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Dravet Syndrome and *SCN1A* gene mutations: a review

Abstract

Introduction: Dravet's Syndrome (DS) is epilepsy syndrome that strikes individuals in early childhood, also known as Severe Myoclonic Epilepsy of Infancy (SMEI). DS clinical presentation involves normal psychomotor development during the first month of life; premature convulsive conditions, beginning mainly during the first year of life; deceleration of psychomotor development later and other neurological deficits, similar to cerebellar ataxia, which ultimately results in a condition of severe disability and therefore individuals unable to live independently. The types of seizures are various and include clonic and tonic seizures, generalized or unilateral; myoclonic seizures and of absences.

Objective: Knowing that DS has as important etiology genetic disorders, this review aims to shed light on the main mutations that occur in the *SCN1A* gene, which considered the main gene related to SMEI and thus to correlate with its phenotype.

Methods: The databases PubMed, Scielo, Medscape and Google Scholar helped searching articles in both Portuguese and English.

Discussion: The *SCN1A* gene has 26 coding exons and translates the subunit 1 of the voltage-dependent neuronal sodium channel protein (Nav1.1). This protein consists of four domains (DI-IV), containing six transmembrane segments each. The subunit of the sodium channel is responsible for the formation of the transmembrane pore that allows the entry of sodium ions into the intracellular medium of the neurons. It is known that there are more than 500 distinct mutations at *SCN1A* gene associated with the DS.

Conclusion: Due to the impact of this syndrome on affected individuals and relatives lives, it is important to study the disease etiology. Therefore, this study is a review of several scientific publications encompassing mutations in the *SCN1A* gene. In conclusion, the main kind of *SCN1A* gene mutations consist of missense and truncating mutations.

Keywords: dravet's syndrome, myoclonic epilepsy, *SCN1A* gene, subunit 1 of the voltage-dependent neuronal sodium channel protein (Nav1.1)

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Introduction

Dravet's Syndrome (DS) is a progressive encephalopathy described in 1978 by Charlotte Dravet, also known as Severe Myoclonic Epilepsy of Infancy (SMEI), an epilepsy syndrome of infantile onset.[1] Common DS clinical features are normal neuropsychomotor development during the first month of life; early symptoms seizures presentation, starting during the first year of life; developmental psychomotor delay; and development of neurological deficits, such as lack of coordination similar to cerebellar ataxia, leading to the development of a severe disability that renders individuals unable to live independently.[2]

There are several types of seizures, including tonic-clonic, absence seizures complex atypical or partial, generalized or unilateral, myoclonic (ranging from a minute to hours, or even comatose) and may occur during wakefulness or during sleep. First, convulsion seizures are often associated with fever, but feverish seizures occur later in the course of the disease. The syndrome is notable for seizure frequency and its resistance to large variety of antiepileptic drugs. Photosensitivity is also a frequent symptom.[2,3]

The clinical characteristics and comorbidities of the syndrome in four patients with DS, including dysautonomia, nutrition issues, autism characteristics, and a high rate of sudden unexpected death in epilepsy (SUDEP) were previously described.[4] In addition, four DS patients presented long Q-T intervals, suspecting of cardiorespiratory arrest associated with SUDEP, and *SCN1A* mutations. Similarly, five of 232 DS patients presented abnormalities or changes in the heart structure and *SCN1A* mutations.[4] That gene is responsible for coding a voltage-dependent neuronal sodium channel.[5]

Estimated disease incidence is 1 in 22,000 births, which fits it into the group of rare diseases (1/2,000). Patients and families with DS must face common problems of a rare disease including, lack of awareness and knowledge, lack and/or diagnostic delay, difficulties in accessing healthcare and medication, and loneliness.[3,5] In addition, about 80% of affected patients harbor *SCN1A* gene mutations.

The ILAE genetics commission report from 2010[6] stated that "post-test genetic counselling is crucial to help the patient understand the test result and begin to digest it in the context of life circumstances"; therefore, it is important review clinical and *SCN1A*related mutations in DS patients.

Methods

This review was compiled using articles, bibliographic reviews and thesis obtained from PubMed, Scielo, Medscape and Google

Scholar databases in both language, Portuguese and English. A webpage for Non-Governmental Organization related to DS was also investigated. Thus, 21 publications involving clinical features, DS pathophysiology, *SCN1A* mutation frequencies, DS diagnosis and epidemiology were included in the present review. In addition, it was added a single publication about *SCN1A* inherited mutations. Most of the studies have discussed the *SCN1A* mutations while some studies also have characterized them.

