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Genetics in epilepsy, Dravet and SUDEP: A systematic review

Abstract

Introduction: Epilepsy is a neurologic condition and its patients have higher mortality rates than healthy individuals. One of the most frequent death causes in epilepsy is SUDEP. Moreover, another cause in epilepsy, although rare, is Dravet Syndrome and it's generally diagnosed in children in their first year of life. In around 70% of the patients there is a genetic inheritance involved and several genes have been described as related to SUDEP and Dravet Syndrome which the most prevalent were DNA and belonged to the voltage-gated channel coding.

Objectives: Identify genes related do Dravet Syndrome, SUDEP and Epilepsy in literature, analyze the convergence of results, and discuss the differences that were found, contributing to the study of genetic mapping.

Methodology: Meta-analysis realized through a bibliographical research in the electronic data banks such as PUBMED, NCBI, Scholar Google and Scielo with the descriptors Epilepsy; Epilepsies, Myoclonic; Polymorphism, Single Nucleotide; MicroRNAs; Death, Sudden. The languages used to filter the articles were English, Spanish and Portuguese. The year was a filtering factor, selecting only articles published in the last 20 years.

Results: About forty (40) genes were found to be SUDEP related and the most relevant was KCNH2, appearing more frequently than other genes. Additionally, in Epilepsy without risk for SUDEP twenty-eight (28) DNA genes were found, which the most frequently mentioned was HCN2, appearing six (6) times. Among Dravet syndrome patients, only two (2) genes were described: SCN1A and SCN9A, both of them were SUDEP risk related. In epilepsy nineteen (19) microRNA genes were found in five (5) different articles.

Project: It was identified genes related to Dravet Syndrome, SUDEP and Epilepsy in literature and was noted that some genes appeared more frequently than others. Among the DNA related genes, the most prevalent were around those belonging to the voltage-gated channel coding, being them sodium, hydrogen and potassium. The results demonstrate that 25% of all articles mentioned SCN1A; 17,5% mentioned HCN2 and 15% mentioned KCNH2. Together these findings provide a basis for further investigation around the role of ionic channels in SUDEP and DS. On the other hand, regarding to MicroRNA linked genes data were scarce. Only five articles described changes on SUDEP and neither described changes compatible with DS. There was no most prevalent mRNA gene.

Conclusion: A range of studies associated DNA mutations with Epilepsy, DS and SUDEP. However, MicroRNA research could not provide concrete evidence on its influence in the development of the epilepsy and epilepsy related conditions. The identification of possible etiological factors can allow a correct and early diagnosis, providing better prognosis and therapeutic outcome, besides it can evaluate the recurrence of the disease in the family. Still, further prospective studies in larger cohorts are required to further define the genetic predisposition to SUDEP, DS and Epilepsy.

Keywords: epilepsy, epilepsies, myoclonic, polymorphism, single nucleotide, microRNAs, death, sudden

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Introduction

Epilepsy is one of the most prevalent neurological diseases, affecting around 50 million patients worldwide is characterized as a predisposition to the occurrence of lasting epileptic seizures and also by the neurobiological, cognitive, psychological and social consequences caused by this condition.[1–3] Patients with this condition have higher mortality rates when compared to healthy individuals and in around 70% of the cases there is a genetic factor involved in the pathogenesis.[2,4] Generalized Seizures, non-adhesion to treatment or drug-resistant epilepsy are the key risk factors to the occurrence of a fatal event.[5]

Epilepsy is a chronic neurologic condition and its etiology is diverse.[6] This disease is responsible for involuntary epileptic seizures due to serious synaptic changes which increases the mortality rates in affected patients.[7] One of the most frequent death causes is the sudden and unexpected death in epilepsy (SUDEP) accounting 17% of all deaths in epilepsy.[8] Moreover, it has an annual incidence rate 1:1000 adults and around 0,2:1000 in children.[8] Its occurrence grows as the number of epileptic seizures increases, in the presence of a night crisis, the longer the time since the beginning of the condition, early onset of the disease and cardiorespiratory comorbidities.[8]

