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NLM Citation: Miller IO, Sotero de Menezes MA. *SCN1A* Seizure Disorders. 2007 Nov 29 [Updated 2022 Feb 17]. 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/

SCN1A Seizure Disorders

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Created: November 29, 2007; Revised: February 17, 2022.

Summary

Clinical characteristics

SCN1A seizure disorders encompass a spectrum that ranges from simple febrile seizures and generalized epilepsy with febrile seizures plus (GEFS+) at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) at the severe end. Phenotypes with intractable seizures including Dravet syndrome are often associated with cognitive decline. Less commonly observed phenotypes include myoclonic astatic epilepsy (MAE), Lennox-Gastaut syndrome, infantile spasms, epilepsy with focal seizures, and vaccine-related encephalopathy and seizures. The phenotype of *SCN1A* seizure disorders can vary even within the same family.

Diagnosis/testing

The diagnosis of an *SCN1A* seizure disorder is established in a proband by identification of a heterozygous pathogenic variant in *SCN1A* by molecular genetic testing.

Management

Treatment of manifestations: Care is best provided by a physician (e.g., pediatric epileptologist) familiar with the pharmacotherapy for this disorder. Seizure control is critical to prevent permanent injury and death. Anti-seizure medication (ASM): clobazam (can be used for treatment of seizures in Lennox-Gastaut syndrome); stiripentol, benzodiazepines, cannabidiol, topiramate, levetiracetam, valproic acid, and ethosuximide. Levetiracetam is often effective, but may make seizures worse in some individuals. Phenobarbital is effective but poorly tolerated because of its effects on cognition. Use of the ketogenic diet to decrease seizure frequency has been beneficial in some affected individuals. Parents are advised to take a CPR course. Routine seizure and personal safety education is indicated.

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Prevention of secondary complications: Use of protective helmets by individuals with atonic seizures or myoclonic-astatic epilepsy. Good sleep hygiene should be encouraged. Persons with epilepsy should be made aware of motor vehicle driving laws.

Surveillance: Serial neuropsychological evaluation for neurologic, cognitive, and behavioral deterioration; EEG monitoring for new or different seizure types; polysomnography should be considered if obstructive or central sleep apnea is suspected.

Agents/circumstances to avoid: ASMs: carbamazepine, lamotrigine, and vigabatrin, which can induce or increase myoclonic seizures; phenytoin, which can induce choreoathetosis; rufinamide may exacerbate seizures as well; acetaminophen, which is hepatotoxic. Activities in which a sudden loss of consciousness could lead to injury or death (e.g., bathing, swimming, driving, or working/playing at heights). Sleep deprivation, which can exacerbate seizures, should be avoided.

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

Genetic counseling

SCN1A seizure disorders are inherited in an autosomal dominant manner. A proband with an *SCN1A* seizure disorder may have an inherited or a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants varies by phenotype: the percentage of probands with an *SCN1A* seizure disorder and an affected parent decreases as the severity of the phenotype in the proband increases; thus, most *SCN1A*-related severe myoclonic epilepsy in infancy (*SCN1A*-SMEI) and ICE-GTC are the result of a *de novo* pathogenic variant. Each child of an individual with an *SCN1A* seizure disorder has a 50% chance of inheriting the pathogenic variant; however, the risk of developing seizures is less than 100% because of reduced penetrance. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant in the family is known.

GeneReview Scope

SCN1A Seizure Disorders: Included Phenotypes [1]
• Generalized epilepsy with febrile seizures plus (GEFS+) • Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) • Intractable infantile partial seizures • Myoclonic astatic epilepsy (MAE) • Severe myoclonic epilepsy in infancy (SMEI) / Dravet Syndrome (DS) • Simple febrile seizures

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

Diagnosis

Suggestive Findings

SCN1A seizure disorders encompass a spectrum of phenotypes that ranges from mild to severe. When the following suggestive features are present, *SCN1A* molecular genetic testing should be considered:

- Precipitation of seizure with fever, warmth, or vaccination
- Prolonged or hemiconvulsive seizures
- Seizure provocation with overstimulation or flashing/patterned visual stimulus

- Worsening of seizures with medications that inhibit sodium channel function as the primary mechanism of action (e.g., carbamazepine, oxcarbazepine, phenytoin, lamotrigine)

These features can be seen in any one of several clinical epilepsy syndromes that can occur in individuals with a heterozygous *SCN1A* pathogenic variant.

Clinical epilepsy syndromes reported in individuals with *SCN1A* seizure disorders (see Clinical Characteristics):

- **Febrile seizures (simple or complex)** may be the first and only manifestation of an *SCN1A* pathogenic variant, although individuals presenting with febrile seizures can also progress to Dravet syndrome. Febrile seizure onset is typically in the first year of life; seizures are prolonged and multiple.
- **Febrile seizures plus (FS+)** is characterized by seizure onset before age one year, persistence beyond age six years, unusual severity (including status epilepticus), and occurrence of unprovoked (e.g., afebrile) seizures of any kind.
- **Generalized epilepsy** caused by *SCN1A* pathogenic variants most often involves tonic, clonic, tonic-clonic, myoclonic, or absence seizures.
- **Generalized epilepsy with febrile seizures plus (GEFS+)**
- **Dravet syndrome**
- **Severe myoclonic epilepsy, borderline (SMEB)**
- **Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC)**
- **Infantile partial seizures with variable foci**

Less common presentations of *SCN1A* seizure disorders

- Epilepsy with focal seizures
- Myoclonic-astatic epilepsy (MAE, Doose syndrome)
- Lennox-Gastaut syndrome
- Infantile spasms
- Vaccine-related encephalopathy and seizures

Establishing the Diagnosis

The diagnosis of an *SCN1A* seizure disorder **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *SCN1A* by molecular genetic testing (see Table 1). Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Because the phenotype of *SCN1A* seizure disorders is indistinguishable from many other inherited disorders with seizures, the recommended molecular genetic testing is an **epilepsy multigene panel**.

Note: Single-gene testing (sequence analysis of *SCN1A*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An epilepsy multigene panel** that includes *SCN1A* 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 this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Single-gene testing.** Sequence analysis of *SCN1A* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Table 1. Molecular Genetic Testing Used in *SCN1A* Seizure Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SCN1A	Sequence analysis [3]	73%-92% [4]
	Gene-targeted deletion/duplication analysis [5]	8%-27% [6, 7, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Estimated value based on subtracting experimental values of deletion frequencies of 8%-27% from 100% (see footnote 5).
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.
6. Using a variety of methods to identify deletions encompassing the *SCN1A* locus in individuals with SMEI who did not have an *SCN1A* pathogenic variant identified on sequence analysis, Madia et al [2006] found deletions in three of 39 (8%), Mulley et al [2006] found deletions in two of 13 (15%), and Suls et al [2006] found deletions in three of 11 (27%). In these three studies a total of eight of 63 (12%) individuals with SMEI who did not have a sequence variant identified on sequence analysis had an identifiable *SCN1A* deletion.
7. Marini et al [2009] found that 12.5% of individuals with Dravet syndrome who did not have a pathogenic variant identified on sequence analysis had copy number variations that were detectable by MLPA.
8. It is not known if the percent of exon and whole-gene deletions is the same for the other phenotypes in the spectrum of *SCN1A* seizure disorders.

Clinical Characteristics

Clinical Description

The natural history of *SCN1A* seizure disorders is strongly influenced by seizure phenotype, which can range from simple febrile seizures and generalized epilepsy with febrile seizures plus (GEFS+) at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) at the severe end [Kimura et al 2005, Mantegazza et al 2005, Fujiwara 2006, Gennaro et al 2006]. The phenotype varies even among family members with the same pathogenic variant (see Figure 1). As a result of this variable expressivity, long-term prognosis is difficult to determine.