Results and discussion

The *SCN1A* gene has 26 coding exons, responsible for encoding of the alpha subunit of the voltage-dependent neuronal sodium channel (Nav1.1 channel protein). In humans, there are 9 different subunits (Nav 1.1-Nav1.9) encoded by the *SCN1A-SCN11A* genes (Figure 1).[7,8] Mutations in these genes are responsible for causing epilepsy, highlighting the *SCN1A* gene in the genesis of DS.[7] The dependent sodium channel voltage opens in response to depolarization membrane, allowing the entry of ions in the in the neuron.[9] This activity is responsible for generate the action potential and propagate the electrical impulses to the synaptic terminals, which results in synaptic transmission. The Nav1.1 channel protein has four homologous domains (DI-DIV), and each domain has 6 transmembrane segments. Its expression occurs predominantly in the GABA inhibitory interneurons, that is, those that secrete the GABA neurotransmitter. Therefore, it is believed that hyperexcitability observed in cases of loss of function of the sodium channel, as observed in the DS and in some of the genetic epilepsy with febrile seizures plus (GEFS+) cases, would be the result of a dysfunction in the circuit's neuronal inhibitors.[8]

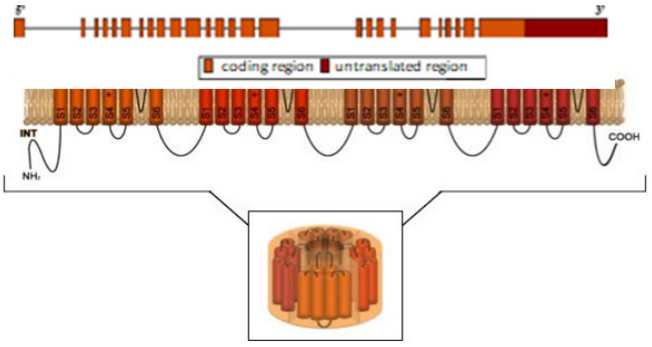

Figure 1 *SCN1A* gene structure and Nav1.1 channel protein. The *SCN1A* gene has 26 coding exons, responsible for encoding of the alpha subunit of the voltage-dependent neuronal sodium channel (Nav1.1 channel protein). The Nav1.1 channel protein has 4 homologous domains (DI-DIV) and each domain has 6 transmembrane segments.[8]

SCN1A gene mutations

According to Gonsales,[8] *SCN1A* gene mutations screening has proved to be highly important for patients with DS, revealing 16 potentially gene deleterious changes totalizing 81 investigated patients (Table 1).[8] The most common mutation type was the missense mutation, which promotes the replacement of waste amino acid in the protein chain. Considering only the number of mutations per protein segment, there is a clear predominance of changes in the pore-forming regions, between segments S5 and S6 and in the N- and C-terminal portions in addition to the segment responsible for detecting voltage (S4) in some domains such as I and IV.[8,10] However, when considering the amount of amino acid residues present in each region, most of the *SCN1A* mutations occurred at the conserved regions of the attenuated protein. Still, the S5-S6 region of the second domain stands out as presenting greater amount of mutations. Still, this approach highlights the frequency of changes in small segments, such as regions DIV/S4-S5 (15 amino acid residues), DIII/S1-S2 (13 residues), DI/S3 (19 residues), DIV/S2- S3 (6 residues) and DI/S4-S5 (16 residues). Larger segments such as DI/S4-S5 (126 residues) and the N- and C-terminal regions (123 and 223 residues, respectively) shows a considerable reduction in *SCN1A* mutation frequency. To date (2017), about 774 mutations in *SCN1A* gene in DS patients has been described.[8]

Table 1 *SCN1A* gene mutation types, localization of the nucleotide changes, and alpha subunit of the voltage-dependent neuronal sodium channel protein phenotype in Dravet's syndrome

Mutation type	Exon/Intron localization	Nucleotide changes	Protein phenotype	References
Missense	Exon4	c.530G>a	p.Gly177Glu	(1)
Missense	Exon5	c.680T>G	p.Ile227Ser	(1)
Missense	Exon26	c.5195C>T	p.Prol1732Leu	(19)
Missense	Exon26	c.5054C>T	p.Ala1685Val	(13)
Missense	Exon15	c.2836C>T	p.Arg946Cys	(19)
Missense	Exon22	c.4313T>C	p.Met1438Thr	(19)
Missense	Exon26	c.5555T>C	p.Met1852Thr	(20)
Missense	Exon26	c.4907G>A	p.Arg1636Gln	(19)
Missense	Exon6	c.829T>C	p.C277R	(8)
Missense	Exon6	c.917A>C	p.H324P	(8)
Missense	Exon13	c.2360T>G	p.M787R	(8)

