UNIVERSITY OF NOTRE DAME | PATIENT ADVOCACY INITIATIVE

A Companion Guide to Cambridge Elements: SCN2A-Related Disorders

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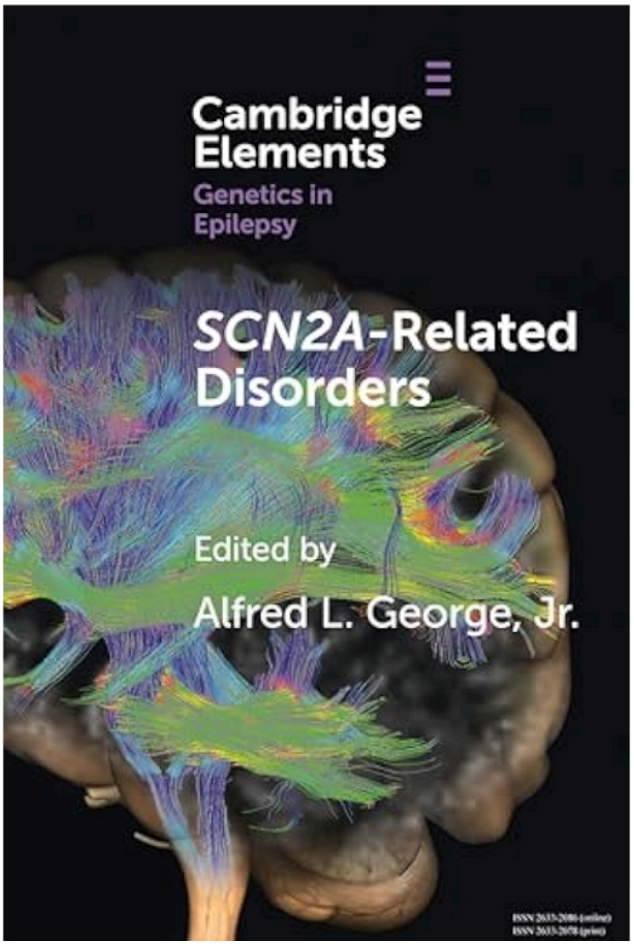

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The Cambridge Elements: SCN2A-Related Disorders explains key concepts such as what SCN2A is, how it affects individuals, and what treatments are available. This companion guide was created to make the information more accessible for families and others without a scientific background by highlighting the main takeaways in a clear and understandable way.

The many ways SCN2A-related disorders affect people

Summary of the Chapter: "Clinical Spectrum and Genotype-Phenotype Correlations," pages 7-20

Changes in the SCN2A gene can cause problems in the brain that can start around birth or later in childhood. These problems are known as neurodevelopmental disorders and can include:

- Epilepsy: Some kids with SCN2A-related disorders will get seizures. Repeated seizures are called epilepsy. **Almost all individuals with SCN2A variants will develop epilepsy at some point in their lives.** Seizures can make muscles stiff (tonic) or move suddenly (clonic). The head and eyes may turn in one direction. They often happen in one part of the brain (focal seizure) and last from 20 seconds to 3 minutes. **Focal seizures are the most common seizure type.**

- Autism Spectrum Disorder / Intellectual Disability: Many kids with SCN2A-related disorders who never have seizures or have them later in childhood will be diagnosed with Autism Spectrum Disorder and/or Intellectual Disability.

- Movement Disorders: Kids with SCN2A-related disorders can have a wide range of movement disorders including sudden, brief, involuntary muscle spasms, tremors, and abnormal movements and postures. This can happen with or without seizures.

Common Conditions Seen With SCN2A-related Disorders (Co-morbidities):

- "Cortical Visual Impairment" (CVI): this is when vision is impaired even though eye structures look normal. Instead, parts of the brain that process vision are impaired.
- "Dysautonomia": Difficulties regulating unconscious, "automatic" processes, like body temperature and heart rate.

How Do Doctors Find Out Someone Has An SCN2A-related Disorder?