Features associated with poor cognitive outcome include early myoclonic and absence seizures [Ragona et al 2011].

Phenotypes with intractable seizures (e.g., Dravet syndrome) usually cause epileptic encephalopathy, a form of progressive dementia. The root cause of the encephalopathy is unknown: the effects on cognition of seizures, the most obvious explanation, cannot be separated from the effects of medication or of an *SCN1A* pathogenic variant [Riva et al 2009].

In addition to having seizures in response to strong environmental stimuli, individuals with *SCN1A* seizure disorders often have an ADHD-like phenotype characterized by impulsivity, inattentiveness, and distractibility. Possibly related to the inability of the GABA system to provide negative feedback on extraneous sensory input, these symptoms tend to be less responsive to conventional stimulant medications.

The phenotypes in *SCN1A* seizure disorders include the following (see Table 2).

Table 2. Seizure Phenotypes in *SCN1A* Seizure Disorders

Seizure Phenotypes	% of Individuals w/Phenotype & Identified *SCN1A* Pathogenic Variant
Intractable childhood epilepsy w/generalized tonic-clonic seizures (ICE-GTC)	70% [1]
Dravet syndrome	33%-90% [2]
Generalized epilepsy w/febrile seizures plus (GEFS+)	5%-10% [3]
Febrile seizures plus (FS+)	Unknown
Simple febrile seizures	Unknown

1. Fujiwara et al [2003]
2. Mulley et al [2005]
3. Marini et al [2007]

Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC). This phenotype is defined as generalized seizures including absence seizures and generalized tonic-clonic seizures with onset in infancy or childhood. However, partial seizures can occur in up to 13% of affected individuals [Bonanni et al 2004]. Localized epilepsy, either alternating hemiconvulsive or complex partial seizures, may also be seen. Children with frequent generalized tonic-clonic seizures often develop cognitive impairment. The distinction between ICE-GTC and Dravet syndrome is not clear, and the former is not included in the ILAE classification system.

Dravet syndrome. Wirrell et al [2017] published guidelines for the clinical diagnosis of Dravet syndrome. Presentation is between age one and 18 months after a period of normal development. Seizures are often prolonged and include recurrent generalized tonic-clonic or hemiconvulsive seizures. Myoclonic seizures are typically seen by age two years. Obtundation status, focal dyscognitive seizures, and atypical absences are often seen after age two years. The seizures are often triggered by hyperthermia (e.g., a hot bath, physical exertion, fever following vaccination), light stimuli, or sodium channel-blocking anti-seizure medication. Status epilepticus is common, and pharmacologic management is difficult. Seizures tend to lessen in severity after puberty; however, they rarely resolve completely.

The initial EEGs are often normal or show nonspecific changes such as generalized slowing, but over time epileptiform activity appears. Patterns can include generalized spike and wave discharges, multiple spike and wave (also referred to as polyspike and wave) discharges, and multifocal spikes (see Figure 2). Brain MRI is typically normal or may show mild generalized atrophy and/or hippocampal sclerosis.

The myoclonic seizures that tend to appear later in the course often coincide with the appearance of cognitive dysfunction, ataxia, and psychomotor regression. Some degree of cognitive impairment is always seen, ranging from moderate to severe, often with marked inattention, impulsivity, and distractibility. Anxiety, obsessive personality traits, and autism spectrum disorder are common. Crouched gait, hypotonia, incoordination, and

impaired dexterity are typically evident by age three to four years. Parkinsonian features of bradykinesia, tremor, and antecollis have been reported in adults with Dravet syndrome [Rilstone et al 2012, Aljaafari et al 2017].

Individuals with Dravet syndrome often develop a crouched gait. In spite of the gait being commonly described as "ataxic," affected individuals are more mobile than one would expect from how crouched they appear. The gait changes tend to be more prevalent in older children. In one study these changes were absent before age five years, but present in 5/10 children ages 6-12 years and in 8/9 children age 13 years or older [Rodda et al 2012]. In one cohort, 5/10 adults with Dravet syndrome had crouched gait [Rilstone et al 2012]. Decreased passive knee extension, increased external tibial torsion, and *pes planovalgus* all progressed [Rodda et al 2012]. Hip internal rotation did not show age-related changes. In one study antecollis was present in 9/14 and parkinsonian gait in 8/14 individuals with Dravet syndrome [Aljaafari et al 2017]. The degree of ataxia in affected individuals is greater than would be expected by the use of anticonvulsant medications alone. Pathogenic variants affecting the pore region appear to be more associated with gait changes [Kanai et al 2004, Rilstone et al 2012].

Severe myoclonic epilepsy, borderline (SMEB). This description is sometimes used for children who have some but not all of the features of Dravet syndrome [Fukuma et al 2004].

Generalized epilepsy. This phenotype is otherwise indistinguishable from idiopathic generalized epilepsy with onset in childhood or adolescence. Generalized epilepsies caused by *SCN1A* pathogenic variants are most often tonic, clonic, tonic-clonic, myoclonic, or absence.

Generalized epilepsy with febrile seizures plus (GEFS+). This term refers to the findings in a family rather than an individual [Arzimanoglou et al 2004]. In a family with GEFS+, epilepsy with variable expressivity and incomplete penetrance is inherited in an autosomal dominant manner. It implies a spectrum from mild (such as febrile seizure alone) to severe (including medically treatable generalized epilepsy, intractable generalized epilepsy, or Dravet syndrome). Intermediate phenotypes with myoclonic epilepsy, absence epilepsy, or focal epilepsy are also included. Individuals with GEFS+ often have febrile seizures (or FS+) in early childhood, followed by occasional tonic, clonic, myoclonic, or absence seizures that respond to medication and remit by late childhood or early adolescence. The proportion of children with GEFS+ whose first seizure occurs in the context of immunization appears to be greater than the proportion of children with febrile seizures unrelated to FS+ and GEFS+.

Febrile seizures plus (FS+). This subset of febrile seizures (simple or complex) is characterized by any of the following features:

- Onset before age one year
- Persistence beyond age six years
- Unusual severity (including status epilepticus)
- Occurrence of unprovoked (i.e., afebrile) seizures of any kind

Febrile seizures. These childhood seizures occur only in association with fever. The epidemiologic definition requires the following:

- Onset on or after age six months
- Resolution by age five years
- Fever higher than 38°C (without other evidence of CNS infection)
- No other identifiable cause

Febrile seizures are divided into simple febrile seizures and complex febrile seizures. Febrile seizures are considered complex if any of the following is present:

- Duration longer than 15 minutes
- Occurrence of more than one seizure within 24 hours

- Presence of any partial (focal) features during the seizure

Febrile seizures with the following criteria are associated with a higher risk for developing Dravet syndrome [Hattori et al 2008]:

- Febrile seizure onset before age seven months
- Five or more febrile seizures
- Prolonged seizure(s) lasting more than ten minutes

The febrile seizure characteristics include hemiconvulsions, partial seizures, myoclonic seizures, and hot water-induced seizures.

Infantile partial seizures with variable foci, also referred to as migrating partial seizures of infancy, cryptogenic focal epilepsy, or severe infantile multifocal epilepsy [Harkin et al 2007]. Multifocal partial seizures are often the first manifestation; however, in some children the first manifestation is febrile seizures. Severity varies and pharmacoresistance is common, but not absolute. Myoclonic seizures are rare but may be precipitated by administration of medications that inactivate the sodium channel, including phenytoin, carbamazepine, or lamotrigine. Cognitive deterioration may occur, especially when seizure control is incomplete. Electroencephalography shows multifocal independent spikes; generalized spike and wave discharges may be seen.

