain until additional efforts are made to determine the early history of each parent, including review of parents' medical records and, if possible, consultation with older relatives to determine if the parent was affected in infancy (but was unaware of the diagnosis as the phenotype did not persist beyond infancy). Therefore, an apparently negative family

history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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 known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Given the rarity of *KCNQ3*-related disorders, little is known about the inter- and intrafamilial phenotypic variability. In most families with *KCNQ3* pathogenic variants, affected members showed a self-limited disease course. However, in the family described by Soldovieri et al [2014] febrile seizures beyond the neonatal period and intellectual deficiency occurred in two of the four affected family members, and in the family described by Miceli et al [2015b] three of the four affected individuals showed intellectual deficits in addition to seizures.
- If the *KCNQ3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

  Note: While parental mosaicism has not been reported in autosomal dominant *KCNQ3*-NDD to date, it is estimated that approximately 10% of individuals (who represent simplex cases) with any form of genetic developmental and epileptic encephalopathy have the disorder as the result of a pathogenic variant inherited from an asymptomatic mosaic parent [Myers et al 2018].
- If the parents have not been tested for the *KCNQ3* pathogenic variant but are clinically unaffected and are known not to have had seizures in infancy or childhood, the risk to the sibs of a proband appears to be low. However, the sibs of a proband with clinically unaffected parents are still at increased risk for a *KCNQ3*-related disorder because of the possibility of reduced penetrance in a parent and the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with an autosomal dominant *KCNQ3*-related disorder has a 50% chance of inheriting the *KCNQ3* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *KCNQ3* pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive *KCNQ3*-NDD are presumed to be heterozygous for a *KCNQ3* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *KCNQ3* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- The heterozygous parents of a child with autosomal recessive *KCNQ3*-NDD are asymptomatic.

Sibs of a proband

- If both parents are known to be heterozygous for a *KCNQ3* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- The heterozygous sibs of a proband with autosomal recessive *KCNQ3*-NDD are asymptomatic.

Offspring of a proband.

- The offspring of an individual with autosomal recessive *KCNQ3*-NDD are obligate heterozygotes (carriers) for a pathogenic variant in *KCNQ3*.
- To date, individuals with autosomal recessive *KCNQ3*-NDD are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *KCNQ3* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *KCNQ3* pathogenic variants in the family.

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 young adults who are known to have, or to be at risk of having, a *KCNQ3* pathogenic variant.
- It is appropriate to offer *KCNQ3* molecular genetic testing to the reproductive partners of individuals known to be heterozygous for a pathogenic variant associated with autosomal recessive *KCNQ3*-NDD, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the *KCNQ3* pathogenic variant(s) have been identified in an affected family member, prenatal 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.

- **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
- **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
- **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. KCNQ3-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KCNQ3	8q24.22	Potassium voltage-gated channel subfamily KQT member 3	KCNQ3 database RIKEE KCNQ2-5-related illness database	KCNQ3	KCNQ3

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 KCNQ3-Related Disorders (View All in OMIM)

121201	SEIZURES, BENIGN FAMILIAL NEONATAL, 2; BFNS2
602232	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 3; KCNQ3

Molecular Pathogenesis

The *KCNQ* potassium channel gene subfamily consists of five members (*KCNQ1-5*), each encoding a subunit of a voltage-gated potassium channel. Each subunit shows distinct tissue distribution and subcellular localization, as well as biophysical, pharmacologic, and pathophysiologic properties [Soldovieri et al 2011].

KCNQ subunits, like other voltage-gated potassium channel subunits, include six transmembrane domains, with cytoplasmic N- and C-terminal regions. In neurons, KCNQ2, KCNQ3, KCNQ4, and KCNQ5 subunits (either as

homomultimers or heteromultimers) represent the molecular basis of the M-current (I_{KM}), a K^+-selective, non-inactivating, and slowly activating/deactivating current [Brown & Adams 1980, Wang et al 1998], showing a critical role in spike-frequency adaptation and neuronal excitability control.

KCNQ3 encodes a voltage-gated potassium channel subunit (KCNQ3 or Kv7.3) mainly expressed in neurons. In heterologous expression systems, currents carried by KCNQ3 homomeric channels are rather small, but are potentiated upon coexpression with KCNQ2 subunits. In the adult nervous system, KCNQ2/KCNQ3 heteromers are believed to be the main constituents of the M-current, a voltage-gated K^+ current that plays important roles in controlling excitability in many central and peripheral neurons [Delmas & Brown 2005]. M-current activation reduces neuronal excitability by stabilizing the membrane potential at values closer to the equilibrium potential for K^+ ions, thus limiting repetitive firing and contributing to spike-frequency adaptation. M-current, somewhat paradoxically, can also augment excitability under some conditions by enhancing availability of the sodium channels driving the neuronal action potential [Battefeld et al 2014]. M-currents are present on both excitatory principal cells and inhibitory interneurons [Lawrence et al 2006, Battefeld et al 2014]. The complexity of M-current roles, which may change with human development, are factors contributing to the phenotypic heterogeneity and age dependence associated with *KCNQ3* [Dirkx et al 2020].

