Introduction

This is the second gene-focused Element of the Cambridge Elements series on Genetics in Epilepsy launched in September 2021 [1]. The goal of this Element is to provide an in-depth, state-of-the-art review of clinical, genetic, basic science, and family perspectives on neurological and neurodevelopmental disorders (NDD) associated with pathogenic variants in *SCN2A*, which encodes a major voltage-gated sodium ion channel (designated $Na_V1.2$) in the brain. The *SCN2A*-related disorders are clinically heterogenous with features ranging from neonatal and infantile onset epilepsy, late onset epileptic encephalopathy, autism spectrum disorder (ASD), and intellectual disability (ID). In addition to phenotype diversity, the widespread use of clinical genetic testing has resulted in more than 1,000 *SCN2A* variants deposited in ClinVar. With the explosion in genetic variant identification has come recognition of genotype–phenotype relationships, which when coupled with experimental demonstration of functional perturbations are guiding new therapeutic approaches. Investigations into the biology of *SCN2A* has led to fundamental discoveries about the physiology and pathophysiology of synaptic connections and neural circuits. As one of the earliest known epilepsy genes, *SCN2A* has emerged as an important genetic factor in neurodevelopment and NDD.

We hope this Element will provide opportunities for families, trainees, and health care professionals to learn about *SCN2A*-related disorders. Subsections of this Element offer complete discussions about clinical features, pathophysiology, genetics, model systems, and treatment. This Element begins with perspectives from parents and caregivers of children with these disorders, made possible by a parent-led advocacy group (the FamilieSCN2A Foundation). The following subsections are devoted to clinical features, genotype–phenotype correlations, basic science, and current and future therapeutic approaches. Thus, this Element on *SCN2A*-related disorders provides a comprehensive and in-depth review of the state of knowledge in this field, which should be valuable to scientists, clinicians, trainees, and families interested in the topic.

In addition to a thorough and informative narrative, this Element is augmented by video content, including interviews with parents of children with *SCN2A*-related disorders (Video 1); with Dr. Matthew State (Professor and Chair, Department of Psychiatry and Behavioral Sciences, University of California, San Francisco) on the genomics of ASD and the discovery of *SCN2A* as a major risk factor (Video 2); and with Dr. Steven Petrou (Professor of Neuroscience, University of Melbourne, and Chief Scientific Officer at Praxis Precision Medicines) on his career evolution from academic

research to a new pharmaceutical company specializing in precision medicine for rare neurological diseases (Video 3).

This was a team effort that we hope provides inspiration to future clinicians, researchers, and patient advocates. We hope you enjoy learning about this important epilepsy gene.

Patient, Family, and Foundation Perspectives

Pathogenic variants in the *SCN2A* gene are associated with a broad spectrum of complex NDD that are collectively designated as *SCN2A*-related disorders. The primary clinical manifestations include epilepsy, ASD, movement disorders, and ID. The severity of these conditions varies among individuals, ranging from mild and well controlled to severe and treatment resistant. Even individuals with mild clinical phenotypes exhibit significant impairments compared to their age-matched peers. Those on the severe end of the spectrum are profoundly affected and heavily reliant on their caregivers for all aspects of daily life. Given the complexity of *SCN2A*-related disorders, clinical care teams are often multidisciplinary, emphasizing the importance of coordinated efforts to optimize care and minimize clinical risks (Figure 1).

FamilieSCN2A Foundation

The FamilieSCN2A Foundation, founded in 2015, is the largest nonprofit patient advocacy organization representing *SCN2A*-related disorders and has the broadest international footprint among other *SCN2A* patient-advocacy groups. Focused on creating an engaged ecosystem, FamilieSCN2A Foundation acts as a central

