

Dravet Syndrome

A GUIDE FOR NEWLY DIAGNOSED FAMILIES

SUPPORTING FAMILIES
FUNDING RESEARCH
ADVANCING TOWARDS A CURE



Dravet Syndrome
Foundation

WWW.DRAVETFOUNDATION.ORG

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About DSF

The Dravet Syndrome Foundation (DSF) was founded by a group of parents with the purpose of expediting research to find a cure and better treatments for their afflicted children in 2009. Since our inception we have added numerous programs and resources to assure that our caregiver and patient community has the education and tools they need to best manage this disease and assure appropriate care.

Thanks to our patient community and the help of our supporters, we have been able to move the needle forward in the field of Dravet syndrome. DSF has funded over \$5.7M in research grants and since 2018 we have seen three new medications receive FDA approval for the treatment of Dravet syndrome.

We hope you will become an active and engaged member of our community and will join us in **Raising Hope Through Research!** www.dravetfoundation.org



Stay Connected

We encourage you to stay connected with DSF for the latest on research, clinical trials, and local events.

You can find us online at:

- dravetfoundation.org
- facebook.com/dravetsyndromefoundation
- twitter.com/curedravet
- instagram.com/dravetsyndromefoundation
- linkedin.com/company/dravet-syndrome-foundation
- youtube.com/dravetsyndromefoundation



Welcome

Receiving a diagnosis of Dravet syndrome or an SCN1A mutation for your child can be a shock and leave you unsure where to turn. We want you to know that your family is not alone in your medical journey. Since 2009, the Dravet Syndrome Foundation (DSF) has been a trusted partner to the patient community. We provide disease information, advocacy resources, patient assistance and support, and research grants.

Make sure to give yourself the time and space to adjust to this diagnosis. Many parents report experiencing a sense of loss or grief. Every patient is affected differently and every family copes differently. There is no right or wrong way to emotionally respond to this diagnosis. When you are ready, DSF is here with everything you need to educate yourself, feel empowered, and allow you to be the best advocate for your child.

Families impacted by Dravet syndrome have helped develop this booklet. While it cannot give you all of the answers to everything you might want to know, it does provide an overview on how Dravet syndrome may impact your daily life and information on resources. Read on to learn more about Dravet syndrome, current best care practices, programs, and resources for your family. We are here to offer empathy and support.

DSF is here for you.

Our Mission

The mission of Dravet Syndrome Foundation (DSF) is to aggressively raise funds for Dravet syndrome and related epilepsies; to support and fund research; to increase awareness; and to provide support to affected individuals and families.



Receiving a Diagnosis

Receiving a confirmed diagnosis of Dravet syndrome can feel absolutely overwhelming. To help you find your footing, DSF has developed this booklet, including our *Newly Diagnosed Checklist*, that will help get you started and connect you with the programs and resources we offer. Additional information can be found on our website at:

www.dravetfoundation.org/caregiver-resources/newly-diagnosed/

We know you have many questions - Will my child always have seizures? Will they take medications forever? Will they outgrow this? Will they ever live independently? No two patients are the same, and Dravet syndrome will impact families differently. However we do know that most patients with a Dravet syndrome diagnosis will always be at a heightened risk for an unprovoked seizure and will experience associated health comorbidities. For this reason, it is important to educate yourself and seek comprehensive treatment from healthcare professionals who understand the spectrum and progression of Dravet syndrome.

We believe this booklet and the enclosed tips will be useful for you, regardless of your child's age. Having the knowledge and resources you need will give you confidence in making healthcare decisions for your child. The internet can be both a blessing and a curse. Be sure to turn to professional organizations such as DSF, government research sites, or medical institutions to assure you are receiving accurate and current information on Dravet syndrome.

While we cannot predict the future, there have been incredible advances in research resulting in new and better treatments. These advances have happened in large part because of the engagement and support of the Dravet syndrome community through DSF. From helping to fund research to participation in clinical trials, we encourage you to become an active member of our community and stay informed.





Understanding Dravet Syndrome

Dravet syndrome is considered to be an epilepsy syndrome with accumulating morbidity. This means that epilepsy is just one part of Dravet syndrome and there are other health conditions which are often found in patients. These include cognitive delays, behavioral difficulties, motor impairment, speech delays/impairment, and issues with sleep. More information on comorbidities often occurring in Dravet syndrome can be found at the back of this booklet and on our website.

Dravet syndrome affects between 1:15,700-1:20,900 people. It was first described in 1978 by Dr. Charlotte Dravet, a French pediatric epileptologist. For the majority of patients, the first seizure occurs in the first year of life and is often accompanied by a fever or illness. This seizure may be prolonged (longer than 5 minutes in length). Prolonged seizures, also known as status epilepticus, require emergency intervention and will most likely involve a child receiving treatment in the ER or being admitted to the hospital. This first seizure may be improperly diagnosed as a febrile seizure and thought unlikely to happen again.

In many cases, the first seizure occurs after vaccination due to the associated fever and immune activation. Dravet syndrome is caused by an underlying genetic mutation, and vaccines do not cause or worsen the trajectory of the disease. It is important to discuss preventative measures to avoid fever, which may cause seizures, surrounding vaccination or other illness with your child's physicians.

Seizures in the first year of life are often tonic clonic (jerking movements), prolonged (status epilepticus), and tend to affect one side of the body. Over time, seizures happen with or without a fever or illness and you may begin to recognize seizure triggers in your child, such as pattern or light sensitivity, overheating, or overexcitement. After the first year, additional seizure types may appear. It is important to learn about these different types of seizures so that you can recognize and report them accurately.

- **Tonic clonic (grand mal)** seizures involve both stiffening and twitching or jerking of a person's muscles.
- **Myoclonic seizures**, are characterized by brief, jerking spasms which may involve one part of the body or the whole body.
- **Atypical absence seizures** begin abruptly, with the patient entering a trance-like state during which they are unresponsive or unaware of their surroundings. Patients may stare blankly into space, or experience automatisms (non-purposeful, repetitive movements such as lip smacking, blinking, or gulping).
- **Complex partial seizures** are focal seizures that start in one area of the brain, but may spread, with the patient losing consciousness during the seizure. Patients may stare blankly into space, or experience automatisms (non-purposeful, repetitive movements such as lip smacking, blinking, or gulping).
- **Status epilepticus** is a seizure that lasts longer than 5 minutes, or having more than one seizure within a 5 minute period, without returning to a normal level of consciousness between seizures. These seizures typically require intervention with a rescue medication, either at home or in a hospital setting to stop them.
- **Non-convulsive status epilepticus (NCSE)** is a state of continuous or repetitive seizures without convulsions. Patients with NCSE have altered mental state. An EEG is needed to confirm the diagnosis.



Over time, you will see changes to your child's seizure patterns. Typically as the child gets older, prolonged seizures lessen. However, patients with Dravet syndrome will remain prone to status epilepticus, particularly with illness. Seizure frequency may increase as prolonged seizures decrease. These seizures may be shorter in duration and not require emergency intervention.

