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SCN1A related phenotypes: Epilepsy and beyond

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Key bullet:

- Dravet syndrome is the most well recognised epilepsy phenotype associated with *SCN1A*
- *SCN1A* has been implicated in other diseases such as hemiplegic migraine, autism spectrum disorder and SUDEP.
- Patients with Dravet syndrome should be evaluated for ASD that often present with a specific phenotype.
- Patients with Dravet Syndrome present with a complex disease showing many symptoms beyond epilepsy.

Abstract

SCN1A, encoding the alpha 1 subunit of the sodium channel, is associated with several epilepsy syndromes and a range of other diseases. SCN1A represents the archetypal channelopathy associated with a wide phenotypic spectrum of epilepsies ranging from Genetic Epilepsy with Febrile Seizures Plus (GEFS+), to developmental and epileptic encephalopathies (DEEs). SCN1A disorders also results in in other diseases such as hemiplegic migraine and autism spectrum disorder (ASD).

DS is the prototypic DEE with an early onset of febrile status epilepticus, hemiclonic or generalized tonic-clonic and later onset of additional seizure types. EEG and MRI are normal at onset. Development is normal in the first year of life but plateaus rapidly with most patients ultimately

having intellectual disability. Epilepsy is drug resistant and necessitates polytherapy. Most pathogenic variants occur *de novo* in the affected child, but they are inherited from mosaic affected or unaffected parents rare cases. The molecular finding of haploinsufficiency is consistent with a loss of function defect in cells and animal models. Although seizures are the most commonly reported symptom in DS, many additional issues critically impact on patients' cognitive and behavioural functioning.

Hemiplegic migraine (HM) is a rare form of migraine with aura, characterized by the emergence of hemiparesis as part of the aura phase. All *SCN1A* mutations reported in Sporadic/Familial HM3 are missense mutations. Most of the experimental results show that they cause a gain of function of $Na_V1.1$ as opposed to the loss of function of the epileptogenic $Na_V1.1$ mutations.
SCN1A and *SCN2A* pathogenic variants have been identified in genetic studies of cohorts of patients with ASD. In addition, ASD features are often reported in patients with Dravet syndrome and other DEEs.

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SCN1A, encoding the alpha 1 subunit of the sodium channel, is associated with a range of human diseases. Since it was first implicated in epilepsy in 2000[1], *SCN1A* has remained the most important epilepsy gene. The most well recognized epilepsy phenotype associated with *SCN1A* is Dravet Syndrome, but it also results in several other epilepsy syndromes, many associated with significant co-morbidities. *SCN1A* has been implicated in other diseases such as hemiplegic migraine and autism spectrum disorder (ASD). Patients with Dravet Syndrome present with a complex disease showing many symptoms beyond epilepsies.

SCN1A **Epilepsies**

SCN1A disorders represent the archetypal channelopathy associated with epilepsy. They result in a wide phenotypic spectrum ranging from self-limited and pharmaco-responsive

epilepsies, such as Genetic Epilepsy with Febrile Seizures Plus (GEFS+), to developmental and epileptic encephalopathies (DEEs). Even within the DEEs, there is a spectrum of severity ranging from Myoclonic-Atonic Epilepsy (MAE) to Dravet syndrome, Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) and Early Onset *SCN1A* DEE. Each has a different range of co-morbidities and prognosis, and intriguing evidence is emerging that they are underpinned by different functional deficits.

Dravet Syndrome

Dravet Syndrome is the prototypic DEE with a mean age of seizure onset of 6 months (upper age limit 15 months)[2]. The infant typically presents with febrile seizures which may be a hemiclonic or generalised tonic-clonic seizure. First seizure can evolve to status in almost half of patients and is often followed by further convulsive seizures. If the infant has hemiclonic seizures, the lateralisation will often vary in different attacks, a critical clue to the diagnosis. Between one and five years of age, additional seizure types appear including focal impaired awareness seizures, absence seizures, myoclonic seizures and episodes of non-convulsive status epilepticus. The early occurrence of multiple seizure types, especially myoclonic seizures, have been shown to be a factor of negative prognosis. Overtime, seizures are might be less triggered by fever and tend to occur during sleep[3]. The EEG is often normal in the first one to two years of life, but then develops generalised spike wave, poly spike wave and multifocal discharges. Patients with Dravet Syndrome typically have drug resistant epilepsy.

