U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Hammer MF, Xia M, Schreiber JM. *SCN8A*-Related Epilepsy and/or Neurodevelopmental Disorders. 2016 Aug 25 [Updated 2023 Apr 6]. 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/

SCN8A-Related Epilepsy and/or Neurodevelopmental Disorders

Michael F Hammer, PhD,[1] Maya Xia, BA,[2] and John M Schreiber, MD[3]

Created: August 25, 2016; Updated: April 6, 2023.

Summary

Clinical characteristics

SCN8A-related epilepsy and/or neurodevelopmental disorders encompasses a spectrum of phenotypes. Epilepsy phenotypes include developmental and epileptic encephalopathy (DEE) associated with severe developmental delays and usually pharmacoresistant epilepsy with multiple seizure types; mild-to-moderate developmental and epileptic encephalopathy (mild/modDEE, or intermediate epilepsy) with partially treatable epilepsy; self-limited familial infantile epilepsy (SeLFIE, also known as benign familial infantile epilepsy or BFIE) with normal cognition and medically treatable seizures; neurodevelopmental delays with generalized epilepsy (NDDwGE); and neurodevelopmental disorder without epilepsy (NDDwoE) with mild-to-moderate intellectual disability (though it can be severe in ~10% of affected individuals). Hypotonia and movement disorders including dystonia, ataxia, and choreoathetosis are common in some phenotypes. Sudden unexpected death in epilepsy (SUDEP) has been reported in some affected individuals.

Diagnosis/testing

The diagnosis of *SCN8A*-related epilepsy and/or neurodevelopmental disorders is established in a proband with suggestive findings and a heterozygous pathogenic variant in *SCN8A* identified by molecular genetic testing.

Management

Targeted therapy: Several studies suggest a favorable response to sodium channel blockers in the *SCN8A*-related epilepsy phenotypes of *SCN8A*-DEE, *SCN8A*-mild/modDEE, and *SCN8A*-SeLFIE.

Supportive care: Seizure control should be managed by a pediatric neurologist with expertise in epilepsy management who is familiar with the pharmacotherapy for *SCN8A*-related epilepsy and aware of how it differs from treatment of similar disorders. Vigorous attempts to control seizures are warranted. Supportive care to

Author Affiliations: 1 Professor of Neurology, BIO5 Institute, University of Arizona, Tucson, Arizona; Email: mfh@email.arizona.edu. 2 COMBINEDBrain, Brentwood, Tennessee; Email: maya@combinedbrain.org. 3 Children's National Hospital, Washington, DC; Email: jschreib@childrensnational.org.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

improve quality of life, maximize function, and reduce complications is recommended, ideally involving multidisciplinary care by specialists in relevant fields.

Surveillance: Periodic evaluations for neurologic, cognitive, and/or behavioral deterioration; monitoring with EEG and other modalities such as video EEG telemetry or ambulatory EEG when new or different seizure types are suspected. Because of the increased risk of SUDEP, monitoring seizures in individuals at higher risk, including those with generalized tonic-clonic seizures and/or nighttime seizures, is warranted.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify those who are at risk for developing seizures. This typically entails targeted molecular genetic testing for the known pathogenic variant(s) in the family.

Pregnancy management: Pregnant women should receive counseling regarding the risks and benefits of using anti-seizure medications during pregnancy; the advantages and disadvantages of increasing maternal periconceptional folic acid supplementation to 4,000 µg daily; the effects of pregnancy on anti-seizure medication metabolism; and the effect of pregnancy on maternal seizure control.

Agents/circumstances to avoid: Several families report worsening of seizures with levetiracetam.

Genetic counseling

SCN8A-related epilepsy and/or neurodevelopmental disorders are inherited in an autosomal dominant manner. Individuals with more severe *SCN8A*-related phenotypes are more likely to have the disorder as the result of a *de novo* pathogenic variant than individuals with milder *SCN8A*-related phenotypes. Each child of an individual with *SCN8A*-related epilepsy and/or neurodevelopmental disorders has a 50% chance of inheriting the *SCN8A* pathogenic variant. Once the *SCN8A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

SCN8A-Related Epilepsy and/or Neurodevelopmental Disorders: Included Phenotypes

Phenotype	*SCN8A*-Related Disorder [1, 2]
Epilepsy ± neurodevelopmental features	Developmental and epileptic encephalopathy (DEE)
	Mild-to-moderate developmental and epileptic encephalopathy (mild/modDEE, also referred to as intermediate epilepsy or IE [2])
	Self-limited familial infantile epilepsy (SeLFIE, also referred to as benign familial infantile epilepsy or BFIE [2])
	Neurodevelopmental disorder with generalized epilepsy (NDDwGE)
Neurodevelopmental disorder	Neurodevelopmental disorder without epilepsy (NDDwoE)

1. For other genetic causes of these phenotypes, see Differential Diagnosis.
2. Johannesen et al [2022]

Diagnosis

No consensus clinical diagnostic criteria for *SCN8A*-related epilepsy and/or neurodevelopmental disorders have been published.

Suggestive Findings

SCN8A-related epilepsy and/or neurodevelopmental disorders encompass a spectrum of phenotypes that range from mild to severe and **should be considered** in probands with the following clinical findings and family history.

Clinical Findings

Epilepsy features

- Childhood-onset seizures: seizure onset variable, ranges from the first few months to the first few years of life
- Development of multiple seizure types, including focal, multifocal, or generalized seizures
- May be intractable in some individuals or treatable (especially using sodium channel blockers)

Clinical epilepsy syndromes reported in individuals with *SCN8A*-related epilepsy and/or neurodevelopmental disorders (see Clinical Characteristics). Five different clinical phenotypes have been identified in individuals with pathogenic *SCN8A* variants:

- Developmental and epileptic encephalopathy (DEE). Severe intellectual disability, usually pharmacoresistant to anti-seizure medications
- Mild-to-moderate DEE (mild/modDEE, also referred to as intermediate epilepsy or IE). Mild-to-moderate intellectual disability, partially treatable epilepsy
- Self-limited familial infantile epilepsy (SeLFIE, also referred to as benign familial infantile epilepsy or BFIE). Normal cognition and medically treatable seizures (not necessarily self-limited)
- Neurodevelopmental disorder with generalized epilepsy (NDDwGE). Mild-to-moderate intellectual disability, frequently with absence and other generalized seizures
- Neurodevelopmental disorder without epilepsy (NDDwoE). Mild-to-moderate intellectual disability (can be severe in ~10% of affected individuals)

Other clinical features

- Motor abnormalities including hypotonia in some individuals
- Movement disorders including dystonia, ataxia, choreoathetosis, or paroxysmal kinesigenic dyskinesia in some individuals
- Cognitive development varies depending on the clinical phenotype and can range from normal to severe cognitive delays. In some individuals, intellectual disability occurs without epilepsy.
- Non-epileptic paroxysmal episodes, including startle-like myoclonus, generalized tremor, or hyperekplexia-like startles
- Language delay, autism spectrum disorder, and behavioral issues may occur with certain epilepsy phenotypes or in the absence of epilepsy.
- Some individuals have severe tone abnormalities, significant gastrointestinal issues, impaired swallow function, and cortical visual impairment with early mortality.

Family History

The proband may represent a simplex case (i.e., a single occurrence in a family) or the family history may suggest autosomal dominant inheritance (e.g., affected males and females in multiple generations). Probands with more severe *SCN8A*-related phenotypes are more likely to represent simplex cases.

Establishing the Diagnosis

The diagnosis of *SCN8A*-related epilepsy and/or neurodevelopmental disorders **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *SCN8A* identified by molecular genetic testing (see Table 1).

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 any likely pathogenic variants. (2) Identification of a heterozygous *SCN8A* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with epilepsy and/or developmental delay or an older individual with epilepsy and/or intellectual disability may begin with a **multigene panel** or **exome sequencing**. Subsequent testing may involve **chromosomal microarray analysis (CMA)**; however, to date, there are very few reported copy number variants in this spectrum. Note: Single-gene testing (sequence analysis of *SCN8A*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An epilepsy or intellectual disability multigene panel** that includes *SCN8A* 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(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an epilepsy or intellectual disability multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing epilepsy or intellectual disability, whereas some multigene panels may not. To date, the majority of reported *SCN8A* pathogenic variants are within the coding region and are therefore likely to be identified on exome sequencing. **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.

Table 1. Molecular Genetic Testing Used in *SCN8A*-Related Epilepsy and/or Neurodevelopmental Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SCN8A	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	~1% (very few reported to date) [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. To date, most *SCN8A* pathogenic variants, including missense variants, splice site variants, and small deletions/duplications, are detectable by sequencing [Rauch et al 2012, Veeramah et al 2012, Allen et al 2013, Carvill et al 2013, de Kovel et al 2014, Estacion et al 2014, Ohba et al 2014, Vaher et al 2014, Blanchard et al 2015, Dyment et al 2015, Fitzgerald et al 2015, Fung et al 2015, Kong et al 2015a, Larsen et al 2015, Mercimek-Mahmutoglu et al 2015, Olson et al 2015, Singh et al 2015, Takahashi et al 2015, Wagnon et al 2015a, Anand et al 2016, Boerma et al 2016, Gardella et al 2016, Malcolmson et al 2016, Butler et al 2017, Han et al 2017, Jain 2017, Wagnon et al 2017, Wang et al 2017, Bagnasco et al 2018, Epilepsy Genetics Initiative 2018, Gardella et al 2018, Pons et al 2018, Wagnon et al 2018, Xiao et al 2018, Denis et al 2019, Epifanio et al 2019, Johannesen et al 2019, Kim et al 2019, Liao et al 2019, Lin et al 2019, Trivisano et al 2019, Wengert et al 2019, Zaman et al 2019, Canafoglia et al 2020, Fatema et al 2020, Ranza et al 2020, Schreiber et al 2020, Alagia et al 2021, Fan et al 2021, Negishi et al 2021, Solazzi et al 2021, Stringer et al 2021, Hu et al 2022, Johannesen et al 2022, Keshri et al 2022, Medlin et al 2022, Peng et al 2022]. Data is also derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020].
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. Small deletions and/or duplications in *SCN8A* have been rarely reported [Berghuis et al 2015, Larsen et al 2015, Wong et al 2021, Johannesen et al 2022].
6. To date, no large chromosomal deletions/duplications have been reported in individuals with *SCN8A*-related epilepsy and/or neurodevelopmental disorders.