As children get older they may begin to experience seizures while sleeping, which can be stressful for parents due to the worry about missed seizures and the risk of SUDEP (sudden unexpected death in epilepsy). While there is no proof that the methods below may reduce the chance of SUDEP, they can provide reassurance for families that they are doing their best to keep their child safe. Examples include:

- A crib or bed with high sides to ensure that the child does not fall or injure themselves during a seizure.
- Sleeping with your child, either in the same room and/or on the same bed.
- Pulse oximeter machines that monitor heart rate and oxygen levels. During a seizure, heart rate increases and oxygen levels drop, and the monitor will sound an alarm, so that parents/caregivers can administer emergency treatment if necessary.
- Movement monitors, ranging from mattress monitors to video cameras to wearables which can alert caregivers to movement from seizures. Visit the DannyDid Foundation for an overview of current monitors. www.dannydid.org
- Nighttime nursing or respite, where staff stays awake to monitor your child.

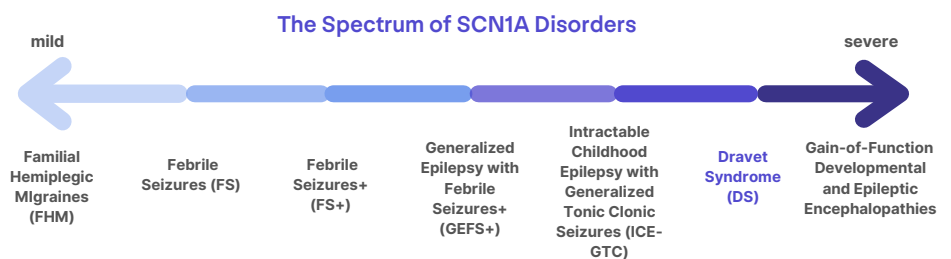




Your Child's Diagnosis

Dravet syndrome is a clinical diagnosis, which means health care providers make the decision on the diagnosis of a patient based on the presentation of symptoms. Often genetic testing is ordered to help aid in diagnosis, either providing clues or confirming a suspected diagnosis.

In over 80% of cases of Dravet syndrome, a mutation in the SCN1A gene is identified. However, mutations in SCN1A are related to a spectrum of disorders, ranging from migraines to several varying degrees of epilepsy syndromes with Dravet syndrome lying at the more severe end of the spectrum.



Since SCN1A mutations can lead to multiple disorders along this spectrum, genetic testing results need to be combined with observations of symptoms to determine the diagnosis. Sometimes the results from genetic testing are more informative than others, depending on the type of mutation, where the mutation is located in the SCN1A gene, and if the mutation has been reported in other patients. Additionally, genetic tests may need to be reviewed over time as genetic knowledge increases from research.

Individuals with Dravet syndrome often have unique mutations in the SCN1A gene that may not have been reported in another patient before, and even two patients with identical mutations do not always have the same outcomes. Researchers are still working to better understand the relationship between a specific SCN1A mutation and the resulting presence of symptoms.

During very early developmental years, it may specifically be difficult to delineate between the epilepsy syndromes at the further end of the spectrum (such as GEFS+ and Dravet syndrome). In Dravet syndrome, many of the non-seizure symptoms do not appear until after seizure onset, leaving the future prognosis difficult to determine at very young ages. Regardless of the eventual outcomes, families will have many similar concerns in early years and the following advice will help prepare you for what challenges may arise and how to navigate those challenges if they do. Even within the diagnosis of Dravet syndrome, there is also a spectrum of variation in the presence and severity of symptoms and comorbidities. Remember every patient is unique and comparisons can be hard to make even when two individuals have an identical mutation.

Approach the diagnosis of Dravet syndrome with anticipatory optimism: understand the potential complications that can be encountered under the diagnosis of Dravet syndrome so that you are prepared with proper interventions when necessary. You can learn more about genetics and associated comorbidities at the back of this booklet.



The **SCN1A gene** holds the instructions to make the **Nav1.1 sodium channel**.

This sodium channel is needed for neurons in the brain to effectively communicate. Humans have two copies of the SCN1A gene, and mutations in one copy of SCN1A that lead to Dravet syndrome usually result in a 50% reduction in the production of the Nav1.1 sodium channel. This type of genetic disorder is called a **haploinsufficiency**.

Receiving a Diagnosis as an Adult

If your child is diagnosed after the age of 18, we recognize that your experience is quite different from parents of young children or infants. You have already gone through testing, early intervention, therapies, waiver programs, and more. You might wonder, why is a diagnosis as an adult so important?

DSF believes a diagnosis at any age is vital to assuring the best quality of life for the patient. It can help answer the questions you have had about your child and their health comorbidities. It can also help with access to treatments and services, especially with the recent approval of several new medications to treat Dravet syndrome and several others currently in clinical trial. A diagnosis helps identify and narrow down strategies for possibly more effective treatments that will afford a better quality of life. It can also lead to much-needed peer support and a community that understands the challenges you face.

Recent improvements to genetic testing, along with lower costs, have greatly improved early diagnosis. However, we know we have many "missing" adult patients from our community who have either gone without a diagnosis or were initially misdiagnosed. We want to make sure that all of our adult patients are counted and that their needs are clearly understood and addressed as part of their overall care management.

At any age, information is power. We need your lived experience and involvement in our community.





A confirmed diagnosis in adulthood is important to the patient and caregiver because it:

- Assists caregivers by assuring they have the needed knowledge of the disease, including the prognosis and disease trajectory, which allows for future planning.
- Helps explain and possibly anticipate comorbidities, to allow for comprehensive care for the patient.
- Guides what is needed for medical transition planning and may help with insurance coverage for specific tests and treatments.
- Supports the need and eligibility for waivers and services such as therapies, funding, adult services, and palliative care, which might require a firm diagnosis.
- Connects you with a community of caregivers who understand your medical journey.
- Allows access to studies, medications, and clinical trials that are disease-specific and not age limited.
- Provides you the opportunity, through DSF, to share your experience with parents of younger patients, as well as to connect with researchers and clinicians who are trying to better understand the disease.

You can find resources for families of adult patients, as well as connect with other caregivers of adults on our website:

www.dravetfoundation.org/what-is-dravet-syndrome/dravet-adult-resources/



Can Genetic Testing Predict my Child's Future?

A common question that parents have after receiving the results of genetic testing is whether the specific mutation can be used to determine the severity or long-term effects on their child's health. Unfortunately, researchers have not been able to make associations between specific mutations in the SCN1A gene and the severity of each individual's presentation of symptoms.

SCN1A mutations cause a spectrum of disorders. Increased access to genetic testing means many families are receiving a genetic diagnosis earlier than ever before. However, mutations in SCN1A can result in a spectrum of epilepsy disorders of varying severity that all present with seizures in young children. In some cases, it may be difficult to predict whether the children will have a classical Dravet syndrome diagnosis, or one of the less severe epilepsy syndromes like GEFS+ (generalized epilepsy with febrile seizures plus). Studies of individuals with SCN1A mutations suggests that the best predictor between Dravet syndrome and some of the other SCN1A-related epilepsies is age at seizure onset rather than mutation type, but much remains to be studied and understood. Mutations that cause Dravet syndrome can occur in many locations across the gene, and many patients have mutations that have not been identified in another patient before.