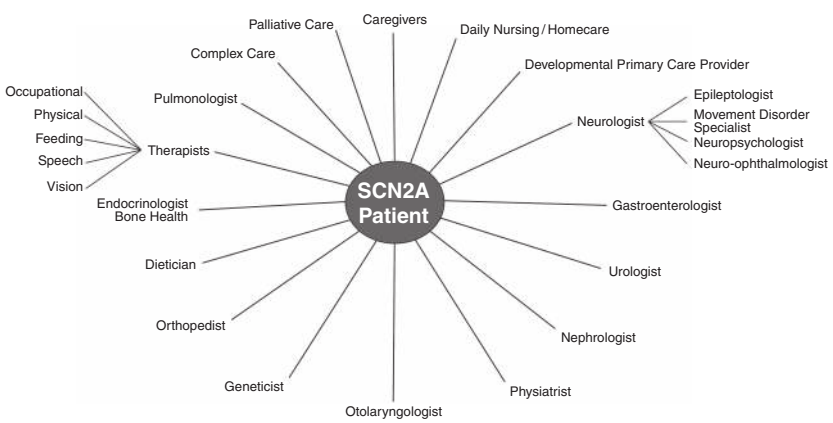

Figure 1 Diagram of multispecialty care of a patient with an *SCN2A*-related disorder.

liaison between patients, caregivers, scientists, clinicians, and industry. They also work in close partnership with other large foundations such as the Simons Foundation and the Chan Zuckerberg Initiative. "Families" is part of the Foundation's name because these rare and devastating conditions affect the entire family. The Foundation strives every day and, in every way, to improve the lives of not only the patients but also the entire family.

The missions of the Foundation are to accelerate research, foster a sense of community, and advocate for improvements in the lives of those affected. The Foundation's vision is centered around achieving effective treatments and cures for all *SCN2A*-related disorders. The core values of the Foundation are urgency, integrity, collaboration, and inclusion. FamilieSCN2A strives to provide families and professionals with the information and tools needed for a rapid and accurate diagnosis as well as the resources needed to tailor treatments based on the patients' and families' goals informed by research knowledge.

Before 2014, there was little hope for children or families diagnosed with an *SCN2A*-related disorder. There were no specialists treating the condition, no support groups for families desperately seeking answers, and no researchers investigating cures. This void created a gravity that pulled together a small group of thoughtful, committed parents who sought to build a better world for their children, and thus the FamilieSCN2A Foundation was born. The Foundation grew quickly as other parents and professionals were inspired and empowered by the stated vision: a world with effective treatments and cures for all *SCN2A*-related disorders. As momentum built, the Foundation attracted board members that shared the core values and missions. A timeline of Foundation milestones is presented in Figure 2.

Advocacy is critical to the mission of FamilieSCN2A. The tenets of their advocacy strategy are: awareness, empowerment, evidence-based research, and equity. Successful advocacy requires awareness within the patient/family community and beyond. Awareness of *SCN2A*-related disorders began with the first online support group using the Facebook platform, which launched in 2013 with just five members. Today, there are more than 1,000 participants. This private, robust group is a safe space for families, patients, and caregivers to share their journey, ask questions, learn from one another, and reduce feelings of isolation. The community of patient caregivers remains a pillar of support for individuals affected by *SCN2A*-related disorders.

To extend awareness beyond families, the FamilieSCN2A Foundation spearheads various awareness initiatives including state proclamations, listening sessions with the Food and Drug Administration (FDA), providing information to policymakers and drug developers, and organizing caregiver testimonies that are intended to raise