Less common phenotypes associated with *SCN1A* pathogenic variants include the following:

- **Myoclonic-astatic epilepsy (MAE, also called Doose syndrome).** This phenotype is defined as the combination of myoclonic, atonic, and atypical absence seizures. Onset is usually after age two years (range: 7 months - 8 years). Although isolated myoclonic seizures as well as tonic seizures can occur, they are not characteristic of this syndrome (which distinguishes them from Lennox-Gastaut syndrome). Development prior to seizure onset is often normal. The course can range from spontaneous seizure resolution without cognitive impairment to intractable seizures with severe intellectual disability [Arzimanoglou et al 2004].
- **Lennox-Gastaut syndrome (LGS).** This phenotype is defined as slow spike-waves on EEG, developmental delay, and multiple types of generalized seizures (particularly atypical absence, tonic, and atonic seizures). LGS usually begins during childhood (ages 2-14 years). Any type of seizure can be seen in this syndrome; status epilepticus is common [Arzimanoglou et al 2004]. Only a minority of persons with the LGS phenotype have an *SCN1A* pathogenic variant, usually in the context of a family in which Dravet syndrome occurs [Singh et al 2001]. This subset remains poorly characterized. It is unclear whether *SCN1A*-associated LGS differs phenotypically from LGS of other etiologies.
- **Infantile spasms.** This phenotype is defined as clustered seizures that show brief (<1 second) axial contractions associated with a slow-wave transient on EEG, often followed by generalized attenuation of the background. Both findings may be intermixed with fast activity. The resting EEG (between seizures) shows high-voltage slowing and a multifocal spike pattern known as hypsarrhythmia [Arzimanoglou et al 2004]. Association of an *SCN1A* pathogenic missense variant with infantile spasms has been reported once [Wallace et al 2003]. The single individual represents fewer than 1% of reported cases, although publication bias makes it difficult to estimate the actual proportion.
- **Vaccine-related encephalopathy and seizures.** This phenotype is defined as sudden onset of seizures and encephalopathy in infants 48 hours after immunization. Berkovic et al [2006] identified an *SCN1A* pathogenic variant in 11/14 children diagnosed with post-vaccine encephalopathy. Tro-Baumann et al [2011] reported that 19 of 70 individuals with an SCN1A pathogenic variant and the Dravet phenotype had a history of seizures following vaccination.

Imaging. Brain MRI is most often normal early in the course of the disease; however, it often evolves to show cortical atrophy, cerebellar atrophy, white matter hyperintensity, ventricular enlargement, hippocampal sclerosis,

or cortical dysplasia [Striano et al 2007]. Individuals with a more severe phenotype early in life often have more atrophic changes seen on MRI later in life.

Genotype-Phenotype Correlations

Given the variable expressivity of *SCN1A* disorders, consistent genotype-phenotype correlations have been infrequently identified.

Pathogenic nonsense variants and missense variants in the voltage sensor or pore region often lead to a more severe phenotype [Zuberi et al 2011, Meng et al 2015]. A truncation variant, however, does not necessarily result in a severe phenotype [Suls et al 2010, Yu et al 2010].

Affected individuals with missense variants in the pore-forming region and truncations in the SCN1A protein are more likely to have gait changes [Kanai et al 2004, Rilstone et al 2012]. These changes may be the result of a direct effect of the *SCN1A* pathogenic variant in the cerebellar Purkinje cells [Catterall et al 2010].

Variants in *SCN9A*, *CACNA1A*, *POLG*, and *CACNB4* have been suggested to play a role in modifying the phenotype of *SCN1A* seizure disorders [Ohmori et al 2008b, Gaily et al 2013, Ohmori et al 2013, Yang et al 2018]; however, the data are insufficient for use in clinical management or prognosis.

Nomenclature

Generalized epilepsy with febrile seizures plus has been referred to as GEFS+, type 2 related to *SCN1A* pathogenic variants.

Intractable infantile partial seizures has been referred to as ICE-GTC.

Dravet syndrome is also known as severe myoclonic epilepsy in infancy (SMEI) or polymorphic myoclonic epilepsy in infancy (PMEI). The term "Dravet syndrome" is preferred over the descriptive names because myoclonic seizures can be absent in children whose seizures are otherwise similar.

Penetrance

SCN1A seizure disorders show incomplete penetrance and variable expressivity.

Penetrance varies by phenotype. For example, Bonanni et al [2004] estimated the penetrance to be 70% for the GEFS+ phenotype, whereas Mantegazza et al [2005] reported the penetrance to be 90% for the familial simple febrile seizure phenotype.

Prevalence

Wu et al [2015] reported a population-based estimate of the incidence of Dravet syndrome of 1:15,000. This is supported by similar estimates in Denmark of 1:22,000 [Bayat et al 2015] and a slightly lower number, 1:40,900, in the UK [Brunklaus et al 2012]. Of all reported seizures following vaccinations in the first year of life, 2.5% (95%CI:1.3 to 3.6%) were a result of *SCN1A* Dravet syndrome [Verbeek et al 2013].

Genetically Related (Allelic) Disorders

Other phenotypes associated with pathogenic variants in *SCN1A*:

- **Interstitial deletions of 2q24-q3** (including a cluster of voltage-gated sodium channel genes: *SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, and *SCN9A*) are associated with tonic focal and myoclonic jerks that tend to appear in infancy and are subsequently followed by seizures mixed in type. The seizures persist up to late childhood and are drug resistant [Grosso et al 2007]. Pereira et al [2004] identified a contiguous deletion

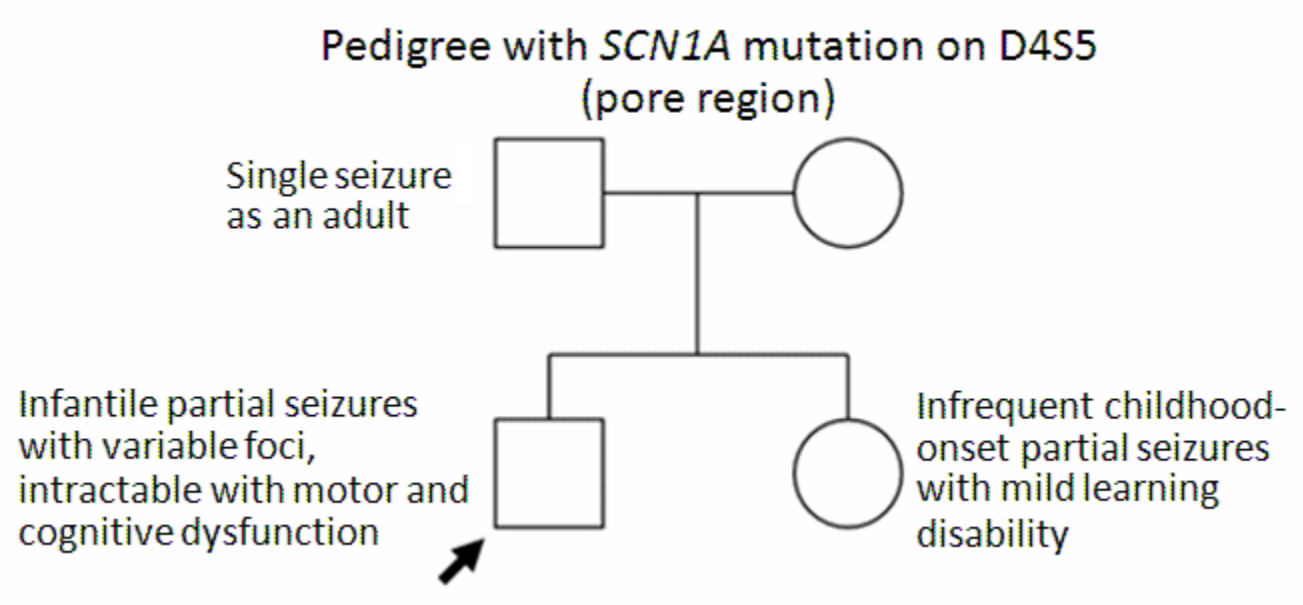

Figure 1. Findings in a family illustrating variable expressivity among individuals with the same pathogenic variant. The proband, a boy (arrow) with febrile convulsions since age seven months, had frequent, difficult-to-control partial seizures beginning at age three years. His sister had infrequent partial seizures starting early in school age. Their father had a single seizure as a young adult. All three had the same pathogenic variant in the fourth domain fifth segment (D4S5) on the pore region of the SCN1A ($Na_V1.1$) protein (see Molecular Pathogenesis) [M Sotero, personal observation].