- Doctors and scientists look at what problems the child is having, and may use brain tests such as an electroencephalogram (EEG) and brain imaging like magnetic resonance imaging (MRI). Genetic testing to identify the specific change in the SCN2A gene will help the doctor with diagnosis and figuring out the best treatment plan.

GLOSSARY

Neurodevelopmental Disorders
A group of disorders with onset during childhood that affect brain development and function.

Epilepsy
Repeated, spontaneous seizures caused by irregular electrical activity in the brain.

Tonic Seizure
A seizure where the body becomes stiff. This can cause a person to fall if standing.

Clonic Seizure
A seizure with sudden, repeated movements of the arms and legs.

Focal Seizure
A seizure that starts in one small part of the brain. Symptoms vary on location. They can be defined based on whether a person stays aware during the seizure.

Autism Spectrum Disorder (ASD)
A neurological and developmental condition affecting how a person communicates, interacts, learns, and behaves.

Intellectual Disability
A neurological and developmental condition limiting cognition, learning, and everyday abilities.

Comorbidities
Diagnoses that can occur along with a "primary" diagnosis of autism, epilepsy, etc.

How Gene Changes Relate to Symptoms:

Doctors and scientists look at how different changes in the SCN2A gene affect kids in different ways. This is called **genotype–phenotype correlation.**

- **What does this mean?**
  - **Genotype:** The specific gene instructions caused by the change in the SCN2A gene. The genes carry instructions to make **proteins**. Proteins make the basis of all our bodies' structures.
  - **Phenotype:** These are the traits you can see in a person because of the way the proteins function in the body.

For SCN2A-related disorders, there is some genotype–phenotype correlation:

- Many kids who have seizures that start early in life may have what is called a **gain-of-function (GOF) variant**. This sort of gene change increases the activity of SCN2A in the brain.
- Kids who have seizures that start later, or never have seizures, are more likely to have a **loss-of-function (LOF) variant.** This sort of gene change decreases the activity of SCN2A in the brain. They are also more likely to have autism spectrum disorder and/or intellectual disability.

But it's not always that simple!

- Many gene changes do not fit neatly into either the GOF or LOF category, but instead have mixed GOF / LOF function effects. These kids can have a wide range of phenotypes depending on the exact change in SCN2A and their own individual genetic background.
- The same gene change (**genotype**) can cause different problems in different kids, even in the same family. Every kid's phenotype is unique.
- And, sometimes, **not all cells have the change**, which is called **mosaicism**, happening in about 6% of cases, making it hard to identify.

Interpretation of SCN2A variants requires the help of a neurologist or geneticist.

Genotype
The specific set of gene instructions a body carries in its DNA..

Phenotype
These are the traits you can see in a person because of the gene information.

Protein
The building blocks of all our bodies' structures.

Gain-of-Function (GOF) Variant
A gene change that makes a protein more functional than usual.

Loss-of-Function (LOF) Variant
A change in genes that makes a protein less functional or non-functional.

Mixed GOF / LOF Variant
A change in a gene that both increases and decreases the function of the protein.

Mosaicism
When some cells in the body have a gene change and others don't. Different kinds of cells are mixed.

Summary: What Parents Need to Know

SCN2A is a gene that helps the brain work. Changes in this gene can cause a range of problems, like seizures, learning delays, autism, movement issues, or trouble walking. Some children have symptoms at birth, while others don't show signs until later. Seizures can be hard to treat, and some medicines might even make them worse, so it's important to know your child's exact gene change. **Genetic testing can help doctors find the best care plan. Even kids with the same gene change can have different symptoms, so every child is unique. Early care, watching for changes, and talking with doctors who know about SCN2A can make a big difference.**

Types of SCN2A-related Disorders (Pages 7-17)

When Brain Symptoms Start

Early (0-3 months old) | **Late (>3 months old)**

Self-Limited Epilepsies (0-2 years old) ⇧

- Most children with this disorder have their first seizure around 3 months old. These seizures may stop by age 1, allowing the children to grow and learn like their peers. About 1 in 5 people with changes in the SCN2A gene have this type. It is often passed down from a parent.

