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SCN1A-Related Seizure Disorders

Ian O Miller, MD
Director, Clinical Neuroinformatics
Miami Children's Hospital
Miami, FL
ian.miller@mch.com

Marcio A Sotero de Menezes, MD
Co-Director, Epilepsy Center
Associate Professor, Neurology and Pediatrics
Children's Hospital and Regional Medical Center
Seattle, WA
marcio.sotero@seattlechildrens.org

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Summary

Disease characteristics. *SCN1A*-related seizure disorders encompass a spectrum that ranges from simple febrile seizures (FS) 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, also known as severe myoclonic epilepsy in infancy (SMEI) or polymorphic myoclonic epilepsy in infancy (PMEI), are usually associated with progressive dementia. Less commonly observed phenotypes include myoclonic-astatic epilepsy (MAE or Doose syndrome), Lennox-Gastaut syndrome (LGS), infantile spasms, and vaccine-related encephalopathy and seizures. The phenotype can vary even within the same family.

Diagnosis/testing. The diagnosis of *SCN1A*-related seizure disorders relies on molecular genetic testing of *SCN1A*. Sequence analysis and deletion testing are available on a clinical basis.

Management. *Treatment of manifestations:* Antiepileptic drugs (AEDs) include benzodiazepines (diazepam and clonazepam), topiramate, and valproic acid. Phenobarbital is effective, but poorly tolerated because of its effects on cognition. *Prevention of secondary complications:* use of protective helmets by individuals with atonic seizures or myoclonic-astatic epilepsy. *Surveillance:* serial neuropsychological evaluation for neurologic, cognitive, and behavioral deterioration; EEG monitoring for new or different seizure types. *Agents/ circumstances to avoid:* AEDs: carbamazepine, lamotrigine, and vigabatrin, which can induce or increase myoclonic seizures; phenytoin, which can induce choreaoathetosis. Activities in which a sudden loss of consciousness could lead to injury or death (e.g., bathing, swimming, driving, or working/playing at heights). *Other:* The AEDs clobazam and stiripentol, used in treatment of SMEI, are not FDA-approved for this use in the US. Sleep deprivation and illness can exacerbate seizures. Persons with epilepsy should be made aware of motor vehicle driving laws.

Genetic counseling. *SCN1A*-related seizure disorders are inherited in an autosomal dominant manner. A proband with an *SCN1A*-related seizure disorder may have a *de novo* mutation. The proportion of cases caused by *de novo* mutations varies by phenotype. The percentage of probands with an *SCN1A*-related seizure disorder and an affected parent decreases as the severity of the phenotype in the proband increases. Most *SCN1A*-related SMEI and ICE-GTC

are the result of a *de novo* heterozygous mutation. Each child of an individual with an *SCN1A*-related seizure disorder has a 50% chance of inheriting the mutation; 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 disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of *SCN1A*-related seizure disorders is complicated by the following three issues involving *SCN1A*-related seizure disorders:

- The phenotypes cover a broad spectrum of severity even within the same family.
- The epilepsy phenotypes are incompletely specific (i.e., phenotypes are seen in other conditions as well).
- Some epilepsy phenotypes refer to features observed in the family, rather than in a particular individual in the family.

Terms used in the literature to describe the phenotypes sometimes differ from the standard epilepsy syndrome terminology as defined by the International League Against Epilepsy (ILAE). Terms used to describe the phenotypes seen in *SCN1A*-related seizure disorders include the following.

Commonly associated phenotypes:

- **Febrile seizures (FS),** which may or may not have features suggestive of an *SCN1A*-related condition described above
- **Generalized epilepsy with febrile seizures plus (GEFS+)**
- **Dravet syndrome,** also known as **severe myoclonic epilepsy in infancy (SMEI)** or **polymorphic myoclonic epilepsy in infancy (PMEI)**

  Note: The term "Dravet syndrome" is preferred because the myoclonic seizures implied by the descriptive name(s) can be absent in children whose seizures are otherwise similar.
- **Severe myoclonic epilepsy, borderline (SMEB)**
- **Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC),** which does not represent an ILAE-defined epilepsy, and is most similar to late-onset Dravet syndrome in the ILAE classification system

  Note: This classification is widely used in the *SCN1A* literature and is thus included for completeness.
- **Infantile partial seizures with variable foci,** also referred to as **migrating partial seizures of infancy**, **cryptogenic focal epilepsy**, or **severe infantile multifocal epilepsy** per Harkin and colleagues (2007)

Less commonly associated phenotypes:

- **Myoclonic-astatic epilepsy (MAE, Doose syndrome),** initially defined conceptually as a group of individuals with a genetic predisposition to generalized epilepsies. In the ILAE classification system it is a superset including Dravet syndrome, benign myoclonic epilepsy, as well as childhood-onset epilepsies with primarily generalized seizures.