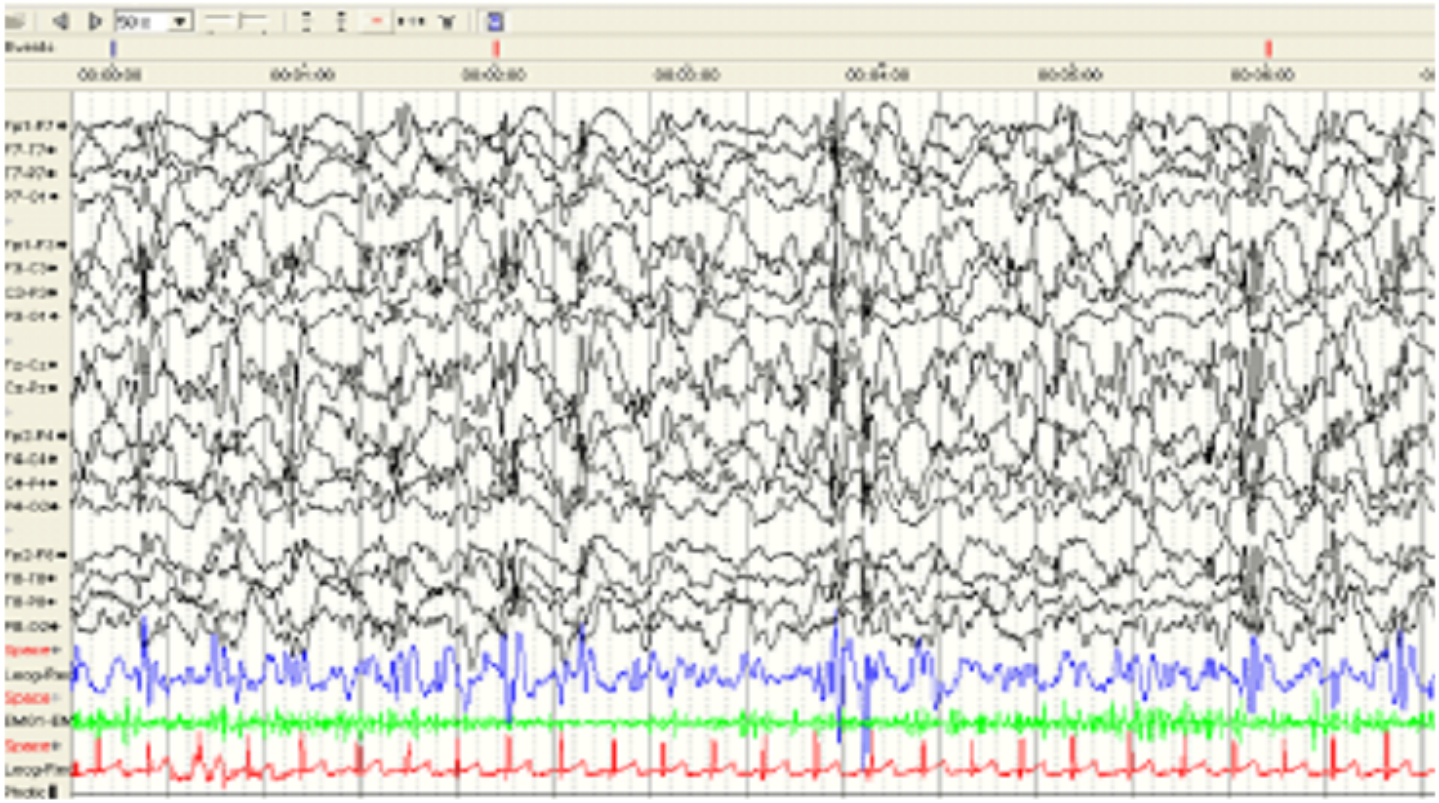

Figure 2. Individuals with Dravet syndrome often have an unusual seizure type that frequently will manifest as obtundation status epilepticus. The EEG during these difficult-to-classify seizures shows an alternation of generalized and focal discharges with variable degrees of secondary generalization.

of *SCN1A* and *SCN2A* in one individual with severe epilepsy, intellectual disability, and dysmorphic features.
- Larger deletions of 2q24.3 are associated with dysmorphic features including microcephaly, ptosis, downslanting palpebral fissures, long eyelashes, micrognathia [Pescucci et al 2007] and digit anomalies in individuals with 2q24-q31 deletions [Boles et al 1995].
- **Duplications of 2q24.2-q3.** Reported duplications involving the cluster of voltage-gated sodium channel genes *SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, and *SCN9A* vary in size. Individuals reported by Goeggel Simonetti et al [2012] presented with focal seizures and epileptic spasms with onset in the neonatal period as early as the third day of life. The seizures were refractory to many anticonvulsant medications such as phenobarbital and levetiracetam, but may respond to valproate [Okumura et al 2011]. In one report the seizures disappeared between ages five to 20 months [Goeggel Simonetti et al 2012, Yoshitomi et al 2015]. Developmental delay is common.
- Familial hemiplegic migraine [Dichgans et al 2005]
- Familial autism [Weiss et al 2003]
- Rasmussen encephalitis associated with the pathogenic variant p.Arg1575Cys [Ohmori et al 2008a]

Differential Diagnosis

The phenotypes typically seen in individuals with an *SCN1A* pathogenic variant are neither necessary nor sufficient to diagnose an *SCN1A* seizure disorder. Other conditions (including those caused by pathogenic variants in other genes) may be associated with the same phenotypes.

It is most important to distinguish *SCN1A* seizure disorders from potentially treatable conditions, including the following [Arzimanoglou et al 2004, Roger et al 2006]:

- Pyridoxine-dependent epilepsy (an autosomal recessive disorder resulting from pathogenic variants in *ALDH7A1*) and B_6-related epilepsies
- Inborn errors of metabolism, including mitochondrial dysfunction, which may be diagnosed by the presence of abnormal serum concentrations of lactate, ketones, ammonia, amino acids, and/or abnormal concentrations of urine organic acids (See Mitochondrial Disorders Overview.)
- Biotinidase deficiency, an autosomal recessive disorder resulting from pathogenic variants in *BTD*, which is usually identified during newborn screening
- Glucose transporter type 1 deficiency syndrome (Glut1 DS), which is diagnosed by low CSF glucose concentrations, and responds to the ketogenic diet. This disorder is caused by mutation of *SLC2A1* and is most commonly autosomal dominant. Rarely, Glut1 DS may be inherited in an autosomal recessive manner.
- Hepatic porphyrias, which usually demonstrate photosensitive porphyrins in the urine and reduced monopyrrole porphobilinogen (PBG) deaminase in red cells (See Acute Intermittent Porphyria, Familial Porphyria Cutanea Tarda, Hereditary Coproporphyria, and Variegate Porphyria.)