In addition, another cause of death in epilepsy, despite rare, is Dravet Syndrome (DS), a spectrum of the disease characterized by the beginning of prolonged seizures in the first year of life; among those with seizures in the first year of life 3-8% have DS.[9,10] In the second year of life, others types of seizures arise.[9] Around 15% of the children with this syndrome dies before reaching the youth. In cases of survival, the seizures occur in monoclonal crisis, of absence and partially complex, as well as cognitive impairment, ataxia and behavioral changes.[11] Unlike other types of seizures, that in many cases it is possible to manage, the same isn't possible in patients with DS, which still does not have a treatment option.[9] Dravet Syndrome is found between 1:20000 and 1:40000 people, with a prevalence two times higher in boys.[10] Furthermore, those that suffer from this disease have 15 times higher risks of a SUDEP occurrence than in other pediatric epilepsies.[9,7] Also, DS can be classified as a channelopathy because 80% of the patients have a mutant SCN1A gene, responsible for codifying a protein that forms the sodium transport channel between the cell membranes.[11]

As mentioned before the epileptic syndromes patients have a genetic inheritance involved in 70% of the cases. Because of that, the main genes were grouped together in a table relating each one to the corresponding pathologies. Scientists started to create patients' genetic maps to research alterations, such as genome-wide single nucleotide polymorphism (SNP), to analyze and identify connected genes to Dravet, SUDEP and Epilepsy, even though the quantity of known genes is inaccurate due its large vastitude and to the dynamics of his new discoveries.

Mapping patient's genome allows the scientific community to widen access to knowledge. Also, it contributes to precision medicine, meaning it individualizes the therapeutic management and prognosis study considering environment and genetics factors. This improves patient's diagnosis as well as treatment efficacy and accuracy.

Objectives

The main goal of this work is to identify genes related to Dravet Syndrome, SUDEP and Epilepsy in literature; to analyze convergence of results; to discuss the differences that were found and to contribute to the study of genetic mapping that allows early diagnosis and improve treatment efficacy.

Methodology

In this meta-analysis study, a range of articles it was investigated through a bibliographical research in the electronic data banks: PUBMED, NCBI, Scholar Google and Scielo with the descriptors Epilepsy; Epilepsies, Myoclonic; Polymorphism, Single Nucleotide; MicroRNAs; Death, Sudden. Also, several arrangements were made among the descriptors and also a manual search along the references of the consulted articles. The languages used to filter the articles were English, Spanish and Portuguese. The year was a filtering factor, selecting only articles published in the last 20 years.

Results

Thirty-seven (37) articles were selected and analyzed. After a more detailed examination and the build of 4 tables composed by twenty-one (21) articles, where it was realized a correlation between the gene involved and the article that cited it, we could notice that some genes appeared more frequently than others, but the mutations were in different regions.

In Dravet only two genes were found: SCN1A and SCN9A, both DNA with locus differences. All of them are related to SUDEP risks. In Epilepsy exactly nineteen (19) microRNA were found in five (5) different articles. Also in Epilepsy, without SUDEP risk, were found twenty-eight (28) DNAs and six (6) of them are different locus of HCN2, two (2) of CDKL5, two (2) of HCN1, two (2) of HCN4, two (2) of KCNH2. About SUDEP DNA genes were found forty (40), the most relevant is KNCH2, because appears in numerous studies. In resume, 21,8% of all mentioned genes are Epilepsy microRNA; 32% are Epilepsy DNA without SUDEP risk; and 45,9% are SUDEP DNA genes; 25% of all articles mentioned SCN1A; 17,5% mentioned HCN2 and 15% mentioned KCNH2.

On the next page the Table 1 exposes the main genes associated to Dravet Syndrome. In addition, the table mentions other genes disorders and its bibliographical references. SCN1A appears in three (3) different articles and locus. The gene mutations are linked to the pathologies: early infantile epileptic encephalopathy type 6 and generalized epilepsy with febrile seizures plus type 2. SCN9A is also related to Dravet Syndrome, and is associated to paroxysmal extreme pain disorder.

Table 1 Dravet syndrome

Gene	Locus	Sudep	Other disorders	Reference
SCN1A	2q24.3	YES	Early Infantile Epileptic Encephalopathy type 6 and Generalized Epilepsy with Febrile Seizures Plus type 2	12
SCN1A	c.4507G>A p(E1503K)	YES	Early Infantile Epileptic Encephalopathy type 6 and Generalized Epilepsy with Febrile Seizures Plus type 2	13
SCN1A	--	YES	Early Infantile Epileptic Encephalopathy type 6 and Generalized Epilepsy with Febrile Seizures Plus type 2_	14
SCN9A	2q24.3	YES	Paroxysmal Extreme Pain Disorder	13

Citation: Rocha MS, Avi PH, Aguiar PHPD, et al. Genetics in epilepsy, Dravet and SUDEP: A systematic review. *J Neurol Stroke.* 2019;9(5):290–298. DOI: 10.15406/jnsk.2019.09.00392

The following Table 2 presents microRNAs associated to Epilepsy. Only five (5) articles and nineteen (19) microRNA were found to be related to the disorder, and most of them couldn't explain the specific function of each microRNA.