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Table continue

Mutation type	Exon/Intron localization	Nucleotide changes	Protein phenotype	References
Missense	Exon21	c.4093G>T	p.G1365C	(8)
Missense	Exon16	c.2963T>G	p.Leu998Arg	(11)
Nonsense	Exon26	c.5674C>T	p.Arg1892X	(13)
Nonsense	Exon5	c.664C>T	p.Arg222X	(1)
Nonsense	Exon12	c.2134C>T	p.Arg712X	(13)
Nonsense	Exon26	c.5177G>A	p.w1726X	(8)
Splicing	Intron 2	IVS2+1A>G	---	(8)
Splicing	Intron 4	IVS4+1G>A	---	(8)
Splicing	Intron 8	IVS8+3G>T	---	(8)
Splicing	Intron 21	IVS21+1G>A	---	(8)
Frameshift	Exon9	c.1242delA	p.I415X	(8)
Frameshift	Exon19	c.3719_3720insGATA	p.I1240fsX1244	(8)
Frameshift	Exon26	c.5329delG	p.V1777fsX1778	(8)
In-frame deletions	Exon2	c.296_313delTCTTCCGGTTCAGTGCCA	p.I99_A104del	(8)
In-frame deletions	Exon 26	c.5489_5491delAGT	p.Q1830_F1831delinsL	(8)

As previously mentioned, regarding the mutations types among 24 publications, the most common was *SCN1A* missense mutation in exon 16.[10] This variant is located within the DII S6 domain of the Scn1a protein and it was a novel *de novo* variant in the *SCN1A* gene.[11] Another publication also has indicated missense (S123R, F1415I) and nonsense/truncating mutations (Y325X, R1407X, R1645X) in DS patients.[2,7] Two other studies[7,8] have described missense mutation (S1231R), and nonsense mutation (R1407X) whereas it mainly targets GABA inhibitory neurons while the electrophysiological properties of pyramidal neurons remain unchanged. Interestingly, the missense mutation (S1231R) has caused a single nucleotide alteration (c.3693T> A).[7] Other common mutation type in DS is the frameshift mutation.[8]

Summarizing, missense mutation consists in one DNA nucleotide change in a way that the nucleotide triplet of which is part changes by encoding an incorrect amino acid.[12] This can change the function of the protein in greater or lesser degree depending on the exon location and the importance of this particular amino acid. Nonsense/truncating mutation may change one of the nucleotides resulting in a termination codon in a way that the nascent protein is prematurely truncated.[12,13] The frameshift mutation can be the result of insertion, duplication, and deletion nucleotides causing a reading grid landing.[12]

It worth to mention that DS less severe phenotype is more commonly associated with missense mutations than nonsense mutations. In addition, missense mutations in pore-forming region tend to result in more severe DS phenotype.[14]

Genetic inheritance of mutations in *SCN1A* gene

The *SCN1A* seizure disorder is normally autosomal dominant disease.[15] A *SCN1A* seizure disorder patient may have an inherited or a *de novo* variant. The percentage of patients with an *SCN1A* seizure disorder with an affected relative decreases as the severity of the phenotype in the patient increases. Thus, most of the *SCN1A*-related SMEI result from a *de novo* variant.[16] Each child with a *SCN1A* seizure disorder has a 50% chance of inheriting the pathogenic variant; however, the risk of developing seizures is less than 100% because of reduced penetrance. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant in the family is known.[16,17]

On study has reported four DS patients harboring two *SCN1A* variants with possibly deleterious effect. One patient presented c.2816ARC/p.His939Pro and c.5364CRA/p.Asn1788Lys variants and other c.3235GRA/p.Val1079Ile variant, which was inherited from his asymptomatic father, and a *de novo* c.2504_2508delTTGAC mutation. The third patient carried the c.4723CRT/p.Arg1575Cys variant, inherited from his asymptomatic mother, and a *de novo* c.1804GRT/p.Glu602X mutation. Finally, the fourth patient presented c.3325CRA/p.Pro1109Thr, inherited from his father, and a *de novo* c.4133delA mutation.[18] It was hypothesized that p.Val1079Ile, p.Pro1109Thr and p.Arg1575Cys were novel rare non-synonymous polymorphisms, but it was not possible define which of the p.His939Pro and p.Asn1788Lys variants constituted the causative mutation, as the parents of the patient were unavailable for genetic analyses. Therefore, both were considered as potential missense mutations.[19]

Other study has evaluated 149 DS patients for *SCN1A* point mutations and both parents were available for genetic analyses.[20] Direct sequencing failed to detect the mutation in either parent in 133 cases out of 149 (89%), indicating that the mutation occurred *de novo* in those patients. For the 15 patients who inherited the mutation, it was inherited from the mother in five cases and from the father in ten. Two siblings (brother and sister) had the same mutation although it was undetectable in their parents. Interestingly, authors have found nine patients with novel recurrent mutations (i.e., an identical mutation