If the family history is negative or unavailable, sporadic epilepsies (i.e., those without a genetic cause) need to be included in the differential diagnosis, as does any cause of epilepsy with nonspecific imaging findings. Some general categories of injury to consider include the following [Arzimanoglou et al 2004, Roger et al 2006]:

- Trauma
- Hypoxia
- Sequelae of meningitis or hemorrhage
- Infectious or autoimmune cerebritis
- Vasculitis
- Paraneoplastic syndrome
- Toxins (including drug withdrawal)

- Endocrinopathy

A positive family history for other individuals with epilepsy significantly increases the likelihood of an inherited epilepsy syndrome [Arzimanoglou et al 2004, Roger et al 2006]. See Table 3.

Table 3. Selected Genes of Interest in the Differential Diagnosis of *SCN1A* Seizure Disorders

Gene	Associated Phenotypes											Clinical Features	
	ADNFLE	ADEAF (ADLTE)	BFIE	BFNE	CAE	EIEE	FEB	GEFS+	JAE	JME	NEE	Overlapping w/ *SCN1A* seizure disorders	Distinguishing from *SCN1A* seizure disorders
SCN1A [1]						+	+	+				NA	NA
CHRNA2	+											Focal seizures may become secondary generalized.	Nocturnal frontal semiology seizures (fast, quick recovery, tonic, hypermotor); onset age: <20 yrs
CHRNA4	+												
CHRNB2	+												
CPA6							+					Epilepsy can incl febrile seizures, focal seizures w/ secondary generalization, & primary generalized seizures	Focal seizures more often auditory, mesiotemporal, or occipitotemporal. Variability can resemble GEFS+, but inheritance pattern is recessive, so pedigree affecting multiple generations is uncommon. Sodium channel medications can be helpful.
CRH	+											Focal seizures may become secondary generalized.	Nocturnal frontal semiology seizures (fast, quick recovery, tonic, hypermotor); onset age: <20 yrs
DEPDC5	+												
EFHC1					+				+			CAE & JAE are seen in some persons w/ *SCN1A*-GEFS+. JAE may evolve to JME.	Staring seizures only; absence of DS, GEFS+, intractable epilepsy features
GABRD					+			+	+	+		Similar to *SCN1A*-GEFS+	May be clinically indistinguishable from *SCN1A* epilepsy

Table 3. continued from previous page.

Gene	Associated Phenotypes											Clinical Features	
	ADNFLE	ADEAF (ADLTE)	BFIE	BFNE	CAE	EIEE	FEB	GEFS+	JAE	JME	NEE	Overlapping w/ *SCN1A* seizure disorders	Distinguishing from *SCN1A* seizure disorders
GABRG2								+				Febrile seizures / GEFS+ phenotype	May be clinically indistinguishable from *SCN1A* epilepsy
KCNQ2				+							+	Some affected persons may show both BECTS & neonatal seizures.	Nocturnal GTC; focal seizures w/ face & limb semiology; absence of DS, GEFS+, intractable epilepsy features; neonatal onset (rare in *SCN1A* seizure disorders)
Gene	**Associated Phenotypes**											**Clinical Features**	
	ADNFLE	**ADEAF (ADLTE)**	**BFIE**	**BFNE**	**CAE**	**EIEE**	**FEB**	**GEFS+**	**JAE**	**JME**	**NEE**	**Overlapping w/ *SCN1A* seizure disorders**	**Distinguishing from *SCN1A* seizure disorders**
KCNQ3			+	+								Focal seizures; typically benign but may be encephalopathic	Neonatal onset (rare in *SCN1A* seizure disorders)
KCNT1	+											Focal seizures may become secondary generalized.	Nocturnal frontal semiology seizures (fast, quick recovery, tonic, hypermotor); onset age: <20 yrs
LGI1		+										Focal seizures may become secondary generalized.	Absence of DS, GEFS+, intractable epilepsy features; very different seizure semiology (auditory, MTLS-like, or occipitotemporal)

Table 3. continued from previous page.

Gene	Associated Phenotypes											Clinical Features	
	ADNFLE	ADEAF (ADLTE)	BFIE	BFNE	CAE	EIEE	FEB	GEFS+	JAE	JME	NEE	Overlapping w/ *SCN1A* seizure disorders	Distinguishing from *SCN1A* seizure disorders
MICAL1		+										Focal seizures may become secondary generalized.	Absence of DS, GEFS+, intractable epilepsy features; very different seizure semiology (auditory, MTLS-like, or occipitotemporal)
PCDH19												Phenotype can be quite similar to Dravet syndrome; often respond to the same medications	X-linked; most symptomatic persons are female; febrile & temperature-induced seizures that tend to occur in clusters; seizure onset usually a little later (age ≥12 mos); may have fewer myoclonic jerks & absence seizures than in *SCN1A* seizure disorders
Gene	**Associated Phenotypes**											**Clinical Features**	
	ADNFLE	**ADEAF (ADLTE)**	**BFIE**	**BFNE**	**CAE**	**EIEE**	**FEB**	**GEFS+**	**JAE**	**JME**	**NEE**	**Overlapping w/ *SCN1A* seizure disorders**	**Distinguishing from *SCN1A* seizure disorders**
RELN		+										Focal seizures may become secondary generalized.	Absence of DS, GEFS+, intractable epilepsy features; very different seizure semiology (auditory, MTLS-like, or occipitotemporal)
SCN1B								+				Febrile seizures / GEFS+ phenotype	Later onset than in *SCN1A* epilepsy
SCN2A			+								+	Intractable seizures; occasionally *SCN1A* epilepsy may show infantile spasms.	Response to Na channel blocker; infantile spasms common

Table 3. continued from previous page.

Gene	Associated Phenotypes											Clinical Features	
	ADNFLE	ADEAF (ADLTE)	BFIE	BFNE	CAE	EIEE	FEB	GEFS+	JAE	JME	NEE	Overlapping w/ *SCN1A* seizure disorders	Distinguishing from *SCN1A* seizure disorders
SCN8A						+						Ataxic gait; intractable seizures; occasionally *SCN1A* epilepsy may show infantile spasms.	Response to Na channel blocker; infantile spasms common; SUDEP frequent
SCN9A							+	+				Dravet syndrome may be seen w/this genotype.	May be clinically indistinguishable from *SCN1A* epilepsy
STX1B								+				Febrile seizures / GEFS+ phenotype	May be clinically indistinguishable from *SCN1A* epilepsy but most affected persons become seizure free later in childhood.

ADLTE = autosomal dominant lateral temporal lobe epilepsy; ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; ADEAF = autosomal dominant partial epilepsy with auditory features; BECTS = benign epilepsy with centrotemporal spikes; BFIE = benign familial infantile epilepsy; BFNE = benign familial neonatal epilepsy; CAE = childhood absence epilepsy; DS = Dravet syndrome; EIEE = early-infantile epileptic encephalopathy; FEB = familial febrile seizures; FLE = frontal lobe epilepsy; GEFS+ = generalized/genetic epilepsy with febrile seizure plus; GTC = generalized tonic-clonic; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; MOI = mode of inheritance; MTLS = mesial temporal lobe seizure; NEE = neonatal epileptic encephalopathy; SUDEP = sudden unexpected death in patients with epilepsy; TLE = temporal lobe epilepsy; XL = X-linked

1. Topic of this *GeneReview*; included for comparison

Familial epilepsy syndromes with an unknown molecular basis may also be considered in the differential diagnosis of *SCN1A* seizure disorders. These syndromes include:

- Childhood occipital epilepsy, which may be associated with focal seizures that become secondary generalized. Unlike *SCN1A* seizure disorders, childhood occipital epilepsy is also associated with seizures with visual hallucinations or tonic components (which spread to the frontal lobe) and O1/2 EEG spikes (OMIM 132090).
- Epilepsy with photoparoxysmal response. Unlike *SCN1A* seizure disorders, epilepsy with photoparoxysmal response is associated generalized idiopathic epilepsy without intractability (OMIM 132100).