Episodic Ataxia (0-3 months old) ⇧

- Rare disorder characterized by sudden trouble walking or balancing, which may be triggered by tiredness, loud sounds, etc.
- Some have severe headaches with weakness on one side.
- Few reports of effective treatment with sodium channel blocking medications.

Early Infantile Developmental and Epileptic Encephalopathy (DEE) (0-3 months old) ⇧

- **Most common type.** Very serious, hard to stop seizures in first 3 months.
- Co-morbidities: trouble seeing, moving, eating, breathing, or keeping a normal body temperature or heart rate.
- Intellectual disability is often severe.
- Some are at risk for serious infections or sudden death from epilepsy, particularly if the EEG shows a burst suppression.

Later-Onset Developmental and Epileptic Encephalopathy (DEE) (> 3 months old) ⇩

- **Second most common type.** Seizures can look like intense shaking or brief blank staring.
- Intellectual disability develops in all affected children after seizures begin and the majority have **severe cognitive impairment.**
- Co-morbidities: autism spectrum disorder, movement symptoms
- Treatment challenges: sodium channel blockers may not help or make seizures worse.

SCN2A-Related Disorders Without Epilepsy (> 3 months old) ⇩

- Difficult to diagnose, often missed.
- Usually not passed down from a parent. This type of variant that occurs spontaneously is called a **de novo** variant.
- Co-morbidities: intellectual disability, autism spectrum disorder

KEY:

- Normal/Near Normal Learning and Growth
- Mild to Severe Learning Problems
- ⇧ Mainly gain-of-function change
- ⇩ Mainly loss-of-function change

How Does SCN2A Work?

Summary of the Chapter: "The Biology of SCN2A," pages 20-34

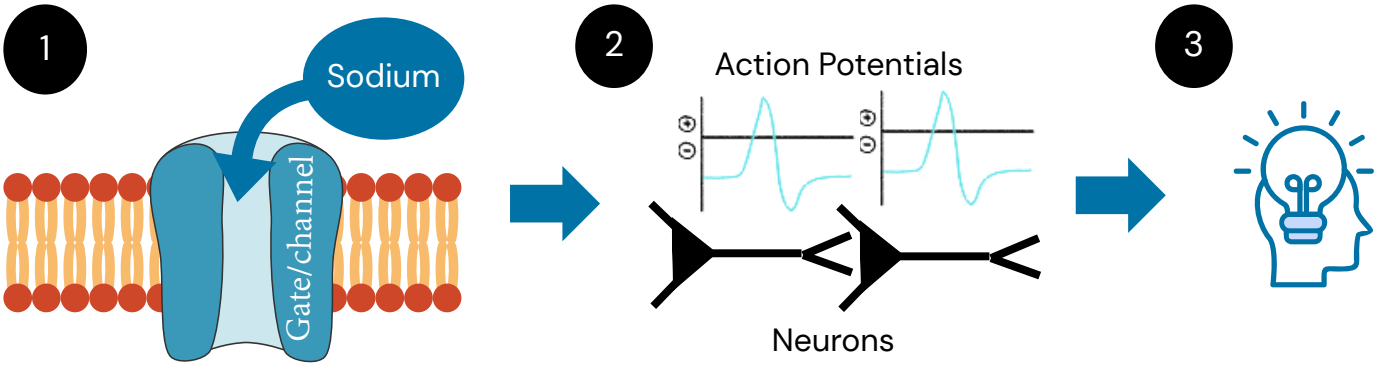
Neurons
Nerve cells that send messages all over your body to allow you to do everything from breathing to talking, eating, walking, and thinking.

Action Potentials (APs)
A burst of electricity that travels through neurons to send messages in the brain and body to help it work.

$Na_V1.2$
The name of the sodium channel that is created by the SCN2A gene. It acts as a gate that lets sodium in and out of neurons.

What Does the SCN2A Gene Do for the Body?