Table 2 microRNA in epilepsy

miRNA	Function	Reference
miR-124	Down regulation	16
miR-34a	Up regulation at BCL-2	16
miR-128	Down regulation in hippocampus	16
miR-132	Up regulation at CA3 in hippocampus	16
miR-134	Down regulation at CREB and BDNF; Up regulation in hippocampus	16
miR-30d-5p	Down regulation; RBMSI - locus 2824.2;	16
miR-92b-3p	Down regulation; ENPP6 - locus 4q35.1;	17
miR-130a-3p	Up regulation	17
miR-146a-5p	Up regulation	17
miR-106b-5p	Down regulation	17
miR-301a-3p	Down regulation	17
miR-let-7d-5p	Down regulation at MIRNLET7D gene	17
miR-23a	Up regulation of TSC1;	18
miR-324-5p	Regulates cell proliferation and stem cell differentiation; targeting GUI and SMO	16
miR-193;	---	19
miR-146a;	---	19
miR-30c;	---	19
miR-466b;	--	19
miR-301a-3p	Down regulation; MAFB- locus 20q12;	20

The upcoming Table 3 demonstrate Epilepsy risk related genes but not linked to SUDEP. Eleven (11) articles and twenty-eight (28) DNAs were found on this topic. These genes have been correlated to other disorders, most of them the different types of Early Infantile Epileptic Encephalopathy, Rigid Spine Muscular Dystrophy, Long QT Syndrome and Brugada Syndrome.

The Table 4 indicates SUDEP associated risk genes. Seven (7) articles and forty (40) DNAs were found treating this theme. These genes have been cited before in other disorders, which most were over the different types of Early Infantile Epileptic Encephalopathy, Long QT Syndrome and Cardiac Arrhythmia.

Table 3 Epilepsy risk genes

Gene	Locus	Risk of slidep	Other disorders	Reference
MECP2	c.473C> T; Xq28; Mutation on p. (T158M);	NO	Refit Syndrome and X-Linked Syndromic Mental Retardation type 13	13
TSC1	9q34.13	NO	Tuberous Sclerosis type 1 and Lymphangioleiomyomatosis	13
CDKL5	c.2277-2A> C; Mosaicism;	NO	_	13
CHD2	c.1618G> A; Alter protein p. (V540I);	NO	Childhood-Onset Epileptic Encephalopathy and Lennox-Gastaut Syndrome	13
TSC2	16p13.3	NO	Focal Cortical Dysplasia type II and Lymphandioleiomyomatosis.	1.3

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Table continued...

Gene	Locus	Risk of slidep	Other disorders	Reference
NRXN1	2p16.3	NO	Pitt-Hopkins-Like Syndrome type 2	13
CSMD3	8q24.11-q24.13	NO	Benign Adult Familial Myoclonic Epilepsy	13
VCL	10q22.2	NO	Dilated Cardiomyopathy 1W and Familial Hypertrophic Cardiomyopathy type 15.	13
CDKL5	Xp22.13	NO	Early Infantile Epileptic Encephalopathy, 2 and Rett Syndrome	13
KCNCQ2	20q13.33	NO	Early Infantile Epileptic Encephalopathy type 7 and Benign Familial Neonatal Seizures type 1	13
KCND2	Not confirmed	NO	Cycloplegia and Gastrointestinal Lymphoma	13
SYNGAP1	6p21.32	NO	Autosomal Dominant Non syndromic Intellectual Disability type 5 and Autosomal Recessive Mental Retardation type 5	13
GNA01	16q13	NO	Early Infantile Epileptic Encephalopathy type 17; Neurodevelopmental Disorder with Involuntary Movements	13
HCN2	GC+CC; rs3752158 locus C; Mutation on p.S632W e p.V246M;	NO	Rigid Spine Muscular Dystrophy type 1 and Epilepsy	21
HCN2	c.1584+7C>T	NO	Rigid Spine Muscular Dystrophy type 1 and Epilepsy	24
HCN2	E515K	NO	Rigid Spine Muscular Dystrophy type 1 and Epilepsy	22
HCN2	Insertion of 4 base pairs into nucleotide 1869 on the linker region of the gene.	NO	Rigid Spine Muscular Dystrophy type 1 and Epilepsy	23
HCN2	R527Q	NO	Rigid Spine Muscular Dystrophy type 1 and Epilepsy	24
HCN1	TT; rs10462087;	NO	Early Infantile Epileptic Encephalopathy type 24 and Undetermined Early-Onset Epileptic Encephalopathy	21
HCN1	A881T	NO	Early Infantile Epileptic Encephalopathy type 24 and Undetermined Early-Onset Epileptic Encephalopathy.	24
SCN1B;	Mutation on p.Arg214Gln-SCN1Bb,p.Ala197Asp SCN1B,p.Cys211Tyr-SCN1B	NO	Early Infantile Epileptic Encephalopathy type 52 and Generalized Epilepsy with Febrile Seizures Plus type 1	25