Clinical Characteristics

Clinical Description

Five different clinical phenotypes have been identified in association with pathogenic *SCN8A* variants. Most individuals have features that fit into one of these five phenotypes:

- Developmental and epileptic encephalopathy (DEE)
- Mild-to-moderate developmental and epileptic encephalopathy (mild/modDEE, also referred to as intermediate epilepsy or IE)
- Self-limited familial infantile epilepsy (SeLFIE, also referred to as benign familial infantile epilepsy or BFIE)
- Neurodevelopmental disorder with generalized epilepsy (NDDwGE)
- Neurodevelopmental disorder without epilepsy (NDDwoE)

To date, more than 500 individuals have been identified with a pathogenic variant in *SCN8A* [Rauch et al 2012, Veeramah et al 2012, Allen et al 2013, Carvill et al 2013, de Kovel et al 2014, Estacion et al 2014, Ohba et al 2014, Vaher et al 2014, Berghuis et al 2015, Blanchard et al 2015, Dyment et al 2015, Fitzgerald et al 2015, Fung et al 2015, Kong et al 2015a, Larsen et al 2015, Mercimek-Mahmutoglu et al 2015, Olson et al 2015, Singh et al 2015, Takahashi et al 2015, Wagnon et al 2015a, Anand et al 2016, Boerma et al 2016, Gardella et al 2016, Lelieveld et al 2016, Malcolmson et al 2016, McNally et al 2016, Møller et al 2016, Trump et al 2016, Arafat et al 2017, Braakman et al 2017, Butler et al 2017, Han et al 2017, Jain 2017, Parrini et al 2017, Rolvien et al 2017, Wagnon et al 2017, Wang et al 2017, Atanasoska et al 2018, Bagnasco et al 2018, Epilepsy Genetics Initiative 2018,

Gardella et al 2018, Ko et al 2018, Kothur et al 2018, Lindy et al 2018, Liu et al 2018, Oates et al 2018, Pons et al 2018, Rim et al 2018, Tsang et al 2018, Wagnon et al 2018, Xiao et al 2018, Balciuniene et al 2019, Costain et al 2019, Denis et al 2019, Encinas et al 2019, Epifanio et al 2019, Jain et al 2019, Jang et al 2019, Johannesen et al 2019, Kim et al 2019, Liao et al 2019, Lin et al 2019, Liu et al 2019, Trivisano et al 2019, Wengert et al 2019, Xie et al 2019, Zaman et al 2019, Canafoglia et al 2020, Fatema et al 2020, Lee et al 2020, Mitta et al 2020, Pergande et al 2020, Ranza et al 2020, Schreiber et al 2020, Alagia et al 2021, Fan et al 2021, Negishi et al 2021, Solazzi et al 2021, Stringer et al 2021, Hu et al 2022, Johannesen et al 2022, Keshri et al 2022, Medlin et al 2022, Peng et al 2022].

The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *SCN8A*-Related Epilepsy and/or Neurodevelopmental Disorders: Comparison of Phenotypes by Select Features

Feature	*SCN8A*-Related Phenotype				
	DEE	Mild-to-moderate DEE	SeLFIE	NDDwGE	NDDwoE
Seizure types	Focal, multifocal, bilateral tonic-clonic, tonic, or infantile spasms	Focal, multifocal, bilateral tonic-clonic, or tonic	Focal, multifocal, bilateral tonic-clonic; may be self-limiting	Absence, bilateral tonic-clonic, or febrile	NA
% w/epilepsy	100%	100%	100%	100%	0%
Median age of epilepsy onset	~3 months	~5 months	~6 months	~42 months	NA
Motor development	Delayed, often nonambulatory	Delayed	Normal	Delayed	Delayed
Speech development	Delayed, often nonverbal	Delayed	Normal to mildly delayed	Delayed	Delayed
Cognition	Moderate-to-severe ID	Mild-to-moderate ID	Normal to mildly delayed	Normal to severe ID (usually mild to moderate)	Normal to severe ID
Other	Hypotonia, CVI, ataxia, GI symptoms	Behavioral issues, ataxia	Paroxysmal kinesigenic dyskinesia	Behavioral issues, ADHD, ASD	ASD
Most common *SCN8A* variant type [1]	GoF	GoF	GoF	LoF	LoF

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CVI = cortical visual impairment; DEE = developmental and epileptic encephalopathy; GI = gastrointestinal; GoF = gain of function; ID = intellectual disability; LoF = loss of function; NA = not applicable; NDDwGE = neurodevelopmental disorder with generalized epilepsy; NDDwoE = neurodevelopmental disorder without epilepsy; SeLFIE = self-limited familial infantile epilepsy

1. Hack et al [2023]

SCN8A-Related Developmental and Epileptic Encephalopathy (*SCN8A*-DEE)

Epilepsy. Age of seizure onset in affected individuals ranges from the first day of life to 22 months (median age: 3 months) [Johannesen et al 2022]. Seizures may occur prenatally, as some mothers reported unusual "drumming" movements in the later stages of pregnancy that are believed to be seizures [Singh et al 2015, Barker et al 2016, McNally et al 2016].

Initial seizure type varies, and most affected individuals develop additional seizure types over time, including the following:

- Focal clonic seizures evolving to bilateral convulsive seizures
- Generalized tonic-clonic seizures
- Tonic seizures
- Infantile spasms
- Myoclonic seizures

Focal seizures in *SCN8A*-DEE are typically prolonged, with prominent hypomotor and autonomic symptoms [Gardella et al 2018] such as facial flushing, sialorrhea, bradycardia, and hypopnea, followed by tachycardia, polypnea, perioral cyanosis, and pallor [Trivisano et al 2019]. This may be followed by asymmetric tonic and clonic or hemiclonic phases, with or without bilateral tonic-clonic convulsions [Gardella et al 2018].

Although both convulsive and nonconvulsive status epilepticus appear to be common [Ohba et al 2014, Kong et al 2015a, Larsen et al 2015, Singh et al 2015, Wagnon et al 2015a, Wagnon et al 2015b, Braakman et al 2017, Gardella et al 2018, Kim et al 2019, Wengert et al 2019, Schreiber et al 2020, Donnan et al 2023], they are not as common as in Dravet syndrome (see *SCN1A* Seizure Disorders) and *SCN2A*-related epilepsy. A recent study of a small cohort of individuals with pathogenic *SCN8A* variants found that the median onset age of convulsive status epilepticus is around eight months, with a rate of 31% of affected individuals, and the median age of nonconvulsive status epilepticus is around 4.3 years, with a rate of 23% [Donnan et al 2023].

Seizure frequencies range from hundreds per day to fewer than one per month. Most affected individuals have refractory seizures and require polytherapy (see Treatment of Manifestations).

Psychomotor development varies from normal prior to seizure onset (with subsequent slowing or regression after seizure onset) to abnormal from birth [Larsen et al 2015, Gardella et al 2018, Denis et al 2019, Encinas et al 2019, Kim et al 2019, Schreiber et al 2020]. Many affected individuals experience marked slowing or arrest in development either for no apparent reason or after an event that occurred before the developmental decline, such as a change in seizure type or change in medication.

Approximately half of affected children learn to sit and walk unassisted; the remainder are nonambulatory. Ataxia and sudden loss of mobility are common in those who are ambulatory.

Most individuals diagnosed with this disorder are younger than age 20 years. For the several individuals who are in their teens, cognitive and motor disabilities persist. The oldest affected individual whom the authors are aware of is age 47 years [Authors, personal communication].

Language development is frequently affected. Most affected individuals speak few or no words and may exhibit anomic aphasia. Many individuals use nonverbal communication strategies as their primary expression method (e.g., crying, vocalizing, reaching/grabbing, behavioral aggression, movements).

Intellectual disability ranges from mild to severe, with about half of affected individuals having severe intellectual disability. Autistic features are noted in some individuals [Larsen et al 2015, Schreiber et al 2020].

Movement abnormalities including hypotonia, dystonia, choreoathetosis, ataxia, spasticity, and increased startle have been described in some affected individuals [Schreiber et al 2020].

Startle and sleep issues. Many children are hyperalert as infants (i.e., more awake and aware of their surroundings than typical infants) and are easily startled. For example, Singh et al [2015] reported a newborn with jittery movements shortly after birth and a pathologically exaggerated startle response to tactile and acoustic stimuli, findings that prompted a suspicion of hyperekplexia. The hyperalert sleep appears to make it difficult for the infant to settle into a deep, healthy sleep. These findings have been reported in several other individuals with *SCN8A*-DEE [Pons et al 2018].

Other associated features reported in some affected individuals include the following:

- Autonomic nervous system dysfunction, including difficulty with temperature regulation and tachypnea
- Hearing issues
- Bone fractures, often associated with prolonged seizures
- Laryngomalacia
- Scoliosis
- Microcephaly
- Cortical visual impairment
- Gum hyperplasia secondary to anti-seizure medication

Sudden unexpected death in epilepsy (SUDEP) has been reported in the literature [Veeramah et al 2012, Estacion et al 2014, Kong et al 2015a, Larsen et al 2015, Johannesen et al 2018, Denis et al 2019, Zaman et al 2019, Donnan et al 2023]. Johannesen et al [2018] examined the likely cause of death in 190 individuals and reported an overall mortality rate of 5.3%. Death was more frequently due to other causes, with definite SUDEP only ascertained in 1.6% of individuals. The cause of SUDEP is unknown but may be related to prolonged seizures, cardiac abnormalities, or brain stem dysfunction.

EEG. Early on, the EEG may be normal or exhibit focal or multifocal epileptiform activity. EEG findings tend to evolve over time, often showing moderate-to-severe background slowing and focal or multifocal sharp waves or spikes, most often in the temporal regions. Some show almost continuous delta slowing in the temporal, parietal, and occipital regions, with superimposed beta frequencies and bilateral asynchronous spikes or sharp waves [Larsen et al 2015, Denis et al 2019, Johannesen et al 2022].

Brain MRI is usually normal at the onset of seizures; however, some individuals may have MRI abnormalities including cerebral atrophy and hypoplasia of the corpus callosum. Some affected individuals have been shown to develop cerebral or cerebellar atrophy in follow-up studies [Larsen et al 2015, Singh et al 2015, Gardella et al 2018, Denis et al 2019, Kim et al 2019, Schreiber et al 2020, Hu et al 2022].

SCN8A-Related Mild-to-Moderate Developmental and Epileptic Encephalopathy (*SCN8A*-mild/modDEE)

SCN8A-mild/modDEE is also referred to as *SCN8A*-related intermediate epilepsy or *SCN8A*-IE.

Epilepsy. Affected individuals usually present within the first few months of life (average age of onset around five months). Seizure types include:

- Focal seizures
- Bilateral tonic-clonic seizures
- Tonic seizures

Seizures are usually partially treatable using sodium channel blockers (see Treatment of Manifestations)

Intellectual disability typically ranges from mild to moderate, but most individuals have mild intellectual disability [Johannesen et al 2019]. Some individuals with intermediate epilepsy are reported to have normal cognition, but many of these individuals may be better classified as having *SCN8A*-related self-limited familial infantile epilepsy, as many are seizure-free on anti-seizure medication.

EEG and MRI brain findings are similar to *SCN8A*-DEE. Affected individuals may also exhibit movement abnormalities, most commonly hypotonia, ataxia, stereotypy, dystonia, and tremor. SUDEP has also been reported in individuals with this phenotype.

SCN8A-Related Self-Limited Familial Infantile Epilepsy (*SCN8A*-SeLFIE)

SCN8A-SeLFIE is also referred to as *SCN8A*-related benign familial infantile epilepsy or *SCN8A*-BFIE.

Epilepsy. Affected individuals usually present within the first year of life (average age of onset is around age 6 months). Seizures may resolve (or individuals may "outgrow seizures") [Gardella et al 2016], but many affected individuals have seizure recurrence and/or require ongoing treatment with anti-seizure medication to remain seizure-free [Anand et al 2016, Gardella et al 2016, Wang et al 2017, Schreiber et al 2020]. Seizure types include:

- Focal seizures
- Focal seizures evolving to bilateral tonic-clonic seizures
- Bilateral tonic-clonic seizures

Seizures are usually treatable using sodium channel blockers (see Treatment of Manifestations.)

Cognitive development is usually normal in affected individuals.

Paroxysmal dyskinesias, triggered by stretching, motor initiation, or emotional stimuli, occurred in five of 16 individuals, with onset in puberty, including in one case series of three families with the p.Glu1483Lys pathogenic variant [Gardella et al 2016].