To see loci and additional genes associated with the phenotypes in Table 3, see the following OMIM Phenotypic Series:

- Epilepsy, familial temporal lobe
- Epilepsy, generalized, with febrile seizures plus (GEFS+)
- Epileptic encephalopathy, early infantile
- Epileptic encephalopathy, infantile or early childhood
- Seizures, benign familial infantile
- Seizures, benign familial neonatal

- Seizures, familial febrile

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *SCN1A* seizure disorder, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neurologic examination
- Cognitive neuropsychological evaluation
- Behavioral neuropsychological evaluation
- Electroencephalogram (EEG), including video EEG telemetry where ictal onset or semiology is unclear
- Consideration of polysomnography if obstructive or central sleep apnea is suspected
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Care is best provided by a physician (e.g., pediatric epileptologist) familiar with the pharmacotherapy for this disorder. Seizure control is critical because children with *SCN1A* seizure disorder are at high risk for sudden unexplained death in epilepsy (SUDEP). In addition, prolonged acute seizures may cause permanent injury [Chipaux et al 2010, Takayanagi et al 2010].

Pharmacologic treatment focuses on the observations that abnormal SCN1A channels disproportionately affect GABA neurons [Yu et al 2006] and that the associated seizures respond optimally to anti-seizure medications (ASMs) that bind to the GABA receptor:

- **Clobazam (0.2-1 mg/kg/day)** is FDA approved for the treatment of seizures in Lennox-Gastaut syndrome.
- **Stiripentol (30-100 mg/kg/day)** is accepted by epileptologists as an effective therapeutic agent in *SCN1A* seizure disorders. It was FDA approved in 2018. It is part of the early standard of care in Europe, and is used in the US after other conventional anticonvulsants have failed. The evidence of effectiveness in *SCN1A* epilepsy is based on double-blind evaluation of seizure reduction in Dravet syndrome [Chiron et al 2000].

  Thanh et al [2002] demonstrated efficacy of the drug when compared with placebo; only moderate side effects including drowsiness, loss of appetite, and occasional neutropenia in infants and young children were observed. In a recent US survey of 82 children with Dravet syndrome, stiripentol was found to be effective in reducing prolonged seizures [Wirrell et al 2013].

  Stiripentol, which acts directly on $GABA_A$ receptors [Quilichini et al 2006], is also a potent inhibitor of the hepatic enzymes CYP3A4, CYP1A2, and CYP2C19. As a result, it increases the serum concentration of several common ASMs, including valproic acid, clobazam, and its metabolite nor-clobazam [Thanh et al 2002]. Doses above 50 mg/kg/day are usually not tolerated when used in conjunction with valproic acid and clobazam.

  Children older than age 12 years may not tolerate stiripentol because of digestive tract side effects and nausea [Thanh et al 2002].
- **Benzodiazepines.** Individuals taking stiripentol must exercise caution in the use of benzodiazepines [Thanh et al 2002]. A single infusion of diazepam and clonazepam appears to be safe [Thanh et al 2002].

- **Cannabidiol.** Two double-blind, randomized, placebo-controlled clinical trials demonstrated efficacy in treating seizures associated with Dravet syndrome [Devinsky et al 2017]. Recommended dose is 5 mg/kg/day divided twice a day for 1 week, then 10 mg/kg/day divided twice a day thereafter, and doses above 20 mg/kg/day when indicated. The median reduction of the frequency of convulsive seizures per month was 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo. At least 50% reduction in convulsive seizure frequency was a seen in 43% of the cannabidiol group and 27% of the placebo arm (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). Cannabidiol significantly reduced the frequency of all seizure types combined (P=0.03), but there was no significant reduction specifically in nonconvulsive seizures. The percentage of individuals who became seizure free was 5% with cannabidiol and 0% with placebo (P=0.08). Diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver function tests occurred more frequently in the cannabidiol group than in the placebo group.
- **Fenfluramine** is a serotonergic [Fuller et al 1988] that had been used for the treatment of Dravet syndrome with success in Belgium; it is not FDA approved for use in the United States. Fenfluramine was used previously for the treatment of obesity. Cardiac complications including valve thickening and pulmonary hypertension led to withdrawal from the US market. However, recent preliminary studies found only trivial cardiac valve thickening [Ceulemans et al 2012, Ceulemans et al 2016]. In a study of 12 individuals with Dravet syndrome (11 with *SCN1A* Dravet syndrome), fenfluramine was combined with valproic acid and in 9/12 individuals it was further combined with benzodiazepines (clobazam, lorazepam), topiramate, lamotrigine, levetiracetam, and ethosuximide. Eight of 12 individuals were seizure-free for more than one year while on fenfluramine (and their other anti-seizure medications). In a five-year follow up of ten individuals with a mean fenfluramine treatment duration of 16.1 years, 7/10 individuals were seizure free longer than two years and 90% of all individuals had an average seizure frequency of less than one seizure per month over the five-year observation period [Ceulemans et al 2016].
- **Topiramate** [Coppola et al 2002]
- **Valproic acid** (10-30 mg/kg/day) [Thanh et al 2002]
- **Ethosuximide** can be effective for absence seizures. The dose is usually limited by gastrointestinal side effects, which can be minimized by more frequent dosing.
- **Levetiracetam** (20-80 mg/kg/day) is often effective, but may make seizures worse in some individuals [Caraballo et al 2010].
- **Potassium bromide** is not FDA approved in the US, but widely used in Japan [Tanabe et al 2008] and Europe (it is approved for use in Germany under the DIBRO-BE mark) with reasonable efficacy at doses of up to 100 mg/kg/day. A non-allergic rash is the most common adverse effect, and dose adjustments must be made slowly because of the long half-life. It will cause an artifactual increase in serum chloride measurements on most laboratory instruments in routine clinical use.
- **Phenobarbital.** Although effective, phenobarbital is poorly tolerated because of its effects on cognition. When it is taken in combination with stiripentol, the serum concentration of phenobarbital is increased because stiripentol slows the metabolism and excretion of barbiturates.
- **Ketogenic diet.** Dressler et al [2010] report that seizures were reduced by more than 50% in 62.5% of persons with Dravet syndrome who stayed on the diet for six months. The findings of Nabbout et al [2011] in 15 individuals also support the use of the ketogenic diet in Dravet syndrome.

Because of the sedating effects of seizure medications and the possibility of respiratory depression (especially with benzodiazepines and barbiturates), parents are advised to take a CPR course. Routine seizure and personal safety counseling is indicated.

Seizures are not always responsive to conventional ASMs. Anecdotal evidence suggests that the following drugs / treatment modalities may be effective for *SCN1A* Dravet syndrome [Dravet et al 2002]:

- Ethosuximide and high-dose piracetam for myoclonic seizures
- Corticosteroids
- Immunoglobulins

Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox. Non-medical interventions that families have reported to be helpful include the following [Nolan et al 2008]:

- Placement of an indwelling venous access device
- Creating a portable microenvironment
- Having a written emergency department protocol
- Establishing emergency routines for the family
- Assigning a parent on call to lessen the effect on the sibs
- Creating personal time to decrease parent stress
- Finding respite care
- Contacting an internet support group

Prevention of Secondary Complications

Individuals experiencing atonic seizures or myoclonic-astatic epilepsy should be advised to wear a protective helmet.