Mutation types affect the gene differently. A mutation in the SCN1A gene may result in varying degrees of impact on health related to how it affects the expression and function of the Nav1.1 sodium channel encoded by SCN1A. Some mutations may result in that copy of the SCN1A gene not being able to produce any of the Nav1.1 sodium channel. Other mutations may just affect how well the Nav1.1 sodium channel is able to move sodium in and out of the cell. A more significant impairment to the sodium channel function may have a greater impact on brain development and communication.

It's not always SCN1A. Mutations in SCN1A are found in approximately 80-90% of patients with Dravet syndrome. The remaining patients diagnosed with Dravet syndrome present with the clinical features of the disorder but may not have an identified genetic mutation or may have a mutation in a related gene.

Other factors may interact with the mutation to affect outcomes.

Even outside of the broad spectrum of disorders that can be caused by SCN1A mutations, there is a lot of variability among individuals diagnosed with Dravet syndrome and the severity of their symptoms and comorbidities. Even two individuals with the same mutation in SCN1A may have very different outcomes.

Researchers are still trying to understand what causes this variability. Some impacts may come from small underlying changes in other genes or unknown environmental inputs. Adults with Dravet syndrome that were treated with contraindicated medications prior to diagnosis may have a more severe presentation, highlighting the importance of early diagnosis and appropriate seizure medications.

Are SCN1A mutations that cause Dravet syndrome inherited?

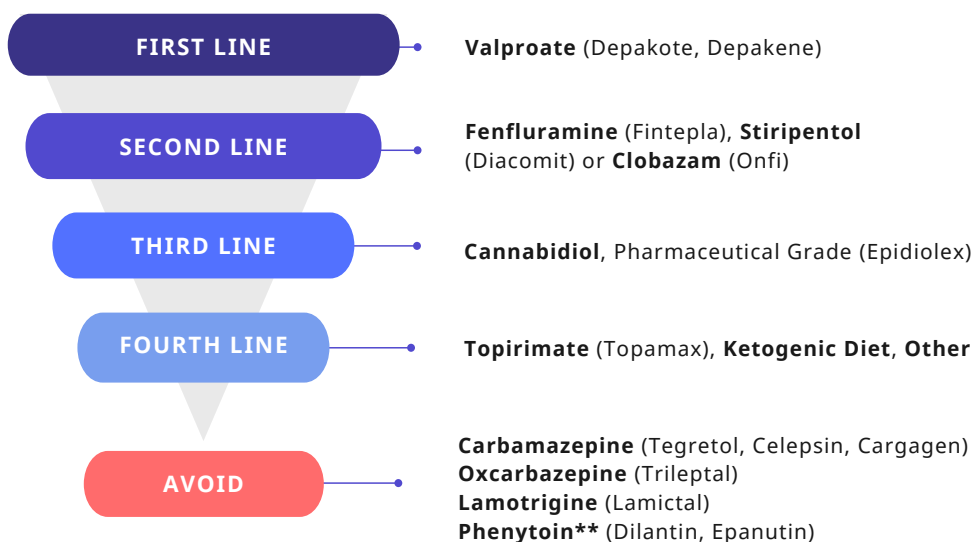
In the majority of cases, mutations in SCN1A that cause Dravet syndrome are not inherited from parents but are new mutations that occurred from random errors in the DNA code of either the sperm, egg, or a cell early in embryonic development. These types of mutations are often referred to as "de novo" which simply means "new." Although rare, there are instances where a mutation has been inherited across multiple generations, often with affected family members displaying varying degrees of migraine or seizure disorders. Another concept called germline mosaicism means that instead of every cell in the body carrying a mutation, only certain populations of cells have the mutation. This means that some cells in the body may have a normal make-up, while others carry a genetic mutation. Mosaicism could lead to a parent carrying a mutation they can pass on without displaying any symptoms themselves. Unfortunately, it is impossible to determine whether an individual has germline mosaicism. While inherited mutations are rare in Dravet syndrome, we encourage families who are planning to have additional children to speak with a genetic counselor. Prenatal diagnosis for pregnancies at increased risk is possible if the mutation in the SCN1A gene in the family is known. This can be done during the pregnancy by testing of fetal cells obtained through CVS (chorionic villus sampling), performed between 10 to 13 weeks of pregnancy, or amniocentesis, performed between 15 to 20 weeks of pregnancy.



Current Treatments

In 2022, a group of international experts on Dravet syndrome formed a treatment consensus indicating which medications they rated to be the most effective in patients with Dravet syndrome (“first line”), as well as second-, third-, and fourth-line therapies that may also be effective. The majority of patients with DS require multiple medications to control their seizures and “control” may not always mean complete seizure freedom. The expert consensus also listed medications that are contraindicated in Dravet syndrome, specifically sodium channel blockers that may worsen seizures since the mutation in the SCN1A gene already reduces activity of the Nav1.1 sodium channel.

Maintenance Anti-Seizure Medications



Based on the 2022 International Treatment Consensus*: **Phenytoin and Fosphenytoin, while not recommended for daily use, are often used in emergency treatment of prolonged seizures with varying success in patients with DS Caution is advised.

The Ketogenic Diet. The ketogenic diet was included in the consensus as a reasonable fourth-line treatment. The ketogenic diet is one of the oldest and most effective treatments for epilepsy, and the use of the ketogenic diet has also been associated with a reduced risk for SUDEP (sudden unexpected death in epilepsy). The diet requires strict ratios of fat, protein, and carbohydrates. Many families have success with the classic or modified ketogenic diet, but adherence can be challenging for some children. A specialized diet should be managed in partnership with your child’s health care providers and an experienced dietician.



Vagus Nerve Stimulation (VNS). A VNS is an implantable device, similar to a pacemaker, that can help reduce seizures by stimulating the vagus nerve with an electrical impulse. At baseline, it sends electrical impulses that help to suppress seizure activity. An external magnet can activate stronger impulses in an attempt to end a prolonged seizure. VNS devices have varied effectiveness depending on the individual patient and their seizure types. VNS is often only considered in Dravet syndrome after other treatments have failed.

Seizure Rescue Medications. Prolonged seizures are a major risk factor in Dravet syndrome, often requiring emergency intervention. You should develop a Seizure Action Plan (SAP) with your child's neurologist that includes detailed instructions of when and how to administer a rescue medication in response to a seizure. Some common rescue medications include: clonazepam (Klonopin), diazepam (Diastat or Valtoco), lorazepam (Ativan), and midazolam (Versed or Nayzilam). At-home rescue medications can be administered in a variety of ways including rectal, nasal, and buccal options depending on the medication. A SAP is important because seizures can be life-threatening. Having a SAP lets others know what to do in an emergency situation and can reduce the time to action during a seizure. Faster response times can reduce risk of prolonged seizures, risk of mortality, and the need for additional rescue medications.