EEG. Initial EEG is often normal [Schreiber et al 2020], though individuals can develop focal or multifocal epileptiform abnormalities [Wang et al 2017].

Brain MRI is typically normal [Schreiber et al 2020].

SCN8A-Related Neurodevelopmental Disorder with Generalized Epilepsy (*SCN8A*-NDDwGE)

Epilepsy. Affected individuals usually present within the first few years of life (average age of onset is around age 42 months). Seizure types include:

- Absence seizures
- Generalized tonic-clonic seizures
- Generalized myoclonic seizures
- Febrile seizures

Seizures are usually not treatable using sodium channel blockers, which may aggravate symptoms of individuals with *SCN8A* loss-of-function (LOF) variants, as in this phenotype. Absence seizures may respond to typical anti-seizure medication (see Treatment of Manifestations).

Cognitive development varies. Most individuals have mild-to-moderate intellectual disability, though approximately 10% of affected individuals have severe intellectual disability.

Some individuals have language delays and behavioral issues.

SCN8A-Related Neurodevelopmental Disorder without Epilepsy (*SCN8A*-NDDwoE)

Individuals with this phenotype typically do not have epilepsy. However, it is important to note that developmental delay may precede seizure onset in *SCN8A*-DEE, *SCN8A*-mild/modDEE, and *SCN8A*-NDDwGE. Epilepsy may develop later (see median age of epilepsy onset in Table 2).

Cognitive development varies from normal to severe delays, though most individuals have moderate intellectual disability.

Other associated features reported in some affected individuals include the following:

- Attention-deficit/hyperactivity disorder
- Autism spectrum disorder

- Microcephaly

Prognosis

It is unknown whether life span in the entire spectrum of *SCN8A*-related epilepsy and/or neurodevelopmental disorders is abnormal. However, in individuals with developmental and epileptic encephalopathy (DEE), early mortality is assessed to be 10.2% [Johannesen et al 2018, Johannesen et al 2022], whereas life span in other *SCN8A*-associated phenotypes is expected to be normal.

Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

SCN8A pathogenic variants can be either gain-of-function (GoF) or loss-of-function (LoF) variants. Several genotype-phenotype correlations have been observed:

- Affected individuals with LoF variants mostly have *SCN8A*-NDDwGE or *SCN8A*-NDDwoE, whereas affected individuals with GoF have *SCN8A*-DEE, *SCN8A*-SeLFIE, or *SCN8A*-mild/modDEE [Hack et al 2023]. The effectiveness of sodium channel blockers for treating epilepsy in these phenotypes is believed to be consistent with the activating effects of the *SCN8A* pathogenic GoF variant [Wagnon & Meisler 2015, Wagnon et al 2015a, Wagnon et al 2015b].
- Several recurrent variants are associated with specific phenotypes (see Table 6):
  - The variants c.2549G>A (p.Arg850Gln) and c.5614C>T (p.Arg1872Trp) are associated with *SCN8A*-DEE.
  - The variants c.4423G>A (p.Gly1475Arg), c.4850G>A (p.Arg1617Gln), c.5615G>A (p.Arg1872Gln), and c.5630G>T (p.Asn1877Ser) are associated with *SCN8A*-mild/modDEE.
  - The variant c.4447G>A (p.Glu1483Lys) is associated with *SCN8A*-SeLFIE.
- All individuals with GoF variants have epilepsy, whereas 50%-70% of individuals with LoF variants have epilepsy [Johannesen et al 2022, Hack et al 2023]. Based on these differences, early mortality has not been observed in individuals with LoF variants to date.

Penetrance

Penetrance for *SCN8A*-related epilepsy and/or neurodevelopmental disorders is unknown but is assumed to be complete.

Nomenclature

Alternate naming conventions for *SCN8A*-related phenotypes have been used in the literature [Johannesen et al 2022]:

- *SCN8A*-related mild-to-moderate developmental and epileptic encephalopathy (*SCN8A*-mild/modDEE) may also be described as *SCN8A*-related intermediate epilepsy (*SCN8A*-IE).
- *SCN8A*-related self-limited familial infantile epilepsy (*SCN8A*-SeLFIE) may also be referred to as *SCN8A*-related benign familial infantile epilepsy (*SCN8A*-BFIE).

Prevalence

The prevalence of *SCN8A*-related epilepsy and/or neurodevelopmental disorders is not known.

The frequency of *SCN8A* pathogenic variants among individuals with DEE was around 1% (51 of 3,489) across multiple independent studies, most of which included several hundred individuals [Allen et al 2013, Carvill et al 2013, Larsen et al 2015, Mercimek-Mahmutoglu et al 2015, Møller et al 2016, Trump et al 2016, Butler et al 2017,

Ko et al 2018, Kothur et al 2018, Lindy et al 2018, Balciuniene et al 2019, Costain et al 2019, Heyne et al 2019, Jang et al 2019, Lee et al 2020, Mitta et al 2020].

A study evaluating the incidence of *SCN8A*-related disorders in the Danish population found an estimated incidence of one in 56,247 [Johannesen et al 2022].

Genetically Related (Allelic) Disorders

Familial myoclonus (OMIM 618364). In one family reported to date, a heterozygous *SCN8A* variant was associated with isolated myoclonus in multiple affected individuals [Wagnon et al 2018].

Differential Diagnosis

Because the phenotypic features associated with *SCN8A*-related epilepsy and/or neurodevelopmental disorders are not sufficient to diagnose these conditions, all genes associated with epilepsy and/or developmental delay / intellectual disability without other distinctive findings should be considered in the differential diagnosis.

See OMIM Phenotypic Series for genes associated with:

- Autosomal dominant intellectual developmental disorders
- Autosomal recessive intellectual developmental disorders
- Nonsyndromic X-linked intellectual developmental disorders
- Syndromic X-linked intellectual developmental disorders
- Developmental and epileptic encephalopathy
- Childhood absence epilepsy
- Familial adult myoclonic epilepsy
- Familial focal epilepsy with variable foci
- Familial temporal lobe epilepsy
- Generalized epilepsy with febrile seizures plus
- Idiopathic generalized epilepsy
- Juvenile absence epilepsy
- Myoclonic juvenile epilepsy

Management

No clinical practice guidelines for *SCN8A*-related epilepsy and/or neurodevelopmental disorders have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SCN8A*-related epilepsy and/or neurodevelopmental disorders, 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 *SCN8A*-Related Epilepsy and/or Neurodevelopmental Disorders

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• EEG to assess EEG background, epileptiform activity, & seizure type (when indicated) • Baseline brain MRI, if not performed already

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Ataxia	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Development	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 behavioral 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 • Tone abnormalities • 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.
Cardiovascular	Consider electrocardiogram or cardiology eval	To assess for cardiac arrhythmias, which have been identified in some persons w/variants of genes encoding other sodium channel subunits & may ↑ risk of SUDEP.
Vision	Ophthalmologic eval	Cortical vision impairment can occur in *SCN8A*-DEE; assess for need for vision therapy.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SCN8A*-related epilepsy &/or neurodevelopmental 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; • 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; SUDEP = sudden unexpected death in epilepsy

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

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Sodium channel blockers represent a targeted treatment option for *SCN8A*-related focal epilepsy phenotypes (*SCN8A*-related developmental and epileptic encephalopathy [*SCN8A*-DEE], *SCN8A*-related mild-to-moderate developmental and epileptic encephalopathy [*SCN8A*-mild/modDEE], and *SCN8A*-related self-limited familial infantile epilepsy [*SCN8A*-SeLFIE]) with onset in the first year of life. See Table 4, **Epilepsy**.

Supportive Care

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 4).

Table 4. Treatment of Manifestations in Individuals with *SCN8A*-Related Epilepsy and/or Neurodevelopmental Disorders

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	• Standardized treatment w/ASM by experienced neurologist • Counsel on SUDEP risk & monitoring for seizures, particularly in persons at higher risk, incl those w/*SCN8A*-DEE & those w/generalized tonic-clonic seizures &/or nighttime seizures.	• Many ASMs may be effective; studies suggest that persons w/focal epilepsy phenotypes (*SCN8A*-DEE, *SCN8A*-mild/modDEE, *SCN8A*-SeLFIE) respond favorably to sodium channel blockers (e.g., phenytoin, valproate, carbamazepine, lacosamide, lamotrigine, rufinamide, & oxcarbazepine). [1] Other classes of ASM may also be useful. • The effectiveness of sodium channel blockers is consistent w/activating effects of *SCN8A* pathogenic GoF variants. [2] 1 study of 4 persons reported positive response to high doses of phenytoin. [3] • Many affected persons are maintained on multiple ASMs w/incomplete seizure control. Vigorous attempts to control seizures w/drug polytherapy are warranted, as children w/DEE are at risk for SUDEP as well as prolonged acute seizures that may cause permanent injury. [4] • Levetiracetam (Keppra®) has been reported by several families to be ineffective or occasionally assoc w/worsening seizures, encephalopathy, &/or developmental regression. [5] However, some may respond favorably, regardless of phenotype. • Education of parents/caregivers [6]
	Other treatments incl corticosteroids, immunoglobulins, vagus nerve stimulation, ketogenic diet, & cannabinoids	When seizures are not responsive to standard ASMs, these drugs / treatment modalities may be effective based on anecdotal data.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Constipation	Eval & treatment by GI specialist	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Sleep	• Eval by sleep &/or ENT specialist for any sleep issues incl sleep apnea • Polysomnography should be considered if obstructive or central sleep apnea is suspected.	• Sleep deprivation & illness can exacerbate *SCN8A*-related seizures; thus, good sleep hygiene should be encouraged. Comorbidity w/ sleep apnea can also occur frequently in persons w/epilepsy, [7] & can influence seizure control, behavior, & cognition. • Because of ↑ risk of SUDEP, some families use oxygen monitoring during sleep.
Aspiration pneumonia	• Swallow eval • Eval by pulmonary & GI	Aspiration pneumonia occurs more commonly in *SCN8A*-DEE.
Respiratory insufficiency/ failure	Respiratory support incl respiratory therapy, supplemental oxygen, positive airway pressure, & ventilatory support	Respiratory insufficiency/failure can occur in *SCN8A*-DEE.
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; GoF = gain of function; *SCN8A*-DEE = SCN8A-related developmental and epileptic encephalopathy; *SCN8A*-mild/modDEE = *SCN8A*-related mild-to-moderate developmental and epileptic encephalopathy; *SCN8A*-SeLFIE = *SCN8A*-related self-limited familial infantile epilepsy; SUDEP = sudden unexpected death in epilepsy

1. Kong et al [2015b], Larsen et al [2015], Boerma et al [2016]

2. Wagnon & Meisler [2015], Wagnon et al [2015a], Wagnon et al [2015b]

3. Boerma et al [2016]

4. Chipaux et al [2010], Takayanagi et al [2010]

5. Schreiber et al [2020]

6. 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.

7. Malow et al [2000]

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.

Neurobehavioral/Psychiatric 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

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with *SCN8A*-Related Epilepsy and/or Neurodevelopmental Disorders

System/Concern	Evaluation	Frequency
Neurologic	• Monitor seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	At each visit
Sleep	Assess for any sleep issues / sleep apnea.	
SUDEP	• Query for factors that ↑ SUDEP risk, incl generalized tonic-clonic seizures & nighttime seizures. • Assess seizure monitoring strategies.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

OT = occupational therapy; PT = physical therapy; SUDEP = sudden unexpected death in epilepsy

Agents/Circumstances to Avoid

Several families of affected individuals report worsening of seizures, encephalopathy, and/or developmental regression with levetiracetam (Keppra®) [Schreiber et al 2020]. However, some may respond favorably to levetiracetam, regardless of the phenotype. Therefore, careful evaluation and follow up by a neurologist is recommended.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

NBI-921352, a $Na_V1.6$ selective sodium channel inhibitor, is currently in Phase II clinical trials for individuals with *SCN8A*-related developmental and epileptic encephalopathy (*SCN8A*-DEE) (NCT04873869) [Johnson et al 2022].