- **Lennox-Gastaut syndrome (LGS)**
- **Infantile spasms**
- **Vaccine-related encephalopathy and seizures**

Note: Because clinical findings alone cannot establish the diagnosis, detection of an *SCN1A* mutation is necessary.

Findings in a family that have some specificity for *SCN1A*-related seizure disorders include the following:

- One or more family members with epilepsy, especially of more than one type
- Febrile seizures before age one year [Bonanni et al 2004]
- Febrile seizures after age six years [Scheffer & Berkovic 1997]
- Febrile seizures with unusual severity (including status epilepticus) [Baulac et al 1999]
- Febrile seizures that precede unprovoked (i.e., afebrile) seizures (which may be generalized tonic-clonic, myoclonic, myoclonic-astatic, or absence) [Scheffer & Berkovic 1997]

Note: Because the suggestive features may occur in some members of the family and not others, a complete family history must be taken.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. The only gene known to be associated with *SCN1A*-related seizure disorders is *SCN1A*; however, similar phenotypes can be seen in other conditions (see Differential Diagnosis).

Clinical testing

- **Sequence analysis.** In most reported cases, PCR amplification of genomic DNA and sequencing of the 26 exons and splice junctions is used to detect *SCN1A* mutations.
- **Deletion testing.** Some individuals with SMEI have large-scale *SCN1A* deletions that are not detected by sequence analysis (see Table 1).

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*SCN1A* sequence variants	73%-92%	Clinical Testing
Deletion testing	*SCN1A* exonic and whole gene deletions	8%-27% [2, 3]	

1. Proportion of affected individuals with a mutation(s) as classified by test method

2. The proportion of all *SCN1A* mutations that are deletions in those with the SMEI phenotype. It is not known if the percent of exonic and whole gene deletions is the same for the other phenotypes in the spectrum of *SCN1A*-related epilepsies.

3. Using a variety of methods to identify deletions encompassing the *SCN1A* locus in individuals with SMEI who did not have an *SCN1A* point mutation 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.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband. Molecular genetic testing of *SCN1A* is warranted in a proband whose family history includes the following:

- More than one member with epilepsy or febrile seizures, especially if multiple phenotypes are present
- Febrile seizures before age one year
- Febrile seizures after age six years
- Febrile seizures with unusual severity (including status epilepticus)
- Febrile seizures that precede unprovoked (i.e., afebrile) seizures (which may be generalized tonic-clonic, myoclonic, myoclonic-astatic, or absence)

Prenatal diagnosis for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Other phenotypes associated with mutations in *SCN1A*:

- Panayiotopolous syndrome [Grosso et al 2007]
- Familial hemiplegic migraine [Dichgans et al 2005]
- Familial autism (see Autism Overview) [Weiss et al 2003]
- A contiguous gene deletion syndrome of severe epilepsy, mental retardation, and dysmorphic features that includes the *SCN1A* and *SCN2A* genes at chromosomal locus 2q23-q24. One affected individual has been described [Pereira et al 2004].

Clinical Description

Natural History

The natural history of *SCN1A*-related epilepsies is strongly influenced by seizure phenotype, which can range from simple febrile seizures (FS) and generalized epilepsy with febrile seizures plus (GEFS+) at the mild end to severe myoclonic epilepsy of infancy (SMEI) 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]. Phenotypes with intractable seizures (e.g., Dravet syndrome) usually cause epileptic encephalopathy, a form of progressive dementia.

The phenotype varies even among family members with the same mutation (Figure 1).

The features and course for the most common phenotypes in *SCN1A*-related epilepsies, summarized in Table 2, include the following:

Febrile seizures (FS), consisting of childhood seizures that 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 greater than 15 minutes
- Occurrence of more than one seizure within 24 hours
- Presence of any partial (focal) features during the seizure

Febrile seizures plus (FS+), a subset of febrile seizures (simple or complex) which have 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

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

Generalized epilepsy with febrile seizures plus (GEFS+), a term that differs from the above terms in that it refers to 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. The range of *SCN1A*-related seizure phenotypes are seen within any family; however, the seizure phenotypes tend toward the mild end of the spectrum [Scheffer & Berkovic 1997] because the more severe seizure types have a reproductive disadvantage and thus are less likely to be familial [Claes et al 2001]. Affected individuals within a family with GEFS+ often present with febrile seizures (or FS+) in early childhood, followed by occasional tonic, clonic, myoclonic, or absence seizures which respond to medication and remit by late childhood or early adolescence. Also the proportion of children whose first seizure occurs in the context of immunization appears to be greater than those in children with febrile seizures unrelated to FS+ and GEFS+.

Dravet syndrome, defined as seizures with onset during the first year of life that do not remit, and usually evolve to include myoclonic seizures

- Early seizures are often prolonged febrile seizures. Seizures can sometimes be provoked by modest hyperthermia (e.g., a hot bath, physical exertion).
- Any seizure type is possible, although generalized tonic-clonic, myoclonic, and hemiconvulsive seizures are most common.
- Myoclonic seizures tend to appear later in the course, often coinciding with the appearance of cognitive dysfunction, ataxia, and psychomotor regression.
- Status epilepticus is common, and pharmacologic management is difficult.
- The initial EEGs are often normal, but over time epileptiform activity appears. Patterns can include generalized spike and wave discharges, multiple spike and wave (synonymous with polyspike and wave) discharges, and multifocal spikes.

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

Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC), 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.

Infantile partial seizures with variable foci, defined as focal seizures beginning in infancy with multiple independent zones of seizure onset involving both hemispheres. Multifocal partial seizures are often the first manifestation; however, some children may present with 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.

Table 2. Phenotype Distribution in *SCN1A*-Related Seizure Disorders

Disorder	Distribution
Simple febrile seizures (FS)	Unknown
Febrile seizures plus (FS+)	Unknown
Generalized epilepsy with febrile seizures plus (GEFS+)	5%-10%
Severe myoclonic epilepsy in infancy (SMEI)	33%-90% [1]
Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC)	70% [2]

1. Mulley et al 2005
2. Fujiwara et al 2003

The features and course for the less common phenotypes associated with *SCN1A* mutations include the following:

Myoclonic-astatic epilepsy (MAE), defined as the combination of myoclonic, atonic, and atypical absence seizures. 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). Age of onset ranges between seven months and eight years, although it most often begins after age two years. Development prior to seizure onset is often normal. The course is variable, and can range from spontaneous seizure resolution without cognitive impairment to intractable seizures with severe mental retardation [Arzimanoglou et al 2004]. In one series of 20 individuals with MAE (including 12 of the original Doose cohort) and 18 controls, three individuals were found to have an *SCN1A* mutation [Ebach et al 2005]. Only one of the three had a phenotype consistent with MAE, leading the authors to conclude that MAE was not predictive of an *SCN1A* mutation.

Lennox-Gastaut syndrome (LGS), 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 (age 2-14 years). Any type of seizure can be seen in this syndrome, and status epilepticus is common [Arzimanoglou et al 2004]. Only a minority of persons with the LGS phenotype have an *SCN1A* mutation, 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 the larger cohort of LGS.

Infantile spasms, 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* missense mutation with infantile spasms has been reported once [Wallace et al 2003]. The single case represents less than 1% of the reported cases, although publication bias makes it impossible to estimate the real proportion.

Vaccine-related encephalopathy and seizures, defined as sudden onset of seizures and encephalopathy in infants 48 hours after immunization. Berkovic et al (2006) reported *SCN1A* mutations in 11/14 children diagnosed with post-vaccine encephalopathy.

Genotype-Phenotype Correlations

Mulley et al (2005) found that most *SCN1A* mutations cluster in the C-terminus and in the pore loops connecting S5 and S6 especially in the first three domains of the protein (Figure 2). Mutations that predict premature protein truncation often lead to a severe phenotype, but no consistent correlation between mutation type, mutation location, and clinical phenotype is found.

An estimated 5% of the mutation-positive SMEI cases have a familial missense *SCN1A* mutation, which is associated with a milder phenotype (i.e., GEFS+) in other family members [Mulley et al 2005].

Penetrance

SCN1A-related seizure disorders show incomplete penetrance and variable expressivity.

Penetrance may vary by phenotype or mutation. For example, Bonanni et al (2004) estimated the penetrance to be 70% for the GEFS+ phenotype, whereas Mantegazza et al (2005) reported a penetrance of 90% for the familial simple febrile seizure phenotype.

Prevalence

The prevalence of *SCN1A*-related seizure disorders is unknown.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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

It is most important to identify potentially treatable conditions, including the following [Arzimanoglou et al 2004, Roger et al 2006]:

- Pyridoxine-dependent seizures and B6-related epilepsies

- "Folinic acid-responsive" seizures, a rare cause of epilepsy that improves with daily folinic acid administration
- 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
- Glucose transporter type 1 deficiency, which is diagnosed by low CSF glucose concentrations, and responds to the ketogenic diet
- Hepatic porphyrias, which usually demonstrate photosensitive porphyrins in the urine and reduced monopyrrole porphobilinogen (PBG) deaminase in red cells

If the family history is negative or unavailable, sporadic epilepsies (i.e., those without 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

If the family history is positive for other individuals with epilepsy, the differential diagnosis should include the following inherited epilepsy syndromes [Arzimanoglou et al 2004, Roger et al 2006]:

- Benign familial neonatal seizures
- Benign familial infantile seizures
- Benign childhood epilepsy with centrotemporal spikes
- Childhood occipital epilepsy
- Absence epilepsies
- Autosomal dominant nocturnal frontal lobe epilepsy
- Familial temporal lobe epilepsies
- Familial focal epilepsy with variable foci

At least seven febrile seizure loci *(FEB1-7*) have been identified (Table 3) [Mantegazza et al 2005]. The phenotype in simple febrile seizures is usually less severe than that of febrile seizures associated with GEFS+ (see Clinical Description, Natural History) [Nakayama & Arinami 2006].

Table 3. Genes and Loci Associated with Simple Febrile Seizures

Locus Name (Gene Symbol)	Chromosomal Locus
FEB1	8q13-q21
FEB2	19p13.3
FEB3 (SCN1A)	2q24
FEB4	5q14-q15
FEB5	6q22-q24
FEB6	18p11.2
FEB7	21q22

The mode of inheritance for most GEFS+ is unknown. Only 5% of affected individuals in a large family with GEFS+ were found to have mutations in *SCN1A* [Mulley et al 2005].

Genetic loci known to be associated with GEFS+ include the following:

- **Voltage-gated sodium channel genes**
  - *SCN1A* [Escayg et al 2000; Escayg et al 2001; Wallace, Scheffer et al 2001]
  - *SCN1B* [Wallace et al 1998, Wallace et al 2002, Audenaert et al 2003]
  - *SCN2A* [Sugawara et al 2001]
- **$GABA_A$ receptor genes**
  - *GABRG2* [Baulac et al 2001; Wallace, Marini et al 2001]
  - *GABRD* [Dibbens et al 2004]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with an *SCN1A*-related seizure disorder, the following evaluations are recommended:

- Neurologic examination
- Cognitive neuropsychological evaluation
- Behavioral neuropsychological evaluation
- Electroencephalogram (EEG), including video EEG telemetry where ictal onset or semiology is unclear

Treatment of Manifestations

Care is best provided by a physician (e.g., pediatric epileptologist) who is familiar with the pharmacotherapy for this disorder.