New Treatments & Research

Several new medications have been approved for use in Dravet syndrome in the last several years: cannabidiol (Epidiolex), stiripentol (Diacomit), and fenfluramine (Fintepla). Not every patient has seen benefit, however these medications have allowed many patients to achieve significantly better levels of seizure control. Patients on some of these medications have also seen improvements in other outcomes besides seizures, but larger studies are still ongoing to understand this better. For epilepsy in general, uncontrolled seizures are often associated with poorer outcomes, so the reduced seizure frequencies associated with these new medications may be changing the future outlook for many patients with Dravet syndrome.



Researchers are continuing to develop new medications that may improve upon current therapy options. In addition to the three medications that have recently been approved, there are several more medications being examined in clinical trials that may help to reduce seizures and improve outcomes for individuals with Dravet syndrome.

Disease-modifying therapies that target the underlying cause of Dravet syndrome, haploinsufficiency of the SCN1A gene, are becoming a reality. Progress on these treatments was initially a challenge because the traditional gene therapy approach for a haploinsufficiency like Dravet syndrome would be to provide a replacement for the mutated gene copy. However, the SCN1A gene that is most commonly mutated in Dravet syndrome is too large to fit in the packaging (called “vectors”) that are used to deliver this type of replacement gene therapy. In addition, delivering a therapy to the cells in the brain that need it can be challenging.



Scientists have been working hard to develop several different types of approaches to overcome these challenges, and some of these therapies have even begun being tested in clinical trials in humans. Research has advanced the delivery vectors that now allow more efficient targeting to the brain. Instead of replacing the mutated copy of the SCN1A gene, many therapeutic approaches are now trying to increase productivity of the healthy copy of SCN1A. For additional details on these approaches, you can visit our website at:

www.dravetgenetherapy.org

It is difficult to predict what the future will hold. In addition to the variability along the spectrum of Dravet syndrome, recently approved medications are helping more patients than ever achieve better seizure control. It is yet to be seen how these new medications may affect the long-term outcomes for patients with Dravet syndrome. Furthermore, the disease-modifying therapies that are being developed to directly target the SCN1A gene could greatly change the outlook for the future. When this booklet was first published in 2021, some of these therapies had already entered clinical trials and several more showed promising results in preclinical cellular and animal models.

Staying connected to DSF will ensure you are up-to-date on all the new treatments in the development pipeline, opportunities to participate in clinical trials, and options for approved medications.

Raising Hope Through Research

DSF Programs & Services

DSF offers resources, education, and programs to help you on this complex medical journey.

DSF Family Network: Register so your family is counted and connected. Members receive updates on new clinical trials, educational events, and fundraising events near them.

www.dsffamilynetwork.org

Parent Support Groups: Register with the DSF Family Network for access to our private parent support groups on Facebook where you can ask questions, find advice, and get support. We offer a primary group with families worldwide, as well as five regional U.S. groups, and a group for caregivers of adult patients.

Biennial Conference: Attend our 3-day event for the unique opportunity to connect with and learn from other families, medical professionals, researchers, and industry partners.

www.dsfconference.org

Day of Dravet Workshops: Learn about the latest in research and treatments, as well as connect with local families at these annual one-day regional events. **www.dayofdravet.org**

DSF Patient Assistance Grants: Learn about grants for necessary medical equipment, therapy devices, and educational aides not covered through private insurance or other assistance programs.

www.dsfpatientassistance.org

Birthday Buddies: Register your loved one with Dravet syndrome and the week of their birthday they will receive a birthday card and a small gift from DSF's mascot, Aurora.

www.dsfbirthdaybuddies.org





Sibling Resources: Explore resources created based on research and inspiration from the community, with guidance from health care providers specializing in Dravet syndrome and mental health experts. www.dsfsupersibs.org

Medical Care: There are specialists and medical centers across the U.S. that offer multidisciplinary care for the treatment of Dravet syndrome. Use our tools to help develop your care team. dravetdoctors.org and dravetcenters.org

Research Grants: These seed grants offer funding for research directly related to Dravet syndrome and fund initial research hypotheses that have not been fully explored. www.dsfresearchgrants.org

Clinical Trials: Research is our best hope for advancing treatments, but research is not just the responsibility of scientists and doctors. It is important that patients participate to whatever extent they are able. www.dravetclinicaltrials.org

Educational Resources: We offer brochures on our website, as well as educational videos on our YouTube channel:

www.dravetfoundation.org/caregiver-resources
www.youtube.com/dravetsyndromefoundation

Resources for Professionals: Share our website with the health care professionals who care for your child. The resources and information found there will be useful for them, especially if they have limited treatment experience with patients with Dravet syndrome.
www.dravetfoundation.org/hcp-resources/

Additional information for Newly Diagnosed: Visit our website for updates and additional information. www.dravetfoundation.org/caregiver-resources/newly-diagnosed/

Newly Diagnosed Checklist

Family & Community

- ☐ When you are ready, share the diagnosis with family and friends. Be sure to direct them to our website for more information.
- ☐ Suggest ways that family and friends can help. They want to help but might not know how to support you. Create and share your list of needs.
- ☐ Connect with your own feelings about what has happened. Talk to your spouse, children, and family members, as well as a therapist.
- ☐ Have a family member or friend accompany you to all healthcare appointments to help with your child or take notes, so you can focus and remember important information.

Advocacy & Support

- ☐ Visit our website at www.dravetfoundation.org for information and support, regardless of your child's age.
- ☐ Visit www.dravetclinicaltrials.org to learn about current clinical trials and how you can participate.
- ☐ Join the DSF Family Network at www.dsffamilynetwork.org to connect with other families and register for programs and resources offered by DSF, including our private parent support groups.
- ☐ Register for a DSF conference, Day of Dravet workshop, or recorded webinars. Visit www.dravetfoundation.org to learn about upcoming events.

Medical

- ☐ Keep a seizure log to share with your child's neurologist. Seizure Tracker - www.seizuretracker.com - is a commonly used tool.
- ☐ See a specialist who understands Dravet syndrome. Our Find a Doctor tool at www.dravetdoctors.org can help.
- ☐ Learn about seizure action plans at www.seizureactionplans.org and develop one with your child's neurologist.
- ☐ Prioritize your child's medical challenges and focus on top concerns. Schedule appointments with specialists for baseline assessments.
- ☐ Discuss SUDEP (sudden unexpected death in epilepsy) with your child's neurologist.
- ☐ Dravet syndrome has its own unique ICD-10 billing codes, which may ease access to new treatments. You can visit www.dravetfoundation.org/hcp-resources/treatment-consensus/ for details.

State Services & Education

- ☐ Check on your state's website for waiver programs as well as Federal and State sources of support.
- ☐ Children younger than 3 can receive Early Intervention services through the State Department of Health.
- ☐ Set up evaluations for ages 3 and older to determine their services in school and to establish an Individualized Education Plan (IEP) or a 504 Plan.
- ☐ Provide school staff with information on Dravet syndrome, along with your child's Seizure Action Plan for emergencies.
- ☐ For caregivers of adults, your state's website will offer a list of disability waivers, financial support, and housing services that are available.
- ☐ Unsure where to start? Begin with your pediatrician or family doctor. Additionally, all schools and hospitals have social workers on staff who can help connect you with appropriate programs in your area.

The Importance of Research

Severe myoclonic epilepsy of infancy (or 'SMEI') was first described in 1978 by Dr. Charlotte Dravet and was renamed in 1989 as Dravet syndrome. By 2001, researchers had discovered that a primary cause of Dravet syndrome was related to mutations in SCN1A, a gene responsible for making sodium channels that affect electrical activity in the brain. Despite this major advancement in the scientific understanding of DS, research was still slow to follow. By 2009, families had come together to form the Dravet Syndrome Foundation (DSF) in an effort to spur and support research efforts towards a better understanding of the underlying causes, the presentation and progression, and the best treatment approaches for Dravet syndrome. DSF has made research a core priority, funding over 5.7 million dollars of research efforts as of 2022. Through the combined efforts of DSF, scientists, clinicians, industry, government, and patient families, research has led to advancements in the care and treatment of those living with Dravet syndrome. While much has been accomplished, there is still great unmet need for patients and their families, underlining the importance of continuing to fund, advocate for, and participate in further research efforts.



The Importance of Basic Science Research

The initial link between Dravet syndrome and mutations in a gene, SCN1A, came from studies of genetic samples from human patients. Following that discovery, scientists used an array of basic science tools and studies to unravel WHY mutations in SCN1A might result in the symptoms of Dravet syndrome. Breakthroughs using cells, fish, and mice have revealed the role of this gene in specific cells in the brain and increased our understanding of how SCN1A is regulated. The development of animal models that mimic the genetics of Dravet syndrome have allowed researchers to investigate more about the cause and symptoms of Dravet syndrome and to screen drugs and therapies that could translate to human treatments. Research advancements have uncovered biological details that are guiding the development of disease modifying therapies that attempt to correct the root genetic cause of Dravet syndrome.



The Importance of Clinical Research

Clinical research, or research directly involving humans, works hand-in-hand with basic research to improve outcomes for patients. Clinical research seeks to better understand or to investigate methods to intervene to improve treatment for a condition or disease. As our understanding of the cause and progression of Dravet syndrome in human patients has grown over the years through clinical research, it has improved standards of clinical care for patients as well as informed the direction of basic science research to focus on particular symptoms and interventions. In turn, basic science discoveries have led to interventional clinical trials of new medications and therapies for Dravet syndrome.

How has research changed the landscape for Dravet syndrome?

- Basic and clinical research continue to improve outcomes for individuals with Dravet syndrome. The breadth and depth of research knowledge has greatly expanded leading to faster diagnoses and better treatments.
- The number of scientific publications with relevance for Dravet syndrome have increased greatly over time, from only 5 publications in 2001 to over 270 publications in 2021.
- The National Institutes of Health (NIH), the government agency responsible for supporting biomedical and public health research, has also increased funding for grants related to Dravet syndrome, with current numbers exceeding \$10 million each year.

These increases in scientific funding and publications are representative of major advancements to the field that have subsequently impacted patient care. A few key examples are outlined below:

- Understanding the genetic cause and clearly defining the symptoms of Dravet syndrome has led to faster diagnoses and avoidance of contraindicated medications.
- The discovery of serotonin (5-HT) as a target for treating seizures is changing the clinical perspective on achievable levels of seizure control in Dravet syndrome and has led to a robust pipeline of potential therapeutics.
- Discovery of unique ways that the SCN1A gene is regulated as well as the identification of the specific cells that require this gene to function has allowed researchers to develop novel approaches to gene-based therapy. Many studies in mouse models support the effectiveness of a variety genetic-based therapies that could be truly disease-modifying.
- DSF has led, supported, and/or raised awareness of countless surveys, interviews, and observational study opportunities. The robust participation of caregivers and patients has enabled clinical knowledge of the full spectrum of impacts of Dravet syndrome, leading to better recognition, resources, and support.





The importance of your involvement in research

Scientific advancements take a lot of time, money, and effort, but things move faster when everyone works together. The patient and caregiver voice are invaluable to direct research efforts where they will matter most to those living with Dravet syndrome. Meaningful results and the success of clinical studies are dependent upon patient and caregiver participation; a population that is “clinical trial ready” is essential to spur additional drug development efforts. Moreover, the determination of families to fund research has made a major impact, which is reflected in the over 5.7 million dollars that DSF has directed towards research since 2009. In addition to the direct funding of research, DSF supports research in a variety of other ways, including acting as a hub to convene all the stakeholders with interest in moving research for Dravet syndrome forward. Staying connected to DSF will help keep you up to date on research efforts and opportunities for participation.

Ready to get involved in research efforts?

You can keep up to date on current research and participation opportunities by staying connected with DSF. We raise awareness through our website listings, Family Network, newsletter, caregiver support groups, Decoding Dravet blog, webinars, conferences, and social media channels.

- Stay up-to-date and consider participation in clinical studies.
- Participate in research surveys or interviews.
- Learn more about research related to Dravet syndrome.
- Help DSF fund more research.

Tips from Families

- Contact utility companies and emergency departments (fire, police, etc.) to let them know that you have a child with special needs, in case of an emergency.
- Contact your state's Department of Motor Vehicles to apply for an accessible parking placard. Your child is eligible. You will have to complete and submit an application signed by a physician.
www.dannydid.org
- Consider cooling vests and towels which are designed to lower body temperature. Families report finding them useful in preventing seizures due to overheating. The DSF Patient Assistance Grant Program covers necessary medical equipment, therapy devices, and educational aids.
www.dsfpatientassistance.org
- Research additional therapy options or specialists, such as therapeutic horseback riding (hippotherapy), aqua therapy, vision therapy, etc.
- Look for a special recreational association in your area with trained staff that provides programs for individuals with disabilities.
- Follow DSF on social media to stay up-to-date. Share posts to help raise awareness and educate others.
- Consider hosting or participating in a live or virtual DSF fundraising event.





Taking Care of the Caregiver

Caregiving can be an emotional roller coaster. Your love and commitment are shown through your caregiving, but the continuous care demands along with worry, exhaustion, and inadequate resources are extremely stressful. Taking responsibility for your own care will help you to cope with the diagnosis and enjoy your child.

