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Phenotypic and genetic spectrum of SCN8A related disorders, treatment options and outcomes

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E.G. and R.S.M. conceived and designed the study, and wrote the manuscript. E.G. collected and analysed the data.

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Key Point Box
- SCN8A pathogenic variants have a wide phenotypic spectrum, ranging from developmental and epileptic encephalopathy to behavioral or movement disorders
- Most patients carry a de novo heterozygous missense SCN8A pathogenic variant
- The epilepsy phenotype ranges from BFIS to severe DEE, including a wide variety of familial and sporadic cases of intermediate severity
- The increased risk of precocious mortality primarily involves the severe DEE phenotype in a critical age range (early childhood)
- Patients benefit from treatment with sodium channel blockers and ketogenic diet

ABSTRACT
Pathogenic variants in *SCN8A* have originally been described in patients with developmental and epileptic encephalopathy (DEE). However, recent studies have shown that *SCN8A* variants can be associated with a broader phenotypic spectrum, including: (1) Patients with early onset, severe DEE, developing severe cognitive and motor regression, pyramidal/extra-pyramidal signs and cortical blindness. Severe *SCN8A*-DEE is characterized by intractable seizures beginning in the first months of life. The seizures are often prolonged focal hypomotor and occur in clusters, with prominent vegetative symptoms (apnea, cyanosis, mydriasis), evolving to clonic or bilateral tonic-clonic manifestations. Spasms-like episodes, cortical myoclonus and recurrent episodes of status epilepticus are also common. EEGs show progressive background deterioration and multifocal abnormalities, predominant in the posterior regions. (2) Sporadic and familial patients with mild-to-moderate intellectual disability, discrete neurological signs and treatable epilepsy. EEG is abnormal in half of the cases, showing multifocal or diffuse epileptiform abnormalities. (3) Familial cases with benign infantile seizures (BFIS), sometimes associated with paroxysmal dyskinesia later in life, with no other neurological deficits, normal cognition and usually normal interictal EEG. (4) Patients without epilepsy but with cognitive and/or behavioral disturbances, or with movement disorders.

Extrapyramidal features, such as dyskinesia, ataxia and choreo-athetosis are common in all groups. Early death has been reported in about 5% of the patients, most often in the subgroup of severe DEE. Premature death occurs during early childhood and often for causes other than sudden unexpected death in epilepsy (SUDEP). All epilepsy subgroups exhibit better seizure control with sodium channel blockers, usually at supra-therapeutic doses in the severe cases. In severe *SCN8A*-DEE, ketogenic diet often has a good effect, whereas Levetiracetam has a negative effect, if any. The familial *SCN8A*-related epilepsies show an autosomal dominant pattern of inheritance, whereas the vast majority of *SCN8A*-DEEs occur de novo.

**Key words:** *SCN8A*, epilepsy, intellectual disability, movement disorders, autism, voltage-gated sodium channels.

**Introduction**

*SCN8A* encodes the α-subunit of the voltage-gated sodium channel, Na,1.6, which is located at the axial initial segment (AIS) and provides the molecular basis for the initiation and propagation of neuronal action potentials. Na,1.6 is widely expressed in the brain, both at cortical and subcortical level. Therefore, it is largely predictable that an *SCN8A* dysfunction may lead to heterogeneous neurological deficits, comprising epilepsy and other neurodevelopmental disorders.
Pathogenic variants in *SCN8A* have originally been described in patients with developmental and epileptic encephalopathy (DEE)\(^1\), accounting for approximately 1% of DEEs\(^2\). The number of *SCN8A*-related phenotypes is rapidly increasing, with the inclusion of *SCN8A* in gene panels and the expanded use of whole exome sequencing for diagnostic assessment of patients with epilepsy syndromes\(^3\). Recently, it became obvious that *SCN8A* could cause more benign forms of epilepsy with normal cognition and treatable seizures\(^4\). Furthermore, rare patients with intellectual disability (ID)\(^5\), autism spectrum disorder (ASD)\(^6,7\) or myoclonus / movement disorders without epilepsy have been reported\(^8\).