The effectiveness of pharmacologic treatment may be improved by the observation that abnormal *SCN1A* channels disproportionately affect GABA neurons [Yu et al 2006], and that associated seizures respond optimally to antiepileptic drugs (AEDs) that bind to the GABA receptor:

- **Clobazam (0.2-1 mg mg/kg/day).** Clobazam is not FDA-approved for this use in the US.
- **Stiripentol (50-100 mg/kg/day).** Stiripentol is not FDA-approved for use in the US, but it is the only medication evaluated in a double-blind severe myoclonic epilepsy in infancy (SMEI) treatment study [Chiron et al 2000]. Thanh et al (2002) demonstrated efficacy of the drug when compared with placebo administration; only moderate side effects including drowsiness, loss of appetite, and occasional neutropenia in infants and young children were observed. Stiripentol acts directly on $GABA_A$ receptors [Quilichini et al 2006], but also has the added benefit of increasing the serum concentration of other common AEDs, including valproic acid, clobazam, and its metabolite nor-clobazam [Thanh et al 2002]. 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].
- **Topiramate** [Coppola et al 2002]
- **Valproic acid** (10-30 mg/kg/day) [Thanh et al 2002]
- **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.

Prevention of Secondary Complications

Routine seizure and personal safety counseling is indicated.

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

Surveillance

Serial neuropsychological evaluation for neurologic, cognitive, and behavioral deterioration is appropriate.

EEG monitoring is appropriate when new or different seizure types are suspected.

Agents/Circumstances to Avoid

Contraindicated antiepileptic drugs (AEDs):

- **Carbamazepine, lamotrigine, and vigabatrin,** which can induce or increase myoclonic seizures [Horn et al 1986; Guerrini et al 1998; Ceulemans, Boel et al 2004]
- **Phenytoin,** as it may induce choreaoathetosis [Saito et al 2001]

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

Testing of Relatives at Risk

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

Therapies Under Investigation

Although clobazam and stiripentol (see Treatment of Manifestations) are widely used in Europe for treatment of seizures in those with *SCN1A*-related SMEI, in the US these therapies are still considered experimental and are not FDA approved.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Sleep deprivation and illness can exacerbate *SCN1A*-related seizures. Thus, good sleep hygiene ought to be encouraged.

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

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

- Ethosuximide and high-dose piracetam for myoclonic seizures
- Triple bromide
- Corticosteroids
- Immunoglobulins
- The ketogenic diet

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

SCN1A-related seizure disorders are inherited in an autosomal dominant manner.

Note: Most *SCN1A*-related severe myoclonic epilepsy in infancy (SMEI) and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) are the result of a *de novo* heterozygous mutation.

Risk to Family Members

Parents of a proband

- A parent of the proband is presumed to have a disease-causing mutation if he/she has additional family members who have seizures.
- A proband with an *SCN1A*-related seizure disorder may have the disorder as the result of a *de novo* mutation. The proportion of cases caused by *de novo* mutations varies by phenotype. The percentage of probands with an *SCN1A*-related 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 who has the same *SCN1A* mutation.
  - Only approximately 5% of probands with SMEI have a parent who has the same *SCN1A* mutation [Wallace et al 2003; Ceulemans, Claes et al 2004; Fukuma et al 2004].
  - Testing of parents of children whohad SMEI and a confirmed *SCN1A* mutation showed that 95% (76/80) of the children had *de novo* mutations. Of the four children who had a parent with the mutation, two had a missense mutation and two had a truncation mutation; the parents were either asymptomatic or had mild epilepsy [Gennaro et al 2003, Nabbout et al 2003].
  - Berkovic et al (2006) found *SCN1A* mutations in 11/14 children diagnosed with post-vaccine encephalopathy; nine of the mutations were *de novo*.
- If a disease-causing mutation found in the proband cannot be detected in DNA extracted from the leukocytes of either parent, the risk of either parent having the mutation 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].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing if the proband has a detectable mutation.
- An apparently negative family history cannot be confirmed until appropriate evaluations have been performed. Although 95% of individuals with *SCN1A*-related GEFS+ have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or because of early death before the onset of symptoms. If the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation 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 upon the genetic status of the proband's parents.
- If a parent of the proband is affected (i.e., has the disease-causing mutation documented by results of molecular genetic testing) or is presumed to have a disease-causing mutation (based on family history), the risk to the sibs of inheriting the mutation is 50%.
- If a sib has epilepsy, he/she is presumed to be affected (and therefore has a disease-causing mutation).

- If a sib does not have epilepsy, the prior probability of the sib having inherited the disease-related mutation is 50%; however, the probability of the sib developing symptoms depends on the penetrance, which can only be estimated. For example, for an estimated penetrance of 70% for the GEFS+ phenotype, the probability of the asymptomatic sib having inherited the disease-causing mutation is 23%.
- If a disease-causing mutation is found in the proband but cannot be detected in the 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].

Offspring of a proband

- Each child of an individual with an *SCN1A*-related seizure disorder has a 50% chance of inheriting the mutation.
- Penetrance is incomplete (see Penetrance) and varies by phenotype.
- The likelihood that the child of an individual with an *SCN1A*-related seizure disorder will develop the same phenotype is the probability of inheriting the mutation (50%) times 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 of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, the other family members are at greater risk than the general population.

Related Genetic Counseling Issues

Interpreting test results in at-risk asymptomatic relatives. Counseling asymptomatic family members who test positive for the family-specific mutation should be done with caution because of reduced penetrance and limited ability to predict phenotype based on molecular genetic testing alone.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions regarding testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis in pregnancies at increased risk for an *SCN1A*-related seizure disorder is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at

approximately ten to 12 weeks' gestation. The disease-related allele must be identified in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of SCN1A-Related Seizure Disorders

Gene Symbol	Chromosomal Locus	Protein Name
SCN1A	2q24	Sodium channel protein type 1 subunit alpha

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for SCN1A-Related Seizure Disorders

182389	SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT; SCN1A
604233	GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS; GEFS+
604403	FEBRILE CONVULSIONS, FAMILIAL, 3; FEB3
607208	SEVERE MYOCLONIC EPILEPSY OF INFANCY; SMEI

Table C. Genomic Databases for SCN1A-Related Seizure Disorders

Gene Symbol	Entrez Gene	HGMD
SCN1A	6323 (MIM No. 182389)	SCN1A

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

SCN1A codes for the alpha subunit (also known as $Na_v1.1$) of the neuronal voltage-gated sodium channel. *SCN1A*-related epilepsy is therefore best conceptualized as a "channelopathy" with seizures (and their sequelae) as its sole 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 (Figure 2). 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 mutations 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, Claes et al 2004; Mulley et al 2006].

Normal allelic variants: The *SCN1A* gene spans approximately 84 Mb of genomic DNA and has a transcript of 8,100 bp (reference sequence NM_006920.4). The gene has 26 exons that encode a protein of 1,998 amino acid residues (reference sequence NP_008851.3). Splicing variability has been reported [Wallace, Scheffer et al 2001].

Pathologic allelic variants:

- **Generalized epilepsy with febrile seizures plus (GEFS+).** GEFS+ cases associated with *SCN1A* mutations are mostly missense and familial [Mulley et al 2005].
- **Dravet syndrome.** Almost half of the mutations associated with the severe myoclonic epilepsy in infancy (SMEI) phenotype are truncating mutations [Mulley et al 2006]. The remainder include missense mutations (39%-43%; fewer than the GEFS+ phenotype, but with a similar topologic distribution within $Na_v1.1$), splice site mutations (7%), and deletions (3%) [adopted from Mulley et al 2005].
- **Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC).** Seven out of ten individuals with ICE-GTC had *SCN1A* missense mutations [Mulley et al 2005]. In the two cases with a familial mutation, the parents had GEFS +.
- **Infantile partial seizures with variable foci.** In the authors' experience, such cases often have missense mutations affecting the pore region or the carboxy-terminus of $Na_v1.1$.
- **Infantile spasms.** The literature cites an isolated case of infantile spasms and an *SCN1A* missense mutation [Wallace et al 2003].
- **Vaccine-related encephalopathy and seizures.** There are five reports of mutations causing $Na_v1.1$ truncation and six reports of missense mutations in conserved regions of $Na_v1.1$ [Berkovic et al 2006].

Normal gene product: See Molecular Genetic Pathogenesis.

Abnormal gene product: The molecular pathogenesis of *SCN1A* is not yet well elucidated. It is an active area of investigation using both cell systems and animal models, and several competing hypotheses have been advanced [Lossin et al 2002, Cossette et al 2003, Rhodes et al 2004, Spampanato et al 2004, Barela et al 2006, Yu et al 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

American Epilepsy Society
342 North Main Street
West Hartford CT 06117-2507
Phone: 860-586-7505
Fax: 860-586-7550
Email: info@aesnet.org
www.aesnet.org

Epilepsy Foundation
8301 Professional Place

East Landover, MD 20785-2238
Phone: 800-EFA-1000 (800-332-1000); 301-459-3700
Fax: 301-577-4941
Email: webmaster@efa.org
www.efa.org

National Institute of Neurologic Disorders and Stroke
Febrile Seizures Fact Sheet
NINDS Epilepsy Information Page

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 29 November 2007 (me) Review posted to live Web site
- 13 October 2006 (msm) Original submission

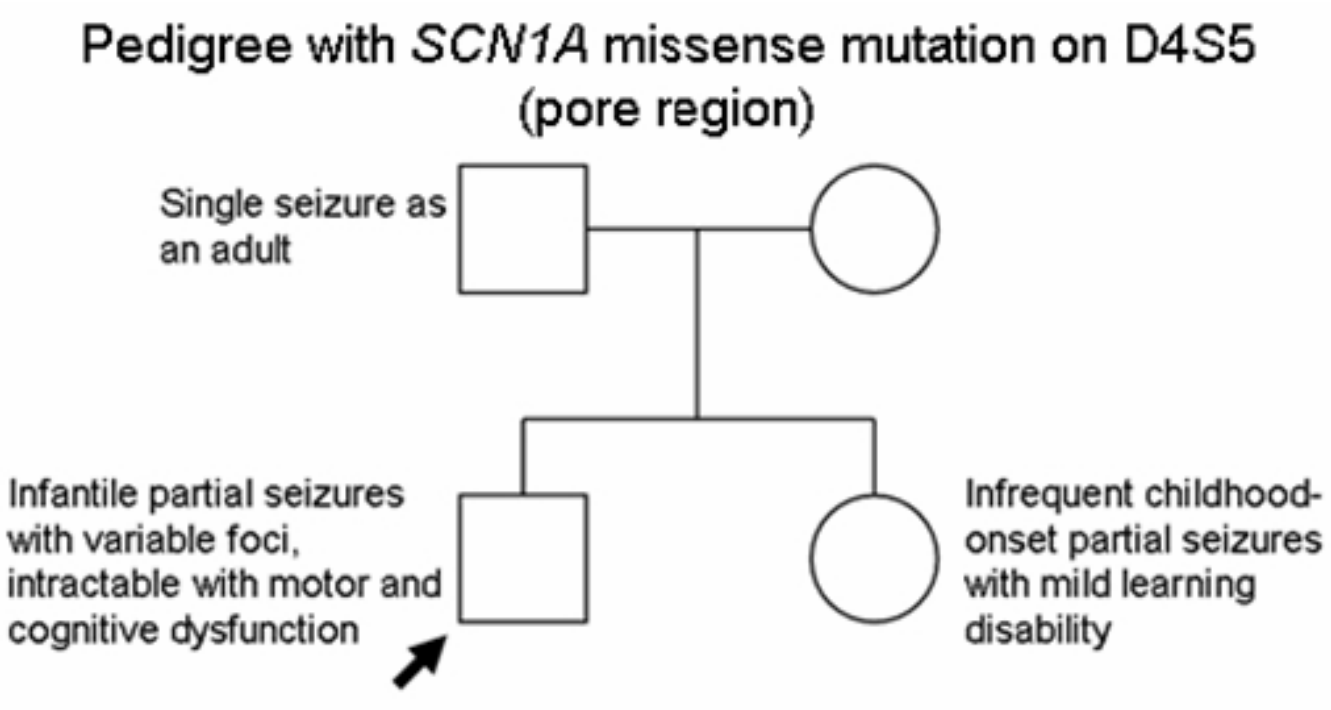

Figure 1. Findings in a family illustrating variable expressivity among individuals with the same mutation. The proband, a boy (arrow) with febrile convulsions since age seven months, had frequent, difficult-to-control partial seizures beginning at age three years. His sister had infrequent partial seizures starting at early school years. Their father had a single seizure as a young adult. All three had the same mutation in the fourth domain fifth segment (D4S5) on the pore region of the *SCN1A* ($Na_v1.1$) protein (see Molecular Genetic Pathogenesis) [M Sotero, personal observation].

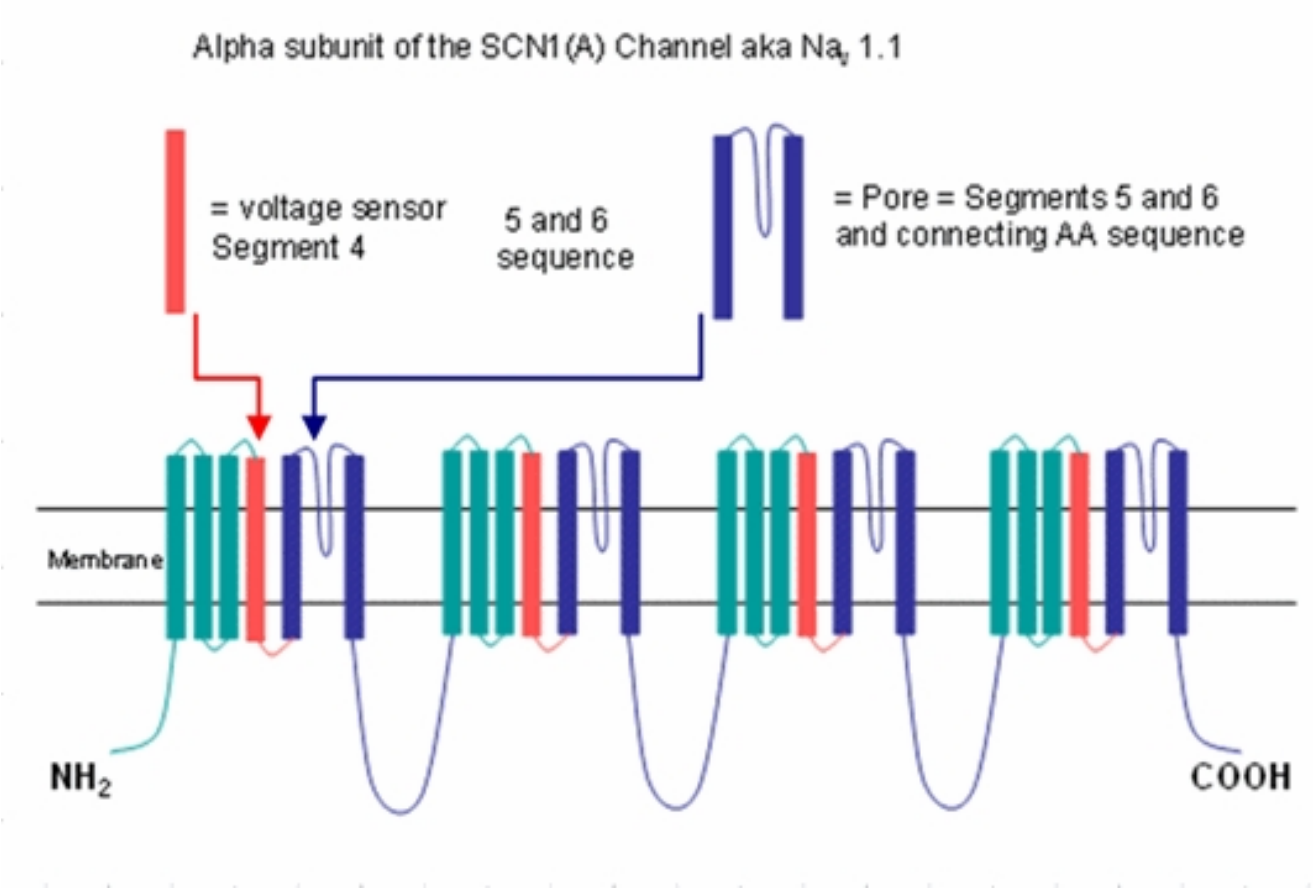

Figure 2. Topologic diagram of $Na_v1.1$, the alpha subunit of the neuronal voltage-gated sodium channel encoded by the *SCN1A* gene. $Na_v1.1$ is 2,000 amino acids in size and has four homologous domains (D1-D4) that fold around a central pore and are connected by cytoplasmic loops. Each domain has 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].