We encourage you to:

- **Reduce and manage your personal stress.** Identify what you can and cannot change, then take action. Even a small change can make a big difference.
 - **Get proper rest and nutrition.** Sleep and a healthy diet are vital components of a person's overall well-being, will reduce your stress, and improve your outlook.
 - **Exercise regularly.** Exercise promotes better sleep, reduces tension and depression, and increases energy and alertness. If finding time for exercise is a problem try to incorporate it into your daily activity.
-
- **Ask for and accept help.** Be prepared with a mental list of simple ways that others could help you. For example, you might ask someone to organize a meal train, help with transportation, or pick up prescriptions.
 - **See a therapist.** A therapist can help you to work through difficult situations, learn coping skills to manage strong feelings like anxiety and depression, and help families to communicate throughout this medical journey.
 - **Keep a journal.** The initial diagnosis of Dravet syndrome can be an avalanche of questions and information. Keep a dedicated journal to write questions, thoughts, phone numbers, medications, and other details you find important. This journal can be used while at an appointment or in the hospital when you are under stress and remembering details can be difficult.

Advice from Other Parents

No one better understands your struggles and challenges than another parent or family living with Dravet syndrome. Here is some advice they have shared:

- Remember who you are fighting for and become your child's best advocate.
- Trust your instincts - you know your child best.
- Remember to take care of yourself, too.
- Don't let your fear hold your child back from life experiences.
- Celebrate the small victories.
- Understand that life with Dravet syndrome may get easier with time.
- Begin early intervention. Make sure your child has the therapies or resources to help with any setbacks.
- Try to see a specialist in Dravet syndrome who is familiar with new treatments.
- Attend a DSF conference or event. Connect with other families you can learn from and share advice with.
- Learn about contraindicated medications for Dravet syndrome and be sure to avoid them to prevent adverse effects.
- You will want to know what the future holds so badly, but that's just impossible with Dravet syndrome.
- There will be good and bad days. Try to remain calm and be patient with your child and yourself.
- Hold onto the hope for the future.
- Remember that your child is unique, and his/her medical journey will not be the same as another child with Dravet syndrome.



Read Dravet Stories on our website at www.dravetstories.org

Siblings

It can be hard for brothers and sisters when a sibling has a chronic illness like Dravet syndrome. Their routines are disrupted. They worry and wonder what is happening and if their sibling will be alright. Oftentimes parents' time is limited by the many needs of their child with Dravet syndrome and siblings can feel unimportant or neglected. This can be upsetting and frustrating for everyone involved. For these siblings, their whole childhood takes a slightly different turn compared to most of their peers. It is important that they have opportunities and tools to help them understand and cope.

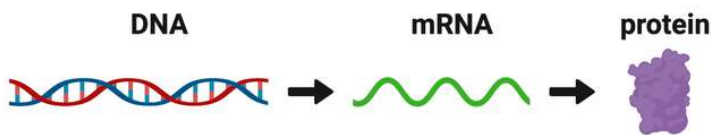


Seeing a seizure can be scary. It is important to talk to siblings about seizures. We suggest working with them to develop a plan for when a seizure strikes. Let them know what they might be asked to do and who they will stay with if you have to head to the emergency room or hospital. Giving them knowledge and allowing them to be a part of the planning empowers them and offers a sense of control. Many children benefit from seeing a professional counselor or therapist who can help them process their fear and complex emotions. The Sibling Support Project offers helpful resources for siblings and families. www.siblingsupport.org

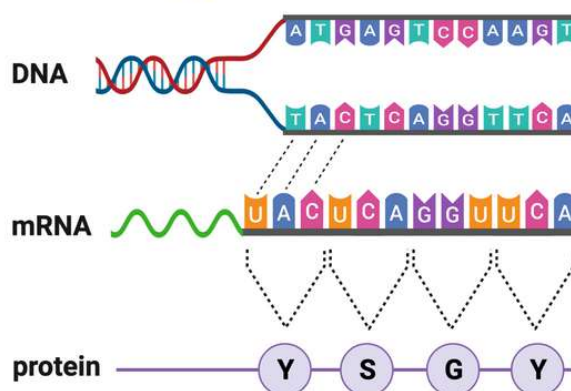
To support siblings in our community, DSF offers a day camp to connect siblings at our biennial conference and Day of Dravet workshops. These in-person events offer an opportunity to connect siblings and address their needs within a fun, safe, and nurturing environment. We also provide resources to support siblings and their parents, and help them navigate this complex situation. Our Parent Resource Guide and Super Sibling VIP kits, for ages 4-10 and ages 11-18, are available at no cost. www.dsfsupersibs.org

Genetics and Dravet Syndrome

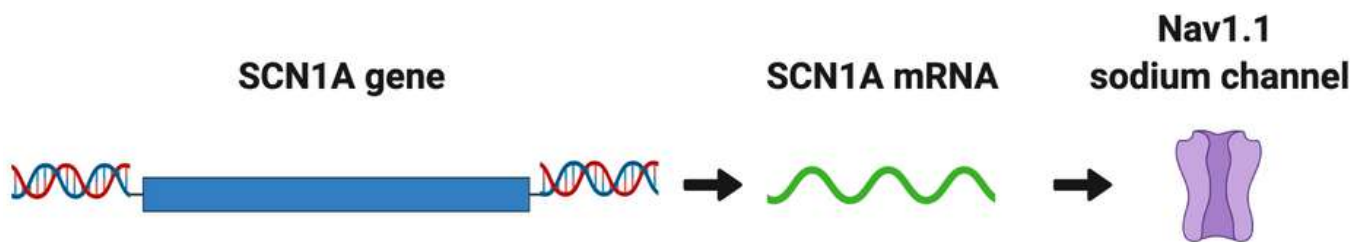
The Basics of Genetics: Your **DNA** encodes two copies of all the genes your body needs to grow and function. Genes are essentially recipes your body uses to make **proteins**. Strands of messenger RNA (**mRNA**) are copied from the DNA with the instructions from a single gene to make a **protein**. Different proteins made from different genes all have unique roles to help cells function correctly.



- If you were to zoom in and look more closely at the twisted DNA strands, you would see the strands are made up of four unique nucleic acids represented by the letters A,T,C,G.
- Sections of the DNA containing individual genes are copied into strands of mRNA.
- The cells then "reads" the letter code, three letters at a time. Each combination of three letters can code for a unique building block of a protein, called an amino acid. The amino acids get assembled according to the code, like beads on a string. Once the building blocks are assembled, the protein "string" is folded up into a shape to do its job.

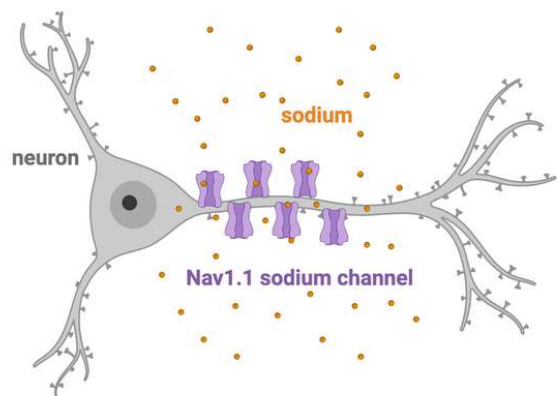


The SCN1A gene: The SCN1A gene is located along a stretch of 160,000 nucleic acids (A,T,C,G) in the DNA (represented here by the solid blue box). Not all of those nucleic acids are necessary for the instructions to make the protein, so as the cell copies the DNA into an mRNA strand, it "cuts and pastes" the sections that contain the vital instructions to a length of about 6,000 nucleic acids. All those remaining sections of the DNA that are not necessary to the protein "recipe" are often still important for the regulation of the gene- telling cells when to make more or less of the gene. The SCN1A mRNA is then "read" by the cell, three letters at a time as described above, to assemble a protein called Nav1.1.