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Table continued...

Gene	Locus	Risk of slidep	Other disorders	Reference
CACNA1 H	—	NO	Familial Hyperaldosteranism type IV and Childhood Absence Epilepsy type 6.	26
HCN4	—	NO	Sick Sinus Syndrome type 2 and Brugada Syndrome type B	26
HCN4	RSSOC	NO	Sick Sinus Syndrome type 2 and Brugada Syndrome type B	27
HCN2	rs7255568	NO	Rigid Spine Muscular Dystrophy type 1 and Epilepsy	21
KCNH2	c.246T>C	NO	Long QT Syndrome type 2 and Short Cif Syndrome type 1	28
KCNH2	p.Pro1034fs (=c.31013108del)	NO	Long QT Syndrome type 2 and Short OT Syndrome type 1	29
KCNQ1	c.817C>T on exon 6	NO	Long Qt Syndrome type 1 and Jervell And Lange-Nielsen Syndrome type 1	30

Table 4 Sudep risk genes

Gene	Locus	Other disorders	Reference
SCN8A	c.2543C> G; Mutation on p. (R850G)	Early Infantile Epileptic Encephalopathy type 13 and Benign Familial Infantile Seizures type 5	13
DEPDC5	c.4427-2A> G	Familial Focal Epilepsy with Variable Foci type 1 and Autosomal Dominant Epilepsy with Auditory Features	13
SCN1 A	c.45070> A; 2q24.3-, Mutation on p. (E1503K);	Early Infantile Epileptic Encephalopathy type 6 and Generalized Epilepsy with Febrile Seizures Plus type 2	13
SCN1A	dbSNP A1067T; Mutation on Nav 1.1	Early Infantile Epileptic Encephalopathy type 6 and Generalized Epilepsy with Febrile Seizures Plus type 2	13
SCN5A	c.1066G> A; p.(D356N), Ala672Asp and Pro2006Ala mutation	Cardiac Arrhythmia, Sudden Infant Death Syndrome and Long at Syndrome type 3.	13
SCN5A	R523C no exon 12;	Cardiac Arrhythmia, Sudden Infant Death Syndrome and Long CI Syndrome type 3	31
KCNT1	c.1038C> A e 9q34.3; Altera p.(F346L);	Nocturnal Frontal Lobe Epilepsy type 5 and Early Infantile Epileptic Encephalopathy type 14.	13
CHRN A4	20q13.33	Nocturnal Frontal Lobe Epilepsy type 1 and Autosomal Dominant Nocturnal Frontal Lobe Epilepsy	32
SCN2A	2q24.3	Benign Familial Infantile Seizures type 3 and Early Infantile Epileptic Encephalopathy type 11	32
HCN4	15q24.1; Mutation on Gly913Arg;	Sick Sinus Syndrome type 2 and Brugada Syndrome type 8	33

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Table continued...