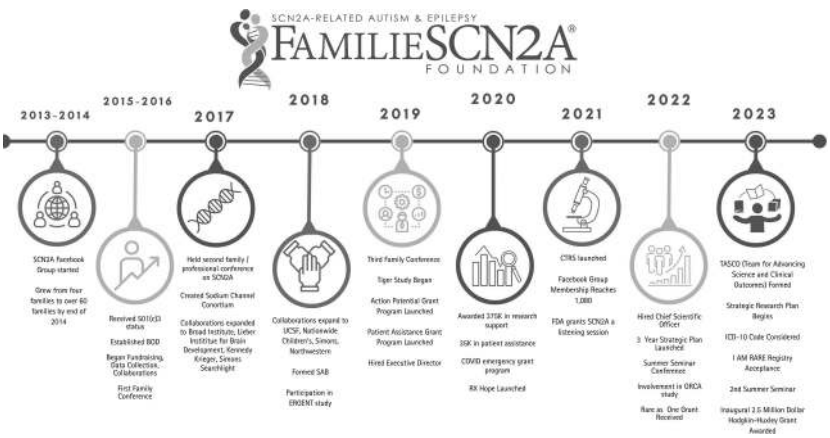

Figure 2 Timeline of major events involving the FamilieSCN2A Foundation.

awareness of the burden of disease. Education, which is vital for a community actively engaged in collaboration with clinicians, scientists, and industry, has been an important Foundation strategy. As such, the FamilieSCN2A Foundation organizes an annual family and professional conference that leaves participants feeling empowered, educated, and hopeful. Supplementing the educational initiatives are programs that support families both emotionally and financially. Initiatives include Family Meet Up Grants, a Birthday Club, and a Patient Assistance Grant program that has awarded more than $65,000 to families since 2015.

The accomplishments of the FamilieSCN2A Foundation include $4 million raised since 2015, 1,200 families supported globally, strategic partnerships with leading academic researchers, a voice with the FDA, representation at international conferences, and a growing attendance at the annual family and professional symposium. Its founders, board members, volunteers, and community (including researchers and clinicians) together have made significant progress in a thoughtful way and committed to changing the world for those affected with *SCN2A*-related disorders.

Family and Caregiver Perspectives

There is a dearth of literature that describes the burden of care and health-related quality of life (HRQoL) as they relate to *SCN2A*-related disorders. While Cohen and colleagues [2] summarized quality of life and its determinants in developmental and epileptic encephalopathies (DEEs), for which *SCN2A* pathogenic variants accounted for 24 percent of the cases (n=42/173), no peer-reviewed HRQoL studies have been published specific to *SCN2A*-related disorders. Given the severity of *SCN2A*-related disorders and their impact on individuals and their families, it is imperative that

additional HRQoL studies be conducted. Further, understanding the lived experiences of patients and their caregivers facing rare neurologic diseases is critical to advancing patient-centered outcomes research and informing clinical trial design. Lived experiences also highlight unmet needs of the *SCN2A*-related disorders community and describe the nuances of the disease beyond clinical care. Thus, this section provides a glimpse into some of the challenges families face on a daily basis and illustrates why the patient voice is a fundamental component that complements the clinical and scientific literature on *SCN2A*-related disorders.

To capture the family perspective, the FamilieSCN2A Foundation interviewed caregivers of individuals with *SCN2A*-related disorders. Interviews were transcribed and edited into a short video that highlights various aspects of the disorder (Video 1).

> *I felt shattered and heartbroken. The doctors did not know anything about this diagnosis. They were new to it but luckily, they did give us all the information of the FamilieSCN2A foundation. That was helpful.*
>
> – Sofia's mom, United States

Video 1 Parents (Sandya Crasta, Liz Hendrickx, Amy Richards, Ashley Taylor, Tracy Umezu) discussing experiences caring for their children with *SCN2A*-related disorders.

A transcript of this video is available in the Appendix. The video file is available at www.cambridge.org/scn2a

In addition, the following paraphrased quotes describe how families felt when they received a diagnosis of *SCN2A*-related disorders.

Terrible. My world just fell apart. I didn't know what to do. Didn't know where to look because in Belgium, there just aren't many cases. The doctors told me not to Google it, and that was pretty scary.

– Charlie's mom, Belgium

I felt a mixture of emotions for the first 23 months of my son's life. He was initially neurotypical, then seizures started. Within two months of seizures starting, we got the diagnosis. I felt overwhelmed. There was a little bit of excitement knowing that there's something that they can possibly treat, but at the same time scary that they knew very little about it. I was scared for the future.