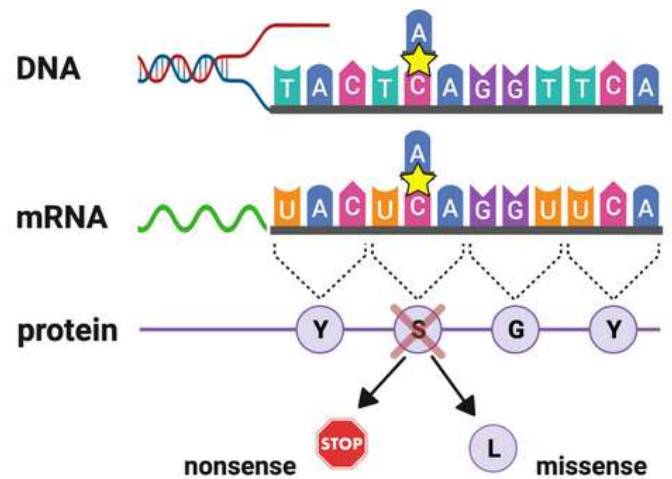
The Nav1.1 Protein: The Nav1.1 protein is a sodium channel. It helps to regulate how much sodium is allowed into the cell. Special types of neurons in the brain particularly rely on the Nav1.1 sodium channel to help them communicate with other neurons correctly.

As with the majority of genes, everyone has two copies of the SCN1A gene. Your neurons need both of these gene copies to make enough of the Nav1.1 sodium channel for neurons to be able to communicate effectively.



Types of Mutations: A mutation is a change to the sequence of nucleic acids in the DNA that alters the amount of the gene that is expressed or the function of the protein it makes. There are several types of mutations in SCN1A that cause Dravet syndrome.

Some mutations change a single letter in the DNA code. The example to the right shows a mutation that changed the 'C' to an 'A.' This caused a major change to the three-letter code; instead of another building block for the protein, now the code says to **STOP** building the protein. This type of mutation is called a **nonsense mutation**.



This early STOP signal can lead to a shortened (or "truncated") form of the Nav1.1 sodium channel that may not function correctly or, in many cases of Dravet syndrome, it is not made at all.

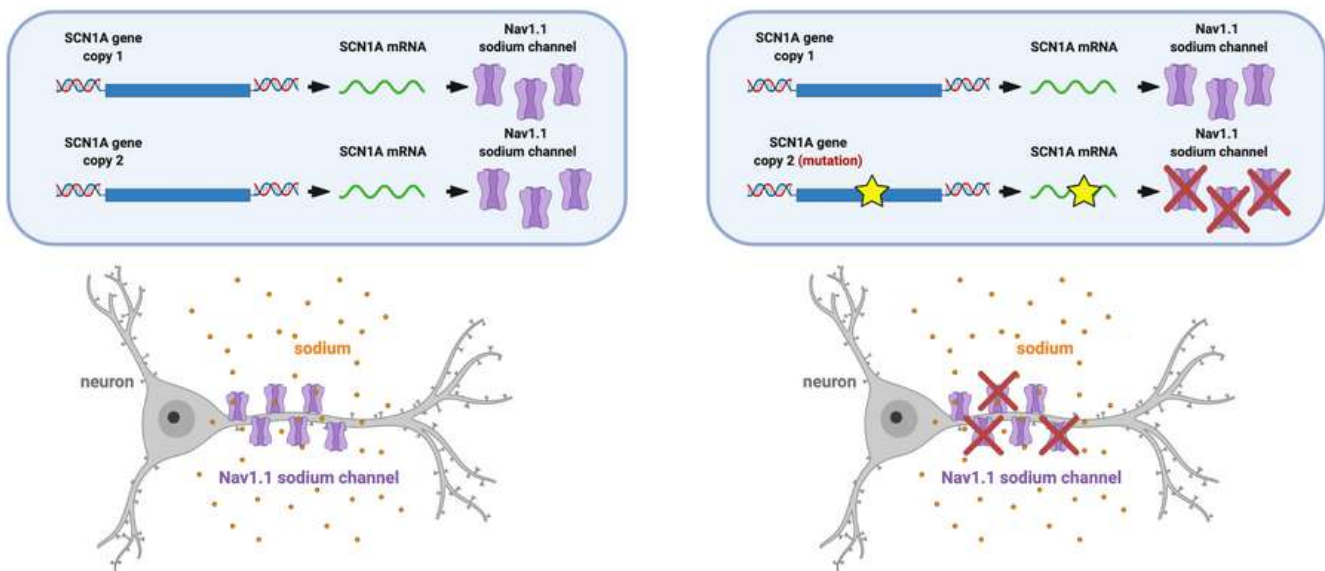
Instead of a stop signal, a different change in the DNA code could lead to another amino acid building block being substituted, such as changing the "S" to an "L" in the example above. This is called a **missense mutation**. Depending on the location and specific change, this may affect the function of the Nav1.1 sodium channel or lead to the cell disposing of the dysfunctional channel.

Other types of mutations are called **insertions** and **deletions**. These occur when, instead of a swap, extra nucleic acids are either added in or deleted from the SCN1A gene. These mutations can vary in size and severity of the effect on the expression and function of the Nav1.1 sodium channel.



Why do SCN1A mutations cause Dravet syndrome? The majority of cases of Dravet syndrome, somewhere between 80-90%, are attributed to a mutation in the SCN1A gene. Generally, these mutations occur in one copy of the gene, leaving one healthy copy of SCN1A. The mutations in SCN1A that cause Dravet syndrome result in 50% of the Nav1.1 sodium channel protein either not being made or not working as efficiently as it should. This kind of disorder is often referred to as a "haploinsufficiency."

This loss of Nav1.1 sodium channel expression or function due to a mutation in the SCN1A gene impairs the ability of certain types of neurons to communicate effectively. Neurons use sodium channels like Nav1.1 to move sodium in and out of the cell; because sodium has a chemical charge, this helps neurons to generate electricity and send communications to other neurons. The primary neuron type that uses the SCN1A gene to make the Nav1.1 sodium channel is called an inhibitory neuron. Inhibitory neurons help to "put the brakes" on the electrical activity of excitatory neurons. When inhibitory neurons are not able to communicate correctly, excitatory neurons may not be able to stop their activity when appropriate, leading to seizures.



Figures created with Biorender.com with some adaptations from "Central Dogma" (2021) Template. Retrieved from <https://app.biorender.com/biorender-templates>

Comorbidities Associated with Dravet Syndrome

On the next several pages you will find an overview of some of the comorbid conditions that are often associated with Dravet syndrome. Not every patient will experience all the symptoms listed, and the severity can differ greatly from one individual to the next. You should learn what to watch for and how to intervene when necessary, but also approach your child's future with optimism.