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in one patient) and 67 patients had mutations that have previously been reported by other authors. However, most mutations occurred *de novo*, indicating that mutations are repetitively generated through specific mechanisms.[17]

In conclusion, *de novo* mutations in *SCN1A* gene occur in approximately 70-90% of all DS patients (2,5,18). Inherited mutations are usually missense and occur often in a parent with a family history of febrile seizures or epilepsy with febrile seizures-plus (GEFS+).[5]

Table 1 shows the main mutations observed in patients with syndrome DS. The literature shows around 80% of affected patients with DS carry a mutation in the *SCN1A* gene at 2q24.3, which encoding a voltage-gated sodium channel, and essential for the excitability of neurons. The majority of these variants are *de novo* mutations described as missense in exon 15 with the nucleotide change c.2836C>T and a protein phenotype p.Arg946Cys. In addition, it was described that mutations in exon 22 and 26, which present another *SCN1A* mutation types with different phenotypes due to the sodium channel alteration. In 5-10% of the cases, the variants are inherited (typically missense mutations), and the diagnosis is considered part of the febrile seizures or GEFS+ spectrum.

A minority of DS patients might have pathogenic variants in other genes such as *PCDH19*, *SCN1B*, *SCN8A*, *HCN1*, *GABRA1*, and *GABRG2*, and other pathologies close to DS should be considered for the differential diagnosis.[19]

Regarding the physiological and phenotypic consequences of the *SCN1A* mutations, it can be pointed out that exon 26 has a great importance in the genesis of DS, and the most cited in the literature. The *SCN1A* nonsense mutation at exon 26 results in the substitution of c.5177G>A/p.W1726X, generating an early termination codon, that corresponds to the pore formation region of the protein; thereby, impairing the inhibitory activity of the affected neurons.[8] The nonsense mutation at exon 26, c.5674C>T/p.Arg1892X, leads to hemiclonic seizures at the age of five months; thereafter, the patient has presented other seizures including myoclonus daily from 1 year to 10 months of age, and generalized tonic clonic seizures starting at 1 year of age. The patient's IQ was 80. The computed tomography and magnetic resonance imaging (MRI) of the patient were normal. The electroencephalogram analysis showed spike-wave complex and poly spike-wave complex. The magnetoencephalography had no cluster dipole.[13]

The missense mutations at exon 26, c.4907G> A/p.Arg1636Gln, have been related to a phenotype of epileptic encephalopathy, myoclonic seizures, dystonia, and spasticity. In addition, when patients present the mutation c.5555T>C, also presented only afebrile generalized seizures. Few patients had myoclonic seizures and some had a clinical picture of SMEI.[20]

Regarding mutations in exon 4, c.530G>A/p.Gly177Glu and exon 5, c.680T>G/p.Ile227Ser, DS patients have presented no history of acquired brain injury, normal cognitive and motor development, emergence of generalized or unilateral febrile or afebrile seizures in the first year of age, myoclonic spasms, intractable epilepsy, psychomotor delay after two years of onset seizures, normal MRI in the first year of seizure disorder, and a minimum follow-up of three years.[1]

Mutations IVS4+1G>A, IVS8+3G>T and IVS21+1G>A have revealed reduction in mutant allele splicing signal values. In addition, these mutations are located in the third nucleotide of the intron, which are less conserved than the first (9). However, the mutation IVS2+1A>G involves a non-canonical sequence of the splicing donor site, i.e., not part of the most common mRNA splicing in eukaryotes. Mutations at splicing sites modify the normal signaling sequence and result in aberrant mRNA transcription, which may affect protein structure and function. However, to clarify this issue, functional or mRNA studies are required, which is difficult to obtain, since the *SCN1A* gene is only expressed in the central nervous system.[15]

Among the insertions and deletions, identified as c.1242delA, c.3719_3720insGATA and c.5329delG, cause the change of the amino acid residues of the protein sequence due to the promotion of premature termination of the chain by an appearance of an early stop codon.[8] If the aberrant transcripts are translated, they would loss 3/4 and half of the protein sequence for the c.1242delA deletion and for the c.3719_3720insGATA insertion, respectively. In addition, the protein sequence would loss the C terminal portion, which is crucial for protein anchoring on the membrane, for the c.5329delG deletion.[8]

Considering only the number of mutations per protein segment, there is a predominance of alterations in the pore formation regions, between segments S5 and S6, and in the N- and C-terminal portions, besides the segment responsible for voltage detection (S4) in some domains like I and IV.

Conclusion

Mutations in the *SCN1A* gene have a significant impact on the DS etiology. The overlapping mutations were missense and nonsense/truncating mutations. Thus, the genetic test in *SCN1A* for DS clinical purposes is highly recommended.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

LFMS and GST: carried out the bibliographic survey and wrote the paper. MMO: wrote the paper. PHPA: conception and design.

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