Sleep deprivation and illness can exacerbate *SCN1A*-associated seizures; thus, good sleep hygiene should be encouraged. Comorbidity with sleep apnea also frequently occurs in individuals with epilepsy [Malow et al 2000], and can influence seizure control, behavior, and cognition.

Although immunization may trigger a seizure, it does not affect the natural course of the disorder. McIntosh et al [2010] looked retrospectively at a cohort of 14 individuals with Dravet syndrome and found no effect of immunization on cognitive outcome. These authors suggest that the immunization schedule not be altered and that the risk for fever following immunization could be reduced by providing a scheduled, long-acting NSAID (e.g., naproxen). The treating neurologist may also consider increasing the anticonvulsant dose(s) temporarily around the time of the immunization.

Surveillance

- Serial neuropsychological evaluation for neurologic, cognitive, and behavioral deterioration is appropriate.
- Clinical examination for scoliosis and impaired gait at each office visit
- EEG monitoring is appropriate when new or different seizure types are suspected.
- Polysomnography should be considered if obstructive or central sleep apnea is suspected.

Agents/Circumstances to Avoid

Several ASMs that are effective for most forms of epilepsy can worsen *SCN1A*-related seizures:

- **Carbamazepine, lamotrigine, and vigabatrin,** which can induce or increase myoclonic seizures [Horn et al 1986, Guerrini et al 1998, Ceulemans et al 2004a]
- **Phenytoin,** which may worsen seizures and can induce choreoathetosis [Saito et al 2001]
- **Rufinamide,** which has a pharmacologic mechanism similar to carbamazepine and phenytoin and may exacerbate seizures as well

- **Acetaminophen,** which is hepatotoxic in overdose. Given the possibility of interaction with anticonvulsant medications, especially valproate and topiramate [Nicolai et al 2008], acetaminophen should be avoided. Any of the NSAIDs are effective as antipyretics, and represent much lower risk.

Activities in which a sudden loss of consciousness could lead to injury or death should be avoided (e.g., bathing, swimming, driving, or working/playing at heights).

Evaluation of Relatives at Risk

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

Pregnancy Management

In addition to the considerations described in Genetic Counseling, other pregnancy-related considerations include the following:

- Risk of major malformations (especially as a result of valproic acid exposure in utero [Samrén et al 1997]) and minor anomalies
- Advantages and disadvantages of increasing maternal periconceptional folic acid supplementation to 4,000 µg daily, particularly when women are taking valproic acid or carbamazepine during pregnancy
- Effect of in utero exposure to anticonvulsants on future cognitive development [Meador et al 2009]
- Effect of anticonvulsants on hormonal methods of birth control
- Effects of anticonvulsants on conception; the risk for complications in mothers who are on anticonvulsants
- Effect of pregnancy on anticonvulsant metabolism
- Effect of pregnancy on maternal seizure control

Pregnancy, family planning, and contraception are issues that should be raised with every female near childbearing age who has epilepsy. These considerations are not unique to or (aside from medication selection) significantly influenced by the presence of an *SCN1A* seizure disorder.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Thalamic deep brain stimulation (DBS) was reported by Andrade et al [2010] in two children with Dravet syndrome with ten-year follow up. One showed "marked improvement" after implantation, whereas the other received no benefit.

Lacosamide has not been studied in *SCN1A* seizure disorders; however, there are theoretic reasons why it may be effective [Curia et al 2009].

Verapamil was reported to help two girls with severe epilepsy resulting from *SCN1A* pathogenic variants [Iannetti et al 2009]; however, it has not been formally studied.

Search ClinicalTrials.gov in the US for access to information on clinical studies for *SCN1A* seizure disorders and a wide range of other diseases and conditions. Search EU Clinical Trials Register in Europe.

Other

Other cannabis-derived compounds (e.g., tetrahydrocannabinol [THC], cannabidivarin [CBDV], tetrahydrocannabivarin [THCV]) have no proven efficacy. Many anecdotal claims have been made regarding THC and THC:CBD ratios, but the episodic and noisy nature of epilepsy requires any data acquired in a non-blinded way to be viewed with extreme caution. Cannabinoids are bioactive and may have psychotropic and/or

systemic side effects; they also may act as an immunosuppressant and an anti-inflammatory in animal models. Clinical trial data regarding safety and efficacy are needed before widespread clinical use is appropriate [Rieder et al 2010, Bergamaschi et al 2011].

Persons with epilepsy should be made aware of local motor vehicle driving laws and physician reporting laws.

Hippocampal sclerosis can occur as a secondary feature of *SCN1A* seizure disorders [Livingston et al 2009], but there is no proven role for surgery given the widespread epileptogenic potential in this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

SCN1A seizure disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- A proband with an *SCN1A* seizure disorder may have the disorder as the result of a *de novo* pathogenic variant or may have inherited an *SCN1A* pathogenic variant from a parent. A parent of the proband is presumed to have an *SCN1A* pathogenic variant if the parent has additional family members who have seizures.
- The proportion of cases caused by a *de novo SCN1A* pathogenic variant differs by phenotype. The percentage of probands with an *SCN1A* seizure disorder and an affected parent decreases as the severity of the phenotype in the proband increases.
  - More than 95% of individuals with GEFS+ have a parent with the same *SCN1A* pathogenic variant.
  - Most *SCN1A* Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) is the result of a *de novo* pathogenic variant [Depienne et al 2009]. Only approximately 5% of probands with Dravet syndrome have a parent with the same *SCN1A* pathogenic variant [Wallace et al 2003, Ceulemans et al 2004b, Fukuma et al 2004].
  - Testing of parents of children who had Dravet syndrome and a confirmed *SCN1A* pathogenic variant showed that in 95% (76/80) of the children the pathogenic variant was *de novo* in the proband. Of the four children who had a parent with the pathogenic variant, two had a missense variant and two had a truncation variant; the parents were either asymptomatic or had mild epilepsy [Gennaro et al 2003, Nabbout et al 2003].
  - Berkovic et al [2006] found an *SCN1A* pathogenic variant in 11/14 children diagnosed with post-vaccine encephalopathy; in nine the variant was *de novo* in the proband.
  - Note: In one series, 75% of *de novo* pathogenic variants originated on the paternally inherited chromosome [Heron et al 2010].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant (i.e., no other affected family members) include molecular genetic testing.
- If a pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to either parent of having the pathogenic variant is low, but greater than that of the general population because of the possibility of germline mosaicism. Germline mosaicism has been documented

[Gennaro et al 2006, Selmer et al 2009, Azmanov et al 2010], and may occur in up to 7% of families with Dravet syndrome [Depienne et al 2010].

- An apparently negative family history cannot be confirmed until appropriate evaluations have been performed. Although 95% of individuals with *SCN1A*-GEFS+ have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, or because of early death before the onset of symptoms. If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be only mildly or minimally affected [Gennaro et al 2006].

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

- If a parent of the proband has the *SCN1A* pathogenic variant (documented by molecular genetic testing) or is presumed to have a pathogenic variant (based on clinical status and/or family history), the risk to the sibs of inheriting the pathogenic variant is 50%.
  - The likelihood that a sib who inherits an *SCN1A* pathogenic variant will develop symptoms depends on penetrance, which can only be estimated (see Penetrance).
  - Seizure phenotype in sibs who inherit an *SCN1A* pathogenic variant is difficult to predict as phenotype can vary among family members with the same pathogenic variant.
- If the *SCN1A* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism [Gennaro et al 2006].
- If a sib has epilepsy, the sib is presumed to be affected (and therefore to have an *SCN1A* pathogenic variant).