– Hudson's mom, United States

I was actually thrilled. It was such a relief to finally figure out what was wrong. I knew from infancy that something was wrong. I always equated it to a juggling act: she has GI reflux, and she's got a tic-like behavior, and she's got apraxia of speech, and she has double hip dysplasia. I kept asking, so then what is it? There has to be something underlying. I just wanted a name for it.

– Erin's mom, United States

The following express the difficulties of having a child affected with a *SCN2A*-related disorder.

Charlotte was born having over 400 seizures a day and she was very prone to illness. As her life went on, she had more and more seizures, and towards the end of her life, she was in status most of the time and her brain wasn't functioning anymore. The hardest part for me was that I am an Intensive Care Unit nurse and knew too much.

– Charlotte's mom, United States

It's kind of like stripping everything away that I had envisioned for my child. I had to re-evaluate what his future might look like. I watched him suffer and was not able to do anything about it. He still pushes through with a smile, but it's challenging to know that there's nothing I can do about it at this moment.

– Hudson's mom, United States

The way families feel about a cure for *SCN2A*-related disorders is expressed by these statements.

I believe in a cure. There are a lot of prayers as well as just the parental force of the FamilieSCN2A foundation that have come together to make me feel hopeful that there would someday be a cure.

– Sofia's mom, United States

I always believe in a cure. That's the main reason why I attend the conferences. That why we're not giving up, why we're going across the globe to find people who understand and who are willing to work with us. That's why I'm screaming from the rooftops telling everyone, "this is what my child has!" I tell every cab driver. I'm here for this, this is my daughter, she has this, I'm telling everyone.

– Charlie's mom, Belgium

> *I think there's going to be a cure. I'm not 100 percent sure it's going to be in her lifetime.*
>
> – Erin's mom, United States

These quotes were in response to asking parents how they have been impacted by FamilieSCN2A Foundation.

> *We ask questions and we get answers that we don't get from our doctors. We get mental as well as emotional support from each other, even coming to the conferences and learning about what the research is done or just meeting other families has been possible through the funding that is available through the FamilieSCN2A Foundation for which I am very grateful.*
>
> – Sophia's mom, United States

> *It's a huge support system knowing that I'm not alone and that there are others that understand my struggle. It's a judgment-free zone. It's a source of hope because I see what the foundation is doing. It gives me hope that people care and they are trying to do something about SCN2A.*
>
> – Hudson's mom, United States

> *I believe that the foundation provides a community of support for our families. It gives families hope and I am really excited at the research that they initiated, to get doctors excited about researching this disease, and putting money towards finding a cure or at least a better quality of life for our kids.*
>
> – Charlotte's mom, United States

In an effort to build upon the interview data, FamilieSCN2A disseminated a questionnaire to their community in March 2023 that asked questions related to the consequences of caregiving. Two specific questions generated data that formed visual representations of (1) how caregivers felt when their children were first diagnosed and (2) what they wished their providers knew about *SCN2A*-related disorders. Figure 3 illustrates word clouds representing these responses.

Given the dearth of literature describing the challenges and consequences of caring for *SCN2A*-related disorders for patients and their families, combined with the speed at which *SCN2A*-related disorders are being studied and the simultaneous growth of the FamilieSCN2A Foundation, we hope this section has provided a thorough overview that highlights various aspects of the disorder and leaves families feeling empowered and health care professionals with valuable insights to navigate the complexities associated with *SCN2A*-related disorders.

Clinical Spectrum and Genotype–Phenotype Correlations

Pathogenic *SCN2A* variants are associated with a range of NDD with or without epilepsy, having symptom onset anytime between the first day of life through later childhood (Figure 4). Due to the variability in clinical presentation, data on

Figure 3 Word clouds generated from caregiver responses. (A) Responses expressing how caregivers felt when their child was first diagnosed. (B) Responses expressing what caregivers wished their health care providers knew about *SCN2A*-related disorders.