Most pathogenic variants in *SCN8A* are missense, clustering in the highly conserved transmembrane domains. Functional studies of selected epilepsy associated *SCN8A* variants, have revealed a gain-of-function (GoF) pathogenic mechanism, causing partial or complete elevated persistent sodium currents, and ultimately hyperactivity of the ion channel\(^1,10-13\). On the opposite, variants causing loss-of-function (LoF) are associated with ID, ASD, myoclonus and ataxia often without epilepsy\(^5,8,13\) (OMIM 614306).

This review aims to systematically characterize the spectrum of *SCN8A*-related phenotypes and examine the possible associations between clinical and genetic factors, treatment options and outcomes.

**Materials and methods**

We searched PubMed, Google Scholar and Embase using the term ‘*SCN8A*’ and included all relevant papers that met the following criteria: (1) clinical studies in humans, (2) report of a *SCN8A* variant and/or protein change, (3) original reports only. Last search date was March 2019. The reference lists of all selected articles, and the full texts of the relevant studies were also examined. To identify duplicates, we used the information about the mutation (cDNA and/or protein change and modality of inheritance), patient’s gender and age at study as well as at seizure onset. All relevant data were extracted from selected articles.

**Results**

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In total, 56 studies met the inclusion criteria, with 235 patients (211 probands and 24 affected family members) whose age ranged from 6 months to 35 years. Six articles reported almost only the genetic data (37 patients) and three reported patients described in better details in other papers. Clinical information was available for 198 published patients (47 studies).

The phenotypic spectrum

The phenotype ranged from movement disorders or ID only to severe DEE. Several degrees of cognitive impairment, myoclonus or extrapyramidal signs, such as paroxysmal dyskinesia, ataxia and choreo-athetosis were common in all groups. Based on the electro-clinical features, we identified phenotypes of variable severity (Fig.1), either sporadic or, in a minority of cases, familial. Only a few papers described patients with a homogeneous SCN8A phenotype whereas most of the studies included patients with phenotypes of different severity or not classified. For an overview of the electro-clinical, genetic and MRI data of these papers, see the Supplementary table. For practical reasons, here we refer only to the studies with homogeneous and deeply phenotyped patients.

Severe DEE phenotype

The severe DEE was the most extensively described and homogeneous phenotype\textsuperscript{15-18}. The median age at epilepsy onset ranged from 43 days to 4 months. Deviations from this range are represented by reports of abnormal fetal jerky movements in utero or by epilepsy onset at the age of 36 months\textsuperscript{16,17}. The onset and early course of epilepsy and neurological symptoms was stormy in 37-73\% of cases\textsuperscript{16,17}, whereas in the other cases epilepsy severity worsened more gradually, with relapsing and remitting periods. In the follow up, all children exhibited cognitive deterioration resulting in severe to profound ID and absent speech, progressive pyramidal/extra-pyramidal signs and progressive cerebral atrophy, axial hypotonia, dystonia/dyskinesia, and myoclonus. A quite typical features was the progressive visual impairment resulting in acquired cortical blindness\textsuperscript{14,16,18-20}. Gastrointestinal disorders were extremely common, ranging from sialorrhea to severe GE reflux, unsafe oral feeding (leading to the use of PEG feeding tube in 50\% of subjects) and constipation. Spontaneous bone fractures occurred in a minority of patients\textsuperscript{16}. Typically, these children experienced severe worsening of the epilepsy and neurological conditions during early childhood, a phase during which early death could occur, and reached a relative stabilization later on, usually at school age\textsuperscript{16}.
Seizures were unprovoked and afebrile and were occurred frequently in clusters and often during sleep. The most common seizure type was focal prolonged seizures, with prominent hypomotor and vegetative symptoms (apnea, brady-/ tachy-cardia, and cyanosis), that may evolve to unilateral tonic or clonic manifestations and ultimately to bilateral tonic and/or clonic seizures. Vegetative seizures might not be recognized, in particular when occurring during sleep, therefore they are often underestimated or reported as tonic, myoclonic or primary generalized tonic clonic seizures. Epileptic spasms-like episodes, epileptic myoclonus, and recurrent non-convulsive status epilepticus were also frequently described.