Offspring of a proband

- Each child of an individual with an *SCN1A* seizure disorder has a 50% chance of inheriting the pathogenic variant.
- Penetrance is incomplete (see Penetrance) and varies by phenotype.
- The likelihood that a heterozygous child of an individual with an *SCN1A* seizure disorder will develop the same phenotype depends on the penetrance for that particular phenotype.
- Individuals with GEFS+ may have offspring who are more severely affected than they are; for example, they may have a child with Dravet syndrome.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has the *SCN1A* pathogenic variant, other family members may be at risk.

Related Genetic Counseling Issues

Interpreting test results in at-risk asymptomatic relatives. Counseling of asymptomatic family members in whom the family-specific pathogenic variant has been identified should include information on reduced penetrance and the limited ability to predict phenotype based on molecular genetic testing alone.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SCN1A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **Dravet Syndrome Foundation**
  Phone: 203-392-1950
  Fax: 203-907-1940
  Email: info@dravetfoundation.org
  www.dravetfoundation.org
- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Febrile Seizures Fact Sheet
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page
- **The International Ion Channel Epilepsy Patient Registry (IICEPR)**
  IICEPR

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. SCN1A-Related Seizure Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SCN1A	2q24.3	Sodium channel protein type 1 subunit alpha	SCN1A gene database	SCN1A	SCN1A

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 SCN1A-Related Seizure Disorders (View All in OMIM)

182389	SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 1; SCN1A
604403	GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS, TYPE 2; GEFSP2
607208	DRAVET SYNDROME; DRVT
619317	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 6B; DEE6B

Molecular Pathogenesis

SCN1A encodes the alpha subunit (also known as $Na_V1.1$) of the neuronal voltage-gated sodium channel. *SCN1A* seizure disorders are therefore best conceptualized as a "channelopathy" with seizures (and their sequelae) as their primary manifestation. The molecular abnormality causes neuronal dysfunction, and ultimately hyperexcitability at the level of the cortical network: the sine qua non of epilepsy.

SCN1A is part of a cluster of sodium channel genes encoded on chromosome 2q24 that includes *SCN2A* and *SCN3A* [Mulley et al 2005]. The alpha subunit of sodium channels forms the membrane pore. Each alpha subunit protein has four domains with six transmembrane segments connected by loops (see Figure 3). Pore-lining residues are found in S5, S6, and the P-loop, the latter connecting S5 with S6. The voltage sensor is in S4, where positively charged residues allow for the sensing of membrane potential changes [Catterall 2000]. Although epilepsy-associated pathogenic variants are found in all parts of $Na_V1.1$, they occur more frequently in the C terminus, to some extent in the N terminus, in the P loops of D1-D5, and in the voltage sensor [Ceulemans et al 2004b, Mulley et al 2006].

Mechanism of disease causation. Pathogenic variants in *SCN1A* seizure disorders can result in either loss of or alteration of channel activity. The pathophysiology is an active area of investigation; it appears likely that the predominant effect is the loss of excitability in inhibitory GABAergic neurons [Escayg & Goldin 2010].

Chapter Notes

Revision History

- 17 February 2022 (sw) Revision: clarifications to Table 2
- 18 April 2019 (sw) Comprehensive update posted live
- 15 May 2014 (me) Comprehensive update posted live
- 10 November 2011 (me) Comprehensive update posted live
- 29 November 2007 (me) Review posted live
- 13 October 2006 (msm) Original submission

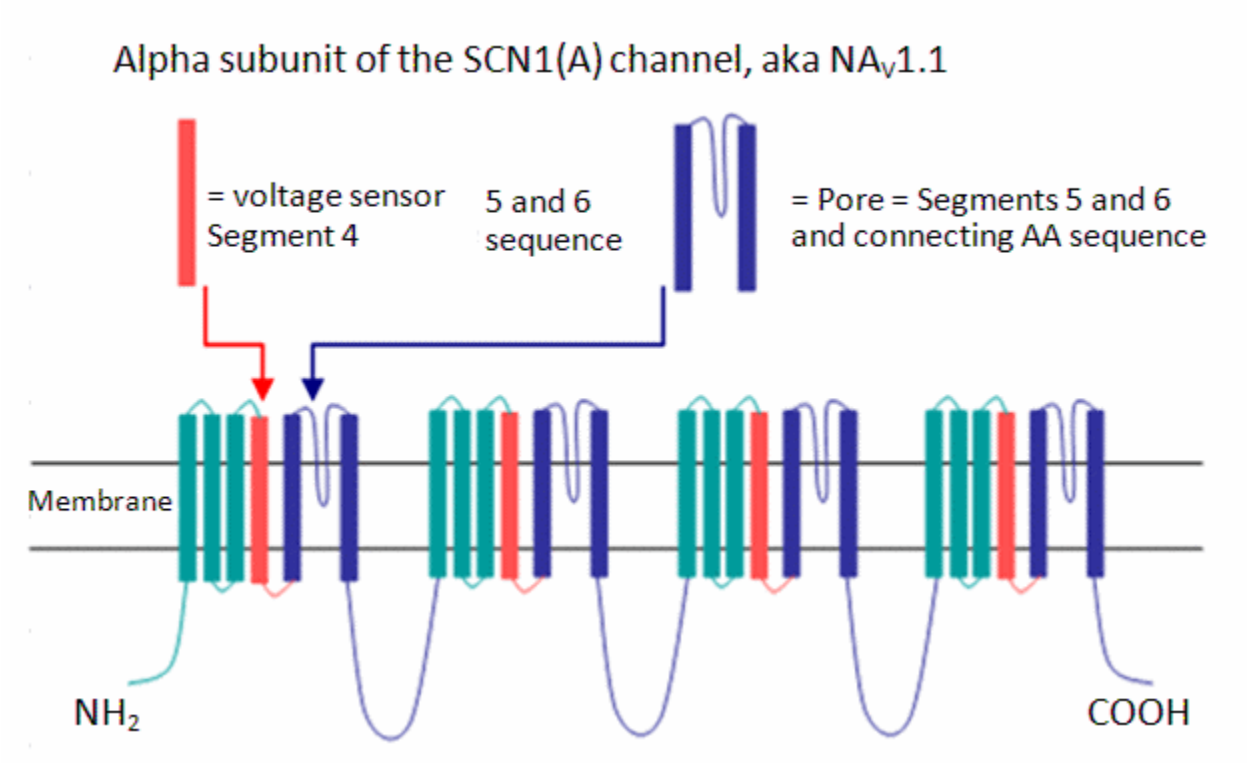

Figure 3. Topologic diagram of $Na_V1.1$, the alpha subunit of the neuronal voltage-gated sodium channel encoded by *SCN1A*. $Na_V1.1$ is 2,000 amino acids in size and has four homologous domains (D1-D4) that fold around a central pore and are connected by cytoplasmic loops. Each domain has six transmembrane segments, S1-S6. The cytoplasmic loop between the third and fourth domain forms the inactivation gate, while the S4 segments make up the voltage sensor. The pore is formed by parts of S5, S6, and the P loop between them. Voltage-gated sodium channels have one or more modulatory beta subunits (230 amino acids each, not pictured) that consist of a single transmembrane segment, an extracellular IgG loop, and a short intracellular C terminus. All voltage-gated sodium channels ($Na_V1.1$ - 1.9) have structural homology [Catterall 2000].

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