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.

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

SCN8A-related epilepsy and/or neurodevelopmental disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with an *SCN8A*-related phenotype have the disorder as the result of a *de novo* *SCN8A* pathogenic variant. Individuals with more severe *SCN8A*-related phenotypes are more likely to have the disorder as the result of a *de novo* pathogenic variant than individuals with milder *SCN8A*-related phenotypes.
- Some individuals diagnosed with an *SCN8A*-related phenotype have the disorder as the result of a pathogenic variant inherited from an affected and/or mosaic parent. Of families in which parental testing was performed, the percentage of individuals with a pathogenic variant inherited from a mosaic and/or affected parent varied by phenotype [Johannesen et al 2022]:
  - 2% (3/166) of individuals with *SCN8A*-related developmental and epileptic encephalopathy (DEE)
  - 10% (3/29) of individuals with *SCN8A*-related mild-to-moderate DEE (also referred to as intermediate epilepsy)
  - 47% (7/15) of individuals with *SCN8A*-related self-limited familial infantile epilepsy (also referred to as benign familial infantile epilepsy)
  - 33% (5/15) of individuals with *SCN8A*-related neurodevelopmental disorder (NDD) with generalized epilepsy
  - 60% (9/15) of individuals with *SCN8A*-related NDD without epilepsy
- If the proband appears to be the only affected family member (i.e., a simplex case), 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 parents using peripheral blood leukocyte-derived DNA may not detect all instances of somatic mosaicism. Molecular genetic tests sensitive enough to detect low-level somatic mosaicism, such as high-coverage next-generation sequencing or allele-specific PCR, should therefore be considered.

  * A parent with somatic and germline mosaicism for an *SCN8A* pathogenic variant may be mildly/minimally affected.

- The family history of some individuals diagnosed with an *SCN8A*-related phenotype may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. 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 clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *SCN8A* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *SCN8A* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be greater than that of the general population because of the possibility of parental mosaicism [Johannesen et al 2022].
- If the parents have not been tested for the *SCN8A* pathogenic variant but are not known to have had manifestations consistent with an *SCN8A*-related phenotype, the sibs of a proband are still presumed to be at increased risk of an *SCN8A*-related phenotype because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual with an *SCN8A*-related phenotype has a 50% chance of inheriting the *SCN8A* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *SCN8A* pathogenic variant, the parent's family members 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SCN8A* pathogenic variant has 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.

- **International SCN8A Alliance**
  www.scn8aalliance.org
- **SCN8A Epilepsy and Related Disorders**
  Email: scn8a.info@gmail.com
  www.scn8a.net
- **The Cute Syndrome Foundation**
  www.thecutesyndrome.com
- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  epilepsy.ca
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Epilepsy and Seizures

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. SCN8A-Related Epilepsy and/or Neurodevelopmental Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SCN8A	12q13.13	Sodium channel protein type 8 subunit alpha	SCN8A @ LOVD	SCN8A	SCN8A

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 SCN8A-Related Epilepsy and/or Neurodevelopmental Disorders (View All in OMIM)

600702	SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 8; SCN8A
614306	COGNITIVE IMPAIRMENT WITH OR WITHOUT CEREBELLAR ATAXIA; CIAT
614558	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 13; DEE13
617080	SEIZURES, BENIGN FAMILIAL INFANTILE, 5; BFIS5

Molecular Pathogenesis

SCN8A encodes the sodium channel protein type 8 subunit alpha (isoform $Na_V1.6$), one of four voltage-gated sodium channels expressed in the human brain and predominantly expressed in excitatory as well as inhibitory neurons. The protein includes four homologous domains with six transmembrane segments each, as well as two large cytoplasmic loops, a short cytoplasmic inactivation gate, and cytoplasmic N-terminal and C-terminal domains (see Figure 1, with exon designations and functional domains marked). The amino acids forming the sodium-specific pore are located in segments S5 and S6 of each domain. The protein is highly conserved through evolution, and the human sequence can be aligned with the bacterial sodium channel, whose crystal structure has been determined.

Most pathogenic variants associated with *SCN8A*-related epilepsy and/or neurodevelopmental disorders result in substitution of a single amino acid (see Figure 2 for a distribution of missense variants). Of the nine pathogenic variants tested functionally, seven resulted in elevated channel activity due to premature channel opening or impaired channel closing. Elevated activity of $Na_V1.6$ leads to neuronal hyperexcitability and seizures in a mouse model of *SCN8A*-related epilepsy with encephalopathy [Wagnon et al 2015b]. $Na_V1.6$ is expressed at a low level in cardiac ventricular myocytes, and cardiac arrhythmia is seen in the mouse model, suggesting that sudden unexplained death in epilepsy may have a cardiac component [Frasier et al 2016].

Mechanism of disease causation

- Gain of function in *SCN8A*-related developmental and epileptic encephalopathy (DEE), *SCN8A*-related mild-to-moderate DEE, and *SCN8A*-related self-limited familial infantile epilepsy
- Loss of function in *SCN8A*-related neurodevelopmental disorder with generalized epilepsy and *SCN8A*-related neurodevelopmental disorder without epilepsy

SCN8A-specific laboratory technical considerations

- *SCN8A* includes 26 coding exons. The approximate position of each exon is indicated in Figure 1. During the first year of postnatal life, the "neonatal" and the "adult" exons are expressed in roughly equal proportions [O'Brien et al 2012].
- There are several alternatively spliced exons: 6A (adult) and 6N (neonatal) that encode segment 3/4 of domain I, as well as alternatively spliced exons 21A and 21N that encode segment 3/4 of domain III.
- Exon 21N is a "poison" exon that contains an in-frame stop codon and encodes a truncated protein terminating in domain III that does not have channel activity. Therefore, the reference sequence for missing exon 21 should not be used for sequence comparisons: NM_001177984.2 (ENST00000545061).
- The most complete full-length reference transcript contains exon 6N and exon 21A: NM_014191.3 (ENST00000354534).

Table 6. Highly Recurrent *SCN8A* Pathogenic Gain-of-Function Variants [1]

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Associated Phenotype
NM_001330260.2 NP_055006.1	c.2549G>A	p.Arg850Gln	*SCN8A*-DEE
	c.4423G>A	p.Gly1475Arg	*SCN8A*-mild/modDEE
	c.4850G>A	p.Arg1617Gln	
	c.5614C>T	p.Arg1872Trp	*SCN8A*-DEE
	c.5615G>A	p.Arg1872Gln	*SCN8A*-mild/modDEE
	c.5630G>T	p.Asn1877Ser	
	c.4447G>A	p.Glu1483Lys	*SCN8A*-SeLFIE

SCN8A-DEE = SCN8A-related developmental and epileptic encephalopathy; *SCN8A*-mild/modDEE = *SCN8A*-related mild-to-moderate developmental and epileptic encephalopathy; *SCN8A*-SeLFIE = *SCN8A*-related self-limited familial infantile 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.
1. Variants known to be present in >15 individuals

Chapter Notes

Author Notes

Michael F Hammer, PhD (scn8a.info@gmail.com), is actively involved in clinical research regarding individuals with *SCN8A*-related epilepsy and related disorders. He would be happy to communicate with persons who have any questions regarding diagnosis of *SCN8A*-related epilepsy and/or neurodevelopmental disorders or other considerations.

John M Schreiber, MD, is actively involved in treating patients with *SCN8A*-related epilepsy and related disorders and is also interested in hearing from clinicians treating families affected by this disorder or in whom no causative variant has been identified through molecular genetic testing.

Contact **Michael F Hammer** (scn8a.info@gmail.com) to inquire about review of *SCN8A* variants of uncertain significance.

The Hammer lab identified the first case of *SCN8A*-related epilepsy and has established a registry and an online database of the clinical features of patients with pathogenic variants in *SCN8A* (www.scn8a.net). The Hammer lab is also performing experiments using mouse models of *SCN8A*-related epilepsy and/or neurodevelopmental disorders.

Acknowledgments

We thank Wishes for Elliott (www.wishesforelliott.com) for funding the first *SCN8A* workshop in association with an American Academy of Neurology meeting in Washington, DC (April 20, 2015).

Author History

Michael F Hammer, PhD (2016-present)
Heather C Mefford, MD, PhD; St Jude Children's Research Hospital (2016-2023)
Miriam H Meisler, PhD; University of Michigan (2016-2023)
John M Schreiber, MD (2023-present)

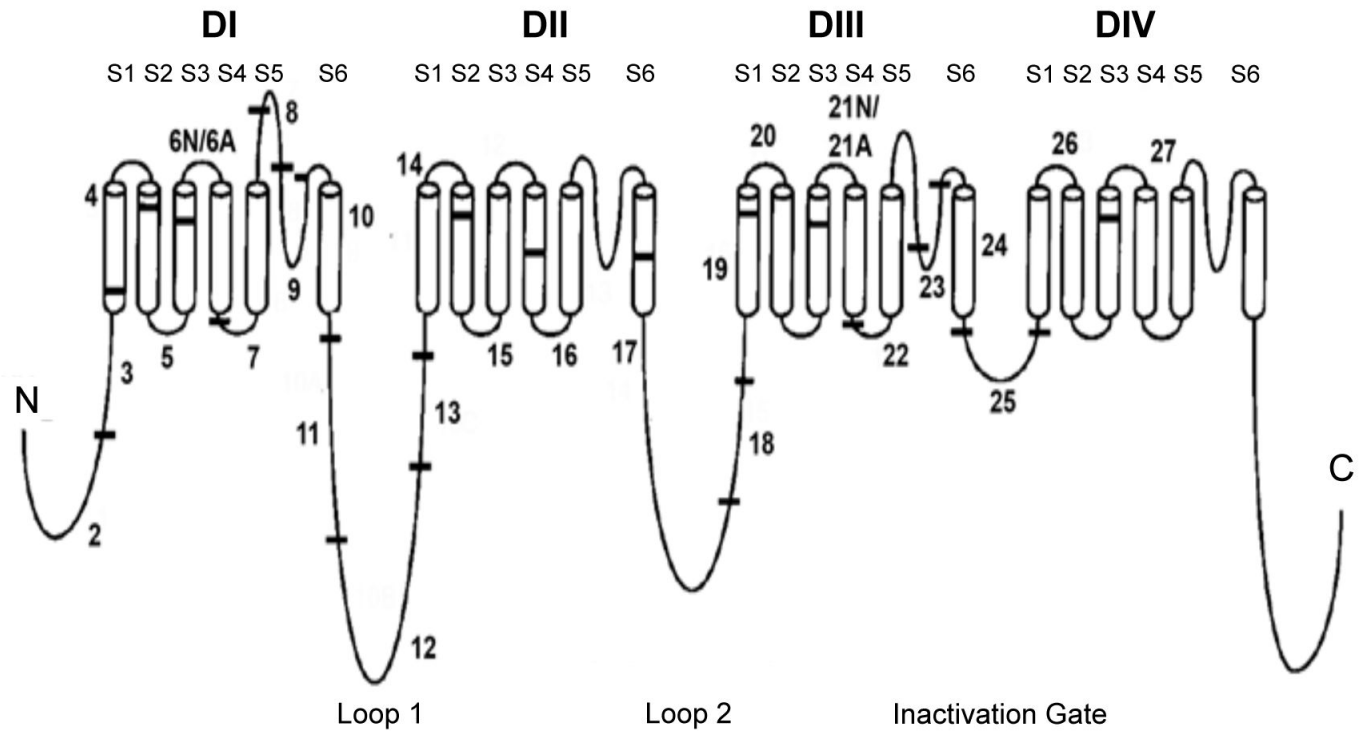

Figure 1. Intron-exon organization of *SCN8A*. Horizontal bars mark the positions of the introns of the sodium channel protein type 8 subunit alpha ($Na_V1.6$) superimposed on the secondary structure of the sodium channel.

Adapted from Plummer et al [1998]

Jacy L Wagnon, PhD; University of Michigan (2016-2023)
Maya Xia, BA (2023-present)

Revision History

- 6 April 2023 (gm) Comprehensive updated posted live
- 25 August 2016 (bp) Review posted live
- 29 September 2015 (mfh) Original submission

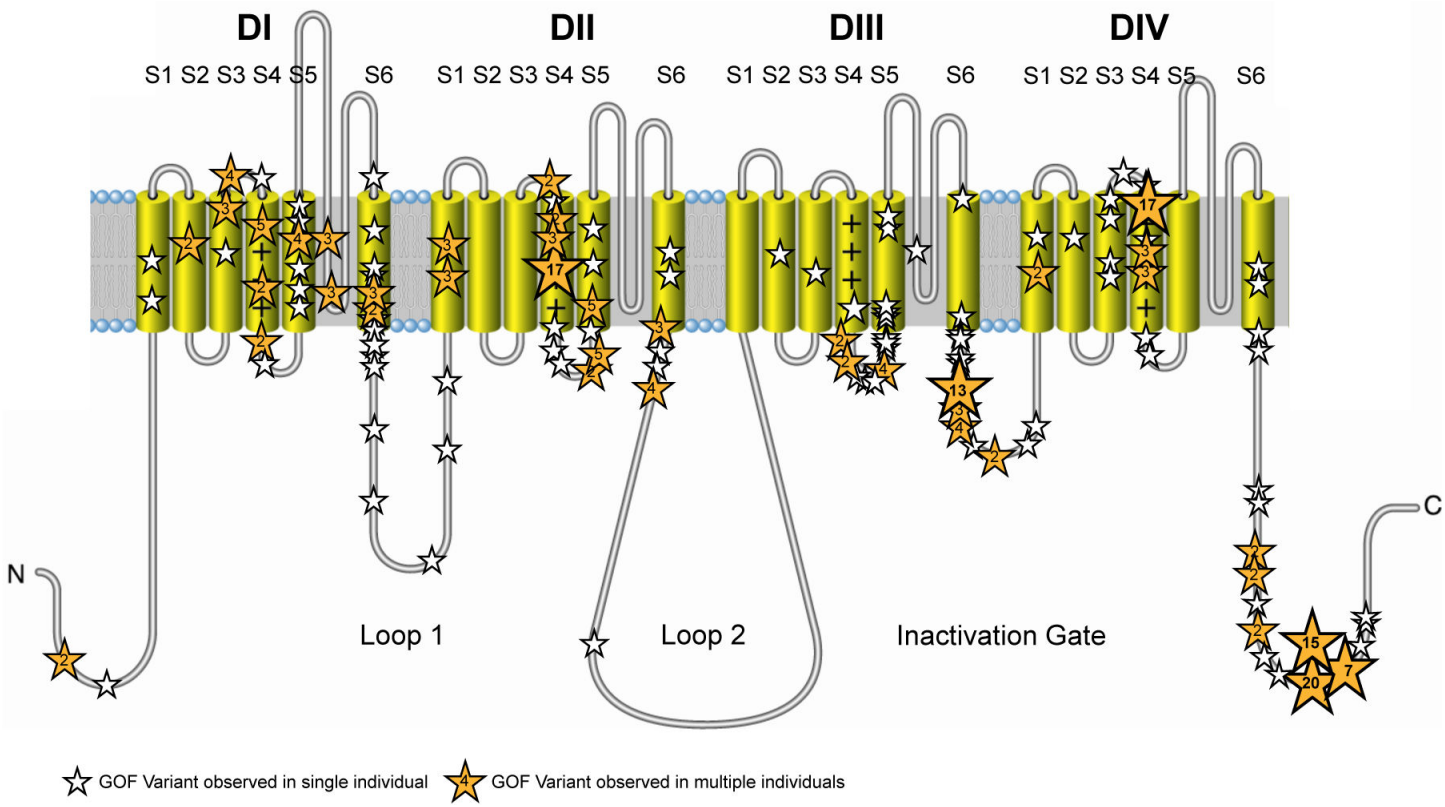

Figure 2. Positions of *SCN8A* missense pathogenic variants in the sodium channel protein type 8 subunit alpha ($Na_V1.6$). The protein has four homologous domains (DI to DIV), each containing six transmembrane segments (S1-S6).

Data from www.scn8a.net

References

Literature Cited

Alagia M, Bernardo P, Genesio R, Gennaro E, Brunetti-Pierri N, Coppola A, Zara F, Striano P, Striano S, Terrone G. Dual diagnosis in a child with familial SCN8A-related encephalopathy complicated by a 1p13.2 deletion involving NRAS gene. Neurol Sci. 2021;42:2115-7. PubMed PMID: 33201365.

Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217-21. PubMed PMID: 23934111.

Anand G, Collett-White F, Orsini A, Thomas S, Jayapal S, Trump N, Zaiwalla Z, Jayawant S. Autosomal dominant SCN8A mutation with an unusually mild phenotype. Eur J Paediatr Neurol. 2016;20:761-5. PubMed PMID: 27210545.

Arafat A, Jing P, Ma Y, Pu M, Nan G, Fang H, Chen C, Fei Y. Unexplained early infantile epileptic encephalopathy in Han Chinese children: next-generation sequencing and phenotype enriching. Sci Rep. 2017;7:46227. PubMed PMID: 28387369.

Atanasoska M, Vazharova R, Ivanov I, Balabanski L, Andonova S, Ivanov S, Pacheva I, Malinov M, Toncheva D. SCN8A p.Arg1872Gln mutation in early infantile epileptic encephalopathy type 13: review and case report. Biotechnol Biotechnol Equip. 2018;32:1345-51.

Bagnasco I, Dassi P, Blé R, Vigliano P. A relatively mild phenotype associated with mutation of SCN8A. Seizure. 2018;56:47-9. PubMed PMID: 29432985.

Balciuniene J, DeChene ET, Akgumus G, Romasko EJ, Cao K, Dubbs HA, Mulchandani S, Spinner NB, Conlin LK, Marsh ED, Goldberg E, Helbig I, Sarmady M, Abou Tayoun A. Use of a dynamic genetic testing approach for childhood-onset epilepsy. JAMA Netw Open. 2019;2:e192129. PubMed PMID: 30977854.

Barker BS, Ottolini M, Wagnon JL, Hollander RM, Meisler MH, Patel MK. The SCN8A encephalopathy mutation p.Ile1327Val displays elevated sensitivity to the anticonvulsant phenytoin. Epilepsia. 2016;57:1458-66. PubMed PMID: 27375106.

Berghuis B, de Kovel CG, van Iterson L, Lamberts RJ, Sander JW, Lindhout D, Koeleman BP. Complex SCN8A DNA-abnormalities in an individual with therapy resistant absence epilepsy. Epilepsy Res. 2015;115:141-4. PubMed PMID: 26220391.

Blanchard MG, Willemsen MH, Walker JB, Dib-Hajj SD, Waxman SG, Jongmans MC, Kleefstra T, van de Warrenburg BP, Praamstra P, Nicolai J, Yntema HG, Bindels RJ, Meisler MH, Kamsteeg EJ. De novo gain-of-function and loss-of-function mutations of SCN8A in patients with intellectual disabilities and epilepsy. J Med Genet. 2015;52:330-7. PubMed PMID: 25725044.

Boerma RS, Braun KP, van den Broek MP, van Berkestijn FM, Swinkels ME, Hagebeuk EO, Lindhout D, van Kempen M, Boon M, Nicolai J, de Kovel CG, Brilstra EH, Koeleman BP. Remarkable phenytoin sensitivity in 4 children with SCN8A-related epilepsy: a molecular neuropharmacological approach. Neurotherapeutics. 2016;13:192-7. PubMed PMID: 26252990.

Braakman HM, Verhoeven JS, Erasmus CE, Haaxma CA, Willemsen MH, Schelhaas HJ. Phenytoin as a last-resort treatment in SCN8A encephalopathy. Epilepsia Open. 2017;2:343-4. PubMed PMID: 29588963.

Butler KM, da Silva C, Shafir Y, Weisfeld-Adams JD, Alexander JJ, Hegde M, Escayg A. De novo and inherited SCN8A epilepsy mutations detected by gene panel analysis. Epilepsy Res. 2017;129:17-25. PubMed PMID: 27875746.

Canafoglia L, Franceschetti S, Granata T, Messina G, Solazzi R, Ragona F, Freri E, Scaioli V, Nardocci N, Gellera C, Panzica F, DiFrancesco JC, Castellotti B. SCN8A splicing mutation causing skipping of the exon 15 associated with intellectual disability and cortical myoclonus. Seizure. 2020;82:56-8. PubMed PMID: 33007625.

Carvill GL, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, Cook J, Khan A, Dorschner MO, Weaver M, Calvert S, Malone S, Wallace G, Stanley T, Bye AM, Bleasel A, Howell KB, Kivity S, Mackay MT, Rodriguez-Casero V, Webster R, Korczyn A, Afawi Z, Zelnick N, Lerman-Sagie T, Lev D, Moller RS, Gill D, Andrade DM, Freeman JL, Sadleir LG, Shendure J, Berkovic SF, Scheffer IE, Mefford HC. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet. 2013;45:825-30. PubMed PMID: 23708187.

Chipaux M, Villeneuve N, Sabouraud P, Desguerre I, Boddaert N, Depienne C, Chiron C, Dulac O, Nabbout R. Unusual consequences of status epilepticus in Dravet syndrome. Seizure. 2010;19:190-4. PubMed PMID: 20172746.

Costain G, Cordeiro D, Matviychuk D, Mercimek-Andrews S. Clinical application of targeted next-generation sequencing panels and whole exome sequencing in childhood epilepsy. Neuroscience. 2019;418:291-310. PubMed PMID: 31487502.

de Kovel CG, Meisler MH, Brilstra EH, van Berkestijn FM, van 't Slot R, van Lieshout S, Nijman IJ, O'Brien JE, Hammer MF, Estacion M, Waxman SG, Dib-Hajj SD, Koeleman BP. Characterization of a de novo SCN8A mutation in a patient with epileptic encephalopathy. Epilepsy Res. 2014;108:1511-8. PubMed PMID: 25239001.

Denis J, Villeneuve N, Cacciagli P, Mignon-Ravix C, Lacoste C, Lefranc J, Napuri S, Damaj L, Villega F, Pedespan J, Moutton S, Mignot C, Doummar D, Lion-François L, Gataullina S, Dulac O, Martin M, Gueden S, Lesca G, Julia S, Cances C, Journel H, Altuzarra C, Ben Zeev B, Afenjar A, Barth M, Villard L, Milh M. Clinical study of 19 patients with SCN8A-related epilepsy: two modes of onset regarding EEG and seizures. Epilepsia. 2019;60:845-56. PubMed PMID: 31026061.