EEG could be normal or mildly abnormal at epilepsy onset, and in all cases it evolved to a progressive background deterioration with epileptic abnormalities and beta intermixed with delta activity, predominant in the posterior regions and enhanced during sleep. The focal seizures had a post-temporo-occipital EEG onset and might migrate from one hemisphere to the other, leading in few cases to the diagnosis of Epilepsy in Infancy with Migrating Focal Seizures (EIMFS).

In the majority of cases, the epilepsy was extremely drug-resistant; nevertheless, a positive response to sodium channel blockers (SCBs), usually at supra-therapeutic doses, has been reported. The most effective drugs were Phenytoin, Carbamazepine, Oxcarbazepine and Benzodiazepines (halting seizure clusters). Levetiracetam usually had a poor effect, or might even result in seizure exacerbation. Inconsistent seizure improvement was observed with other SCBs, such as Lamotrigine and Topiramate. Rarely SCBs (Lamotrigine, Carbamazepine) lead to seizure aggravation. Single patients experienced transient benefit with Zonisamide, Stiripentol, Lacosamide, Rufinamide, and Perampanel. Spasms might benefit from high-dosages of Prednisolone/Adrenocorticotropic hormone and Vigabatrin. The ketogenic diet was effective in about one half of patients who tried it and was successfully used to stop NCSE. Cannabidiol was without benefit (see Supplementary table a).

Benign epilepsy phenotype (BFIS)

We have firstly identified three unrelated families with a total of 16 members (3 probands) who presented with benign SCN8A-related familial infantile seizures (BFIS). Five family members developed paroxysmal kinesigenic dyskinesia (PKD) later in life. All BFIS patients had the same missense variant, Glu1483Lys. Recently, the same variant was also found in a Chinese family with...
a similar phenotype\textsuperscript{23}. A second pathogenic variant, Asn1877Ser, has been reported both in BFIS and in sporadic cases with drug responsive focal epilepsy\textsuperscript{6,24,25} (Table 1 and Supplementary table a).

All affected individuals manifested self-limiting seizures during the first years of life (range 6-12 months of age) and did not require prolonged antiepileptic treatment. Interictal EEG was either normal or showed rare epileptiform abnormalities (Fig.2A). Cognition and psychomotor development were normal in all patients but one. One third of patients had single unprovoked seizures later in life and one-third developed paroxysmal dyskinetic / dystonic episodes in puberty, triggered by stretching, motor initiation or by emotional stimuli, and rapidly controlled by low doses of carbamazepine. Although these dyskinetic episodes fulfilled the clinic diagnostic criteria for PKD, in one patient the ictal video-EEG recording suggested an epileptic nature\textsuperscript{4}.

The spectrum of intermediate epilepsies

In between these two extremes of the \textit{SCN8A} epilepsy spectrum, an increasing number of sporadic and familial patients with a milder epilepsy phenotype has emerged, with extended seizure-free periods, mild to moderate ID and mild or absent neurological deficits\textsuperscript{6,18,24,26}. We recently collected a large series of patients with intermediate \textit{SCN8A} phenotypes, underlying their clinic heterogeneity\textsuperscript{27}. Their mean age at epilepsy onset was approximately 14 months (range 1.5 months to 7 years).

Seizure semiology, based on the clinical charts, included focal and generalized seizures (bilateral tonic clonic, atypical absences and seizures with tonic, myoclonic or atonic component), as well as epileptic spasms and isolated episodes of non-convulsive status epilepticus (NCSE) in a minority of patients. Seizure severity did not progress over time\textsuperscript{27}.