Gene	Locus	Other disorders	Reference
HCN2	Mutations on Phe738Cys, PRO802Leu and Pro802ser;	Rigid Spine Muscular Dystrophy type 1 and Epilepsy	33
KCNH2	7q36.1; Mutation Arg176Trp and Arg1047Leu;	Long QT Syndrome type 2 and Short OT syndrome type 1	33
KCNA1	12p13.32;	Episodic Ataxia type 1 and 'Isolated Autosomal Dominant 1-tvpomannesemia Glaudemans type	32
KCNQ1	11p15.5-p15.4;	Long at Syndrome type 1 and Jervell And Lange- Nielsen Syndrome type 1	32
COL18A1	21q22.3	Knobloch Syndrome type 1	32
JUP	17q21.2	Naxos Disease and Familial Arrhythmogenic Right Ventricular Dysplasia type 12	32
SPTAN1	9q34.11	Early Infantile Epileptic Encephalopathy type 5 and Focal Epilepsy	32
SCARB2	4q21.1	Epilepsia mioclonica progressiva type 4	32
CNTNAP2	7q35-q36	Sindrome da epilepsia focal por displasia cortical; Sindrome Pitt-Hopkins;	32
GNAI2	3p21.31	Taquicardia ventricular id idiopatica, Adenoma hipofisario secretor de ACTH;	32
KCTD7	7q11.21	Myoclonic Progressive Epilepsy type 4 and Unvercicht-Lundborg Syndrome	32
DPP6	7q36.2	Autosomal Dominant Mental Retardation type 3 and Paroxysmal Familial Ventricular Fibrillation type 2	32
PCDH19	Xq22.1	Childhood Absence Epilepsy and Early Infantile Epileptic Encephalopathy type 9	34
RYR2	nsSNP Q2958R	Catecholaminergic Polymorphic Ventricular Tachycardia type 1, with or without Atrial Dysfunction and/or Dilated Cardiomyopathy and Familial Arrhythmogenic Right Ventricular Dysplasia type 2	35
RYR2	GABRG3 Duplication	Catecholaminergic Polymorphic Ventricular Tachycardia type 1, with or without Anal Dysfunction and/or Dilated Cardiomyopathy and Familial Arrhythmogenic Right Ventricular Dysplasia type 2	36
RYR3	nsSNP C1288Y	Familial Arrhythmogenic Right Ventricular Dysplasia type 2 and Central Core Myopathy	35
5-HT	nsSNP R260H	_	35
CACNA1 A	p.R2241W; p.A951V	_	34
CACNA1C	p.P2421V; 19p13	Timothy Syndrome and Brugada Syndrome type 3	34
EFHC1	_	Myoclonic Juvenile Epilepsy and Juvenile Absence Epilepsy type 1.	34
SCN11A	p.C844Y	Familial Episodic Pain Syndrome type 3 and Hereditary Sensory and Autonomic Neuropathy type VII	34
SCN10A	p.M1267R	Familial Episodic Pain Syndrome type 2 and Sodium Channelopathy-Related Small Fiber Neuropathy	34
FBN 1	_	Stiff Skin Syndrome and Marfanoid-Progeroid- Lipodystrophy Syndrome	34
SCN4A	p.R1828C	Paramyotonia Congenita Of Von Eulenburg and Potassium-Aggravated Myotonia	34
ARRB2	_	Whim Syndrome and Bardet-Biedl Syndrome type 19	36
ANK2	4q25-q26	Arrhythmia, Ankyrin-B-Related Cardiac Arrhythmia and Long Qt Syndrome type 1	36
COL18A1	21q22.3	Knobloch Syndrome type 1	36
CNTNAF2	7q35-q36	Pitt-Hopkins-Like Syndrome type 1 and Autism type 15	36
CASK	Xp11.4	Mental Retardation and Microcephaly with Pontine and Cerebellar Hypoplasia, FG Syndrome type 4	36

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Project

Genes related to Dravet Syndrome, SUDEP and Epilepsy have been identified in literature and was noted that some of them appeared more frequently than others. The results demonstrate that 25% of all articles mentioned SCN1A; 17,5% mentioned HCN2 and 15% mentioned KCNH2.

Among the DNA related genes, the most prevalent were around those belonging to the voltage-gated channel coding, being them sodium, hydrogen and potassium. The Sodium voltage-gated channels (SCN) appeared more frequently, being cited fourteen times which four of them were SCN1A. Also, mutations in SCN1B, SCN2A, SCN5A, SCN8A, SCN9A, SCN10A, SCN11A, despite less recurrent were also described. The Hydrogen voltage-gated channels (HCN) were mentioned in twelve occasions of which seven pointed to HCN2. Besides, variations were also seen in HCN1 and HCN4. Finally, the Potassium voltage-gated channels were reported in nine occasions of which three were about KCNH2. Moreover, mutations have been cited in KCNH1, KCNQ1, KCNT1, KCNQ2, KCNA1, KCND2. Together these findings provide a basis for further investigation around the role of ionic channels in SUDEP and DS.

SCN1A

It is related to DS, also denominated as early childhood epileptic encephalopathy type 6.[11–13] In this disease, particularly, there are 12 possibilities of deleterious alterations observed, being 50% missense type (c.829T> C, c.971A> C, c.2360T> G, c.4093G> T, c.5178G> T and c .5434T> C), 25% splice sites (IVS2 + 1A> G, IVS4 + 1G> A and IVS8 + 3G> T), 17% frameshift type (c.3719_3720insGATA and c.1242delA), 8% deletion of a triplet (c.5489_5491delAGT).[14] Mutations provide a great risk of SUDEP, because this is a rare and severe progressive encephalopathy without concrete treatment.[13,14,29,37]

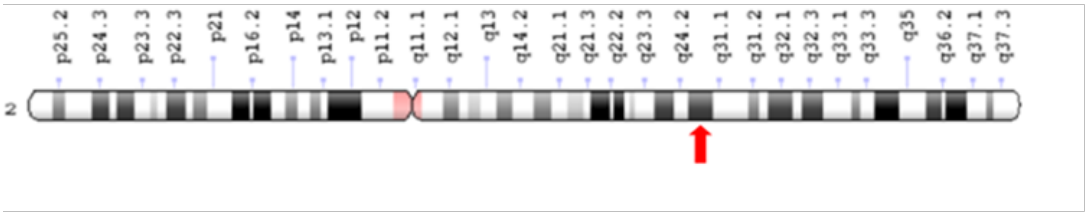

Image 1 Cytogenetic location of SCNA1 gene: 2q24.3. Adapted from: Genetics Home Reference.[38]

Modifications in SCN1A gene are also linked to generalized epilepsy associated with febrile seizures type 2.[14,37] According to article research**,** the proteins responsible for the composition of Nav1.1 (voltage-dependent sodium channel type I, alpha subunit) are modified, also altering the synaptic functions of cells.[13,14]

KCNH2

With the intention of connecting canalopathic epilepsy with cardiac arrhythmias, the KCNH2 gene was experimented.[29] Observed modifications in 7q36.1, which changes Arg176Trp and Arg1047Leu13; also p.Pro1034fs (c.3101_3108del), in this case there is a premature stop codon that gives the degradation order of mutated mRNA; the missense heterozygous mutation (c.246T> C) in the second exon of the gene leads in the alteration of isoleucine (p.I82T).[28,29,33] This is a gene responsible for the composition of Kv1.1, potassium channels, and its alterations are linked to type 2 long and short QT syndromes, as well the epilepsies.[28,29,33]

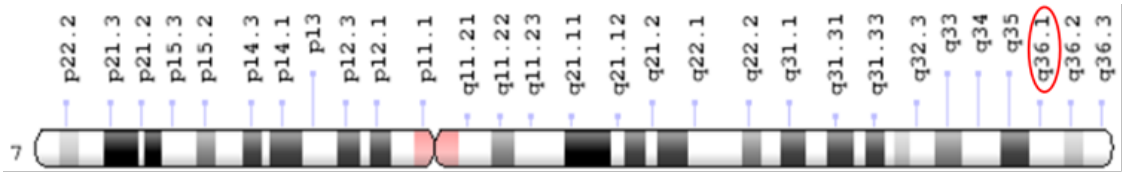

Image 2 Cytogenetic location of KCNH2 gene: 7q36.1. Adapted from: Genetics Home Reference.39

Theories suggest the concept of cardiocerebral channelopathy, because they are the sites of highest expression of proteins encoded by the KCNH2 gene.[28] The hERG channels, encoded by KCNH2, can regulate neuronal triggering and are particularly active in astrocytes: disturbances of this channel may confer susceptibility to recurrent seizure activity.[28,40–42]