- The SCN2A gene is like a "recipe" within your body that is responsible for making tiny gates called channels in the walls of brain cells (neurons). These gates are crucial in helping neurons develop and communicate.
- The name for the specific channel that the SCN2A gene creates is $Na_V1.2$.
- $Na_V1.2$ allows for sodium to go in and out of neurons. When this happens, it helps neurons send fast messages called action potentials (APs).
- These APs are brief electrical signals that allow neurons to send information all over the body, **messages that help us think, learn, move, and feel.** When these channels do not work properly, there may be problems with how neurons send messages.
- Changes in the SCN2A gene will cause the $Na_V1.2$ channels to function differently, and these changes can be GOF variants, LOF variants, or mixed GOF / LOF variants.



What Do SCN2A Variants Do?

- Gain-of-function (GOF) variants change the channels so that too much sodium is allowed into the cell. This change is most often found in kids who have seizures early in life.
- Loss-of-function (LOF) variants change the channels so that not enough sodium is allowed into the cell. This change if often associated with autism spectrum disorder and intellectual disability.
- Mixed GOF / LOF variants can show some changes that increase sodium and others that decrease sodium, leading to complicated effects on phenotype.

The Role of $Na_V1.2$ Changes with Age:

- As kids grow, the role of $Na_V1.2$ in neurons changes a little. Because of this, $Na_V1.2$ may play a slightly different role in early versus late childhood, and these differences may affect how variants in SCN2A cause different issues at different ages.

Summary: What Parents Need to Know

The SCN2A gene is responsible for making protein 'gates' within the brain that help neurons communicate. These gates allow sodium to go in and out when needed, giving us the ability to move, think, and feel. The gates are found in different areas and are responsible for different roles. **Changes to the SCN2A gene will cause these gates to work differently, which can lead to different conditions.** Some changes will lead to increased activity, or **gain-of-function**, which may result in seizures. Others will result in decreased activity, or **loss-of-function**, and this may cause autism spectrum disorder or intellectual disability. How these gates work changes with age, so how an SCN2A variant affects an individual can change with age too.

Treatments of Conditions Related to SCN2A

Summary of the Chapter: "Treatments of SCN2A-related Disorders" pages 34-43

SCN2A-related Disorder Therapy Treatments

- Primary treatments are aimed at seizure control.
- Secondary treatments include supportive therapies for symptoms related to ASD and ID, such as occupational, physical, and speech therapies.

Anti-seizure Therapy Treatments

- Seizures at birth or before 3 months are commonly seen with **gain-of-function (GOF)** variants, these are usually treated with **sodium channel blockers**, such as phenytoin and carbamazepine.
- Individuals with **loss-of-function (LOF)** variants may also have seizures, which tend to begin later in infancy or in early childhood and do not generally respond to sodium channel blockers. There is no general agreement on the best anti-seizure medications for **LOF variants**.
- **BUT**, not all GOF or LOF variants follow this trend and may have seizures that start earlier or later, and some variants are difficult to categorize and treat because they exhibit features of both GOF and LOF (mixed GOF/LOF).

Possible Treatments in Progress for Gain-of-Function Variants

Small Molecule Drugs

- A **small molecule drug** is in **phase 2 clinical trials.** It is a more specific sodium channel blocker than those currently used for treatment.

Sodium Channel Blockers
A class of drugs that slow or block the transfer of sodium in and out of cells, decreasing signal activity. These help treat conditions like cardiac arrhythmia, epilepsy, and neuropathic pain.

Small Molecule Drugs
A small medicine that can easily enter cells to fix problems in the body. These are typical drug store medicines like pills.

Clinical trials
Research study that tests if a new treatment or medicine is safe and works well. There are usually 3 steps or phases of a clinical trial before the medicine is available to the public.

Phase 1
The first step of a clinical trial tests the new drug's safety and dose range.

Phase 2
The second step of a clinical trial tests whether the new drug works, and further tests its safety.

Phase 3
The third step of a clinical trial expands the tests of whether the new drug works into larger groups of people.