Development is normal in the first year of life although some subtle development abnormalities are reported as oculo motor coordination deficit if infants undergo psychomotor testing. but plateaus between one and two years of age, with most patients ultimately having intellectual disability. The degree of intellectual disability varies from severe in about half of the patients, to moderate in the large majority of the others. Rare patients with mild learning disabilities or normal intellect have been recognised[4]. In terms of motor development, children walk a little late at 16-18 months, and they have more pronounced physiological ataxia. After puberty, they often develop subtle spasticity with a crouch gait[5]. Other issues in some patients include behaviour problems and autistic features. More than 80% of patients with Dravet Syndrome have pathogenic variants (or mutations) in *SCN1A*, making it the epilepsy syndrome with the highest yield on genetic testing[6]. About

half of the patients have truncation variants and half missense variants; genotype does not appear to be useful clinically helping to shape specific therapy or to predict prognosis[7]. While Sanger sequencing or next generation sequencing reveal most of the causative pathogenic variants, about 3% of patients have pathogenic copy number variants, either microdeletions or duplications that can be missed without appropriate testing[8]. Recently, a novel mechanism has been invoked where a poison exon, previously hidden in an intron, affects protein splicing in neurons[9].

Most pathogenic variants occur *de novo* in the affected child, but in fewer than 10% of cases, they are inherited from mosaic affected or unaffected parents[10]. In some cases, they may inherit the pathogenic variant in a dominant manner in the setting of a family history of GEFS+ [11]. The molecular finding of haploinsufficiency is consistent with a loss of function defect in cells and animal models.

Myoclonic-Atonic Epilepsy (MAE)

Myoclonic-atonic epilepsy, described by Doose, is a genetic generalized epilepsy that begins in children aged between 7 months and 6 years, often with explosive onset of multiple seizure types[12]. Seizures include the hallmark drop attacks due to myoclonic, atonic and myoclonic-atonic components. Other seizure types include absence seizures, generalized tonic-clonic seizures, and tonic seizures in the more severely affected children. Non-convulsive status epilepticus is common. The EEG shows 2-4 Hz generalized spike-wave activity; a 4-7 Hz theta rhythm is prominent in the parietal regions together with an occipital 4 Hz rhythm[13]. Outcome is highly variable, ranging from normal intellect to severe intellectual disability. Only a small percentage of patients with MAE have pathogenic variants in *SCN1A*, including the original GEFS+ family [14]. EMA phenotype was also reported in a few cases of SCN2A[15].

Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)

This rare disorder begins at a mean age of 2 months and is characterised by focal seizures which migrate clinically and electrically from one hemisphere to the other [16]. Seizures are extremely frequent and infants typically have profound developmental impairment. Rare patients with *SCN1A* mutations have been reported [17; 18]. The major causal gene is *KCNT1*, responsible for almost half of cases[19]. However, this syndrome has emerged to be highly

genetically heterogeneous for another half of cases with more than 20 genes implicated, with most mutations arising *de novo*, although recessive inheritance is seen for specific genes.

Early Onset *SCN1A* DEE

This is the most severe of the *SCN1A* DEEs with seizures beginning at 8-12 weeks of age[20]. Infants present with hemiclonic seizures or generalised tonic-clonic seizures. Epileptic spasms and tonic seizures are frequent in infancy and childhood; in contrast, epileptic spasms are not seen in Dravet Syndrome and nocturnal tonic seizures are not usually seen until adult life. Patients with this syndrome also have generalised tonic-clonic seizures, myoclonic seizures and convulsive status epilepticus. More cases and pathogenic variants were recently recognised with this but it is much less common than DS.
It is not clear if development is ever truly normal in these infants but developmental delay is apparent by 16 weeks of age. These children are far more profoundly impaired than children with Dravet Syndrome as they are non-verbal and non-ambulant. They develop a movement disorder between 9 weeks and 20 months of age which is hyperkinetic in nature with prominent chorea, dystonia and orofacial myoclonus. The EEG is initially normal but then develops generalised spike wave and multifocal epileptiform activity. To date most of the patients with this early onset *SCN1A* DEE have a recurrent *de novo* missense mutation, Thr226Met. There are other rare pathogenic variants that are being increasingly recognised that cause this profound syndrome.

From a mechanistic point of view, it is well known that Dravet Syndrome is associated with loss of *SCN1A* function. In contrast this early onset *SCN1A* DEE is associated with gain of function[21]. Thr226Met channels exhibit hyperpolarising shifts of both the activation and inactivation curves, together with enhanced fast inactivation. Berecki and colleagues found that current stimulation that produced repetitive action potential firing in control neurons, resulted in depolarisation block and cessation of action potential firing in Thr226Met model neurons. These physiological studies show that, from a biophysical perspective, the Thr226Met variant produces gain-of-function but, paradoxically, causes interneurons to more readily develop depolarisation block and produce a functional dominant negative interaction. It thereby produces more profound disinhibition compared with the haploinsufficiency that is characteristic of Dravet Syndrome. This profound phenotype has more corollaries with the

phenotypes of *SCN8A* encephalopathy and early infantile *SCN2A* encephalopathy, where children often have profound impairment associated with a severe movement disorder.

Genetic Epilepsy with Febrile Seizures Plus (GEFS+)

GEFS+ was first recognised in 1997 in large families with dominant inheritance of Febrile Seizures (FS) and self-limited, pharmacoresponsive seizure disorders in most family members[22]. FS is the most common phenotype in GEFS+ families, followed by Febrile Seizures Plus (FS+). FS+ refers to children where febrile seizures occur outside the normal limits of classical FS (6 months to 6 years) or where afebrile generalized tonic-clonic seizures occur as well as febrile convulsive seizures.

In GEFS+ families, there may be DEEs in some family members such as MAE and Dravet syndrome [23]. Small and large families have been reported around the world and the heterogeneous spectrum of GEFS+ phenotypes have grown to include focal seizures without preceding FS and also Genetic Generalized Epilepsies [24].

SCN1A was first discovered in GEFS+ families [1]. About 20% of reported families have pathogenic variants in *SCN1A*. GEFS+ does not always occur in a familial context; patients with GEFS+ phenotypes may have *de novo SCN1A* mutations [25]. Comparing three genes implicated in GEFS+ families, *SCN1A, SCN1B* and *GABRG2, SCN1A* families had an earlier age of onset of FS and FS+ in the first year of life compared with families with *SCN1B* mutations, consistent with gene-specific effects [26].

Common epilepsies

Given the marked genetic heterogeneity of the epilepsies as a whole, large numbers of cases are required to assess if *SCN1A* is relevant to the common types of epilepsy. Two different approaches employed by large consortia have implicated *SCN1A* as playing a role.

Whole exome sequencing of a large number of unrelated individuals with the common epilepsies, genetic generalized epilepsies (GGE) and non-acquired sporadic epilepsies, sought to determine if there was an excess burden of rare genetic variation in all protein-encoding genes [27]. They compared 525 familial and 662 sporadic non-acquired focal epilepsies with

3877 controls. Only *DEPDC5* showed genome-wide significance in familial cases, but *SCN1A* was fourth on the list of genes that showed more ultrarare variation than in controls, suggesting that it may become significant with a much larger number of cases. No gene showed genome-wide significance for the 640 familial GGE cases compared with 3877 controls, but *SCN1A* was seventh on the list and could become significant with far more cases. It was not surprising that the number of cases was underpowered to produce significant findings and whole exome sequencing of 20,000 cases is underway with the EPI25 consortium which promises to yield more significant results.

The International League Against Epilepsy Consortium on Complex Epilepsies performed a meta-analysis of genome-wide association studies on 8696 cases and 26,157 controls [28]. When all patients with epilepsy were included, that is both GGE and focal epilepsy cohorts, a locus at chromosome 2q24.3 was identified. This finding implicates *SCN1A* and suggests it may act pleiotropically to raise the risk for epilepsy more broadly. This approach has recently been expanded to a genome-wide mega-analysis of 15,212 individuals with epilepsy compared with 29,677 controls and confirmed the chromosome 2q24.3 locus harbouring *SCN1A* [29]. This locus is now significant for all epilepsies, GGE and focal epilepsies independently although it is not clear if the signal is due to several genes including *SCN1A*, *SCN2A* and *SCN3A*.

Non-epilepsy *SCN1A* Phenotypes

SCN1A pathogenic variants have also been reported in patients with other neurological disorders such as hemiplegic migraine and ASD. In patients with Dravet syndrome, the high frequency of ASD, gait disorders and Sudden Unexpected Death in Epilepsy (SUDEP) is also linked to *SCN1A* mutations and is supported by preclinical and clinical data.

Hemiplegic Migraine

Hemiplegic migraine is a rare form of migraine with aura and can be subdivided into familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM). FHM is an autosomal dominant type of migraine with aura, characterized by the presence of hemiparesis as part of the aura phase. The clinical manifestations of hemiplegic migraine range from attacks with short-duration hemiparesis to severe forms with recurrent coma and prolonged hemiparesis,

permanent cerebellar ataxia, epilepsy, transient blindness, and mental retardation. Diagnosis relies on a careful patient history and exclusion of potential causes of symptomatic attacks [30]. The pathophysiology of HM involves cortical spreading depression (CSD), a self-regenerating wave of transient neuronal hyperactivity leading to long-lasting (tens of seconds to a few minutes) neuronal and glial depolarization with suppression of firing propagating across the cortex at 2–3 mm/minute, much slower than epileptic discharges [31].

Familial and sporadic HM (S/FHM) are caused by mutations of different genes. S/FHM3 is due to heterozygous pathogenic variants of the $Na_V1.1$ voltage-gated sodium channel (*SCN1A*) [32]. Some genes have been implicated in both epilepsy and migraine[33], however, usually patients with FHM do not have seizures. Numerous studies have been undertaken to find out why a mutation in the same gene leads to different phenotypes[34].

Around 80 patients have been published carrying sporadic or familial FHM3 *SCN1A* mutations and few had both HM and epilepsy. In contrast to FHM due to *CACNA1A* and *ATP1A2* mutations, in the few patients with FHM3 carrying *SCN1A* mutations and presenting with seizures, HM attacks are always independent from seizures and in general the two phenotypes do not overlap temporally [34]. Moreover, most of the pathogenic *SCN1A* mutations cause different types of epilepsy without migraine . The functional effect of the *SCN1A* mutations might partially explain the different phenotypes. Cellular and animal models of truncating and missense Nav1.1 mutations causing severe epileptic phenotypes cause complete loss of function of the channel, consistently with haploinsufficiency [35] . This results in decreased excitability of GABAergic interneurons leading to reduced inhibition and network hyperexcitability, culminating in seizures [36]. All *SCN1A* mutations reported in S/FHM3 are missense mutations. Most of the experimental results show that they cause a gain of function of $Na_V1.1$ [37]. Cellular and animal data point to increased excitability of GABAergic neurons in S/FHM3, a different mechanism from that seen with epileptogenic $Na_V1.1$ mutations.

Autism Spectrum Disorder (ASD)

Evidence from studies in familial and sporadic ASD has strongly pointed to a genetic etiology. *SCN1A* and *SCN2A* pathogenic variants have been identified in genetic studies of cohorts of patients with ASD [38]. In addition, loss of function variants of these two genes were

significantly identified in one study targeting postmortem brain DNA sequencing of patients with ASD compared to controls [39].

ASD features have been reported in patients with Dravet syndrome, but were defined as 'autistic traits' often without using standardized tools. Depending on the type of assessment, rates of 'autistic traits' vary from 8.3% to 61%[40]. Most studies have reported lack of verbal communication with 10 to 79% of patients showing social problems, such as poor peer relationships, withdrawn behaviour, lack of emotional reciprocity, difficulty negotiating social rules and excessive familiarity[37]. Restricted and unusual interests, like obsessions, perseverations or self-stimulation, are reported in 24 to 69% of patients [41].

Two studies assessed ASD in children with Dravet syndrome using standardized tools: the first with DSM-IV and ICD-10 criteria, the Childhood Autism Rating Scale diagnosis tool and Autism Behavior Checklist [41] and the second with gold standard tools (Autism Diagnosis Interview Revised, i.e. ADI-R or Autism Diagnosis Observation Scale 2, i.e. ADOS-2)[40]. Both studies confirmed the occurrence of ASD in 24%-40% of children. This is lower than in an adult study where ASD was diagnosed in 61.5% [42]. The underestimation of ASD in the pediatric series could be due to relative preservation of communicative and social skills such as social smiling, and a lower rate of the repetitive behavior typically seen in ASD [40].

Scn1a$^{+/-}$ mice are a well-defined Dravet syndrome model exhibiting both thermally-induced seizures and spontaneous seizures, in addition to other symptoms such as autism-like behavior [43]. Emerging data report a decrease in the autistic behavior of the DS animal model by enhancing GABAergic properties in inhibitory neurons [44]. Cannabidiol (CBD) showed a similar rescue effect of Dravet syndrome symptoms with increased inhibitory neurotransmission potentially mediated by GPR55 (G protein coupled receptor)[45]. No human data are available to date on this possible improvement of social cognition with the therapies.

SUDEP (Sudden Unexpected Death in EPilepsy) and other SCN1A-related death

SUDEP is the most common cause of death that is related to epilepsy. It is defined as "a sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in

patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicologic cause of death"[46]. Data obtained from human studies and animal models have pointed to alterations in respiratory, cardiac, and brain function as three possible mechanistic areas in SUDEP[47]. The report of two cases of SUDEP in a family with genetic epilepsy syndrome generalized epilepsy with febrile seizures plus (GEFS+) while segregating a novel variant in *SCN1A* gene is a rare example of familial SUDEP[48]. The possible role of SCN1A in SUDEP is reported in animal models and human studies of patients with DS. Patients with DS face an increased risk of premature mortality estimated to affect about 4–12% of children[49-51]. Patients with DS seem predisposed to SUDEP with the implication of autonomic dysfunction, as evidenced by depressed heart rate variability[52-53] and increased P- and QT-interval dispersion[54]. *Scn1a* deficient mice models mirror the human phenotype, exhibiting spontaneous seizures, autonomic instability, and seizure-driven vagal activation preceding sudden death[55-56]. Another mouse model carrying the human mutation *SCN1A-R1407X*[57] displayed a 21% premature death rate, spontaneous seizures, and a prolonged QT interval[57]. Cardiac arrhythmias often preceded apparent convulsive seizures in this model indicating that some *SCN1A* variants could predispose to sudden death through neurocardiac or sole cardiac mechanisms[57,58]

The role of SCN1A dysfunction in sudden death without diagnosed epilepsy is also highlighted by a few cases. Two reports describe cases with sudden unexpected death in infancy and childhood with no previous reported epilepsy[59,60]. The first report includes 2 cases of sudden infant death syndrome (SIDS) with no prior history of seizure with *SCN1A* variants, functionally shown to cause protein-altering changes in channel function[59]. The other describes a case of sudden unexplained death in childhood (SUDC) in a child who was reported to have febrile seizures before dying suddenly and unexpectedly. His sibling was diagnosed with Dravet Syndrome due to a pathogenic variant in *SCN1A* that was thought to be *de novo*, and it was later found on a research basis that the father was mosaic and that the same pathogenic variant was present in the child who died[60].

Dravet syndrome: Core concepts beyond seizures

Cohort studies show that patients with Dravet syndrome and *SCN1A* mutations share features that go beyond purely seizures' related damage[61]. Patients present with developmental disability, behavioral and psychiatric disorders as well as gait disturbance and speech

disorder. Dravet syndrome impacts significantly on both patients' and caregivers' lives[62,63]. We identified core domains to measure the impact on both patients and caregivers dealing with DS[64,65]Although seizures were the most commonly reported symptom in DS, many additional issues critically impact on patients' cognitive and behavioural functioning, as attested to by both caregivers and physicians. These issues might also have variable impact in relation to patient age[63]. The five major domains of concern from French caregivers and healthcare professionals were: seizures, expressive communication and receptive communication of the child, impact on daily activities, and social functioning of the caregiver[64] This study was followed by further analysis of this conceptual disease model in four additional countries: USA, UK, Italy and Australia[65]. Themes identified showed similarity with the French conceptual model with minor differences between countries that likely reflect variations in health care systems. These key impacts of Dravet syndrome on children and caregivers should be targeted as critical outcomes in the evaluation of new therapies.

Disclosure of Conflicts of Interest

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

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.

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