The interictal EEG was normal in one-half of patients or normalized at follow up. In the other patients, the EEG showed focal/multifocal and diffuse epileptiform abnormalities, as well as, in some cases, discrete beta activity in the posterior regions, reminiscent of what observed in severe \textit{SCN8A}-DEE (personal observation) (Fig.2B). Epileptiform activity was enhanced by, or present only during sleep\textsuperscript{6,26}. The focal EEG abnormalities during sleep could mimic those of genetic (“benign”) focal epilepsies of childhood\textsuperscript{26}.

These patients had normal cognition or mild ID, attention deficit hyperactivity disorder (ADHD) and ASD/autistic features were also reported. Mild to moderate neurological symptoms were typically present, namely gait disturbances / ataxia, tremor / myoclonus, hypotonia, movement
disorders and sleep disturbances. These patients display a spectrum of phenotypes, sharing the benign evolution of epilepsy and neurological symptoms.

We recently reported that 58% of these patients achieved seizure freedom, in an age ranging between 4 and 10 years (data available for six patients). In particular, 36% were seizure free on therapy with SCBs either in monotherapy or in combination. Monotherapy was sufficient in the majority of cases. Carbamazepine, Lamotrigine and Valproate (standard / low doses) gave the best results. Single patients became seizure free on Phenytoin, Vigabatrin, Ethosuximide, Phenobarbital, Levetiracetam and even a small dose of Cannabidiol.

Patients with cognitive and/or behavioral disturbances without epilepsy

A few patients harboring an SCN8A variant without epilepsy have been described so far. Eight patients had mild to moderate ID, comorbid ASD or ADHD and discrete neurological symptoms including unstable gait / ataxia, hypotonia, and speech delay. In addition, two of the patients developed movement disorders with oro-bucco-lingual dyskinesia, choreiform movements or tremor. Furthermore, one family with five affected members presented with childhood onset, upper limb action-induced subcortical myoclonus (bursts lasting 50-200 msec) without seizures or cognitive impairment. The myoclonus was alcohol-responsive in one family member.

Outcome and early mortality

SUDEP was initially estimated to occur in about 10% of SCN8A patients. However, recently, the SUDEP rate has been recalculated, and resulted lower than for SCN1A-Dravet syndrome (5.1 versus 9.32/1000-person-years, respectively). Thirteen patients with SCN8A-related early mortality have been reported so far (Fig. 3). Only one them died of definite SUDEP at the age of 15 years. Two additional young patients (17 and 19 years old) had a possible/probable SUDEP and two children (26 months and 5 years old) died after a prolonged seizures, which suggests a possible SUDEP. In total 5 out of 235 (2.1%) patients with pathogenic SCN8A mutations died of definite or possible SUDEP. All of them had uncontrolled seizures; they may have both severe or milder neurological symptoms. One child succumbed at the age of 17 months under unknown circumstances, which did not exclude a possible SUDEP.

The remaining seven children died between age 15 months and 5 years and 6 months. All of them had severe DEE, uncontrolled seizures and progressive neurologic deterioration (Fig. 3). Although they all had several risk factors for SUDEP (e.g. prolonged seizures mainly during sleep, prominent vegetative ictal symptoms, frequent evolution to secondary bilateral tonic-clonic seizures), none of...
them died of SUDEP. Three children died because of lower respiratory tract infections\textsuperscript{16} and respiratory failure\textsuperscript{31} and one of septicemia\textsuperscript{17}. Three further patients passed during subsequent prolonged seizures\textsuperscript{16,20} or status epilepticus\textsuperscript{16}. Although in previous study\textsuperscript{16}, we observed that ictal brady-/tachy-cardia were common features in patients with drug resistant $SCN8A$ epilepsy, we did not document any “critical” ictal ECG alteration. On the opposite, ictal respiratory alterations, consisting of irregular breathing, apnea and cyanosis, were usually prominent and in some cases needed resuscitation.

**(B) The mutational landscape of $SCN8A$-related disorders**

$SCN8A$-related epilepsies are autosomal dominant disorders, in which the affected individuals are heterozygous for the $SCN8A$ variant. $SCN8A$ is one of the most prevalent epilepsy genes, accounting for 1% of all DEEs and 3% of early onset DEEs\textsuperscript{17}. In the vast majority of patients with $SCN8A$-DEE, the variant arises \textit{de novo}, however, in rare cases the variant has been inherited from an unaffected mosaic parent\textsuperscript{18}. $SCN8A$ is highly intolerant to variation in the general population with a pLI of 1.00 and missense $z$-score of 7.94 in the gnomAD database. Almost all reported variants are missense, with the exception of three nonsense, one splice site variant predicted to cause an in-frame deletion and one mosaic deletion of exon 2-14\textsuperscript{27,28,33,34}. Pathogenic variants are spread throughout the entire gene, however most of them are clustering in the highly conserved transmembrane domains, the inactivation gate, and the C-terminus of the affected ion channel\textsuperscript{16,18}. There is no obvious explanation for the almost complete lack of identification of truncating $SCN8A$ variants, both in control and in disease cohorts. One explanation might be, that truncating variants could result in phenotypes that are less likely to undergo genetic testing, such as e.g. learning difficulties or mild ID without seizures or other neurological features.

**Recurrent variants and genotype–phenotype association**

Nine recurrent variants, seen in four or more unrelated patients, have been described (Table 1) so far, accounting for approximately 25% of all reported cases. Most of these variants are associated with DEE, which could be due to an ascertainment bias as patients with severe phenotypes are more likely to undergo genetic testing. Especially the arginine at position 1872 seems to represent a mutational hotspot, as different types of recurrent amino acid substitutions have been detected (R1872L/Q/W). The majority of patients with a variant at Arg1872 have a devastating DEE with moderate to severe ID, speech impairment, hypotonia, microcephaly, dystonia. However, recently a family with three affected individuals with Arg1872Gln and an intermediate phenotype with a treatable epilepsy and only learning difficulties have been described\textsuperscript{27}, illustrating that genotype-
phenotype correlation is not straightforward. A few variants have also been associated with milder phenotypes, e.g. Gly1483Lys and Asn1877Ser. The Gly1483Lys variant has been reported in sixteen members from three unrelated families with BFIS\(^4\). The Asn1877Ser variant has been reported in a few families with BFIS or a treatable focal epilepsy and normal cognition\(^6,24\). However, it has also been seen in a patient with drug resistant focal epilepsy and mild ID\(^35\). In contrast to the mild SCN8A-related epilepsies associated with Gly1483Lys and Asn1877Ser, the Ile1327Val variant has been reported in four unrelated patients with a devastating neonatal or even intrauterine onset DEE associated with severe to profound ID, hypotonia and movement disorder\(^3,15,31,36\).

Functional analysis

Only a few SCN8A variants have been functionally tested so far. However, the results from these studies indicate that variants causing increased firing in neurons (GoF) cause mild or severe epilepsy with or without ID, whereas those decreasing firing (LoF) cause DD, ID or autism alone without seizures\(^1,9-13,28\). Furthermore, one variant causing partial LoF has been associated with autosomal dominant upper limb isolated myoclonus without seizures or cognitive impairment\(^8\).

Discussion

Pathogenic variants in SCN8A have originally been described in patients with DEE, accounting for approximately 1-3% of DEEs\(^2,17\). Nevertheless, the amount of SCN8A-related phenotypes is rapidly increasing, with the inclusion of SCN8A in gene panels and the expanded use of whole exome sequencing for diagnostic assessment of patients with epilepsy syndromes.

The phenotype consists of a continuum of neurological conditions, resulting from different combinations of the cardinal symptoms: epilepsy, ID, motor disorders and autistic features. We confirm the lack of an overt association between the type or location of a SCN8A variant and the severity of the clinical symptoms. Although the spectrum of phenotypes represents a continuum, distinguishing clinical subgroups makes some clinical and prognostic speculations possible.

Patients belonging to the severe end of the phenotypic spectrum of SCN8A-DEEs have a quite homogeneous phenotype consisting of drug resistant epilepsy, with an earlier median age at onset (4 months, versus 14 months in the intermediate phenotypes), severe ID, progressive pyramidal/extra-pyramidal signs, acquired cortical blindness and severe gastrointestinal symptoms\(^14,16,20\). In parallel, the EEG shows a rapid background deterioration, multifocal epileptiform abnormalities and abundant
beta activity, predominant in the post-temporo-occipital regions\textsuperscript{16}. This electro-clinical pattern appears to be quite peculiar of \textit{SCN8A}-DEE, even though not pathognomonic.

During early childhood, these patients experience a stormy worsening of their epilepsy, and develop a progressive cognitive and neurological deterioration as well as a progressive cerebral atrophy. The recurrence of prolonged episodes of subsequent focal seizures without full recovery or continuous seizure activity usually lasting several hours or even days (NCSE) is common and can contribute to a dramatic and irreversible neurological decline\textsuperscript{16,18,20}. The NCSE is often difficult to treat, and life threatening\textsuperscript{16,18,20}. An aggressive and prompt treatment, which might require high doses of Phenytoin, may be necessary\textsuperscript{11,34}. Awareness of this trend towards an age-related worsening is important both for counseling the families, for the potential therapeutic implications and possibly also for early death prevention.

From the first description\textsuperscript{1}, \textit{SCN8A}-DEE has been associated with an increased risk for early mortality due to SUDEP. This was also suggested from the similarities between \textit{SCN8A} and \textit{SCN1A}, and supported by a \textit{SCN8A} mouse model of SUDEP\textsuperscript{37}. No obvious correlation has been found between early mortality and the position of the \textit{SCN8A} variant, the age at seizure onset, seizure type, or clinical severity or association with other genetic abnormalities\textsuperscript{27}.

Based on the first reports, SUDEP was estimated to occur in about 10\% of \textit{SCN8A} epilepsy patients. However, later studies showed that the early mortality rate in \textit{SCN8A} epilepsy was significantly lower\textsuperscript{30}, and that SUDEP was the cause of less than on half of the cases of early death\textsuperscript{16,30}.

The early mortality rate is higher in patients with a severe \textit{SCN8A}-DEE; this is likely the reason why the early mortality rate have been overestimated in the studies mainly including severe \textit{SCN8A}-DEE patients. Interestingly, these patients have a “critical period” during early childhood, with relentless worsening of their epilepsy and neurological condition\textsuperscript{16}. Early death most often occurs during this “critical” age, often due to respiratory failure that ultimately is fatal\textsuperscript{16,30} and / or because of subsequent uncontrolled seizures and NCSE\textsuperscript{16,18,20} (Fig. 3). Ictal cyanosis and respiratory alterations are common in these patients, giving the suspicion that an ictal respiratory failure might be the mechanism contributing to early death.

Patients with a milder \textit{SCN8A} epilepsy phenotype seem to have a more stable epilepsy course, and mild or no neurological deterioration. The EEG can be normal, multifocal or even mimic features of genetic (“benign”) focal epilepsies of childhood\textsuperscript{26}. Following a recent description of a large cohort of patients with an intermediate \textit{SCN8A} phenotype, it can be expected that the number of these
patients will likely increase in the next few years, allowing to better delineate the broad \( SCN8A \) spectrum.

At the very benign end of the \( SCN8A \) epilepsy spectrum, a few families with BFIS have been reported \(^4,23\), in otherwise normal subjects with a normal or almost normal interictal EEG. The video-EEG findings during an episode of “epileptic” paroxysmal kinesigenic dyskinesia in one BIFS family member provide interesting insights into the complex cortico-subcortical excitability in these patients. Only two \( SCN8A \) variants Gly1483Lys and Asn1877\(^4,23\), have so far been associated with this benign condition.

Since \( SCN8A \) is primarily included in epilepsy gene panels, \( SCN8A \) patients without epilepsy are rarely detected and this drawback likely hampers their recognition.

**Differences between patients with \( SCN1A \), \( SCN2A \) and \( SCN8A \) mutations**

The peculiar clinical features of the severe \( SCN8A \)-DEE (cortical blindness, tetraparesis, dyskinesia), the interictal EEG pattern (multifocal epileptiform and beta activity with posterior predominance) and the ictal semiology has never been reported in \( SCN2A \)-epileptic encephalopathy \(^38,39\) and differ from those of Dravet syndrome (DS)\(^40\) and of epilepsy syndromes within the generalized epilepsy with febrile seizures plus (GEFS+) spectrum. In addition, fever sensitivity is a hallmark of \( SCN1A \) related epilepsies, and is lacking in \( SCN8A \) patients.

Pathogenic \( SCN8A \)-DEE variants have most often a GoF mechanism, whereas GEFS+ or DS are associated with LoF variants in \( SCN1A \) resulting in reduced inhibitory interneurons activity, ultimately leading to a network disinhibition. In contrast to \( SCN8A \), the genotype/phenotype correlations in \( SCN2A \) patients are more straightforward, where DEE with an early infantile onset (<3 months of life) and DEE with later onset (≥3 months) have opposite functional effects (GoF and LoF respectively), and consequently opposite response to SCBs, effective only in early infantile \( SCN2A \) epilepsies\(^39\).

**Treatment options**

As mentioned previously, functional studies have indicated so far that epilepsy-associated \( SCN8A \) variants are causing GoF, and in line with these findings, several reports have demonstrated that patients have respond preferentially to SCBs, especially to supra-therapeutic doses of Oxcarbazepine or Phenytoin\(^18,19\). However, seizure outcome in \( SCN8A \)-DEE is generally poor, meaning that development of new targeted therapies, including specific Nav1.6 blockers, remains a
research priority. Interestingly, a recent study has shown that the sodium channel modulator GS967 might to be an effective treatment of SCN8A-DEE in mice\textsuperscript{41,42}. In a high-throughput drug screening study in a SCN8A GoF cell line, ninety drugs were found to significantly inhibit the sodium influx\textsuperscript{43}. Four drugs of potential clinical interest (Amitriptyline, Carvedilol, Nilvadipine, and Carbamazepine) were further investigated and demonstrated concentration-dependent inhibition of the sodium channel currents. These studies are conferring hope for more effective targeted therapies for patients with SCN8A-related epilepsies.

In conclusion, the \textit{SCN8A} phenotypic and genetic spectrum begins now to take shape, including a wide range of phenotypes that share some key symptoms (ID, epilepsy, myoclonus, ataxia / dyskinesia). Further studies in larger cohorts of patients are needed to fully understand genotype-phenotype correlations and further functional studies are necessary to understand the different \textit{SCN8A}-mediated disease mechanisms.

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\textbf{Disclosure of Conflicts of Interest}

None of the authors has any conflict of interest to disclose.

\textbf{Ethical Publication Statement}

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

\textbf{Web resources:}

- Scopus (https://www.scopus.com/home.uri)
- Embase (https://www.embase.com/login)

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References


Figure legends

**Figure 1**: The phenotypic spectrum of SCN8A-related disorders (only probands included)

BFIS= benign familial infantile seizures; DEE=developmental and epileptic encephalopathy