Antisense Oligonucleotide (ASO)

- **Antisense Oligonucleotide** therapies target the SCN2A gene and interferes with the process that turns the gene into the Nav1.2 channel protein. Decreasing the number of channels, hopefully, decreases the patient's symptoms.
- Worked in mice and is currently in **clinical trials** to test in humans.
- But, there are some unanswered questions as to whether ASOs will be a useful therapy. This is because:
  - ASOs can be difficult to administer, requiring injections into the spine every 2-3 months to maintain drug levels in the brain.
  - It is still not known if ASOs can be designed to block the right levels of SCN2A to eliminate seizures without also causing LOF symptoms (the Goldilocks principle).

Possible Treatments in Progress for Loss-of-Function Variants:

CRISPR-Cas9 Activation (CRISPRa)

- **CRISPR-Cas9 Activation** targets and activates the SCN2A gene, creating more copies of the $Na_V1.2$ channel.
- This was tested in mice and helped with loss-of-function symptoms without causing negative side effects (especially seizures).
- An early clinical trial to test this for SCN1A in humans began in 2022.

Other Possible Treatments for GOF, LOF, and Mixed Variants:

Others Ways to Lower Expression of a SCN2A

- **RNA interference** and **CRISPR interference**. These approaches could work in a similar way as ASOs to make less $Na_V1.2$ channels.
- **Base editing** and **prime editing** are promising technologies for fixing the variants directly. These treatments are promising but are still in the early stages of development.

Challenges to Clinical Trial Design in SCN2A-related Disorders:

- Clinical trials for rare diseases can be challenging, and the wide variety of variants and symptoms experienced by the SCN2A community makes it even more challenging.
- Seizure control has been used in the past as an **outcome measure**, but seizure control in SCN2A-related disorders does not necessarily rescue the developmental phenotype.
- It is important target other outcome measures, including developmental achievement, sleep, quality of life, and behavior, among others, to make sure that these other symptoms are being accounted for and treated.

Antisense Oligonucleotide (ASO)
A treatment technique using synthetic genetic material to block a protein from being made.

CRISPR-Cas9 Activation (CRISPRa)
A treatment technique that can activate a gene, increasing the amount of protein being made.

RNA interference (RNAi)
A treatment technique where small pieces of genetic material can stop a protein from being made.

CRISPR interference (CRISPRi)
A treatment technique that can stop a very specific protein from being made.

Base and Prime Editing
Treatments that directly target and change DNA to correct variants.

Outcome Measure
A change in health used to test whether the medicine or treatment is working in a clinical trial.

Summary: What Parents Need to Know

There are currently no treatments that are specifically made for SCN2A, but there are anti-seizure therapies and supportive therapies. GOF variants will respond best to sodium channel blockers but this could be dangerous for LOF variants, so knowing your child's genotype is extremely important. There are treatments being developed currently that aim to directly treat SCN2A, either at the level of genes or by making more or less of the $Na_V1.2$ protein. Clinical trials for SCN2A-related disorders are challenging, but collecting more data from families on developmental phenotypes will help researchers include these symptoms in future clinical trials.

Navigating SCN2A-Related Disorders: Types of Questions to Ask Your Medical Team

- "What type of SCN2A variant does my child have (gain-of-function, loss-of-function, mixed-function)? Should other family members be tested?"
- "What are the treatment options specific to my child's SCN2A mutation type?"
- "We 'd like to be partners in decision-making—how can we stay informed and involved?"
- "What are the goals of this treatment, and what should we expect?"
- "How much input will we have in adjusting the treatment plan over time?"
- "Are there any rare but serious complications we should be aware of?"
- "What are the known side effects or risks—short-term and long-term?"
- "Are there any alternatives to this option that we should consider?"
- "Is my child eligible for any clinical trials or natural history studies?"
- "What are the risks, benefits, and goals of participating in a clinical trial? Will trial participation affect our access to standard care?"

Your space for questions, notes, and concerns for your next appointment: