Epilepsy is a disease characterized by abnormal brain activity and a predisposition to generate epileptic seizures, leading to neurobiological, cognitive, psychological, social, and economic impacts for the patient. There are several known causes for epilepsy; one of them is the malfunction of ion channels, resulting from mutations. Voltage-gated sodium channels (NaV) play an essential role in the generation and propagation of action potential, and malfunction caused by mutations can induce irregular neuronal activity. That said, several genetic variations in NaV channels have been described and associated with epilepsy. These mutations can affect channel kinetics, modifying channel activation, inactivation, recovery from inactivation, and/or the current window. Among the NaV subtypes related to epilepsy, NaV1.1 is doubtless the most relevant, with more than 1500 mutations described. Truncation and missense mutations are the most observed alterations. In addition, several studies have already related mutated NaV channels with the electrophysiological functioning of the channel, aiming to correlate with the epilepsy phenotype. The present review provides an overview of studies on epilepsy-associated mutated human NaV1.1, NaV1.2, NaV1.3, NaV1.6, and NaV1.7.

Keywords: channelopathies, epilepsy, ion channel, mutation, sodium channel

INTRODUCTION

Epilepsy is a disease known worldwide, affecting around 70 million people in the world (Thijs et al., 2019). It has been considered a disease and no longer a disorder or a family of disorders since 2014 by International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) (Falco-Walter et al., 2018). Epilepsy is conceptually defined as a disease in which an individual has at least two unprovoked or reflex seizures in a period greater than 24 h apart, one unprovoked or reflex seizure and a probability of having another seizure similar to the general recurrence risk after two unprovoked seizures (greater than or equal to 60%) over the next ten years or an epilepsy syndrome (Fisher et al., 2014).

When abnormal brain activity begins in one or more identified regions, epilepsy is called focal, whereas, when it occurs in both hemispheres with a wide distribution, it is called generalized. Finally, when it cannot be classified as either focal or generalized, it is called unknown (Devinsky et al., 2018).
Epilepsy can affect anyone, regardless of gender, age, and income levels (Saxena and Li, 2017). Understanding the etiology of epilepsy is crucial for clinical management of patients and for conducting neurobiological research that will direct future therapies (Thomas and Berkovic, 2014). The ILAE Task Force has defined six etiologic categories; they are not hierarchical and more than one might often apply (structural, genetic, infectious, metabolic, immune, and unknown) (Falco-Walter et al., 2018).

Among those genetically caused, it is possible to identify several epilepsy-related genes (Lindy et al., 2018). For example, voltage-gated potassium channel, voltage-gated calcium channel and voltage-gated chloride channel genes, GABA receptors, nicotinic acetylcholine receptors, polymerase (DNA) Gamma genes and voltage-gated sodium channel genes (Deng et al., 2014).

Voltage-gated sodium channels (NaV) can be found mainly in the central nervous system (CNS), peripheral nervous systems (PNS), skeletal, and cardiac muscles (Huang et al., 2017). NaVs are distributed throughout the body and play an important role in the generation and propagation of action potential (Wang et al., 2017b). Structurally, NaVs are composed by an α subunit organized in four homologous ligated domains (DI-DIV), each domain composed by six transmembrane segments (S1-S6), and one or more β subunits associated by non-covalent interactions or disulfide bond (Abdelsayed and Sokolov, 2013; Gilchrist et al., 2013; Catterall, 2017; Bouza and Isom, 2018; Jiang et al., 2020).

The domains of an α subunit present a high degree of conservation with each other, presenting the region known as the voltage sensor domains (VSD) located in transmembranes S1-S4, especially S4 helix, which contains positively charged residues, and the pore-forming (PM) domain located in S5-S6 segments, structuring a four VSD around a central pore (Ahern et al., 2016).

The S4 helix of DI, DII, and DIII domains moves faster than the S4 helix of DIV during membrane depolarization, and this asynchronous movement is an essential feature in the steady activation voltage-dependent process, which provokes movement of S4-S5 intracellular links followed by the displacement of the S6 segments to initiate Na⁺ influx (Goldschens-Ohm et al., 2013; Oelstrom et al., 2014). The movement of the S4 helix of DIV initiates the process of fast inactivation, since the movement of the voltage sensor in domain DIV is associated with the displacement of an intracellular loop between DIII and DIV within an IFM (isoleucine, phenylalanine, and methionine) motif that binds intracellular to PM and terminate Na⁺ influx (Capes et al., 2013; Clairefeuille et al., 2019). A second type of reversible inactivation occurs after repetitive or prolonged stimulation and results in steady-state inactivation whose asymmetric movement of S6 segments collapses the pore (Payandeh et al., 2012; Zhang et al., 2012; Gamal El-Din et al., 2013; Silva and Goldstein, 2013; Ghovanloo et al., 2016). Consequently, electrophysiological changes such as increased current density, shifting steady-state activation, and inactivation to negative and positive values, respectively, enhanced persistent current, accelerated recovery from inactivation, and delayed fast inactivation can cause gain-of-function (GoF) in the channel. Also, decreased current density, positive shift in steady-state activation, negative shift in steady-state inactivation, and slower recovery from inactivation can cause loss-of-function (LoF) (Mantegazzia et al., 2005; Liao et al., 2010; Lossin et al., 2012; Catterall, 2014b; Vanoye et al., 2014; Wagnon et al., 2017; Yang et al., 2018; Zaman et al., 2018; Wengert et al., 2019; Zhang S. et al., 2020).

Currently, there are nine different alpha subtypes of NaVs (NaV1.1-NaV1.9), and mutations in these channels can cause diseases known as channelopathies (Catterall et al., 2010). NaV1.1 (SCN1A), NaV1.2 (SCN2A), NaV1.3 (SCN3A), NaV1.6 (SCN8A) and NaV1.7 (SCN9A) are genes whose mutations are related to epilepsy. So far, there is no correlation of mutations in NaV1.4 (SCN4A), NaV1.5 (SCN5A), NaV1.8 (SCN10A), and NaV1.9 (SCN11A) with epilepsy, which is to be expected, since these channels are mainly expressed in skeletal muscles, cardiac tissues, dorsal root ganglia, trigeminal sensory neurons, nociceptive neurons of the dorsal root and trigeminal ganglia, respectively (Brunklaus et al., 2014). Both α and β subunits (SCN1B) have been reported as the cause of epilepsy phenotype (Meisler et al., 2010; Kaplan et al., 2016).

NaV channels rank amongst the 2% most conserved proteins in the human genome, with an extremely low rate of coding variation, accounting for nearly 5% of known epileptic encephalopathies (Petrovskii et al., 2013; Mercimek-Mahmutoglu et al., 2015; Lek et al., 2016; Heyne et al., 2019). Pathogenic mutated residues are situated in the highly evolutionarily conserved portions of the channel: transmembrane segments, intracellular inactivation gate loop, and the proximal 2/3 of the C-terminal domain (Blanchard et al., 2015; Wagnon and Meisler, 2015). The final 1/3 portion of the C-terminal and cytoplasmic interdomain loops 1 and 2 are less conserved (Denis et al., 2019). The proximal 2/3 of the C-terminal are involved in the interaction of several binding sites for proteins and accessory molecules, like beta subunits β1 and β3, fibroblast growth factors (molecules implicated in neural development), calmodulin (regulatory protein in neuronal function and hyperexcitability) and G protein (Bähler and Rhoads, 2002; Spampanato, 2004; Wittmack et al., 2004; Laezza et al., 2009; Yang et al., 2010). Moreover, the C-terminal has been shown to interact with the inactivated channel via ionic interaction between its positively charged residues and negatively charged residues at the inactivation gate. A shift in any of the charges can brake electrostatic interaction and affect normal channel inactivation (Nguyen and Goldin, 2010; Shen et al., 2017; Johnson et al., 2018).

The N-terminal region seems to play a more important role on protein trafficking than on channel activity. This domain interacts with the light chain of microtubule-associated protein MAP1B, facilitating the traffic of the NaV channel to the neuronal cell surface (O’Brien et al., 2012; Blanchard et al., 2015). In addition, mutation in the N-terminal leads to protein retention in the endoplasmic reticulum (Sharkey et al., 2009).

Newer genomic approaches, especially next generation sequencing (NGS), improve the rate and reduce the costs associated with genetic epilepsy diagnosis, since traditional
cytogenetic and microarray-based tests are lengthy, expensive, and diagnostic yield is incredibly low (Veeramah et al., 2013; Allen et al., 2016; Sands and Choi, 2017; Orsini et al., 2018). The use of gene panels and whole-exome sequencing (WES) provides a powerful tool to change the paradigm of genetic epilepsy diagnosis (Ng et al., 2010; Clark et al., 2018). These techniques have been widely used to elucidate suspected inherited neurological diseases in the last years, contributing to dramatically increase the number of patients diagnosed with genetic epilepsy. Both mendelian and de novo genetic epilepsy can be detected with these methods, but doubtless, de novo mutations are the most prevalent mutations related to epilepsy-related voltage-gated sodium channel mutations.

Gene therapy is promising as an effective approach to treat genetic diseases. Personalized epilepsy therapies are in development and have shown promising results, ranging from antisense oligonucleotides and small peptides to modulation of gene expression through epigenetics (Riban et al., 2009; Tan et al., 2017; Stoke Therapeutics, 2018; Perucca and Perucca, 2019). Even eating habits may be related to an improvement in the patient's clinical condition. Ketogenic diet has been described as an effective treatment in epilepsy (Gardella et al., 2018). Moreover, the combination of traditional antiepileptic drugs with new compounds displayed a synergic and improved efficacy, since these molecules do not compete for the same interaction site (Bialer et al., 2018). Each specific epilepsy-related NaV isoform will be presented and discussed in detail in the following sections.

NaV1 MUTATIONS

NaV1.1

The SCN1A gene encodes for the α subunit NaV1.1, and is allocated at the 2q24.3 chromosome between 165,984,641 and 166,149,161 base pairs, same gene cluster of SCN2A-SCN3A genes, being the most frequent target of mutation in genetic epilepsy syndromes (OMIM#182389) (Malo et al., 1991; Malo et al., 1994; Catterall et al., 2010). NaV1.1 is widely expressed in the CNS, predominant in inhibitory GABAergic interneurons, regulating neuronal excitability, and the reduction of its activity is one of the factors that cause epileptic diseases due to imbalance between inhibition and excitation (Yu et al., 2006; Verret et al., 2012; Tai et al., 2014; Rubinstein et al., 2015).

Epilepsy syndromes, such as generalized epilepsy with febrile seizures plus (GEFS+; Online Mendelian Inheritance in Man [OMIM] #604233), severe myoclonic epilepsy (SME) and SMEI, also known as Dravet syndrome (OMIM #607208), are associated with mutations in the SCN1A gene (Escayg and Goldin, 2010; Meng et al., 2015; Huang et al., 2017).

In the SCN1A mutation database (http://www.caae.org.cn/gzneurosci/scn1adatabase/data), among 1727 mutations described for the SCN1A gene, 1528 are related to epileptic diseases (Table 1 and for the full description of mutations in the SCN1A gene, see Supplementary Table S1). Among the epilepsy-related mutations, 945 are related to severe myoclonic epilepsy of infancy (SMEI), 263 are related to severe myoclonic epilepsy (SME), 151 are related to severe myoclonic epilepsy borderline (SMEB), 18 are related to partial epilepsy (PE), 31 are related to partial epilepsy and febrile seizures plus (PEFS+), 8 are related to generalized epilepsy (GE), and 55 are related to generalized epilepsy with febrile seizures plus (GEFS+).

Mutations in the NaV1.1 channel are described in almost all regions of the protein and may cause GoF or LoF (Goldin and Escayg, 2010; Meng et al., 2015). Among the 52 mutations in SCN1A related to epilepsy with functional studies, 35 mutations (67.30%) exclusively display characteristics of LoF, 6 mutations (11.53%) display characteristics unique to GoF, and 11 mutations (21.15%) display characteristics of GoF+LoF, whereas, in GoF+LoF mutations, the main characteristic that gives GoF features is enhanced persistent current, present in 10 out of the 11 GoF+LoF mutations listed (Tables 1 and S1).

Due to the role of the NaV1.1 channels in the regulation of electrical excitability by the inhibitory interneurons, prescription of AEDs non-selective sodium channel blockers (SCB) for SMEI or GEFS + syndromes is contraindicated, for it may aggravate crises due to the enhanced suppress status of the NaV1.1 channels (Catterall, 2014a; Shi et al., 2016; Knupp and Wirrell, 2018; Zibro et al., 2018). The first-line drug-based therapy for SCN1A epilepsy diseases is the enhancement of postynaptic GABAergic transmission with allostERIC activation of GABA_A receptors as target by Clobazam and/or an increase in GABA concentration in synaptic cleft resulting from increased GABA production and decreased GABA degradation as target by Valproic acid (Catterall, 2014a; Hammer et al., 2016; Knupp and Wirrell, 2018; Musto et al., 2020). Antisense nucleotides (ASO) therapy to increase mRNA of SCN1A for NaV1.1 channel expression in normal levels is a promising strategy for genetic disorders involving haploinsufficiency (Hsiao et al., 2016; Stoke Therapeutics, 2018). Drug-resistant Dravet syndrome cases may thrive on alternative therapeutic strategies based on ketogenic diets (Nabbout et al., 2011; Wu et al., 2018). A recent study with 20 patients with medically intractable Dravet syndrome caused by missense, non-sense, insertion, deletions and splicing mutations presents efficacy during three months of treatment in 17 patients, decreasing seizure frequency in more than 50% (Yan et al., 2018). Besides that, Epidiolex is an FDA approved CBD-based drug approved in June 2018 for the treatment of severe forms of epilepsy, as Dravet and Lennox-Gastaut syndromes (U.S. Food and Drug Administration [website], 2018). Clinical trials using CBD in DS and LGS shown reduced frequency of seizures in monthly average (Lattanzi et al., 2020; Morano et al., 2020). Voltage-gated sodium channel are inhibit by CBD in low micromolar concentrations, IC50 between 1.9 and 3.8 μM, NaV1.4 and NaV1.1 being the most sensitive channels to CBD, 1.9 and 2.0 μM respectively, probably the mechanism of action is reducing channel availability due shift to more hyperpolarized potential in steady-state inactivation (Ghovanloo et al., 2019).

NaV1.2

NaV1.2 is encoded by the SCN2A gene (Wolff et al., 2017). It is located on chromosome 2q24.3 (Shi et al., 2009) and expressed in the CNS (Catterall, 2014a), especially in excitatory neurons (Syrbe et al., 2016) and glutamatergic neurons (Sanders et al.,
| Variant   | Location | Mutation | Disease                  | Alteration on biophysical properties or/and Clinical report | Reference                                                                 |
|-----------|----------|----------|--------------------------|--------------------------------------------------------------|---------------------------------------------------------------------------|
| Inherited mutation |
| A27T      | N-terminal | Missense | GEFS+ SMEB               | Diffuse spikes, prevailing in posterior regions (EEG)        | (Nicita et al., 2010)                                                   |
| L61P      | N-terminal | Missense | DS                       | Febrile seizures                                            | (Halvorsen et al., 2016)                                                 |
| F63L      | N-terminal | Missense | DS                       | Severe developmental delay                                  | (Nicita et al., 2010)                                                   |
| F90S      | N-terminal | Missense | DS                       | Multifocal spikes, frontal-dominant spike-waves complex (EEG)| (Sun et al., 2008; Wang et al., 2012; Xu et al., 2014; Butler et al., 2017b) |
| S103G     | N-terminal | Missense | SME                      | Ataxia                                                     | (Fujitomi, 2003; Ebrahimi et al., 2010; Tonekaboni et al., 2013)          |
| S106F     | N-terminal | Missense | Focal epilepsy           | Right temporal parietal occipital slow-wave and generalized spike-wave complex (EEG) | (Barba et al., 2014)                                                   |
| M145T     | DI (S1)   | Missense | Unidentified epilepsy    | Decrease current density                                   | (Mantegazza et al., 2005; Colosimo et al., 2007)                          |
| L193F     | DI (S3)   | Missense | GEFS+ SMEB               | Generalized tonic-clonic seizures                           | (Cui et al., 2011)                                                      |
| V244L     | DI (S4-S5) | Missense | DS                       | Myoclonic seizures                                          | (Mimura et al., 2006)                                                   |
| R377Q     | DI (S5-S6) | Missense | GEFS+                    | Generalized tonic-clonic seizures                           | (Zucca et al., 2008; Xu et al., 2015; Cetica et al., 2017; Lindy et al., 2018) |
| F412I     | DI (S6)   | Missense | GEFS+ SMEB               | Febrile seizure                                            | (Ebrahimi et al., 2010; Tonekaboni et al., 2013)                          |
| K488EfsX6 | DI-DII    | FrameShift | GEFS+                    | NR                                                         | (Yang et al., 2017)                                                      |
| R542Q     | DI-DII    | Missense | GEFS+ SME                | NR                                                         | (Escayg et al., 2001; Weiss et al., 2003; Combi et al., 2009; Orsico et al., 2009; Wang et al., 2012; Lee et al., 2014; Lal et al., 2016) |
| R618C     | DI-DII    | Missense | PEFS+                    | Generalized tonic-clonic seizures                           | (Brunklaus et al., 2015)                                                 |
| Y790C     | DI (S1-S2) | Missense | GEFS+                    | Multifocal epilepsy and bilateral bursts of 3-4 Hz spike and wave (EEG) | (Annesi et al., 2003; Orsico et al., 2009; Bechi et al., 2015; Bennett et al., 2017) |
| R859H     | DI (S4)   | Missense | GEFS+                    | Shift steady-state activation and inactivation to more negative values | (Volkers et al., 2011; Myers et al., 2017a; Lindy et al., 2018)          |
| S1084C    | DI-DIII   | Missense | Juvenile myoclonic epilepsy | Paroxysmal generalised polyspike-and- wave complexes with myoclonic seizures (EEG) | (Jingami et al., 2014)                                                   |
| T1174S    | DI-DIII   | Missense | FHIM FS                  | Shift steady state activation to more positive values        | (Scayg et al., 2001; Gargus and Tournay, 2007; Yordanova et al., 2011; Rostone et al., 2012; Celet et al., 2013; Lal et al., 2016) |
| V1353L    | DI (S5)   | Missense | PEFS+ GEFS+              | Non-functional channel                                      | (Wallace et al., 2001; Lossin et al., 2003; Bennett et al., 2017)        |
| A1429S    | DIII      | Missense | N-terminal               | No definitive epileptic spikes (EEG)                        | (Sone et al., 2012)                                                     |
| R1596H    | DIV (S2-S3) | Missense | GEFS+                    | Generalized spike-wave complexes (EEG)                      | (Hoffman-Zacharska et al., 2015)                                         |
| I1656M    | DIV (S4)  | Missense | GEFS+                    | Shift steady state activation to more positive values       | (Lossin et al., 2003)                                                   |
| G1674S    | DIV (S5)  | Missense | FS+                      | Febrile seizure                                            | (Saitoh et al., 2015a)                                                   |
| De novo mutation |
| Q3X       | N-terminal | Nonsense | DS                       | Generalized tonic clonic seizures                           | (Claes et al., 2003; Lim et al., 2011)                                    |
| G58X      | N-terminal | Nonsense | DS                       | Autistic characteristics; Hyperactivity                      | (Barba et al., 2014)                                                     |
| Y65X      | N-terminal | Nonsense | DS                       | Generalized tonic-clonic seizures                           | (Zucca et al., 2008)                                                    |
| E75D      | N-terminal | Nonsense | DS                       | Slow-spike-wave complexes (EEG)                             | (Arat et al., 2017)                                                     |

(Continued)
| Variant | Location | Mutation | Disease | Alteration on **biophysical properties** or/and **Clinical report** | Reference |
|---------|----------|----------|---------|-------------------------------------------------|-----------|
| L80_D81del | N-terminal | Inframe deletion | DS | Pharmacoresistant | (Usluer et al., 2016) |
| D81N | N-terminal | Missense | DS | Severe Motor and mental delay | (Usluer et al., 2016) |
| I91T | N-terminal | Missense | DS | Frontal-dominant spike-waves complex (EEG) | (Sun et al., 2008; Xu et al., 2014) |
| G96EfsX24 | N-terminal | FrameShift | NR | Genetic generalized epilepsy with intellectual disability | (Fry et al., 2016) |
| R101Q | N-terminal | Missense | DS | Psychomotor retardation | (Fukuma et al., 2004; Harkin et al., 2007; Marini et al., 2007; Depienne et al., 2008; Sun et al., 2010; Zuberi et al., 2011; Wang et al., 2012; Tonekaboni et al., 2013; Lee et al., 2014; Djemidi et al., 2016) |
| A104V | N-terminal | Missense | DS | Epileptic discharges, slow spike and weave; sharp wave, sharp and slow wave complex (EEG) | (Kwong et al., 2012; Myers et al., 2017a) |
| R118S | N-terminal | Missense | DS | Generalized tonic-clonic seizures | (Zucca et al., 2008) |
| F144YfsX5 | DI (S1) | Frameshift | SME | Moderate psychomotor retardation | (Fukuma et al., 2004; Zuberi et al., 2011; Wang et al., 2012; Vileneuve et al., 2014) |
| M145DfsX4 | DI (S1) | Frameshift | SME | Generalized tonic-clonic seizures without any provoked factors | (Yu et al., 2010) |
| G177E | DI (S2-S3) | Missense | SME | Non-functional channel | (Nabbout et al., 2003; Ohmori et al., 2006; Usluer et al., 2016) |
| L180X | DI (S2-S3) | Nonsense | DS | Focal spike wave (EEG) | (Liu et al., 2018) |
| W190X | DI (S3) | Nonsense | DS | Febrile, partial, generalized tonic-clonic and myoclonic seizures | (Marini et al., 2007; Kwong et al., 2012) |
| S213W | DI (S3-S4) | Missense | Epilepsy | Febrile and afebrile seizures | (Butler et al., 2017a) |
| R219SfsX57 | DI (S4) | Missense | DS | Generalized tonic-clonic seizures | (Claes et al., 2001) |
| R222X | DI (S4) | Missense | SME | No measurable current | (Claes et al., 2001; Nabbout et al., 2003; Fukuma et al., 2004; Harkin et al., 2007; Depienne et al., 2008; Orrico et al., 2009; Zuberi et al., 2011; Wang et al., 2012; Xu et al., 2014; Esterhuizen et al., 2018) |
| I227S | DI (S4) | Missense | SME | Epileptiform discharges on both sides and spikes/poly-spikes during photic stimulation (EEG) | (Claes et al., 2001; Nabbout et al., 2003; Fukuma et al., 2004; Harkin et al., 2007; Depienne et al., 2008; Orrico et al., 2009; Zuberi et al., 2011; Lindy et al., 2018) |
| A239V | DI (S4-S5) | Missense | SME | Generalized tonic-clonic seizures | (Claes et al., 2001; Nabbout et al., 2003; Fukuma et al., 2004; Harkin et al., 2007; Depienne et al., 2008; Orrico et al., 2009; Zuberi et al., 2011; Wang et al., 2012; Yu et al., 2010) |
| W280R | DI (S5-S6) | Missense | DS | Febrile seizures | (Nabbout et al., 2003; Wang et al., 2012; Liu et al., 2018) |
| P281L | DI (S5-S6) | Missense | DS | Moderate mental retardation | (Depienne et al., 2008; Gokben et al., 2017; Lindy et al., 2018) |
| E311X | DI (S5-S6) | Nonsense | DS | Haploinsufficiency | (Orrico et al., 2009) |
| G329E | DI (S5-S6) | Missense | SME | Generalized tonic-clonic seizures | (Myers et al., 2017a) |
| D366E | DI (S5-S6) | Missense | DS | Generalized tonic-clonic seizures | (Fujimura, 2003; Depienne et al., 2008; Zuberi et al., 2011) |
| W384R | DI (S5-S6) | Missense | SME | Generalized tonic-clonic seizures | (Zucca et al., 2008) |
| T391P | DI (S6-S7) | Missense | SME | Generalized tonic-clonic seizures | (Zuberi et al., 2011; Wang et al., 2012; Verbeek et al., 2013) |
| R393H | DI (S6-S7) | Missense | SME | Generalized tonic-clonic seizures | (Claes et al., 2003; Marini et al., 2007; Sun et al., 2010; Zuberi et al., 2011; Lemke et al., 2012; Rilstone et al., 2012; Wang et al., 2012; Xu et al., 2014; Djemidi et al., 2016; Haginoya et al., 2018) |
| V422L | DI (S6) | Missense | EE | Psychomotor developmental delay | (Ohashi et al., 2014) |

*(Continued)*
| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|---------|----------------------------------------------------------|-----------|
| Y426N   | DI-DII   | Missense | DS      | Decreased current density shift stead-state inactivation to more negative values Delayed recovery from inactivation | (Nabbout et al., 2003; Ohmori et al., 2006; Allen et al., 2016) |
| L433fsX16 | DI-DII   | FrameShift | Myoclonic astatic epilepsy | Generalized tonic-clonic seizures | (Ebach et al., 2005) |
| E435X   | DI-DII   | Nonsense | DS      | Myoclonic seizures | (Fukuma et al., 2004; Wang et al., 2012) |
| Q554H   | DI-DII   | Missense | DS      | Generalized tonic-clonic seizure Atypical absence | (Skjei et al., 2015) |
| S662X   | DI-DII   | Nonsense | PEFS+ | Generalized tonic-clonic seizures Febrile seizures Generalized tonic-clonic Severe intellectual disability | (Yu et al., 2010) |
| W738X   | DI-DII   | Nonsense | SME    | Generalized tonic-clonic seizures Severe mental retardation | (Kwong et al., 2012; Xu et al., 2014) |
| T808S   | DII (S2) | Missense | ICEGTC | Rare sharp waves in left temporal (EEG) Increase current density Delay recovery from inactivation Focal spike activity (EEG) | (Fujisawa, 2003; Rhodes et al., 2005) |
| S843X   | DII (S3) | Nonsense | DS      | Multifocal epilepsy Hemiconic Cardiac arrest Severe intellectual disability | (Carranza Rojo et al., 2011; Barba et al., 2014) |
| T932X   | DII (S5-S6) | Nonsense | SME    | Generalized tonic-clonic seizures Severe mental retardation Moderate psychomotor retardation | (Claes et al., 2003; Dhamija et al., 2014) |
| M934I   | DII (S5-S6) | Missense | DS      | Status epilepticus Generalized tonic-clonic seizures Complex partial seizures | (Claes et al., 2003; Ohmori et al., 2006) |
| R946C   | DII (S5-S6) | Missense | SME    | Post trauma epilepsy Laterralized tonic-clonic seizures | (Claes et al., 2003; Ohmori et al., 2006) |
| R946S   | DII (S5-S6) | Missense | SMEB   | Severe non-functional Channel | (Saitoh et al., 2015a; Saitoh et al., 2015b) |
| R946H   | DII (S5-S6) | Missense | PEFS+ | Non-functional Channel | (Fukuma et al., 2004; Harkin et al., 2007; Depienne et al., 2008; Liao et al., 2010a; Verbeek et al., 2011; Volkers et al., 2011; Zuberi et al., 2011; Wang et al., 2012; Verbeek et al., 2013) |
| C959R   | DII (S5-S6) | Missense | SMEB   | Post trauma epilepsy Non-functional Channel | (Claes et al., 2003; Ohmori et al., 2006) |
| V971L   | DII (S6) | Missense | SMEB   | Post trauma epilepsy Myoclonic seizures Apneic spells | (Poryo et al., 2017) |
| V982L   | DII (S6) | Missense | SMEB   | Focal epilepsy | (Singh et al., 2009; Saitoh et al., 2012; Saitoh et al., 2015a; Saitoh et al., 2015b) |
| V983A   | DII (S6) | Missense | ICEGTC | Multifocal spikes, high voltage slow-waves (EEG) Reduced current density Shift steady-state inactivation to more positive values Accelerated recovery from inactivation | (Fujisawa, 2003; Rhodes et al., 2005) |
| V983AfsX2 | DII (S6) | FrameShift | SMEB   | Enlarged extracerebral gap (MRI) | (Wang et al., 2017b) |
| L986F   | DII (S6) | Missense | SMEB   | Non-functional channel | (Claes et al., 2001; Lossin et al., 2003) |
| L991VfsX2 | DII (S6) | FrameShift | SMEB   | Febrile, partial, generalized tonic-clonic, myo-clonic seizures | (Kwong et al., 2012) |
| Variant      | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|--------------|----------|----------|---------|-------------------------------------------------------------|-----------|
| N1011I       | DII-DIII | Missense | ICEGTC  | Rare sharp waves in lateral-temporal (EEG) Reduced current density Shift steady state inactivation to more negative values | (Fujiwara, 2003; Rhodes et al., 2005) |
| D1046MfsX9   | DII-DIII | FrameShift | DS      | Diffuse cerebral edema (Computed tomography) Generalized clonic seizures | (Myers et al., 2017b; Claes et al., 2001) |
| S1100KfsX8   | DII-DIII | FrameShift | DS      | Severe mental retardation | (Depienne et al., 2008; Hernández Chávez et al., 2014) |
| S1104X       | DII-DIII | Missense | DS      | Febrile seizures | (Depienne et al., 2008; Hernández Chávez et al., 2014) |
| E1153X       | DII-DIII | Nonsense  | DS      | Focal epilepsy with frontal-lateral activity (EEG) Severe mental retardation Intractable seizures despite multiple anti-epileptic drugs | (Hernández Chávez et al., 2014; Willemsen et al., 2012) |
| E1176NfsX32  | DII-DIII | FrameShift | DS      | Severe intellectual disability | (Hirai et al., 2007; Butler et al., 2017b) |
| R1213X       | DII-DIII | Nonsense  | SME      | Rare spikes, multifocal spikes and spike-wave complex (EEG) | (Claes et al., 2001) |
| L1230P       | DIII (S1) | Missense | DS      | Focal spike-wave complex (EEG) Febrile seizures | (Liu et al., 2018) |
| F1263L       | DII (S2) | Missense | SMEB     | Rare spike-wave complex and poly spike-waves complex (EEG) | (Fujiwara, 2003) |
| R1636Q       | DIV (S4) | Missense  | DS      | Epileptic encephalopathy Myoclonic seizures | (Harkin et al., 2007; Butler et al., 2017b) |
| V1637E       | DIV (S4) | Missense  | DS      | Episodic status epilepticus triggered by fever Generalized tonic-clonic seizures | (Nishi et al., 2010; Zuberi et al., 2011) |
| F1671fsX8    | DIV (S4-S5) | FrameShift | DS      | Severe mental retardation | (Claes et al., 2001; Sugawara et al., 2002; Depienne et al., 2008; Riva et al., 2009) |
| A1685D       | DIV (S5) | Missense  | DS      | Spike-wave complex (EEG) Non-functional channel Myoclonic seizures Atypical absence | (Fukuma et al., 2004; Wang et al., 2012; Cetica et al., 2017) |
| Y1694C       | DIV (S5) | Missense  | DS      | Myoclonic seizures Severe psychomotor retardation | (Verbeek et al., 2013) |
| L1717P       | DIV (S6-S7) | Missense  | SME      | Generalized tonic-clonic seizure Severe psychomotor retardation | (Wu et al., 2015) |
| T1722A       | DIV (S6-S7) | Missense  | DS      | Myoclonic, hemiconvulsive, focal seizures | (Petrelli et al., 2012) |
| C1741S       | DIV (S6-S7) | Missense  | TLE-MTS  | Febrile status epilepticus | (Tiefes et al., 2019) |
| G1754R       | DIV (S6-S7) | Missense  | DS      | Focal seizures Hemiconvulsions | (Petrelli et al., 2012) |
| S1768R       | DIV (S6-S7) | Missense  | DS      | Absences and tonic-clonic seizures | (Willemsen et al., 2012) |
| E1881X       | C-terminal | Missense  | SMEB     | Febrile and generalized seizures | (Villeneuve et al., 2014) |

Non genetic origin mutations reported*

| Variant      | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|--------------|----------|----------|---------|-------------------------------------------------------------|-----------|
| G177DfsX4    | DI (S2-S3) | FrameShift | DS      | Generalized tonic-clonic seizures | (Fujiwara, 2003) |
| V207G        | DI (S3) | Missense  | EE      | Early-onset multifocal seizures Generalized tonic seizures | (Dacoud et al., 2016; Le Gal et al., 2014) |
| D249E        | DI (S4-S5) | Missense  | DS      | Generalized tonic seizures | (Le Gal et al., 2014) |
| N275K        | DI (S5) | Missense  | PEFS+   | Absences; Mental retardation Hippocampal volume loss (MR) | (Kim et al., 2014) |
| T363R        | DI (S5-S6) | Missense  | DS      | Generalized tonic-clonic seizures | (Zuberi et al., 2011; Le Gal et al., 2014) |
| N416I        | DI (S6) | Missense  | DS      | Focal spike-wave (EEG) Multifocal spikes (EEG) | (Zhou et al., 2018; Haginoya et al., 2018) |

*Non genetic origin mutations reported: Mutations described through clinical diagnosis, but the mutation type (Mendelian or de novo) were not reported, mainly due to the lack of parents to perform genotyping and difficulty in contacting the family. Generalized epilepsy with febrile seizures plus (GEFS+); Febrile seizures (FS); Febrile seizures plus (FS+); Lennox-Gastaut syndrome (LGS); Dravet syndrome (DS); Borderline severe myoclonic epilepsy (SMEB); Severe myoclonic epilepsy (SME); Familial hemiplegic migraine (FHM); Partial epilepsy with antecedent FS (PEFS); Intractable childhood epilepsy with generalized tonic-clonic seizures (ICGTC); Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC); Epileptic encephalopathy (EE); Malignant migrating partial seizures of infancy (MMPSI); Temporal lobe epilepsy (TLE); Mesial temporal sclerosis (MTS); Not Reported (NR); Domain (D); Segment (S); Electroencephalography (EEG); Magnetic resonance imaging (MRI).
More than 100 mutations have already been described for this gene, with approximately 300 patients studied yet (Reynolds et al., 2020) (Table 2). The most common diseases related with SCN2A mutation are West syndrome (WS; OMIM #308350), epilepsy of infancy with migrating focal seizures (EIMFS; OMIM #616645), and benign familial neonatal-infantile seizures (BFNIS; OMIM #607745) (Perucca and Perucca, 2019).

Although epilepsy-related mutations are present throughout the channel, several hotspots such as the ion selectivity filter, the voltage-sensing domain, the intracellular N-terminal, and the C-terminal domain can be highlighted (Sanders et al., 2018). NaV1.2 channels are expressed in the excitatory neurons; therefore, GoF mutations are related to epilepsy because it causes neuronal hyperexcitability. On the other hand, LoF mutations are related to autism and intellectual disability phenotype (Ben-Shalom et al., 2017). Nevertheless, some studies have already related loss of function to epilepsy, as described by Lossin and co-workers (2012) with R1312T mutation (Lossin et al., 2012).

| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/ and Clinical report | Reference |
|---------|----------|----------|---------|---------------------------------------------------------------|-----------|
| Inherited mutation | | | | | |
| R19K | N-terminal | Missense | FS+ | Febrile seizures | (Ito et al., 2004) |
| R36G | N-terminal | Missense | BFS | Partial seizure with eye deviation | (Wolff et al., 2017) |
| I172V | DI (S2) | Missense | FS | Focal seizures | (Saitoh et al., 2015a) |
| R188W | DI | Missense | FS+ | Generalized tonic or chronic tonic seizures | (Ito et al., 2004) |
| A202V | DI | Missense | BFNS | Focal seizures | (Wolff et al., 2017) |
| V208E | DI | Missense | BFS | Positive shifts of both activation and inactivation curves | (Berkovic et al., 2004; Scalmanni et al., 2006; Zara et al., 2013) |
| R223Q | DI (S4) | Missense | BFS | Focal spikes, bifrontal slow wave activity (EEG) | (Herlenius et al., 2007) |
| F328V | DI (SS-S6) | Missense | SMEB | Status epilepticus | (Shi et al., 2009; Saitoh et al., 2015a) |
| Q383E | DI | Missense | BFS | Seizures in early infancy | (Syrbe et al., 2016) |
| E430Q | DI-DII | Missense | BFS | Focal spikes and bifrontal slow wave activity (EEG) | (Herlenius et al., 2007) |
| A467T | DI-DII | Missense | GEFS+ | Loss of consciousness | (Liu et al., 2018) |
| R524Q | DI-DII | Missense | FS | Right parietal-occipital sharp waves (EEG) | (Ito et al., 2004) |
| V992I | DI (SS) | Missense | BFS | Generalized tonic-clonic seizures | (Berkovic et al., 2004; Scalmanni et al., 2006; Misra et al., 2008; Zara et al., 2013) |
| N1001K | DI-DIII | Missense | BFS | Tonic body extension | (Berkovic et al., 2004; Scalmanni et al., 2006; Misra et al., 2008; Zara et al., 2013) |
| L1003I | DIII-DIII | Missense | BFS | Shift steady state activation and inactivation to more positive values | (Berkovic et al., 2004; Scalmanni et al., 2006; Misra et al., 2008; Zara et al., 2013) |
| R1319Q | DIII (S4) | Missense | BFS | Increased persistent Na+ current | (Berkovic et al., 2004; Scalmanni et al., 2006; Misra et al., 2008; Zara et al., 2013) |
| E1321K | DIII | Missense | BFS | Shift steady state activation to more positive values | (Berkovic et al., 2004; Scalmanni et al., 2006; Misra et al., 2008; Zara et al., 2013) |
| L1330F | DIII (S4-S5) | Missense | BFS | Delayed fast inactivation | (Herlenius et al., 2007) |
| L1563V | DIV | Missense | BFS | Increase in neuronal excitability | (Lauzmann et al., 2013) |
| Y1589C | DIV (S2-S3) | Missense | BFS | Shift steady state inactivation to more positive values | (Berkovic et al., 2004; Scalmanni et al., 2006; Misra et al., 2008; Zara et al., 2013) |
| I1596S | DIV (S3) | Missense | BFS | Central and posterior focal spikes (EEG) | (Herlenius et al., 2007) |
| K1641N | DIV | Missense | BFS | Focal seizures with secondary generalization | (Zara et al., 2013) |

(Continued)
| Variant Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|------------------|----------|---------|---------------------------------------------------------|-----------|
| R102X            | N-terminal | Nonsense | EE | Shift steady state inactivation to more negative values, Decrease of available channel | (Kamiya, 2004; Ogiwara et al., 2009) |
| N132K            | DI        | Missense | EOEE | Tonic-clonic seizures | (Matalon et al., 2014) |
| M136I            | DI        | Missense | EIMFS | Focal seizures, Spasms | (Carvill et al., 2013; Howell et al., 2015) |
| E169G            | DI (S2)   | Missense | EOEE | Multifocal spikes (EEG), Febrile seizure, Myoclonic seizure, Focal seizure | (Nakamura et al., 2013) |
| W191C            | DI        | Missense | EIMFS | Frequent multifocal spikes (EEG) | (Su et al., 2018) |
| F207S            | DI        | Missense | BNS | Tonic-clonic seizures, Clonic seizures, Spasms | (Wolff et al., 2017) |
| G211D            | DI        | Missense | WS | NR | (Kodera et al., 2013) |
| N212D            | DI (S3-S4)| Missense | OS and WS | Eyelid myoclonic, Spasms | (Nakamura et al., 2013) |
| R220G            | DI        | Missense | EE | Generalized tonic-clonic seizures, Generalized spike and slow wave (EEG) | (Mercimek-Mahmutoglu et al., 2015) |
| T227I            | DI        | Missense | WS | Tonic seizures, Apneic seizures, Spasms | (Wolff et al., 2017) |
| T236S            | DI (S4-S5)| Missense | OS | Focal seizure | (Nakamura et al., 2013) |
| A240S            | DI        | Missense | EIMFS | Focal seizures | (Howell et al., 2015) |
| M252V            | DI (S5)   | Missense | BFNIS | Increased persistent current, Accelerated of recovery from fast inactivation, Accelerated of recovery from slow inactivation | (Liao et al., 2010b) |
| V261M            | DI (S5)   | Missense | BFNIS | Enhanced persistent current, Faster recovery from inactivation | (Liao et al., 2010b) |
| A286T            | DI (S5)   | Missense | EOEE | Multifocal spikes (EEG) | (Nakamura et al., 2013) |
| V423L            | DI (S6)   | Missense | OS | Change in slope of steady-state activation curve, Enhanced persistent current | (Wolff et al., 2017) |
| E430G            | DI-DII    | Missense | OS | Generalized tonic-clonic seizures | (Matalon et al., 2014) |
| E717G fs*30      | DI-DII    | Splice site | EE | Cerebral and cerebellar atrophy | (Horvath et al., 2016) |
| G828V            | DII       | Missense | BNS | Focal seizures, Clonic seizures, Autonomic seizures, Tonic-clonic seizures, Multifocal spikes (EEG) | (Wolff et al., 2017) |
| R853Q            | DII (S4)  | Missense | WS | Reduced transient current amplitude and density, Shift steady state inactivation to more negative values, Decreased persistent current | (Samanta and Ramakrishnaiah, 2015; Wolff et al., 2017; Berecki et al., 2018; Mason et al., 2019) |
| R856L            | DII       | Missense | EIMFS | Focal seizures | (Howell et al., 2015) |
| R856Q            | DII       | Missense | OS | Tonic seizures | (Wolff et al., 2017) |
| S863F            | DII       | Missense | BNS and Focal epilepsy | Generalized tonic-clonic seizures | (Wolff et al., 2017) |
| I873M            | DII       | Missense | EIEE | Abnormal electroretinogram | (Trump et al., 2016) |
| N876T            | DII (S4-S5)| Missense | OS and WS | Spasms, Focal seizure | (Nakamura et al., 2013) |
| L881P            | DII       | Missense | WS and LGS | Tonic seizures, Atypical absences | (Wolff et al., 2017) |

(Continued)
| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|---------|----------------------------------------------------------|------------|
| G882R   | DII      | Missense | EIMFS   | Unilateral tonic-clonic                                   | (Wolff et al., 2017) |
| G882E   | DII      | Missense | EIMFS   | Autonomic seizures                                        | (Wolff et al., 2017) |
|         |          |          |         | Hemidonic seizures                                       |            |
|         |          |          |         | Myoclonic seizures                                        |            |
|         |          |          |         | Clonic seizures                                           |            |
| V887A   | DII      | Missense | OS      | Intractable infantile epilepsy                            |            |
|         |          |          |         | Tonic-clonic seizures and absences                        | (Wolff et al., 2017) |
| G899S   | DII (S5) | Missense | Intractable infantile epilepsy                            |            |
|         |          |          |         | Shift steady-state activation to more positive values     |            |
|         |          |          |         | Increased slop factor                                     |            |
| K905N   | DII      | Missense | EIMFS   | Focal seizures                                            | (Howell et al., 2015) |
|         |          |          |         | Muscle tone                                               |            |
| F928C   | DII      | Missense | EIMFS   | Focal seizures                                            | (Carvill et al., 2013; Howell et al., 2015) |
| H930Q   | DII      | Missense | MAE     | Tonic-clonic seizures                                     | (Wolff et al., 2017) |
|         |          |          |         | Atonic seizures                                           |            |
|         |          |          |         | Myoclonic-atonic seizures                                 |            |
|         |          |          |         | Tonic seizures                                            |            |
|         |          |          |         | Atypical absences                                         |            |
| N976K   | DII      | Missense | EE      | Focal seizures                                            | (Howell et al., 2015) |
| S987I   | DII      | Missense | EIEE    | Focal and tonic seizures                                   | (Trump et al., 2016) |
|         |          |          |         | Muscle tone                                               |            |
|         |          |          |         | Reduced current density                                   |            |
| G999L   | DII-DIII | Missense | Infantile epilepsy                                     |            |
|         |          |          |         | Diffuse slowing with high-amplitude bursts of activity (EEG)| (Foster et al., 2017) |
| E999K   | DII-DIII | Missense | EIEE    | Generalized seizures with burst suppression               | (Trump et al., 2016) |
| E999V   | DII-DIII | Missense | EIEE    | NR                                                       | (Allen et al., 2016; Trump et al., 2016) |
|         |          |          |         | Muscle tone                                               |            |
| I1021Y.fs*16 | DII-DIII | Frameshift | LGS   | NR                                                       | (Carvill et al., 2013) |
| E1211K  | DII (S1) | Missense | WS      | Shift steady-state activation and inactivation to more negative values | (Ogiwara et al., 2009; Wong et al., 2015) |
|         |          |          |         | Slower recovery from inactivation                          |            |
| K1260E and K1260Q (Mosaic) | DII | Missense | EIEE    | NR                                                       | (Trump et al., 2016) |
| R1312T  | DII (S4) | Missense | DS      | Reduced current density                                   | (Shi et al., 2009; Lossin et al., 2012) |
|         |          |          |         | Shift steady-state activation and inactivation to more negative values |            |
|         |          |          |         | Enhanced closed-state inactivation                        |            |
|         |          |          |         | Slowed recovery from inactivation                          |            |
| M1323V  | DIII     | Missense | OS and WS | Multifocal spikes (EEG)                                  | (Nakamura et al., 2013) |
| V1326D  | DIII     | Missense | EIMFS   | Focal seizures                                            | (Dhamija et al., 2013) |
| S1336Y  | DIII     | Missense | OS and WS | Modified hypersrrhythmia                                  | (Nakamura et al., 2013) |
| M1338T  | DIII (S4) | Missense | OS      | Spasms                                                   | (Nakamura et al., 2013) |
|         |          |          |         | Multifocal spikes (EEG)                                   |            |
| L1342P  | DIII     | Missense | IOEE    | Progressive brain atrophy                                 | (Hackenberg et al., 2014) |
|         |          |          |         | Short tonic seizures                                      |            |
|         |          |          |         | Multifocal sharp wave activity (EEG)                      |            |
| I1473M  | DIII (S6) | Missense | SNEE    | Shift steady-state inactivation to more negative values   | (Ogiwara et al., 2009) |
| Q1479P  | DIII-DIV | Missense | EIEE    | NR                                                       | (Trump et al., 2016) |
| V1528Cfs*7 | DIII-DIV | Frameshift | LGS   | Tonic-clonic seizures                                     | (Wolff et al., 2017) |
|         |          |          |         | Status epilepticus                                        |            |
| Q1531K  | DIII-DIV | Missense | BNS     | Clonic seizures                                           | (Wolff et al., 2017) |
|         |          |          |         | Generalized tonic-clonic seizures                          |            |
| I1537S and M1538I | DIV | Missense | OS and WS | Clonic seizures                                           | (Foster et al., 2017) |
| M1548V  | DIV      | Missense | OS and WS | Generalized tonic-clonic seizures                          | (Wolff et al., 2017) |
| G1593R  | DIV      | Missense | EIMFS   | Focal seizures                                            | (Howell et al., 2015) |
| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|---------|-------------------------------------------------------------|-----------|
| F1597L  | DIV (S3) | Missense | EIIMFS  | Shift steady-state activation to more negative values       | (Wolff et al., 2017) |
| D1598G  | DIV (S3) | Missense | SME     | Severe intellectual disability                              | (Need et al., 2012) |
| P1622S  | DIV (S3-S4) | Missense | MAE     | Shift steady-state inactivation to more negative values     | (Wolff et al., 2017) |
| T1623N  | DIV (S3-S4) | Missense | OS and WS | Multifocal spikes (EEG)                                     | (Nakamura et al., 2013) |
| V1627M  | DIV    | Missense | EIIMFS  | Focal seizures                                             | (Wolff et al., 2017) |
| G1634V  | DIV    | Missense | OS      | Focal seizures                                             | (Howell et al., 2015) |
| I1640S  | DIV    | Missense | EE      | Tonic seizures                                             | (Wolff et al., 2017) |
| L1650P  | DIV    | Missense | EIEE    | NR                                                          | (Trump et al., 2016) |
| A1652P  | DIV    | Missense | WS      | Generalized tonic-clonic seizures                           | (Wolff et al., 2017) |
| S1656F  | DIV    | Missense | LGS     | Generalized tonic-clonic seizures                           | (Fukasawa et al., 2015) |
| L1660W  | DIV    | Missense | Acute encephalopathy | Tonic-clonic convulsions Frequent spikes and sharp waves in the right fronto-temporal regions (EEG) Cerebellar atrophy (MRI) | (Fukasawa et al., 2015) |
| Q1811E  | C-terminal | Missense | OS      | Generalized tonic-clonic seizures                           | (Wolff et al., 2017) |
| L1829F  | C-terminal | Missense | EIEE    | NR                                                          | (Trump et al., 2016) |
| H1853R  | C-terminal | Missense | OS      | Generalized tonic-clonic seizures                           | (Martin et al., 2014) |
| R1882L  | C-terminal | Missense | Epilepsy | Generalized and irregular spike wave and polyspike wave activity (EEG) Focal and generalized tonic-clonic seizures with opisthotonus, bradycardia, and cyanosis | (Baasch et al., 2014) |
| R1882G  | C-terminal | Missense | BIS     | Shift steady-state inactivation to more positive values Increase current density and protein production | (Carvill et al., 2013; Schwarz et al., 2016; Wolff et al., 2017) |
| R1882Q  | C-terminal | Missense | EIEE    | Increased current density                                    | (Trump et al., 2016; Berecki et al., 2018; Mason et al., 2019) |
| D25Nβ1 | β subunit | Substitution | GEFS+ | Inhibits the increment of functional expression of NaCh currents Abolishes the shift of the voltage dependence of activation and inactivation | (Baroni et al., 2018) |

*human embryonic kidney 293 (HEK) cells co-expressing human Nav1.2 sodium channels and D25Nβ1

Chromosome 2q24.3
Portions of the SCN2A and SCN3A genes

Chromosome 24.3q31.1
58 known genes including SCN2A, SCN1A, SCN3A, SCN9A and SCN7A

Non genetic origin mutations reported*

| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|---------|-------------------------------------------------------------|-----------|
| V213D  | DI (S4) | Missense | EOEE    | Focal seizure Focal spikes (EEG)                             | (Nakamura et al., 2013) |

*Continued*
| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|---------|----------|---------|-------------------------------------------------------------|-----------|
| T218K   | DI      | Missense | EIMFS   | Focal seizures, Spasms                                      | (Howell et al., 2015) |
| D649N   | DI-DII  | Missense | DS      | NR                                                          | (Wang et al., 2012) |
| V752F   | DI-DII  | Missense | Absence epilepsy | Increased current density | Shift steady-state activation and inactivation to more negative values | (Oliva et al., 2014) |
| M1128T  | DI-DIII | Missense | AERPPS  | Generalized convulsive seizure, Shift toward negative values | (Kobayashi et al., 2012) |
|         |         |          |         | Slow background activity and rare multifocal spikes over the right temporal and bilateral frontopolar regions (EEG) | |
|         |         |          |         | Brain edema (Cranial computed tomography) | |
| G1522A  | DIII-DIV| Missense | EE      | Absence seizures, Generalized spike and waves (EEG) | (Mercimek-Mahmutoglu et al., 2015) |
| R1629L  | DIV (S4)| Missense | EOE    | Focal seizure | | (Nakamura et al., 2013) |
| R1918H  | C-terminus | Missense | GEFS+    | Generalized tonic-clonic seizures, Delayed fast inactivation, Increased persistent current when expressed in Xenopus oocytes | (Haug et al., 2001) |
| GAL879-881QQQ | DII (S4-S5) (rat brain) | Missense | Epilepsy | | (Kearney et al., 2001) |
| R85C    | Extracellular immunoglobulin-like domain (β1 subunit) | Substitution | GEFS+ | Fail to modulate fast inactivation kinetics | (Xu et al., 2007) |
| R85H    | Extracellular immunoglobulin-like domain (β1 subunit) | Substitution | GEFS+ | Fail to modulate fast inactivation kinetics | (Xu et al., 2007) |
| C121W   | Ig-like domain (β1 subunit) | Substitution | GEFS+ | Destabilization of steady-state inactivation, Disrupts the thermoprotective role of the β1 subunit on channel availability | (Egri et al., 2012; AbdelSayed and Sokolov, 2013) |
| Chromosome 2q24.3 Involves the SCN2A and SCN3A genes | Chromosome | Duplication (1.77 Mb) | EOE | Multifocal spikes (EEG), Epileptic spasms | (Baumer et al., 2015) |
| Chromosome 2q24.3-q31.1 47 genes involved including SCN1A, SCN2A, SCN3A, SCN7A and SCN9A | Chromosome | Deletion (10.4-Mb) | Severe epilepsy | Epileptic seizure with pale, atonic periods followed by a spasm-like out-throwing of both arms, Predominantly right-sided epileptiform activity (EEG) | (Davidsson et al., 2008) |

*Non genetic origin mutations reported: Mutations described through clinical diagnosis, but the mutation type (Mendelian or de novo) were not reported, mainly due to the lack of parents to perform genotyping and difficulty in contacting the family. Generalized epilepsy with febrile seizures plus (GEFS+); Benign familial neonatal-infantile seizures (BFNIS); Benign familial neonatal seizures (BFNS); Benign familial infantile seizures (BIFS); Benign neonatal seizures (BNS); Benign infantile seizures (BIS); Febrile seizures (FS); Febrile seizures plus (FS+); Epilepsy of infancy with migrating focal seizures (EIIMFS); Ohtahara syndrome (OS); West syndrome (WS); Lennox-Gastaut syndrome (LGS); Dravet syndrome (DS); Borderline severe myoclonic epilepsy (SMEB); Severe myoclonic epilepsy (SME); Early-onset epileptic encephalopathies (EEOE); Acute encephalitis with refractory, repetitive partial seizures (AEFRPPS); Early infantile epileptic encephalopathy (EIEE); myoclonic-atonic epilepsy; Infantile onset epileptic encephalopathy (IOEE); Sporadic neonatal epileptic encephalopathy (SNEE); Epileptic encephalopathy (EE); Not Reported (NR); Domain (D); Segment (S); Electrophysiology (EEG); Magnetic resonance imaging (MRI).
Normally, LoF SCN2A gene mutations for epilepsy are related to late-onset epilepsy; however, the mechanism of action is unclear (Mason et al., 2019).

In some cases, NaV1.2 seizures are not controlled not even by various antiepileptic drugs, as with the patient described by Syrbe and colleagues (2016). The proband, even after being treated with oxcarbazepine (OXC), valproic acid, topiramate, sulthiamine, phenytoin, among other drugs, kept on having seizures (Syrbe et al., 2016). Furthermore, the SCB drugs can assist the patient during the treatment as described by Gorman and King (2017). The patient had seizures controlled after administration of phenytoin (Gorman and King, 2017). In addition, Musto et al. (2020) cite benefits treatments using SCB such as carbamazepine, mexiletine, oxcarbazepine, phenytoin, lidocaine, and lamotrigine for patients with early onset epilepsies (Musto et al., 2020). Besides, Peters and colleagues studied a substance commercially used as an antianginal drug (human heart) called ranolazine that has been shown to affect NaV1.2 channels, reducing macroscopic currents and delaying the recovery of fast and slow inactivation of the NaV1.2 channel, consequently with more future studies ranolazine could be a efficacious therapy for epilepsy (Peters et al., 2013).

Drugs can be important to modulate channel kinetics for both GoF and LoF, but some precautions must be observed. For example, the degree of conservation between subtypes, such as NaV1.2 and other sodium channels as NaV1.5 and the excessive decrease in channel function or the excessive increase in function obtained by the drug (Sanders et al., 2018).

Organizations like the FamilialSCN2A Foundation (www.scn2a.org) might be essential in the search for new treatments. Understanding the genotype-phenotype of gain and loss of function is essential because science-patient relationship may be helpful in the search for new therapies (Sanders et al., 2018).

**NaV1.3**

SCN3A is a gene that encodes for type 3 voltage-gated Na⁺ channel α subunit, the NaV1.3, located on human chromosome 2q24, in a cluster with SCN1A and SCN2A (Holland et al., 2008). NaV1.3 is expressed predominantly in the CNS during embryonic and neonatal development, being extremely low or sometimes undetectable in postnatal individuals. Subsequently, during infancy, it is gradually replaced by increased expression of the NaV1.1 isoform (Felts et al., 1997; Whitaker et al., 2000; Cheah et al., 2013; Zaman et al., 2018). On the other hand, studies regarding nervous system injury and neuropathic pain showed an increasing presence of NaV1.3 channels in affected tissues, suggesting a pivotal role of these transmembrane proteins in these processes and diseases (Hains et al., 2003; Waxman and Hains, 2006; Black et al., 2008). For the reasons mentioned above, in the last decades, NaV1.3-associated pathogenesis has been restricted to pain. Recently, a genetic linkage between NaV1.3 mutated variants and epilepsy has been suggested, especially in cryptogenic epilepsy cases (OMIM#182391).

K354Q was the first described NaV1.3 epilepsy-related mutation that revealed harmful electrophysiological alterations (Holland et al., 2008; Estacion et al., 2010). In fact, mutations can change many functional characteristics of NaV1.3 affecting biophysical properties differently; however, these changes result predominantly in neuronal hyper-responsiveness (Table 3) (Cummins and Waxman, 1997; Chen et al., 2000; Cummins et al., 2001; Sun et al., 2007). Previous reports correlate heterozygous variants in SCN3A in association with moderate forms of epilepsy, while homozygosis is related with severe cognitive damage and premature mortality, resulting in a broad range of epileptic phenotypes (Estacion and Waxman, 2013; Vanoye et al., 2014; Lamar et al., 2017).

Different hereditary mutations on NaV1.3 have been reported to date in patients with epilepsy. In general, the biophysical characterization of these mutations reveals GoF, only one mutation (N302S) is related with LoF (Chen et al., 2015), but both GoF and LoF may lead to an increased seizure susceptibility (Lamar et al., 2017).

Moreover, several de novo mutations in SCN3A have been described in the last three years, related with severe infantile neurological dysfunctions and cognitive impairments. These mutations may alter the functionality of NaV1.3 channels, neurons organization, migration, and proliferation during the embryonic development (Smith et al., 2018). Epileptic encephalopathy and polymicrogyria are the main features related with these pathogenic variants, and, so far, polymicrogyria was not reported in other channelopathies, being an exclusive characteristic of SCN3A mutants (Inuzuka et al., 2019).

There is a lack of clinical data on SCN3A-related epilepsies, especially regarding treatment and the use of specific medication. However, in vitro studies reported that mutations related with GoF effect respond favorably to treatment using SCB, like phenytoin, carbamazepine, lacosamide, and topiramate (Sun et al., 2007; Sheets et al., 2008; Colombo et al., 2013; Zaman et al., 2018). The anticonvulsant valproic acid represents a novel and promising epigenetic therapeutic approach (Tan et al., 2017). The compound modulates the SCN3A gene through methylation, downregulating the expression of NaV1.3 and, consequently, decreasing biophysical alterations in the channel.

**NaV1.6**

The SCN8A gene encodes for type 8 voltage-gated Na⁺ channel α subunit, the NaV1.6, located in chromosome 12q13.13. The first case of SCN8A pathogenic variant associated with epilepsy was reported eight years ago (Veeramah et al., 2012). Thereafter, due to advances in genome sequencing technology, especially the WES, the number of epilepsy diagnosis associated with NaV1.6 mutations has increased significantly (OMIM #600702), with more than 300 patients diagnosed with SCN8A epilepsy mutations and nearly 200 different putative spots of mutations described, totaling over 100 published reports (Table 4). A website developed especially to present SCN8A epilepsy and related diseases (www.scn8a.net) was created to provide information to families, clinicians, and researchers, gathering news and recent publications on the subject in a private forum for family interaction, to answer questions, strengthening the ties between the community and the researchers.

NaV1.6 is expressed since prenatal, during fetal development (Plummer et al., 1997). Shortly after birth, expression begins to increase, reaching maximum levels during the first years of life. This
### TABLE 3 | SCN3A-related epilepsies identified in clinical patients through WES and/or NGS.

| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|---------|------------------------------------------------------------|-----------|
| **Inherited mutation** | | | | | |
| K354Q | DI | Missense | CCE | Enhanced persistent current and current amplitude provokes by ramp protocol | (Holland et al., 2008; Estacion et al., 2010) |
| R357Q | DI (SS-S6) | Missense | Focal epilepsy | Reduced current density | (Vanoye et al., 2014) |
| R621C | DI-DII | Missense | BECTS | Enhanced current amplitude provokes by ramp voltage protocol | (Vanoye et al., 2014) |
| E1111K | DII-III | Missense | Focal epilepsy | Enhanced current amplitude provokes by ramp voltage protocol | (Vanoye et al., 2014) |
| M1323V | DII (SS-S6) | Missense | Focal epilepsy | Enhanced current amplitude provokes by ramp voltage protocol | (Vanoye et al., 2014) |
| C121W | b1 subunit mutation* | Extracellular Ig loop | Substitution | Resistant to enter into close-state inactivation | (Lucas et al., 2005) |
| **Chromosome 2q24.3 Involves the SCN1A, SCN2A, and SCN3A genes** | | | | | |
| | | | | | |
| **Chromosome 2q24.3 Involves the SCN1A, SCN2A, and SCN3A genes** | | | | | |
| | | | | | |
| **Chromosome 2q23.3q24.3 Involves the SCN2A and SCN3A genes** | | | | | |
| | | | | | |
| **De novo mutation** | | | | | |
| L247P | DI | Missense | Childhood focal epilepsy | Reduced current density associated with low protein expression | (Lamar et al., 2017) |
| I875T | DI (S4-S5) | Missense | EE | Enhanced persistente current | (Miyatake et al., 2018; Smith et al., 2018; Zaman et al., 2018) |
| P1333L | DII | Missense | EIEE | Shift steady-state activation and inactivation to more negative values | (Trujillano et al., 2017; Zaman et al., 2018) |
| M1765I | DIV | Missense | Refractory epilepsy | Myoclonus and epileptic spasms | (Inuzuka et al., 2019) |
| V1769A | DIV (S6) | Missense | EIEE | Enhanced persistent current | (Zaman et al., 2018) |
| chromosome 2q24.3 Involves the SCN1A, SCN2A, and SCN3A genes | chromosome Deletion (1.1 Mb) | | WS | Shift steady-state activation to more negative values | (Chong et al., 2018) |
| **Non genetic origin mutations reported*** | | | | | |
| N302S | DI | Missense | GEFS+ | Shift steady-state activation and inactivation to more positive values | (Chen et al., 2015) |
| D766N | DII (S2) | Missense | Focal epilepsy | Increased current amplitude by ramp voltage protocol | (Vanoye et al., 2014) |

*Non genetic origin mutations reported: Mutations described through clinical diagnosis, but the mutation type (Mendelian or de novo) were not reported, mainly due to the lack of parents to perform genotyping and difficulty in contacting the family. Cryptogenic childhood epilepsy (CCE); Benign epilepsy with centro-temporal spikes (BECTS); Generalized epilepsy with febrile seizures plus (GEFS+); West syndrome (WS); Febrile seizures (FS); Benign familial neonatal-infantile seizures (BFNIS); Benign familial neonatal seizures (BFNS); Dravet syndrome (DS); Epileptic encephalopathy (EE); Early infantile epileptic encephalopathy (EIEE); Not Reported (NR); Domain (D); Segment (S); Electroencephalography (EEG).
TABLE 4 | SCN8A-related epilepsies identified in clinical patients through WES and/or NGS.

| Variant     | Location | Mutation | Alteration on biophysical properties or/and Clinical report | Reference                                      |
|-------------|----------|----------|-------------------------------------------------------------|-------------------------------------------------|
| **Inherited mutation** |          |          |                                                             |                                                 |
| K101R       | N-terminus | Missense | NR                                                          | (Butler et al., 2017b)                          |
| I137M       | D1 (S1)   | Missense | NR                                                          | (Johannessen et al., 2019)                      |
| T164M       | D1 (S2)   | Missense | NR                                                          | (Butler et al., 2017a)                          |
| G269R       | D1 (S5)   | Missense | Non-functional channel                                      | (Wengert et al., 2019)                          |
| R530W       | D1 (S6)-DII (S1) | Missense | NR                                                          | (Olson et al., 2015)                            |
| N544 fs*39  | D1 (S6)-DII (S1) | Frameshift | NR                                                          | (Johannessen et al., 2019)                      |
| S702T       | D1 (S6)-DII (S1) | Missense | NR                                                          | (Jang et al., 2019)                             |
| G822R       | D1 (S3)   | Missense | Non-functional channel                                      | (Wengert et al., 2019)                          |
| V891M       | D1 (S5)   | Missense | NR                                                          | (Johannessen et al., 2019)                      |
| L1290V      | D1 (S1) (S3-S4) | Missense | NR                                                          | (Carvill et al., 2013)                          |
| L1331V      | D1 (S5)   | Missense | NR                                                          | (Larsen et al., 2015)                           |
| T1360N      | D1 (S5-S6) | Missense | Shift steady-state inactivation to more negative values     | (Wengert et al., 2019)                          |
| E1442K      | D1 (S5-S6) | Missense | NR                                                          | (Liu et al., 2018)                              |
| I1464T      | D1 (S6)-DIV (S1) | Missense | NR                                                          | (Johannessen et al., 2019)                      |
| G1476D      | D1 (S6)-DIV (S1) | Missense | NR                                                          | (Han et al., 2017)                             |
| E1483K      | D1 (S6)-DIV (S1) | Missense | NR                                                          | (Gardella et al., 2016)                         |
| I1583T      | DIV (S3)  | Missense | Shift steady-state activation to more positive values       | (Berghuis et al., 2015)                         |
| V1598A      | DIV (S4)  | Missense | Shift steady-state activation to more positive values       | (Wang et al., 2017a)                            |
| R1638C      | DIV (S4)  | Missense | Shift steady-state activation to more positive values       | (Wengert et al., 2019)                          |
| N1877S      | C-Terminus | Missense | NR                                                          | (Butler et al., 2017b; Johannessen et al., 2019) |
| R1904C      | C-Terminus | Missense | NR                                                          | (Schreiber et al., 2020)                        |
| **De novo mutation** |          |          |                                                             |                                                 |
| Exons 2-14  | –        | Deletion | NR                                                          | (Berghuis et al., 2015)                         |
| c.-8A > G UTR | 5′ UTR | Eight base pairs change upstream of start codon | NR | (Johannessen et al., 2019) |
| c.4296A>G  | D1 (S5-S6) | Splice-site mutation | Shift steady-state inactivation to more negative values | (Zaman et al., 2019) |
| M139I      | D1 (S1)   | Missense | Shift steady-state inactivation to more negative values     | (Zaman et al., 2019)                            |
| I142V      | D1 (S1)   | Missense | NR                                                          | (Denis et al., 2019)                            |
| A205E      | D1 (S1)   | Missense | NR                                                          | (Kim et al., 2019)                              |
| F210L      | D1 (S1)   | Missense | NR                                                          | (Mercimek-Mahmutoglu et al., 2015)               |
| V211L      | D1 (S3)   | Missense | NR                                                          | (Denis et al., 2019)                            |
| V211A      | D1 (S3)   | Missense | NR                                                          | (Berkovic et al., 2018)                         |
| L213P      | D1 (S3)   | Missense | NR                                                          | (Denis et al., 2019)                            |
| G214D      | D1 (S3)   | Missense | NR                                                          | (Allen et al., 2015)                            |
| N215R      | D1 (S3-S4) | Missense | NR                                                          | (Larsen et al., 2015)                           |
| N215D      | D1 (S3-S4) | Missense | NR                                                          | (Deciphering Developmental Disorders Study, 2015) |
| V216D      | D1 (S3-S4) | Missense | NR                                                          | (Onba et al., 2014)                             |
| R223G      | D1 (S4)   | Missense | Reduced current density                                    | (de Kovel et al., 2014; Berkovic et al., 2018; Denis et al., 2019) |
| I231T      | D1 (S4)   | Missense | NR                                                          | (Berkovic et al., 2018)                         |
| S232P      | D1 (S4)   | Missense | NR                                                          | (Wang et al., 2017a)                            |
| T239S      | D1 (S4-S5) | Missense | NR                                                          | (Moller et al., 2016)                           |
| I240V      | D1 (S4-S5) | Missense | NR                                                          | (McNally et al., 2016)                          |
| L257V      | D1 (S5)   | Missense | NR                                                          | (Schreiber et al., 2020)                        |
| F2605      | D1 (S5)   | Missense | NR                                                          | (Larsen et al., 2015; Boerma et al., 2016)      |
| C261F      | D1 (S5)   | Missense | NR                                                          | (Kim et al., 2019)                              |

(Continued)
| Variant | Location | Mutation | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|-------------------------------------------------------------|-----------|
| L267S   | Di (S5)  | Missense | NR                                                          | (Malcolmson et al., 2016) |
| G317A   | Di (S5-S6) | Missense | NR                                                          | (Denis et al., 2019) |
| F360A   | Di (S5-S6) | Missense | NR                                                          | (Rolvien et al., 2017) |
| M367V   | Di (S5-S6) | Missense | NR                                                          | (Lindy et al., 2018) |
| N374K   | Di (S5-S6) | Missense | Shift steady-state activation to more negative values        | (Johannesen et al., 2019; Zaman et al., 2019) |
| T386R   | Di (S5-S6) | Missense | NR                                                          | (Lindy et al., 2018) |
| Y401H   | Di (S6)   | Missense | NR                                                          | (Gardella et al., 2018) |
| L405M   | Di (S6)   | Missense | NR                                                          | (Denis et al., 2019) |
| L407F   | Di (S6)   | Missense | NR                                                          | (Fung et al., 2015; Zhang et al., 2015) |
| A408T   | Di (S6)   | Missense | NR                                                          | (Trump et al., 2016; Denis et al., 2019) |
| V410L   | Di (S6)   | Missense | NR                                                          | (Larsen et al., 2015) |
| L483F   | Di (S6)   | Missense | Slight shift steady-state activation to more negative values | (Zaman et al., 2019) |
| E587Ter | Di (S6)-DII (S1) | Nonsense | NR                                                          | (Schreiber et al., 2020) |
| I763V   | DII (S1)  | Missense | Decreased current density                                   | (Estacion et al., 2014; Gardella et al., 2018; Lindy et al., 2018) |
| V791F   | DII (S2)  | Missense | NR                                                          | (Xie et al., 2019) |
| V842E   | DII (S4)  | Missense | NR                                                          | (Lindy et al., 2018) |
| S845F   | DII (S4)  | Missense | NR                                                          | (Lindy et al., 2018) |
| F846S   | DII (S4)  | Missense | NR                                                          | (Ohba et al., 2014) |
| R850Q   | DII (S4)  | Missense | Shift steady state inactivation to more negative values     | (Fung et al., 2015; Zhang et al., 2015; Kim et al., 2019; Pan and Cummins, 2020; Schreiber et al., 2020) |
| R850E   | DII (S4)  | Missense | NR                                                          | (Wang et al., 2017a) |
| R850L   | DII (S4)  | Missense | NR                                                          | (Gardella et al., 2018) |
| L864V   | DII (S4)  | Missense | NR                                                          | (Gardella et al., 2018) |
| L875Q   | DII (S5)  | Missense | NR                                                          | (Allen et al., 2013) |
| A890T   | DII (S5)  | Missense | NR                                                          | (Fung et al., 2015; Larsen et al., 2015; Zhang et al., 2015) |
| V891M   | DII (S5)  | Missense | Impaired inactivation                                       | (Wang et al., 2017a) |
| V960D   | DII (S6)  | Missense | NR                                                          | (Larsen et al., 2015) |
| L971V   | DII (S6)  | Missense | NR                                                          | (Kim et al., 2019) |
| S978R   | DII (S6)-DIII (S1) | Missense | Shift steady-state activation to more negative values | (Blanchard et al., 2015; Boerma et al., 2016) |
| N984K   | DII (S6)-DIII (S1) | Missense | Shift steady-state activation to more negative values | (Blanchard et al., 2015; Boerma et al., 2016) |
| G1050S  | DII (S6)-DIII (S1) | Missense | NR                                                          | (McMichael et al., 2015) |
| S1073N  | DII (S6)-DIII (S1) | Missense | NR                                                          | (Lindy et al., 2018) |
| E1201K  | DII (S1)  | Missense | NR                                                          | (Johannesen et al., 2019) |
| V1274M  | DII (S3)  | Missense | NR                                                          | (Jiang et al., 2019) |
| V1315M  | DII (S4-SS) | Missense | Shift steady-state activation to more negative values | (Trump et al., 2016; Bagnasco et al., 2018; Denis et al., 2019) |
| N1318S  | DII (S4-SS) | Missense | NR                                                          | (Johannesen et al., 2019; Lin et al., 2019) |
| A1319S  | DIII (S4-SS) | Missense | NR                                                          | (Lindy et al., 2018) |
| A1319D  | DIII (S4-SS) | Missense | NR                                                          | (Johannesen et al., 2019) |
| A1323S  | DIII (S4-SS) | Missense | NR                                                          | (Trump et al., 2016) |
| A1323T  | DIII (S4-SS) | Missense | NR                                                          | (Johannesen et al., 2019) |
| I1327V  | DIII (S4-SS) | Missense | NR                                                          | (Vaher et al., 2013; Singh et al., 2015; Trump et al., 2016) |
| N1329D  | DIII (S4-SS) | Missense | NR                                                          | (Butler et al., 2017b) |

(Continued)
| Variant       | Location   | Mutation       | Alteration on biophysical properties or/and Clinical report                                                                 | Reference                                                                 |
|--------------|------------|----------------|-------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| V1330M       | DIII (S4-S5) | Missense       | NR                                                                                                                     | (Schreiber et al., 2020)                                                 |
| L1332R       | DIII (S5)   | Missense       | NR                                                                                                                     | (Butler et al., 2017b)                                                   |
| P1428_K1473del | DIII (S5-S6) | Missense       | Non-functional channel                                                                                                | (Larsen et al., 2013)                                                   |
| G1451S       | DIII (S5)   | Missense       | NR                                                                                                                     | (Blanchard et al., 2015; Denis et al., 2019)                               |
| N1466K       | (S6)       | Missense       | NR                                                                                                                     | (Ohba et al., 2014)                                                     |
| N1466T       | (S6)       | Missense       | NR                                                                                                                     | (Ohba et al., 2014)                                                     |
| Q1477K       | (S6)       | Missense       | NR                                                                                                                     | (Møller et al., 2016; Gardella et al., 2018)                              |
| G1475R       | (S6)-DIV (S1)| Missense      | Increased persistent current                                                                                         | (Hussain et al., 2016; Ortiz Madinaveitia et al., 2017; Wang et al., 2017a;|                                          |
|              |            |                |                                                                                                                         | Gardella et al., 2018; Lindy et al., 2018; Xiao et al., 2018; Kim et al., 2019; Trivisano et al., 2019; Zaman et al., 2019; Ranza et al., 2020; Schreiber et al., 2020) |
| G1476S       | (S6)-DIV (S1)| Missense      | NR                                                                                                                     | (Lindes et al., 2015)                                                   |
| I479V        | (S6)-DIV (S1)| Missense      | NR                                                                                                                     | (Larsen et al., 2015; Lindy et al., 2018; Schreiber et al., 2020)         |
| E483K        | (S6)-DIV (S1)| Missense      | Shift steady-state activation to more negative values                                                                  | (Johannesen et al., 2019)                                                |
| A1491V       | (S6)-DIV (S1)| Missense      | Increased current amplitude provoked by slow voltage ramp protocol                                                        | (Gardella et al., 2018; Lindy et al., 2018; Zaman et al., 2019)           |
| M1494T       | (S6)-DIV (S1)| Missense      | NR                                                                                                                     | (Kim et al., 2019)                                                      |
| K1496M       | (S6)-DIV (S1)| Missense      | NR                                                                                                                     | (Gardella et al., 2018)                                                 |
| M1529V       | DIV (S1)   | Missense       | NR                                                                                                                     | (Johannesen et al., 2019)                                                |
| H532F        | DIV (S1)   | Missense       | NR                                                                                                                     | (Møller et al., 2016; Gardella et al., 2018)                              |
| M1536I       | DIV (S1)   | Missense       | NR                                                                                                                     | (Lindy et al., 2018)                                                    |
| F1547V       | DIV (S1)   | Missense       | NR                                                                                                                     | (Gardella et al., 2018)                                                 |
| F1588L       | DIV (S3)   | Missense       | NR                                                                                                                     | (Johannesen et al., 2019)                                                |
| V1592L       | DIV (S3)   | Missense       | NR                                                                                                                     | (Larsen et al., 2015; Ranza et al., 2020)                                 |
| S1596C       | DIV (S3)   | Missense       | NR                                                                                                                     | (Fung et al., 2015; Zhang et al., 2015; Boerma et al., 2016)              |
| I1605R       | DIV (S3)   | Missense       | NR                                                                                                                     | (Larsen et al., 2015)                                                   |
| T1614A       | (S3-S4)    | Missense       | NR                                                                                                                     | (Johannesen et al., 2019)                                                |
| R1617Q       | (S3-S4)    | Missense       | Increased persistent current                                                                                         | (Rauch et al., 2012; Ohba et al., 2014; Dymant et al., 2015; Fung et al., 2015; Larsen et al., 2015; Zhang et al., 2015; Fung et al., 2017; Lindy et al., 2018; Johannesen et al., 2019; Schreiber et al., 2020) |
| R1620L       | DIV (S4)   | Missense       | NR                                                                                                                     | (Rossi et al., 2017)                                                    |
| L1621W       | DIV (S4)   | Missense       | NR                                                                                                                     | (Fung et al., 2015)                                                    |
| Q1625R       | DIV (S4)   | Missense       | NR                                                                                                                     | (Deciphering Developmental Disorders Study, 2015)                         |
| L1630P       | DIV (S4)   | Missense       | NR                                                                                                                     | (Schreiber et al., 2020)                                                |
| I1631N       | DIV (S4)   | Missense       | NR                                                                                                                     | (Lindy et al., 2018)                                                    |
| M1645I       | DIV        | Missense       | NR                                                                                                                     | (Zhang et al., 2015)                                                    |
| A1650T       | DIV        | Missense       | NR                                                                                                                     | (Ohba et al., 2014; Larsen et al., 2015; Parrini et al., 2017; Gardella et al., 2018; Trivisano et al., 2019) |
| A1650V       | DIV        | Missense       | NR                                                                                                                     | (Lindy et al., 2018; Johannesen et al., 2019)                            |
| F1754S       | DIV (S6)   | Missense       | NR                                                                                                                     | (Trump et al., 2018)                                                    |
| V1758A       | DIV (S6)   | Missense       | Shift steady-state activation to more positive values                                                                | (Balciuniene et al., 2019; Johannesen et al., 2019; Zaman et al., 2019)  |
| N1759T       | DIV (S6)   | Missense       | NR                                                                                                                     | (Kim et al., 2019)                                                     |
| A1763G       | DIV (S6)   | Missense       | NR                                                                                                                     | (Denis et al., 2019)                                                    |
| I1764M       | DIV (S6)   | Missense       | NR                                                                                                                     | (Gardella et al., 2018)                                                 |

(Continued)
| Variant | Location | Mutation | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|-------------------------------------------------------------|-----------|
| N1768D  | C-Terminus | Missense | Increased spontaneous firing Paroxysmal depolarizing-shift-like complexes, Increased firing frequency Increased persistent current | (Veeramah et al., 2012) |
| V1771I  | C-Terminus | Missense | NR | (Johannesen et al., 2019) |
| Q1801E  | C-Terminus | Missense | NR | (Larsen et al., 2015) |
| R1820X  | C-Terminus | Nonsense | NR | (Møller et al., 2016; Johannesen et al., 2019) |
| R1831Q  | C-Terminus | Missense | NR | (Liu et al., 2018) |
| R1831W  | C-Terminus | Missense | NR | (Jiang et al., 2019) |
| T1852I  | C-Terminus | Missense | NR | (Lindy et al., 2018; Heyne et al., 2019) |
| L1865P  | C-Terminus | Missense | NR | (Trump et al., 2016) |
| R1866Q  | C-Terminus | Missense | Enhanced persistent current Increase peak current density Shift steady-state activation to more negative values Shift steady-state inactivation to more positive values | (Larsen et al., 2015; Horvath et al., 2016; Hussain et al., 2016; Arafat et al., 2017; Atanasoska et al., 2018; Lindy et al., 2018) |
| R1872W  | C-Terminus | Missense | Enhanced persistent current Increased peak current density Shift steady-state activation to more negative values Shift steady-state inactivation to more positive values | (Ohba et al., 2014; Larsen et al., 2015; Takahashi et al., 2015; Gardella et al., 2018; Denis et al., 2019; Kim et al., 2019; Zaman et al., 2019) |
| N1877S  | C-Terminus | Missense | NR | (Anand et al., 2016; Panini et al., 2017; Wang et al., 2017a; Lindy et al., 2018; Costain et al., 2019; Epifanio et al., 2019; Jain et al., 2019; Ranza et al., 2020) |
| P1878S  | C-Terminus | Missense | NR | (Lindy et al., 2018) |

Non genetic origin mutations reported*:

| Variant | Location | Mutation | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|-------------------------------------------------------------|-----------|
| R45Q    | N-terminus | Missense | NR | (Encinas et al., 2019; Heyne et al., 2019) |
| A108fsXTer7 | N-terminus | Truncated gene | NR | (Encinas et al., 2019) |
| T166L   | D1 (S2)  | Missense | NR | (Encinas et al., 2019) |
| I202N   | D1 (S3)  | Missense | NR | (Butler et al., 2017a) |
| V211L   | D1 (S3)  | Missense | NR | (Encinas et al., 2019) |
| V211A   | D1 (S3)  | Missense | NR | (Encinas et al., 2019) |
| R220H   | D1 (S4)  | Missense | NR | (Oates et al., 2018) |
| R223S   | D1 (S4)  | Missense | NR | (Encinas et al., 2019) |
| T239A   | D1 (S4-S5) | Missense | NR | (Encinas et al., 2019) |
| I240V   | D1 (S4-S5) | Missense | NR | (Encinas et al., 2019) |
| I240L   | D1 (S4-S5) | Missense | NR | (Encinas et al., 2019) |
| L257V   | D1 (S5)  | Missense | NR | (Encinas et al., 2019) |
| L267V   | D1 (S5)  | Missense | NR | (Denis et al., 2019) |
| I268L   | D1 (S5)  | Missense | NR | (Encinas et al., 2019) |
| F360A   | D1 (S5-S6) | Missense | NR | (Encinas et al., 2019) |
| M367V   | D1 (S5-S6) | Missense | NR | (Encinas et al., 2019) |
| R381Q   | D1 (S5-S6) | Missense | NR | (Encinas et al., 2019) |
| E587Ter | D1 (S5-S6) | Nonsense | NR | (Encinas et al., 2019) |
| T386R   | D1 (S5-S6) | Missense | NR | (Encinas et al., 2019; Schreiber et al., 2020) |
| S399P   | D1 (S6)  | Missense | NR | (Encinas et al., 2019; Heyne et al., 2019) |
| V410L   | D1 (S6)  | Missense | NR | (Encinas et al., 2019) |
| Y414F   | D1 (S6-D1) | Missense | NR | (Butler et al., 2017a) |
| E416K   | D1 (S6-D1) | Missense | NR | (Encinas et al., 2019) |
| Q417P   | D1 (S6-D1) | Missense | NR | (Encinas et al., 2019) |
| R530Q   | D1 (S6-D1) | Missense | NR | (Encinas et al., 2019) |
| E587Ter | D1 (S6-D1) | Nonsense | NR | (Encinas et al., 2019) |

(Continued)
| Variant  | Location | Mutation | Alteration on biophysical properties or/and Clinical report | Reference |
|----------|----------|----------|-------------------------------------------------------------|-----------|
| R598W    | Di (S6)-DII (S1) | Missense | NR                                                          | (Encinas et al., 2019) |
| G692R    | Di (S6)-DII (S1) | Missense | NR                                                          | (Encinas et al., 2019) |
| I763V    | DII (S1) | Missense | Shift steady-state activation to more negative values        | (Estacion et al., 2014) |
| T767I    | DII (S1) | Missense | Shift steady-state activation to more negative values        | (Encinas et al., 2019) |
| L840P    | DII (S3-S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| L840F    | DII (S3-S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| S645F    | DII (S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| L864V    | DII (S4-S5) | Missense | NR                                                          | (Trivisano et al., 2019) |
| I868T    | DII (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
| A874T    | DII (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
| E936K    | DII (S6) | Missense | NR                                                          | (Johannessen et al., 2019) |
| L969M    | DII (S6) | Missense | NR                                                          | (Encinas et al., 2019) |
| Y1241C   | DII (S2) | Missense | NR                                                          | (Encinas et al., 2019; Johannessen et al., 2019) |
| S1308P   | DII (S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| V1315M   | DII (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
| L1320F   | DII (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019; Schreiber et al., 2020) |
| A1323P   | DII (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
| I1327V   | DII (S4-S5) | Missense | NR                                                          | (Oates et al., 2018) |
| M1328T   | DII (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
| N1329D   | DII (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
| G1451S   | DII (S6) | Missense | NR                                                          | (Encinas et al., 2019) |
| G1461V   | DII (S6) | Missense | NR                                                          | (Encinas et al., 2019; Schreiber et al., 2020) |
| N1466K   | DII (S6)-DIV (S1) | Missense | NR                                                          | (Encinas et al., 2019) |
| F1467C   | DII (S6)-DIV (S1) | Missense | NR                                                          | (Encinas et al., 2019) |
| Q1479V   | DII (S6)-DIV (S1) | Missense | NR                                                          | (Encinas et al., 2019) |
| A1491V   | DII (S6)-DIV (S1) | Missense | Shift steady-state activation to more negative values       | (Encinas et al., 2019; Trivisano et al., 2019) |
| M1492V   | DII (S6)-DIV (S1) | Missense | NR                                                          | (Encinas et al., 2019; Ranza et al., 2020) |
| Q1501K   | DII (S6)-DIV (S1) | Missense | NR                                                          | (Encinas et al., 2019) |
| Splice donor | DII (S6)-DIV (S1) | Truncated gene | NR                                                          | (Encinas et al., 2019) |
| c.4419+1A>G | DII (S6)-DIV (S1) | Truncated gene | NR                                                          | (Encinas et al., 2019) |
| M1536I   | DIV (S1) | Missense | NR                                                          | (Encinas et al., 2019) |
| V1592L   | DIV (S3) | Missense | NR                                                          | (Encinas et al., 2019) |
| I1594L   | DIV (S3) | Missense | NR                                                          | (Encinas et al., 2019) |
| S1596C   | DIV (S3) | Missense | NR                                                          | (Encinas et al., 2019) |
| T1614A   | DIV (S3-S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| R1617Q   | DIV (S4) | Missense | Enhanced persistent current Increased peak current density Shift steady-state activation to more negative values Shift steady-state inactivation to more positive values | (Encinas et al., 2019) |
| R1617P   | DIV (S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| G1625R   | DIV (S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| L1630P   | DIV (S4) | Missense | NR                                                          | (Encinas et al., 2019) |
| F1642C   | DIV (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
| A1650T   | DIV (S4-S5) | Missense | NR                                                          | (Trivisano et al., 2019) |
| A1650V   | DIV (S4-S5) | Missense | NR                                                          | (Encinas et al., 2019) |
channel is widely expressed in the nodes of Ranvier of myelinated axons and in the distal part of the axon initial segments (AIS), although they are also ubiquitously present throughout the central and peripheral nervous systems, in both excitatory and inhibitory neurons (Caldwell et al., 2000; Oliva et al., 2012). For these reasons, NaV1.6 is one of the most common subtype of voltage-gated sodium channels found in the central nervous system (Caldwell et al., 2000). In humans, the distal AIS is the specialized membrane region in neurons where action potentials are triggered. Overexpression of Nav1.6 in the AIS has been shown to cause an increase in spontaneous and repetitive firing (Hu et al., 2009; Sun et al., 2013), a possible explanation for why SCN8A mutations in epilepsy patients are predominantly GoF and affect the action potential threshold. On the other hand, the functional importance of Nav1.6 in inhibitory interneurons is not clear yet, but evidence indicates a role for Nav1.6 in establishing synaptic inhibition in the nervous system circuits. Mutations in SCN8A are associated with early-infantile epileptic encephalopathy type 13 (EIEE13; OMIM #614558), a phenotypically heterogeneous early onset epilepsy, with seizure onset happening before 18 months of age (Hammer et al., 2016). Patients typically develop intellectual disability, developmental delay, and movement disorders (Ohba et al., 2014; Gardella et al., 2016; Johannesen et al., 2018). Co-occurrence of autism spectrum disorders, severe juvenile osteoporosis, bradycardia, cerebral visual impairment, and gastrointestinal disorders have been reported in rare cases (Larsen et al., 2015; Hammer et al., 2016; Rolvien et al., 2017; Gardella et al., 2018). Sudden unexpected death in epilepsy (SUDEP) has also been linked to SCN8A mutations, described as the most common cause of death in epilepsy patients. Reports have suggested that patients with SCN8A-related epilepsy have increased risk of SUDEP, ranging from 1% to 10% (Hammer et al., 2016; Wang et al., 2017a; Gardella et al., 2018; Johannesen et al., 2018). One possible correlation of SUDEP with SCN8A-related epilepsy is the presence of NaV1.6 in heart muscles and tissues, being broadly expressed within ventricular myocytes (Maier et al., 2002). Single mutations may affect heart function, causing failure of the cardiorespiratory system and, consequently, death (Haufe et al., 2005; Noujaim et al., 2012). Most recently, few cases of SCN8A-related epilepsies with “milder” phenotype were associated with benign familial infantile seizures-5 (BFIS5; OMIM #617080) (Anand et al., 2016; Gardella et al., 2016; Han et al., 2017).

An increase in new described variants made some mutation patterns visible. Wagnon and co-workers observed numerous cases of the same epileptogenic mutation, and suggested that CpG dinucleotides are mutation hotspots that, through enzymatic processing and epigenetic methylation, can convert cytosine to thymine, such as arginine residues 1617 and 1872 (Wagnon and Meisler, 2015). The prominent number of new variant cases in Arg850 indicates this residue as a new hotspot, since the arginine codon holds a CpG dinucleotide. In addition to these mutation hotspots, residues I763, I1327, G1475, A1650, and N1877 do not present CpG dinucleotides in their codon; however, they can be considered recurrent mutations in view of its high repetition cases in literature (Table 4).

The mutation at position c.- 8A>G produces a pathogenic variant, despite not being inside the gene, or promoter regions,
transcriptional and translational sites. This mutation was detected in an untranslated region outside of the Kozak consensus sequence (Johannesen et al., 2019). Its role in SCN8A-related epilepsy is still unclear; however, it may change RNA stability, modulate transcriptional factors and promoters, modify the initiation of translation, or work as an enhancer or silencer in the splicing pattern. For all the reasons mentioned above, Nav1.6 variants are predominantly harmful, and the same mutation can lead to different phenotypes, hampering the correlation of genotypes with phenotypes (Blanchard et al., 2015).

SCN8A mutations can be both GoF and LoF, which will likely require different approaches and targets. Even in patients with the same SCN8A mutation, the response to the same drug treatment can differ. Surprisingly, most SCN8A-related epilepsies respond favorably to channel blockers. Phenytoin and lacosamide are SBCs widely used in SCN8A mutations with GoF effect, while carbamazepine exhibited positive seizure control in a patient with NaV 1.6 mutation and LoF effect. (Blanchard et al., 2015; Wagnon and Meisler, 2015; Hammer et al., 2016; Perucca and Perucca, 2019).

Phenytoin demonstrated effectiveness in decreasing seizure episodes in several patients with SCN8A-related epilepsies, however, side effects during prolonged use are very common (Boerma et al., 2016; Braakman et al., 2017). A recent study of a DS model using zebrafish demonstrated the use of the channel blocking compound MV1312, which is 5–6 fold selectivity of NaV1.6 over NaV1.1–1.7, reduced burst movement phenotype and the number of epileptiform events, activity similar to that described with the use of a selective NaV1.1 activator AA43279 (Weuring et al., 2020). Selective Nav1.6 blockers may represent a new therapeutic strategy for DS patients. In addition, two precise and promising drugs have been described recently: XEN901 and GS967. XEN901 is an arylsulfonamide highly selective and potent NaV1.6 inhibitor that binds specifically in voltage sensor domain IV, avoiding recovery from inactivation. GS967 is a NaV1.6 modulator that inhibits the persistent sodium current and exhibits a protective effect (Baker et al., 2018).

The SCN9A gene encodes for the NaV1.7 channel, located in chromosome 2q24 (Yang et al., 2018). NaV1.7 is expressed preferentially in the PNS but is also expressed in the CNS (Cun et al., 2017). Pan disorder mutations with GoF or/and Clinical report Reference

| Variant | Location | Mutation | Disease | Alteration on biophysical properties or/and Clinical report | Reference |
|---------|----------|----------|---------|----------------------------------------------------------|-----------|
| Q10R    | N-terminal | Missense | GEFS+   | Fabryte and afebrile seizures                              | (Cen et al., 2017) |
| G327E   | DI       | Missense | Epilepsy | Generalized tonic-donic seizures                          | (Yang et al., 2018) |
| N641Y   | DI- DII  | Missense | FS      | Reduced electroconvulsive seizure thresholds (Knocking mice) | (Singh et al., 2009; Zhang S. et al., 2020) |
|         |          |          | FS      | Increased corneal kindling acquisition rates (Knocking mice) |           |
|         |          |          | FS      | Increased current density                                  |           |
|         |          |          | FS      | Faster recovery from inactivation                          |           |
|         |          |          | FS      | More susceptible to clonic and tonic seizures induced by electrical stimulation (mice) | (Yang et al., 2018) |
| I1901fs | C-terminal | Frameshift | Epilepsy | Generalized tonic-donic seizure                            |           |
| K655R   | DI-DII   | Missense | FS      | Enhanced persistent current                                | (Zhang S. et al., 2020) |
| W1150R  | DI-DIII  | Missense | FS      | Faster recovery from inactivation                          | (Zhang S. et al., 2020) |
|         |          |          | FS      | Increased current density                                  |           |
|         |          |          | FS      | Enhanced persistent current                                |           |
|         |          |          | FS      | Focal seizures with secondary generalization               |           |
|         |          |          |         | High potential spike activity, paroxysmal release, and d frequency power enhancement (EEG) |           |
seizure with fever, treated with sodium valproic acid, and a LoF mutation I1901fs was observed (Yang et al., 2018) (Table 5).

Variants of NaV1.7 have been related with febrile seizure or GEFS+ (Cen et al., 2017; Zhang S. et al., 2020) and even as asymptomatic (Singh et al., 2009). However, SCN9A can act as a putative modifier of NaV1.1 gene; consequently, it can elevate the severity of patients’ phenotype (Guerrini et al., 2010; Parihar and Ganesh, 2013). Some NaV1.7 mutations could probably contribute to generate a genetic susceptibility to a known epilepsy disease called Dravet syndrome, in a multifactorial way, as a modifier gene (Singh et al., 2009; Doty, 2010; Mulley et al., 2013; Cen et al., 2017; Zhang T. et al., 2020). That said, some rare cases of DS found in patients can be understood (Mulley et al., 2013). For example, even parents with mild phenotype had children with severe cases (Guerrini et al., 2010).

CONCLUSION AND FUTURE PERSPECTIVES

The past two decades have enabled remarkable progress in understanding monogenic epilepsies. NaV-related epilepsies are diseases of phenotypic heterogeneity, since sodium channels are found in both the CNS and the PNS, but with different expression ranges. The lack of a clear genotype-phenotype correlation to help guide patient counseling and management by healthcare professionals makes it very complex, and often expensive, to determine a correct diagnosis. Consequently, identify the monogenic mutation in individual patients with epilepsy is important not only for diagnosis and prognosis, but also for a correct treatment approach (Mei et al., 2017; Reif et al., 2017).

Susceptibility to specific treatments may be different depending on the disease’s features, diverging even in patients who share the same phenotype and/or mutation (Weber et al., 2014). The use of innovative tools that facilitate and prevent diagnostic delay in patients with epilepsy of unknown etiology onset is crucial. WES has proved to be a valuable tool to circumvent the lack of an accurate and fast diagnosis to epilepsies caused by monogenic mutation, and also cheapen and drastically anticipate diagnosis. This genetic diagnostic tool may reduce traditional investigation costs by 55 to 70%, besides avoiding further pre-surgical evaluation and epilepsy surgery (Kothur et al., 2018; Oates et al., 2018). In addition to the financial impact, it can anticipate diagnosis from nearly 3.5 years to 21 days, optimizing management and health care support (Oates et al., 2018).

Effective and safe drugs for the treatment of monogenic epilepsy are still an unmet clinical need. The drugs currently available in the pharmaceutical market are only palliative methods for a temporary control of the disease symptoms, and few patients will benefit from the existing pharmacotherapy, since a great number of patients treated with antiepileptic channel blockers showed no improvement in clinical conditions. Also, most treated patients exhibited manifold side effects, and the prolonged use of these medications proved to be harmful (Boerma et al., 2016; Braakman et al., 2017). Several examples of novel and promising candidate compounds to be used in personalized medicine, such as precision therapies, have been suggested. A previously study demonstrated that CBD at 1μM inhibit preferably resurgent currents but transient current in Nav1.6 WT and also inhibit peak resurgent current in Nav1.6 mutant N1768D, with less effect in current density and without alters voltage dependence of activation (Patel et al., 2016) Possibly the modulation of CBD over mutations in SCN8A that promotes a phenotype with increased resurgent currents would cause a reduction in the causative excitability of epileptic seizures. CBD also showed its ability to preferential inhibit resurgent currents in the Nav1.2 channel (Mason and Cummins, 2020). Due the role of Nav1.2 and Nav1.6 in excitatory neurons, preferentially inhibition in resurgent currents by CBD could possibly reduce the excitability in that subset of neurons and decrease the frequency of seizures by a change in threshold of activation and repetitive fire (Lewis and Raman, 2014). Peptides derived from scorpion and spider venom are well known modulator tools in neuroscience and showed specific capacity to regulate most NaV subtypes related with monogenic epilepsy, unlike the available promiscuous drugs that generally interact with any NaV channel isoform (Schiavon et al., 2006; Israel et al., 2018; Richards et al., 2018; Tibery et al., 2019; Zhang et al., 2019). Bioengineering tools, like antisense oligonucleotides capable to regulate NaV1.1 channels expression, and the peptide Hm1, that modulates the function of this subtype of sodium channel, are some innovative treatment examples (Richards et al., 2018; Stoke Therapeutics, 2018).

However, there is still a long path toward the development of efficacious treatments for NaV-related epilepsies. Recent studies offered a better understanding of the complexity of the phenotypic and genetic spectrum, which has only just begun to be elucidated. Biomolecular diagnostic tools will drastically reduce the developmental and cognitive effects caused by misdiagnosis and late diagnosis, and maybe, in the upcoming years, the treatment for inherited NaV-related epilepsies will be conducted ideally in utero, during the prenatal stage. Moreover, further functional studies, with greater cohorts of patients, represent an urgent medical need for a better understanding of the correlations between genotype and clinical symptoms, as well as the different NaV-related epilepsies mechanisms. These studies will improve clinical efficacy and promote safety diagnostic strategies, as well as develop prognosis prediction in the near future.

AUTHOR CONTRIBUTIONS

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.01276/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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