**Figure 2**: Interictal EEG

The graphs on the top show the percentages of patients with abnormal EEG at epilepsy onset and at follow up, in each SCN8A subgroup. (A) The interictal EEG features in patients with severe SCN8A-DEE consist of background slowing, polymorphic delta and beta activity (18–20 Hz, typically in trains lasting 200–600 msec), and multifocal spike and slow waves, predominant in the posterior quadrants (see boxed region). (B) Patients with an intermediate epilepsy phenotype may have quite heterogeneous EEG features, in some cases reminding the features of the severe phenotype. The picture shows bilaterally in the parieto-occipital regions: trains of beta and delta activity, and focal spike and slow waves (boxed region), with or without spreading diffuse (C) Patients with SCN8A-BFIS have very rare or none interictal epileptiform abnormalities. The EEG shows a diffuse spike and wave complex with maximum amplitude in the frontal regions. The amplitude maps show the onset in the left posterior quadrant (i)-(ii)-(iii). [EEG parameters: sensitivity 150 μV/mm, band-pass filter 1–70 Hz, 50 Hz notch on]

The table at the bottom of the figure summarizes the main clinical features of the different SCN8A epilepsy phenotypes. (sz= seizure; mo= months; y= years; d= day; F= focal; TCS= tonic-clonic seizures; M= myoclonic seizures/ epileptic myoclonus; Abs= absences; T= tonic seizures; AT= atonic seizures; Sp= spasms)

**Figure 3**: Early mortality

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Age and cause of death in the 13 published patients with SCN8A-related early mortality. Of note, in the majority of the cases death occurred at an age ranging from 1 to 5 years, in patients with a severe DEE phenotype (during their stormy worsening phase), and was due to causes other than SUDEP. (a) Veeramah et al, 2012; (b) Vaher et al, 2014; (c) Kong et al, 2015; (d) Larsen et al, 2015; (e) Wang et al, 2017; (f) Gardella et al, 2018; (g) Xiao et al, 2018; (h) Denis et al, 2019). See also the Supplementary table (a).

Table 1: recurrent disease-causing variants observed in four or more unrelated patients

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Number of patients</th>
<th>Most common phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ile763Val</td>
<td>5</td>
<td>Variable phenotype from treatable infantile onset epilepsy with normal cognition to intractable epilepsy, moderate ID, ataxia, hypotonia</td>
</tr>
<tr>
<td>Arg850Gln/Leu</td>
<td>5</td>
<td>Severe DEE with infantile onset, severe ID, no speech, hypotonia</td>
</tr>
<tr>
<td>Ile1327Val</td>
<td>4</td>
<td>Severe DEE with neonatal onset, severe ID, no speech, hypotonia +/- dystonia and dyskinesia</td>
</tr>
<tr>
<td>Gly1475Arg</td>
<td>10</td>
<td>Variable phenotype from treatable infantile onset epilepsy with normal cognition to DEE with severe ID, speech impairment, hypotonia +/- dystonia</td>
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<tr>
<td>Gly1483Lys</td>
<td>1 sporadic case + 3 families</td>
<td>BFIS with normal cognition, increased risk of later onset PKD or treatable sporadic epilepsy with normal cognition</td>
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<td>Mutation</td>
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<tr>
<td>Arg1617Gln</td>
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<td>Ala1650Val/Thr</td>
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<tr>
<td>Arg1872Gln/Trp/Leu</td>
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<tr>
<td>Asn1877Ser</td>
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<td>21</td>
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<td>4 sporadic cases + 3 families</td>
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<table>
<thead>
<tr>
<th>Phenotype</th>
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<tr>
<td>Variable phenotype from treatable infantile onset epilepsy with normal cognition to DEE with severe ID, speech impairment, hypotonia +/- dystonia</td>
</tr>
<tr>
<td>Severe DEE with infantile onset, severe to profound ID, no speech, hypotonia +/- dystonia and dyskinesia</td>
</tr>
<tr>
<td>Severe and intermediate DEE with infantile onset, moderate to severe ID, speech impairment, hypotonia, +/-dystonia</td>
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<tr>
<td>BFIS or treatable, infantile onset epilepsy with mild ID +/- ataxia</td>
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<tr>
<td>Category</td>
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<td>BFIS</td>
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<tr>
<td>Intermediate</td>
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<tr>
<td>Severe DEE</td>
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<td>Unclassified</td>
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