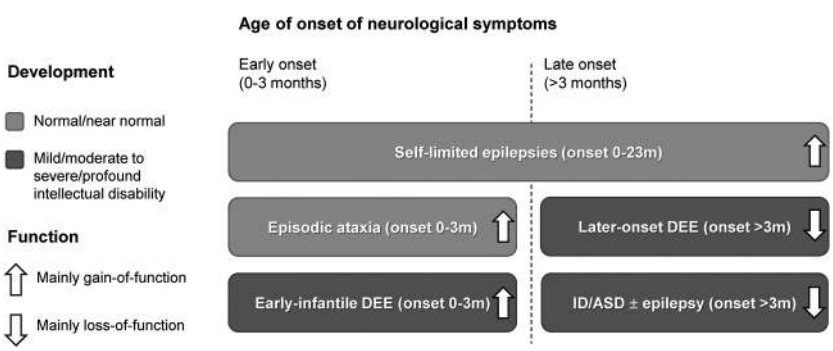

Figure 4 Clinical spectrum of *SCN2A*-related disorders. Black-shaded boxes indicate phenotypes associated with normal development. Unshaded boxes indicate phenotypes associated with mild or moderate to severe or profound ID. Arrows indicate predominant associated functional effects of *SCN2A* variants in each condition. Typical age of onset is given in months (m) and generally refers to the onset of seizures.

the incidence of *SCN2A*-related disorders is not complete. For example, epilepsy patient cohorts exclude cases of NDD that do not have seizures. Expanded genetic testing that includes a wider spectrum of NDD will likely reveal an even greater genotype and phenotype diversity.

In a meta-analysis of genetic findings discovered using next generation sequencing-based gene panels, *SCN2A* was the fourth most commonly implicated gene in monogenic epilepsy (after *SCN1A*, *KCNQ2*, and *CDKL5*) accounting for 7 percent of cases [3]. By comparison, *SCN1A*-associated epilepsy accounted for nearly three times as many cases (19 percent). The incidence of *SCN1A*-associated epilepsy was accurately estimated as 1 per 12,200 live births from a population-based cohort study in Scotland [4]. Based on the assumption that *SCN1A*-associated epilepsy is approximately three times more common than *SCN2A*-associated epilepsy, one might expect the incidence of *SCN2A*-related epilepsy to be in the range of 1 in 30,000 to 50,000 live births. An estimate of 1 per 78,608 live births for *SCN2A*-related epilepsy was based previously on observing seven cases of *SCN2A*-related epilepsy diagnosed in the single national Danish testing center between 2006 and 2014 [5].

A comparable incidence estimate of *SCN2A*-related NDD comes from the UK Deciphering Developmental Disorders (DDD) study [6,7], a national multicenter study in which participants with a wide range of developmental disorders underwent whole exome sequencing (WES). The DDD incidence estimate includes *SCN2A*-related NDD without epilepsy as a feature, but excludes self-limited and familial epilepsy cases. Analyzing the first 4,293 families in the DDD study, the authors estimated that 42 percent of the cohort carried a disease-causing de novo variant in any gene. They further estimated that a de novo variant can be expected to result in a developmental disorder between 1 in 213–448 births. Because 19 study participants with *SCN2A*-related NDD were among these 4,293 families, the incidence of *SCN2A*-related NDD can be estimated as 1 per 47,000 to 100,000 live births.

Nearly all individuals with *SCN2A* variants develop epilepsy at some point in their life. It is estimated that about half of individuals with *SCN2A*-related NDD will present with seizures in the neonatal period [5,8], and 80 percent will develop seizures within the first six months of life [5,8]. Focal seizures are the most common seizure type, reported in 90 percent of individuals, and epileptic spasms occur in up to 50 percent of individuals with *SCN2A*-related NDD [8]. Nearly 80 percent of individuals with *SCN2A*-related epilepsy have comorbid developmental delay [8]. Mosaicism is estimated to occur in 6.4 percent of pathogenic *SCN2A* variants, present at only 11.6 percent of variant reads (range: 11.6–39.5 percent) [9].