Donnan AM, Schneider AL, Russ-Hall S, Churilov L, Scheffer IE. Rates of status epilepticus and sudden unexplained death in epilepsy in people with genetic developmental and epileptic encephalopathies. Neurology. 2023;100:e1712-e1722. PubMed PMID: 36750385.

Dyment DA, Tetreault M, Beaulieu CL, Hartley T, Ferreira P, Chardon JW, Marcadier J, Sawyer SL, Mosca SJ, Innes AM, Parboosingh JS, Bulman DE, Schwartzentruber J, Majewski J, Tarnopolsky M, Boycott KM, et al. Whole-exome sequencing broadens the phenotypic spectrum of rare pediatric epilepsy: a retrospective study. Clin Genet. 2015;88:34-40. PubMed PMID: 25046240.

Encinas AC, Moore IM, Watkins JC, Hammer MF. Influence of age at seizure onset on the acquisition of neurodevelopmental skills in an SCN8A cohort. Epilepsia Open. 2019;60:1711-20.

Epifanio R, Zanotta N, Giorda R, Bardoni A, Zucca C. Novel epilepsy phenotype associated to a known SCN8A mutation. Seizure. 2019;67:15-17. PubMed PMID: 30851583.

Epilepsy Genetics Initiative. De novo variants in the alternative exon 5 of SCN8A cause epileptic encephalopathy. Genet Med. 2018;20:275-81. PubMed PMID: 29121005.

Estacion M, O'Brien JE, Conravey A, Hammer MF, Waxman SG, Dib-Hajj SD, Meisler MH. A novel de novo mutation of SCN8A (Nav1.6) with enhanced channel activation in a child with epileptic encephalopathy. Neurobiol Dis. 2014;69:117-23. PubMed PMID: 24874546.

Fan HC, Lee HF, Chi CS. SCN8A encephalopathy: case report and literature review. Neurol Int. 2021;13:143-50. PubMed PMID: 33915942.

Fatema K, Rahman MM, Faruk O. SCN8A mutation in infantile epileptic encephalopathy: report of two cases. J Epilepsy Res. 2020;9:147-51.

Fitzgerald T, Gerety S, Jones W, van Kogelenberg M, King D, McRae J, Morley K, Parthiban V, Al-Turki S, Ambridge K, Barrett D, Bayzetinova T, Clayton S, Coomber E, Gribble S, Jones P, Krishnappa N, Mason L, Middleton A, Miller R, Prigmore E, Rajan D, Sifrim A, Tivey A, Ahmed M, Akawi N, Andrews R, Anjum U, Archer H, Armstrong R, Balasubramanian M, Banerjee R, Baralle D, Batstone P, Baty D, Bennett C, Berg J, Bernhard B, Bevan A, Blair E, Blyth M, Bohanna D, Bourdon L, Bourn D, Brady A, Bragin E, Brewer C, Brueton L, Brunstrom K, Bumpstead S, Bunyan D, Burn J, Burton J, Canham N, Castle B, Chandler K, Clasper S, Clayton-Smith J, Cole T, Collins A, Collinson M, Connell F, Cooper N, Cox H, Cresswell L, Cross G, Crow Y, D'Alessandro M, Dabir T, Davidson R, Davies S, Dean J, Deshpande C, Devlin G, Dixit A, Dominiczak A, Donnelly C, Donnelly D, Douglas A, Duncan A, Eason J, Edkins S, Ellard S, Ellis P, Elmslie F, Evans K, Everest S, Fendick T, Fisher R, Flinter F, Foulds N, Fryer A, Fu B, Gardiner C, Gaunt L, Ghali N, Gibbons R, Gomes Pereira S, Goodship J, Goudie D, Gray E, Greene P, Greenhalgh L, Harrison L, Hawkins R, Hellens S, Henderson A, Hobson E, Holden S, Holder S, Hollingsworth G, Homfray T, Humphreys M, Hurst J, Ingram S, Irving M, Jarvis J, Jenkins L, Johnson D, Jones D, Jones E, Josifova D, Joss S, Kaemba B, Kazembe S, Kerr B, Kini U, Kinning E, Kirby G, Kirk C, Kivuva E, Kraus A, Kumar D, Lachlan K, Lam W, Lampe A, Langman C, Lees M, Lim D, Lowther G, Lynch S, Magee A, Maher E, Mansour S, Marks K, Martin K, Maye U, McCann E, McConnell V, McEntagart M, McGowan R, McKay K, McKee S, McMullan D, McNerlan S, Mehta S, Metcalfe K, Miles E, Mohammed S, Montgomery T, Moore D, Morgan S, Morris A,

Morton J, Mugalaasi H, Murday V, Nevitt L, Newbury-Ecob R, Norman A, O'Shea R, Ogilvie C, Park S, Parker M, Patel C, Paterson J, Payne S, Phipps J, Pilz D, Porteous D, Pratt N, Prescott K, Price S, Pridham A, Procter A, Purnell H, Ragge N, Rankin J, Raymond L, Rice D, Robert L, Roberts E, Roberts G, Roberts J, Roberts P, Ross A, Rosser E, Saggar A, Samant S, Sandford R, Sarkar A, Schweiger S, Scott C, Scott R, Selby A, Seller A, Sequeira C, Shannon N, Sharif S, Shaw-Smith C, Shearing E, Shears D, Simonic I, Simpkin D, Singzon R, Skitt Z, Smith A, Smith B, Smith K, Smithson S, Sneddon L, Splitt M, Squires M, Stewart F, Stewart H, Suri M, Sutton V, Swaminathan G, Sweeney E, Tatton-Brown K, Taylor C, Taylor R, Tein M, Temple I, Thomson J, Tolmie J, Torokwa A, Treacy B, Turner C, Turnpenny P, Tysoe C, Vandersteen A, Vasudevan P, Vogt J, Wakeling E, Walker D, Waters J, Weber A, Wellesley D, Whiteford M, Widaa S, Wilcox S, Williams D, Williams N, Woods G, Wragg C, Wright M, Yang F, Yau M, Carter N, Parker M, Firth H, FitzPatrick D, Wright C, Barrett J, Hurles M. Large-scale discovery of novel genetic causes of developmental disorders. Nature. 2015;519:223-8. PubMed PMID: 25533962.

Frasier CR, Wagnon JL, Bao YO, McVeigh LG, Lopez-Santiago LF, Meisler MH, Isom LL. Cardiac arrhythmia in a mouse model of sodium channel SCN8A epileptic encephalopathy. Proc Natl Acad Sci U S A. 2016;113:12838-43. PubMed PMID: 27791149.

Fung LW, Kwok SL, Tsui KW. SCN8A mutations in Chinese children with early onset epilepsy and intellectual disability. Epilepsia. 2015;56:1319-20. PubMed PMID: 26235738.

Gardella E, Becker F, Møller RS, Schubert J, Lemke JR, Larsen LH, Eiberg H, Nothnagel M, Thiele H, Altmüller J, Syrbe S, Merkenschlager A, Bast T, Steinhoff B, Nürnberg P, Mang Y, Bakke Møller L, Gellert P, Heron SE, Dibbens LM, Weckhuysen S, Dahl HA, Biskup S, Tommerup N, Hjalgrim H, Lerche H, Beniczky S, Weber YG. Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. Ann Neurol. 2016;79:428-36. PubMed PMID: 26677014.

Gardella E, Marini C, Trivisano M, Fitzgerald MP, Alber M, Howell KB, Darra F, Siliquini S, Bölsterli BK, Masnada S, Pichiecchio A, Johannesen KM, Jepsen B, Fontana E, Anibaldi G, Russo S, Cogliati F, Montomoli M, Specchio N, Rubboli G, Veggiotti P, Beniczky S, Wolff M, Helbig I, Vigevano F, Scheffer IE, Guerrini R, Møller RS. The phenotype of SCN8A developmental and epileptic encephalopathy. Neurology. 2018;91:e1112-24. PubMed PMID: 30171078.

Hack JB, Horning K, Juroske Short DM, Schreiber JM, Watkins JC, Hammer MF. Distinguishing loss-of-function and gain-of-function SCN8A variants using a random forest classification model trained on clinical features. Neurol Genet. 2023;9:e200060. PubMed PMID: 37152443.

Han JY, Jang JH, Lee IG, Shin S, Park J. A novel inherited mutation of SCN8A in a Korean family with benign familial infantile epilepsy using diagnostic exome sequencing. 2017;47.

Heyne HO, Artomov M, Battke F, Bianchini C, Smith DR, Liebmann N, Tadigotla V, Stanley CM, Lal D, Rehm H, Lerche H, Daly MJ, Helbig I, Biskup S, Weber YG, Lemke JR. Targeted gene sequencing in 6994 individuals with neurodevelopmental disorder with epilepsy. Genet Med. 2019;21:2496-503. PubMed PMID: 31056551.

Hu C, Luo T, Wang Y. Phenotypic and genetic spectrum in Chinese children with SCN8A-related disorders. Seizure. 2022;95:38-49. PubMed PMID: 34979445.

Jain P. Novel SCN8A mutation in a girl with refractory seizures and autistic features. Neurol India 2017;65:180-1. PubMed PMID: 28084268.

Jain P, Gulati P, Morrison-Levy N, Yau I, Alsowat D, Otsubo H, Ochi A, Whitney R. "Breath holding spells" in a child with SCN8A-related epilepsy: expanding the clinical spectrum. Seizure. 2019;65:129-30. PubMed PMID: 30685519.

Jang SS, Kim SY, Kim H, Hwang H, Chae JH, Kim KJ, Kim JI, Lim BC. Diagnostic yield of epilepsy panel testing in patients with seizure onset within the first year of life. Front Neurol. 2019;10:988. PubMed PMID: 31572294.

Johannesen KM, Gardella E, Encinas AC, Lehesjoki AE, Linnankivi T, Petersen MB, Lund IC, Blichfeldt S, Miranda MJ, Pal DK, Lascelles K, Procopis P, Orsini A, Bonuccelli A, Giacomini T, Helbig I, Fenger CD, Sisodiya SM, Hernandez-Hernandez L, Krithika S, Rumple M, Masnada S, Valente M, Cereda C, Giordano L, Accorsi P, Bürki SE, Mancardi M, Korff C, Guerrini R, von Spiczak S, Hoffman-Zacharska D, Mazurczak T, Coppola A, Buono S, Vecchi M, Hammer MF, Varesio C, Veggiotti P, Lal D, Brünger T, Zara F, Striano P, Rubboli G, Møller RS. The spectrum of intermediate SCN8A-related epilepsy. Epilepsia. 2019;60:830-44. PubMed PMID: 30968951.

Johannesen KM, Gardella E, Scheffer I, Howell K, Smith DM, Helbig I, Møller RS, Rubboli G. Early mortality in SCN8A -related epilepsies. Epilepsy Res. 2018;143:79-81. PubMed PMID: 29677576.

Johannesen KM, Liu Y, Koko M, Gjerulfsen CE, Sonnenberg L, Schubert J, Fenger CD, Eltokhi A, Rannap M, Koch NA, Lauxmann S, Krüger J, Kegele J, Canafoglia L, Franceschetti S, Mayer T, Rebstock J, Zacher P, Ruf S, Alber M, Sterbova K, Lassuthová P, Vlckova M, Lemke JR, Platzer K, Krey I, Heine C, Wieczorek D, Kroell-Seger J, Lund C, Klein KM, Au PYB, Rho JM, Ho AW, Masnada S, Veggiotti P, Giordano L, Accorsi P, Hoei-Hansen CE, Striano P, Zara F, Verhelst H, Verhoeven JS, Braakman HMH, van der Zwaag B, Harder AVE, Brilstra E, Pendziwiat M, Lebon S, Vaccarezza M, Le NM, Christensen J, Grønborg S, Scherer SW, Howe J, Fazeli W, Howell KB, Leventer R, Stutterd C, Walsh S, Gerard M, Gerard B, Matricardi S, Bonardi CM, Sartori S, Berger A, Hoffman-Zacharska D, Mastrangelo M, Darra F, Vøllo A, Motazacker MM, Lakeman P, Nizon M, Betzler C, Altuzarra C, Caume R, Roubertie A, Gélisse P, Marini C, Guerrini R, Bilan F, Tibussek D, Koch-Hogrebe M, Perry MS, Ichikawa S, Dadali E, Sharkov A, Mishina I, Abramov M, Kanivets I, Korostelev S, Kutsev S, Wain KE, Eisenhauer N, Wagner M, Savatt JM, Müller-Schlüter K, Bassan H, Borovikov A, Nassogne MC, Destrée A, Schoonjans AS, Meuwissen M, Buzatu M, Jansen A, Scalais E, Srivastava S, Tan WH, Olson HE, Loddenkemper T, Poduri A, Helbig KL, Helbig I, Fitzgerald MP, Goldberg EM, Roser T, Borggraefe I, Brünger T, May P, Lal D, Lederer D, Rubboli G, Heyne HO, Lesca G, Hedrich UBS, Benda J, Gardella E, Lerche H, Møller RS. Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications. Brain. 2022;145:2991-3009. PubMed PMID: 34431999.

Johnson JP, Focken T, Khakh K, Tari PK, Dube C, Goodchild SJ, Andrez JC, Bankar G, Bogucki D, Burford K, Chang E, Chowdhury S, Dean R, de Boer G, Decker S, Dehnhardt C, Feng M, Gong W, Grimwood M, Hasan A, Hussainkhel A, Jia Q, Lee S, Li J, Lin S, Lindgren A, Lofstrand V, Mezeyova J, Namdari R, Nelkenbrecher K, Shuart NG, Sojo L, Sun S, Taron M, Waldbrook M, Weeratunge D, Wesolowski S, Williams A, Wilson M, Xie Z, Yoo R, Young C, Zenova A, Zhang W, Cutts AJ, Sherrington RP, Pimstone SN, Winquist R, Cohen CJ, Empfield JR. NBI-921352, a first-in-class, NaV1.6 selective, sodium channel inhibitor that prevents seizures in Scn8a gain-of-function mice, and wild-type mice and rats. Elife. 2022;11:e72468. PubMed PMID: 35234610.

Keshri S, Goel AK, Shah S, Garg AK. A novel SCN8A mutation in a case of early-onset infantile epileptic encephalopathy: a case report. Acta Biomedica Atenei Parmensis. 2022;92:e2021261.

Kim HJ, Yang D, Kim SH, Kim B, Kim HD, Lee JS, Choi JR, Lee ST, Kang HC. Genetic and clinical features of SCN8A developmental and epileptic encephalopathy. Epilepsy Res. 2019;158:106222. PubMed PMID: 31675620.

Ko A, Youn SE, Kim SH, Lee JS, Kim S, Choi JR, Kim HD, Lee ST, Kang HC. Targeted gene panel and genotype-phenotype correlation in children with developmental and epileptic encephalopathy. Epilepsy Res. 2018;141:48-55. PubMed PMID: 29455050.

Kong W, Zhang Y, Gao Y, Liu X, Gao K, Xie H, Wang J, Wu Y, Zhang Y, Wu X, Jiang Y. SCN8A mutations in Chinese children with early onset epilepsy and intellectual disability. Epilepsia. 2015a;56:431-8. PubMed PMID: 25785782.

Kong W, Zhang Y, Jiang Y. In response: SCN8A mutations in Chinese children with early onset epilepsy and intellectual disability. Epilepsia. 2015b;56:1320. PubMed PMID: 26235739.

Kothur K, Holman K, Farnsworth E, Ho G, Lorentzos M, Troedson C, Gupta S, Webster R, Procopis PG, Menezes MP, Antony J, Ardern-Holmes S, Dale RC, Christodoulou J, Gill D, Bennetts B. Diagnostic yield of targeted massively parallel sequencing in children with epileptic encephalopathy. Seizure. 2018;59:132-40. PubMed PMID: 29852413.

Larsen J, Carvill GL, Gardella E, Kluger G, Schmiedel G, Barisic N, Depienne C, Brilstra E, Mang Y, Nielsen JE, Kirkpatrick M, Goudie D, Goldman R, Jahn JA, Jepsen B, Gill D, Docker M, Biskup S, McMahon JM, Koeleman B, Harris M, Braun K, de Kovel CG, Marini C, Specchio N, Djemie T, Weckhuysen S, Tommerup N, Troncoso M, Troncoso L, Bevot A, Wolff M, Hjalgrim H, Guerrini R, Scheffer IE, Mefford HC, Moller RS; Euro ERESCCRP. The phenotypic spectrum of SCN8A encephalopathy. Neurology. 2015;84:480-9. PubMed PMID: 25568300.

Lee J, Lee C, Ki C, Lee J. Determining the best candidates for next-generation sequencing-based gene panel for evaluation of early-onset epilepsy. Mol Genet Genomic Med. 2020;8:e1376. PubMed PMID: 32613771.

Lelieveld SH, Reijnders MRF, Pfundt R, Yntema HG, Kamsteeg EJ, de Vries P, de Vries BB, Willemsen MH, Kleefstra T, Löhner K, Vreeburg M, Stevens SJC, van der Burgt I, Bongers EMHF, Stegmann APA, Rump P, Rinne T, Nelen MR, Veltman JA, Gilissen C. Meta-analysis of 2,104 trios provides support for 10 new genes for intellectual disability. Nat Neurosci. 2016;19:1194-6. PubMed PMID: 27479843.

Liao YF, Liao CH, Chu YJ, Fan PC. Pharmacotherapy and electroencephalographic evolution in SCN8A encephalopathy: a case report. J Formos Med Assoc. 2019;118:1266-7. PubMed PMID: 31010614.

Lin KM, Su G, Wang F, Zhang X, Wang Y, Ren J, Wang X, Yao Y, Zhou Y. A de novo SCN8A heterozygous mutation in a child with epileptic encephalopathy: a case report. BMC Pediatr. 2019;19:400. PubMed PMID: 31672125.

Lindy AS, Stosser MB, Butler E, Downtain-Pickersgill C, Shanmugham A, Retterer K, Brandt T, Richard G, McKnight DA. Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. Epilepsia. 2018;59:1062-71. PubMed PMID: 29655203.

Liu J, Tong L, Song S, Niu Y, Li J, Wu X, Zhang J, Zai CC, Luo F, Wu J, Li H, Wong AHC, Sun R, Liu F, Li B. Novel and de novo mutations in pediatric refractory epilepsy. Mol Brain. 2018;11:48. PubMed PMID: 30185235.

Liu Y, Schubert J, Sonnenberg L, Helbig KL, Hoei-Hansen CE, Koko M, Rannap M, Lauxmann S, Huq M, Schneider MC, Johannesen KM, Kurlemann G, Gardella E, Becker F, Weber YG, Benda J, Møller RS, Lerche H. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. Brain. 2019;142:376-90. PubMed PMID: 30615093.

Malcolmson J, Kleyner R, Tegay D, Adams W, Ward K, Coppinger J, Nelson L, Meisler MH, Wang K, Robison R, Lyon GJ. SCN8A mutation in a child presenting with seizures and developmental delays. Cold Spring Harb Mol Case Stud. 2016;2:a001073. PubMed PMID: 27900360.

Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. Neurology. 2000;55:1002-7. PubMed PMID: 11061259.

McNally MA, Johnson J, Huisman TA, Poretti A, Baranano KW, Baschat AA, Stafstrom CE. SCN8A epileptic encephalopathy: detection of fetal seizures guides multidisciplinary approach to diagnosis and treatment. Pediatr Neurol. 2016;64:87-91. PubMed PMID: 27659738.

Medlin LC, Bello-Espinosa L, MacAllister WS. Neuropsychological profiles of two patients with differing SCN8A-pathogenic variants. Appl Neuropsychol Child. 2022;11:561-6. PubMed PMID: 32853054.

Mercimek-Mahmutoglu S, Patel J, Cordeiro D, Hewson S, Callen D, Donner EJ, Hahn CD, Kannu P, Kobayashi J, Minassian BA, Moharir M, Siriwardena K, Weiss SK, Weksberg R, Snead OC 3rd. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. Epilepsia. 2015;56:707-16. PubMed PMID: 25818041.

Mitta N, Menon RN, McTague A, Radhakrishnan A, Sundaram S, Cherian A, Madhavilatha G, Mannan AU, Nampoothiri S, Thomas SV. Genotype-phenotype correlates of infantile-onset developmental & epileptic encephalopathy syndromes in South India: a single centre experience. Epilepsy Res. 2020;166:106398. PubMed PMID: 32593896.

Møller RS, Larsen LHG, Johannesen KM, Talvik I, Talvik T, Vaher U, Miranda MJ, Farooq M, Nielsen JEK, Lavard Svendsen L, Kjelgaard DB, Linnet KM, Hao Q, Uldall P, Frangu M, Tommerup N, Baig SM, Abdullah U, Born AP, Gellert P, Nikanorova M, Olofsson K, Jepsen B, Marjanovic D, Al-Zehhawi LIK, Peñalva SJ, Krag-Olsen B, Brusgaard K, Hjalgrim H, Rubboli G, Pal DK, Dahl HA. Gene panel testing in epileptic encephalopathies and familial epilepsies. Mol Syndromol. 2016;7:210-9. PubMed PMID: 27781031.

Negishi Y, Aoki Y, Itomi K, Yasuda K, Taniguchi H, Ishida A, Arakawa T, Miyamoto S, Nakashima M, Saitsu H, Saitoh S. SCN8A-related developmental and epileptic encephalopathy with ictal asystole requiring cardiac pacemaker implantation. Brain Dev. 2021;43:804-8. PubMed PMID: 33827760.

Oates S, Tang S, Rosch R, Lear R, Hughes EF, Williams RE, Larsen LHG, Hao Q, Dahl HA, Møller RS, Pal DK. Incorporating epilepsy genetics into clinical practice: a 360 evaluation. NPJ Genomic Med. 2018;3:13.

O'Brien JE, Sharkey LM, Vallianatos CN, Han C, Blossom JC, Yu T, Waxman SG, Dib-Hajj SD, Meisler MH. Interaction of voltage-gated sodium channel Nav1.6 (SCN8A) with microtubule-associated protein Map1b. J Biol Chem. 2012;287:18459-66. PubMed PMID: 22474336.

Ohba C, Kato M, Takahashi S, Lerman-Sagie T, Lev D, Terashima H, Kubota M, Kawawaki H, Matsufuji M, Kojima Y, Tateno A, Goldberg-Stern H, Straussberg R, Marom D, Leshinsky-Silver E, Nakashima M, Nishiyama K, Tsurusaki Y, Miyake N, Tanaka F, Matsumoto N, Saitsu H. Early onset epileptic encephalopathy caused by de novo SCN8A mutations. Epilepsia. 2014;55:994-1000. PubMed PMID: 24888894.