Most *KCNQ3*-related epilepsy phenotypes are caused by single-nucleotide pathogenic variants, with a preponderance of missense variants. Heterozygous truncating variants in *KCNQ3* have not been clearly associated with a disease phenotype, except for one report of an intragenic deletion affecting three individuals in a family [Sands et al 2016]. This is in contrast with *KCNQ2*, in which large intragenic deletions and splice site, frameshift, and stop gain pathogenic variants represent about two thirds of pedigrees of SLFNE [Millichap et al 2016]. Moreover, while homozygous deletions/frameshifts in *KCNQ2* have never been reported, most likely because of their lethality, neonatal-onset epilepsy and developmental delay have been described in individuals carrying homozygous *KCNQ3* frameshift variants, each inherited by an unaffected parent [Kothur et al 2018, Lauritano et al 2019]. In addition, one individual with early-onset developmental encephalopathy (DEE) with severe nonverbal cognitive impairment and spastic quadriparesis had two Kv7.3 missense variants (p.Val359Leu and p.Asp542Asn) in *trans* [Ambrosino et al 2018, Weckhuysen & George 2022]. Altogether, these data provide genetic evidence for the hypothesis that *KCNQ3* pathogenic variants are better tolerated than *KCNQ2* pathogenic variants in humans. In addition to the described pathogenetic mechanism, different developmental patterns of expression between the two genes (with *KCNQ2* being expressed at earlier stages when compared to *KCNQ3*), as well as other factors such as inclusion/exclusion of both genes in panels for developmental and epileptic encephalopathy, diagnostic next-generation sequencing coverage, and epistatic compensation, may contribute to the lower incidence of epilepsy-associated variants described for *KCNQ3* when compared with *KCNQ2*.

In addition to *KCNQ3*, all other *KCNQ* genes have a role in human genetic disease:

- *KCNQ1*. Long QT syndrome (LQTS-1) [Wang et al 1996], familial atrial fibrillation [Chen et al 2003], and short QT syndrome [Bellocq et al 2004]
- *KCNQ2*. The main locus for SLFNE, and a common cause for early infantile epileptic encephalopathy (See *KCNQ2*-Related Disorders.)
- *KCNQ4*. Expressed mainly in the cochlea and central auditory pathways, causing a rare form of nonsyndromic autosomal dominant hearing loss (DFNA2) [Kubisch et al 1999]
- *KCNQ5*. Widely distributed in brain, skeletal muscle, and smooth muscle. Pathogenic variants have been found in unrelated individuals with intellectual disability, two of whom also have epilepsy [Lehman et al 2017, Nappi et al 2022, Wei et al 2022].

Mechanism of disease causation

- *KCNQ3*-SLFNE and *KCNQ3*-SLFIE. Mild loss of function

- *KCNQ3*-NDD. Severe loss or gain of function

Table 7. *KCNQ3* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_004519.3 NP_004510.1	c.680G>A	p.Arg227Gln	Reported in assoc w/DD & ASD [Deciphering Developmental Disorders Study 2017, Sands et al 2019]
	c.688C>T	p.Arg230Cys	Pathogenic variants at this amino acid site have been reported in persons w/ASD & DD w/ & w/o epilepsy [Rauch et al 2012, Allen et al 2013, Bosch et al 2016, Deciphering Developmental Disorders Study 2017, Sands et al 2019, Trinh et al 2019].
	c.688C>A	p.Arg230Ser	
	c.689G>A	p.Arg230His	
	c.989G>T	p.Arg330Leu	Pathogenic variants at this amino acid site have been reported in a family w/early-onset epilepsy & neurocognitive deficits (p.Arg330Leu) & in 2 families w/typical SLFNE (p.Arg330Cys) [Li et al 2008, Miceli et al 2015a].
	c.988C>T	p.Arg330Cys	
	c.1599dup	p.Phe534IlefsTer15	Homozygous *KCNQ3* frameshift pathogenic variant identified in a child w/neonatal-onset epilepsy & DD [Lauritano et al 2019]

ASD = autism spectrum disorder; DD = developmental delay
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

Author Notes

Sarah Weckhuysen (sarah.weckhuysen@uantwerpen.vib.be) is actively involved in clinical research regarding individuals with *KCNQ3*-related neurodevelopmental disorders (NDD). She would be happy to communicate with persons who have any questions regarding diagnosis of *KCNQ3*-related NDD or other considerations.

Acknowledgments

The authors acknowledge funding from the following agencies for supporting their studies: the Italian Ministry for University and Research (MUR) (PRIN 2017ALCR7C), #NEXTGENERATIONEU (NGEU), National Recovery and Resilience Plan (NRRP), Project MNESYS (PE0000006 – A Multiscale Integrated Approach to the Study of the Nervous System in Health and Disease), the Italian Ministry of Health (Project GR-2016-02363337 and RF-2019-12370491), the European Commission H2020 (UNICOM – 875299), FWO (1861419N and G041821N), KCNQ2e.v., and the European Joint Programme on Rare Disease JTC 2020 (TreatKCNQ).

Author History

Giulia Bellini, PhD; Second University of Naples (2014-2017)
Edward C Cooper, MD, PhD (2017-present)
Giangennaro Coppola, MD; University of Salerno (2014-2017)
Nishtha Joshi, BDS, MPH (2017-present)
Francesco Miceli, PhD (2014-present)
Emanuele Miraglia del Giudice, MD; Second University of Naples (2014-2017)
Maria Virginia Soldovieri, PhD (2014-present)

Maurizio Taglialatela, MD, PhD (2014-present)
Sarah Weckhuysen, MD, PhD (2017-present)

Revision History

- 28 September 2023 (gm) Comprehensive update posted live
- 7 September 2017 (ha) Comprehensive update posted live
- 22 May 2014 (me) Review posted live
- 26 September 2013 (mt) Original submission

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