Developmental, Cognitive, and Speech-Language Delays. Developmental milestones are generally on track during the first year of life, but by school age, children with Dravet syndrome have varying degrees of developmental delays that may impact learning, cognition, speech, language, and motor development. Young children may experience regression or slowing of skills. Studies of teens and adults with Dravet syndrome indicate the majority of patients have moderate to severe intellectual disability. Early intervention and access to special education supports in school years are important to ensure each child reaches their full potential. Participation in physical therapy, occupational therapy, and speech therapy is encouraged, based on the patient's development and needs.



While the underlying genetic cause of Dravet syndrome (a mutation in the SCN1A gene) likely contributes to these delays, there may also be impacts from seizure frequency and severity, side effects of medications, or the use of contraindicated medications (such as sodium channel blockers that might be utilized before a diagnosis is received). Awareness of Dravet syndrome is increasing and, with advances in genetics and genetic testing, children are receiving diagnoses earlier than ever. Additionally, new medications have been approved for Dravet syndrome in recent years that are helping many patients to achieve better seizure control than was possible in the past. It remains to be seen if access to appropriate care and improved therapies during early development will improve the long-term outcomes for children and adults with Dravet syndrome.



Behavioral Issues. Autistic-like traits, Attention Deficit Disorder (ADD), or Attention Deficit Hyperactivity Disorder (ADHD) are common in Dravet syndrome. Your child may be predisposed to perseverate or become obsessive about specific things. Irritability and aggressive behavior are also common, and while challenging at all stages, these behaviors can become particularly difficult to navigate as children grow larger in size and reach adulthood. Unlike some other traits shared with autism, patients with Dravet syndrome are often overly social, although some may prefer interactions with adults versus peers. There are also reports of depression or anxiety, especially as children approach teen and adult years. Families often consult with behavioral therapists or implement behavioral therapy routines, and medication may help with behavioral and mental health concerns to varying degrees. A neuropsychiatrist or neuropsychologist can help navigate the available options, and it may be helpful to find a provider who will form a collaborative relationship with your child's neurologist to best manage their care and any medication changes.

Motor Impairments and Gait Disruptions. Issues with movement, balance, and gait, as well as low muscle tone and impaired dexterity, may become apparent as children develop, and these issues often progress throughout their lifetime. Adults with Dravet syndrome often have a "crouched gait" and in some cases may require assistance with mobility. Children should be screened for gait issues regularly. Support from physical and occupational therapy is often recommended and some patients utilize orthotic devices. Encouraging play activity that involves the whole body may be beneficial to retaining mobility. Many families recommend therapeutic horseback riding (hippotherapy) and aquatic therapy to help develop and maintain core strength. Unfortunately, the progression of these issues is not well understood and there are not expert recommendations for the best treatment approaches. It is not uncommon for patients to use adaptive strollers as they get older to assist with traveling over long distances or for recovery after a seizure. As patients age, some of their movement and gait issues may appear similar to Parkinsonian-like symptoms, and early research has suggested some patients may respond favorable to dopaminergic medications used in Parkinson's disease.

Growth and Nutrition Issues. Individuals with Dravet syndrome may be smaller in stature and weight than the average for their age group, and this disparity may increase with age. Studies have suggested that some patients may have abnormal endocrine or metabolic function. Caregivers regularly report issues with decreased appetite as well as decreased muscle tone that may affect the child's ability to eat and drink. Additionally some seizure medications can affect appetite, metabolism, or nutrient absorption. If your child is experiencing these issues, they may be referred to specialists such as an endocrinologist or a gastroenterologist. It is not uncommon for patients to have gastronomy tubes, also know as g-tubes or PEG tubes, placed surgically if poor muscle tone or appetite affects nutrient intake and overall growth. These tubes allow for feeding as well as for delivery of oral medications, and may be placed temporarily or permanently depending on the patient's needs.



Sleeping Difficulties. Issues surrounding sleep are a concern in Dravet syndrome. Sleep disturbances can be common across many developmental epilepsy syndromes and often the circadian clock (or the internal daily rhythm) appears to be altered. Your child may struggle to have a regular sleep pattern, which can be difficult for the entire family. Treatment options are limited, but some families have found melatonin supplementation under the guidance of their physician to be helpful. In addition, seizure activity during the night or in sleep can become increasingly common as children age. If nocturnal seizure activity occurs in a regular pattern, some families discuss options for changing medication dosages and times with their neurologist to provide the best coverage during at-risk times of the day or night. Many families choose to utilize night-time monitors such as a baby monitor, pulse oximeter, or seizure detection device. Seizure detection is important, as prolonged seizures without intervention could increase the risk of status epilepticus (prolonged seizures) or SUDEP (sudden unexpected death in epilepsy). You should discuss options with your child's neurologist and check for resources to assist with the costs, such as the DSF Patient Assistance Grant program. www.dsfpatientassistance.org



Chronic infections. Caregivers report their children appear more susceptible to infection, and some limited evidence suggests immune dysregulation may be associated with Dravet syndrome. Infection, with or without fever, may be a seizure trigger. Using anti-fever medications or add-on anti-seizure medications (often called "bridge medication") during illness may be necessary to avoid increases in seizure activity. Speak with your child's neurologist about plans to manage seizures during any periods of illness.

Dysautonomia. Dysautonomia is when your body is unable to regulate certain autonomic body processes such as body temperature, heart rate, and digestive processes. It is not understood why this occurs commonly in Dravet syndrome. Because drastic changes in temperature or overheating can be a seizure trigger for many children and adults with Dravet syndrome, families often take additional precautions such as avoiding particularly hot or cold water, attempting to tightly control the ambient temperatures of their homes, and utilizing cooling vests. The underlying cause of dysautonomia is not well understood. Your health care provider may prescribe medication aimed at controlling symptoms.

Cardiac issues. There have been limited studies on the heart in Dravet syndrome, but some evidence suggests there could be changes in heart rate and/or heart rhythms. The SCN1A gene is also used by cells in the heart, perhaps explaining these risks. Some researchers think the increased risk of SUDEP (sudden unexpected death in epilepsy) in Dravet syndrome may be related to these subtle changes in heart regulation. Cardiac health should be closely monitored and referral to a cardiologist may be recommended if any issues arise. A newly approved medication for Dravet syndrome (fenfluramine) also requires that cardiac health is closely monitored. Patients taking this medication are required to have echocardiograms every 6 months to monitor for risk of valvular heart disease.



Next Steps

- Visit our webpage for the Newly Diagnosed at: www.dravetfoundation.org/caregiver-resources/newly-diagnosed/ for additional information. Our website also offers regular updates on research and clinical trials, as well as access to all of our programs and resources.
- Follow us on social media and subscribe to our newsletters to stay up to date on resources and events.
- Remember, support comes in many forms and your needs will change over time.
- We are here to support you! We will meet you where you are in your journey and help you take the next step at each stage.

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