Olson HE, Tambunan D, LaCoursiere C, Goldenberg M, Pinsky R, Martin E, Ho E, Khwaja O, Kaufmann WE, Poduri A. Mutations in epilepsy and intellectual disability genes in patients with features of Rett syndrome. Am J Med Genet A. 2015;167A:2017-25. PubMed PMID: 25914188.

Parrini E, Marini C, Mei D, Galuppi A, Cellini E, Pucatti D, Chiti L, Rutigliano D, Bianchini C, Virdò S, De Vita D, Bigoni S, Barba C, Mari F, Montomoli M, Pisano T, Rosati A, Guerrini R, et al. Diagnostic targeted resequencing in 349 patients with drug-resistant pediatric epilepsies identifies causative mutations in 30 different genes. Human Mutation. 2017;38:216-25. PubMed PMID: 27864847.

Peng BW, Tian Y, Chen L, Duan LF, Wang XY, Zhu HX, Shi KL, Zheng KL, Shen HL, Liang W, Li XJ, Chen WX. Genotype-phenotype correlations in SCN8A-related epilepsy: a cohort study of Chinese children in southern China. Brain. 2022;145:e24-e27. PubMed PMID: 35230384.

Pergande M, Motameny S, Özdemir Ö, Kreutzer M, Wang H, Daimagüler HS, Becker K, Karakaya M, Ehrhardt H, Elcioglu N, Ostojic S, Chao CM, Kawalia A, Duman Ö, Koy A, Hahn A, Reimann J, Schoner K, Schänzer A, Westhoff JH, Schwaibold EMC, Cossee M, Imbert-Bouteille M, von Pein H, Haliloglu G, Topaloglu H, Altmüller J, Nürnberg P, Thiele H, Heller R, Cirak S. The genomic and clinical landscape of fetal akinesia. Genet Med. 2020;22:511-23. PubMed PMID: 31680123.

Plummer NW, Galt J, Jones JM, Burgess DL, Sprunger LK, Kohrman DC, Meisler MH. Exon organization, coding sequence, physical mapping, and polymorphic intragenic markers for the human neuronal sodium channel gene SCN8A. Genomics. 1998;54:287-96. PubMed PMID: 9828131.

Pons L, Lesca G, Sanlaville D, Chatron N, Labalme A, Manel V, Arzimanoglou A, de Bellescize J, Lion-François L. Neonatal tremor episodes and hyperekplexia-like presentation at onset in a child with SCN8A developmental and epileptic encephalopathy. Epileptic Disord. 2018;20:289-94. PubMed PMID: 30078772.

Ranza E, Z'Graggen W, Lidgren M, Beghetti M, Guipponi M, Antonarakis SE, Absoud M, Goyal S, Pal DK, Korff CM. SCN8A heterozygous variants are associated with anoxic-epileptic seizures. Am J Med Genet. 2020;182:1209-16. PubMed PMID: 32040247.

Rauch A, Wieczorek D, Graf E, Wieland T, Endele S, Schwarzmayr T, Albrecht B, Bartholdi D, Beygo J, Di Donato N, Dufke A, Cremer K, Hempel M, Horn D, Hoyer J, Joset P, Ropke A, Moog U, Riess A, Thiel CT, Tzschach A, Wiesener A, Wohlleber E, Zweier C, Ekici AB, Zink AM, Rump A, Meisinger C, Grallert H, Sticht H, Schenck A, Engels H, Rappold G, Schrock E, Wieacker P, Riess O, Meitinger T, Reis A, Strom TM. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet. 2012;380:1674-82. PubMed PMID: 23020937.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rim JH, Kim SH, Hwang IS, Kwon SS, Kim J, Kim HW, Cho MJ, Ko A, Youn SE, Kim J, Lee YM, Chung HJ, Lee JS, Kim HD, Choi JR, Lee ST, Kang HC. Efficient strategy for the molecular diagnosis of intractable early-onset epilepsy using targeted gene sequencing. BMC Med Genomics. 2018;11:6. PubMed PMID: 29390993.

Rolvien T, Butscheidt S, Jeschke A, Neu A, Denecke J, Kubisch C, Meisler MH, Pueschel K, Barvencik F, Yorgan T, Oheim R, Schinke T, Amling M. Severe bone loss and multiple fractures in SCN8A-related epileptic encephalopathy. Bone. 2017;103:136-43. PubMed PMID: 28676440.

Schreiber JM, Tochen L, Brown M, Evans S, Ball LJ, Bumbut A, Thewamit R, Whitehead MT, Black C, Boutzoukas E, Fanto E, Suslovic W, Berl M, Hammer M, Gaillard WD. A multi-disciplinary clinic for SCN8A-related epilepsy. Epilepsy Res. 2020;159:106261. PubMed PMID: 31887642.

Singh R, Jayapal S, Goyal S, Jungbluth H, Lascelles K. Early-onset movement disorder and epileptic encephalopathy due to de novo dominant SCN8A mutation. Seizure. 2015;26:69-71. PubMed PMID: 25799905.

Solazzi R, Castellotti B, Canafoglia L, Messina G, Magri S, Freri E, Ragona F, Franceschetti S, Di Francesco JC, Gellera C, Granata T. Paroxysmal tonic upgaze in a child with SCN8A-related encephalopathy. Epileptic Disord. 2021;23:643-7. PubMed PMID: 34259158.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Stringer RN, Jurkovicova-Tarabova B, Souza IA, Ibrahim J, Vacik T, Fathalla WM, Hertecant J, Zamponi GW, Lacinova L, Weiss N. De novo SCN8A and inherited rare CACNA1H variants associated with severe developmental and epileptic encephalopathy. Molecular Brain. 2021;14:126. PubMed PMID: 34399820.

Takahashi S, Yamamoto S, Okayama A, Araki A, Saitsu H, Matsumoto N, Azuma H. Electroclinical features of epileptic encephalopathy caused by SCN8A mutation. Pediatr Int. 2015;57:758-62. PubMed PMID: 25951352.

Takayanagi M, Haginoya K, Umehara N, Kitamura T, Numata Y, Wakusawa K, Hino-Fukuyo N, Mazaki E, Yamakawa K, Ohura T, Ohtake M. Acute encephalopathy with a truncation mutation in the SCN1A gene: a case report. Epilepsia. 2010;51:1886-8. PubMed PMID: 20491869.

Trivisano M, Pavia GC, Ferretti A, Fusco L, Vigevano F, Specchio N. Generalized tonic seizures with autonomic signs are the hallmark of SCN8A developmental and epileptic encephalopathy. Epilepsy Behav. 2019;96:219-23. PubMed PMID: 31174070.

Trump N, McTague A, Brittain H, Papandreou A, Meyer E, Ngoh A, Palmer R, Morrogh D, Boustred C, Hurst JA, Jenkins L, Kurian MA, Scott RH. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. J Med Genet. 2016;53:310-7. PubMed PMID: 26993267.

Tsang MH, Leung GK, Ho AC, Yeung KS, Mak CC, Pei SL, Yu MH, Kan AS, Chan KY, Kwong KL, Lee SL, Yung AW, Fung CW, Chung BH. Exome sequencing identifies molecular diagnosis in children with drug-resistant epilepsy. Epilepsia Open. 2018;4:63-72. PubMed PMID: 30868116.

Vaher U, Noukas M, Nikopensius T, Kals M, Annilo T, Nelis M, Ounap K, Reimand T, Talvik I, Ilves P, Piirsoo A, Seppet E, Metspalu A, Talvik T. De novo SCN8A mutation identified by whole-exome sequencing in a boy with neonatal epileptic encephalopathy, multiple congenital anomalies, and movement disorders. J Child Neurol. 2014;29:NP202-6. PubMed PMID: 24352161.

Veeramah KR, O'Brien JE, Meisler MH, Cheng X, Dib-Hajj SD, Waxman SG, Talwar D, Girirajan S, Eichler EE, Restifo LL, Erickson RP, Hammer MF. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am J Hum Genet. 2012;90:502-10. PubMed PMID: 22365152.

Wagnon JL, Barker BS, Hounshell JA, Haaxma CA, Shealy A, Moss T, Parikh S, Messer RD, Patel MK, Meisler MH. Pathogenic mechanism of recurrent mutations of SCN8A in epileptic encephalopathy. Ann Clin Transl Neurol. 2015a;3:114-23. PubMed PMID: 26900580.

Wagnon JL, Barker BS, Ottolini M, Park Y, Volkheimer A, Valdez P, Swinkels MEM, Patel MK, Meisler MH. Loss-of-function variants of SCN8A in intellectual disability without seizures. Neurol Genet. 2017;3:e170. PubMed PMID: 28702509.

Wagnon JL, Korn MJ, Parent R, Tarpey TA, Jones JM, Hammer MF, Murphy GG, Parent JM, Meisler MH. Convulsive seizures and SUDEP in a mouse model of SCN8A epileptic encephalopathy. Hum Mol Genet. 2015b;24:506-15. PubMed PMID: 25227913.

Wagnon JL, Meisler MH. Recurrent and non-recurrent mutations of SCN8A in epileptic encephalopathy. Front Neurol. 2015;6:104. PubMed PMID: 26029160.

Wagnon JL, Mencacci NE, Barker BS, Wengert ER, Bhatia KP, Balint B, Carecchio M, Wood NW, Patel MK, Meisler MH. Partial loss-of-function of sodium channel SCN8A in familial isolated myoclonus. Hum Mutat. 2018;39:965-9. PubMed PMID: 29726066.

Wang J, Gao H, Bao X, Zhang Q, Li J, Wei L, Wu X, Chen Y, Yu S. SCN8A mutations in Chinese patients with early onset epileptic encephalopathy and benign infantile seizures. BMC Med Genet. 2017;18:104. PubMed PMID: 28923014.

Wengert ER, Tronhjem CE, Wagnon JL, Johannesen KM, Petit H, Krey I, Saga AU, Panchal PS, Strohm SM, Lange J, Kamphausen SB, Rubboli G, Lemke JR, Gardella E, Patel MK, Meisler MH, Møller RS. Biallelic inherited SCN8A variants, a rare cause of SCN8A-related developmental and epileptic encephalopathy. Epilepsia. 2019;60:2277-85. PubMed PMID: 31625145.

Wong JC, Butler KM, Shapiro L, Thelin JT, Mattison KA, Garber KB, Goldenberg PC, Kubendran S, Schaefer GB, Escayg A. Pathogenic in-frame variants in *SCN8A*: expanding the genetic landscape of *SCN8A*-associated disease. Front Pharmacol. 2021;12:748415. PubMed PMID: 34867351.

Xiao Y, Xiong J, Mao D, Liu L, Li J, Li X, Luo H, Liu L. Early-onset epileptic encephalopathy with de novo SCN8A mutation. Epilepsy Res. 2018;139:9-13. PubMed PMID: 29128679.

Xie H, Su W, Pei J, Zhang Y, Gao K, Li J, Ma X, Zhang Y, Wu X, Jiang Y. De novo SCN1A, SCN8A, and CLCN2 mutations in childhood absence epilepsy. Epilepsy Res. 2019;154:55-61. PubMed PMID: 31054517.

Zaman T, Abou Tayoun A, Goldberg EM. A single-center SCN8A-related epilepsy cohort: clinical, genetic, and physiologic characterization. Ann Clin Transl Neurol. 2019;6:1445-55. PubMed PMID: 31402610.

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.