HCN2

It is the gene responsible for coding the H channel, subunit number 2, for activated cations by cyclic nucleotide and for hyperpolarization**,**[21–23] has high sensitivity to cAMP modulation, and is located especially in the thalamus and trunk region. Studies have identified modifications in HCN2 Gs rs7255568 and rs3752158 alleles in genetically generalized epilepsies (GGEs) determined, regarding to controls (p=0.039, p=0.027, respectively).[21] Only rs7255568 was linked to risks of childhood absence epilepsy (CAE) (p=0.028) and juvenile myoclonic epilepsy (JME) (p=0.02).[21] While rs3752158 is linked to the risk of generalized tonic-clonic seizures, JME and febrile seizures, in all C and GC + CC alleles.[21,33] Changes in the two previously mentioned alleles, as well as variations of R527Q in HCN2 exon 5 are also present in congenital rigid spine muscular dystrophy.[21,33] There are few studies that address R527Q and these are not conclusive when its importance in GGEs.[21,33] Regarding idiopathic generalized epilepsy (IGE) in the HCN2 gene, numerous variants

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were found, the most prevalent was the substitution of amino acids R527Q in exon 5.[21,24]

The intron 5 variant (c.1584 + 7CNT) was related to epilepsy from family history studies.[21] Such research leads us to believe that changes in channels with this variant cause a decrease in conductance-voltage.[24] It was identified a type of missense mutation in exon 5 of the HCN2 gene, which causes mutation of the E515K protein, which may be related to sporadic generalized epilepsy. Such mutation involves the Glu515 residue, which is of great importance for channel functionality, as it is involved in triggering. Alterations imply loss of channel function, increasing its excitability at rest.[22] It was identified 4 base pair insertion, TTCA, in nucleotide 1669 in exon 6 of the HCN2 gene at the ion channel.[23] This mutation compared when naturally occurred and when induced provide base shifting and the addition of 41 amino acids and a different stop codon.[23] Producing, therefore, absence epilepsy and ataxia, both of early manifestation.[23]

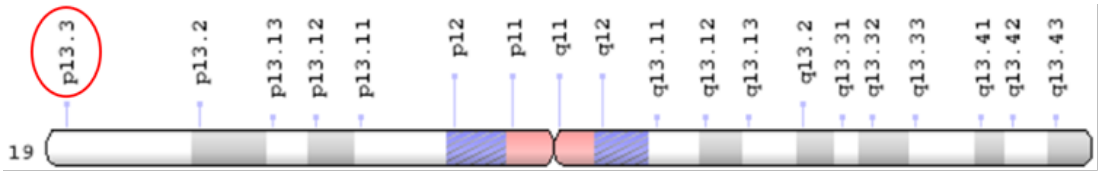

Image 3 Cytogenetic location of HCN2 gene: 19p13.3. Adapted from: Genetics Home Reference.40

On the other hand, regarding to MicroRNA linked genes data were scarce. Only five articles described changes on SUDEP and neither described changes compatible with DS. The changes cited covered the genes: miR-124, miR-34a, miR-128, miR-132, miR-134, miR-30d-5p, miR-92b-3p, miR-130a-3p, miR-146a-5p, miR-301a-3p, miR-let-7d-5p, miR-23a, miR-324-5p, miR-193, miR-146a, miR-30c, miR-466b. There was no most prevalent gene.[16–20]

Conclusion

In this meta-analysis, the tables made it possible to assemble the main genetic components that, mutated, may express different conditions (Tables 1-4). We report a range of studies associating DNA alterations with epilepsy, DS and SUDEP (Tables 1,3 & 4). This series of highly scrutinized DNA analyses will allow advances in early diagnosis.[23,33] For DS, only two genes were found, SCN1A and SCN9A, both related to the risk of SUDEP (Table 1). For epilepsy with or without risk of SUDEP were found mainly SCN1A, HCN2, KCH2 (Table 3). However, research involved in mRNA didn't provide concrete evidence on the influence on different diseases investigated, only suggested the possibility of interference (Table 2).

The combination of genetic effects with susceptibility factors for developing other mutations contributes to the increased risk of SUDEP (Table 1). The pathological relation between brain and heart in SUDEP is evident, because the review demonstrates that K^+ and Na^+ channels suffer strong genetic interference, and, such channelopathies lead to high mortality when there is no adequate treatment.[13,28,31,32,37] The correlation of SUDEP with other syndrome allows an accurate diagnosis search.[23,28,33]

Genetic tests to prove the disease are highly recommended for patients with DS and epilepsy.[9,13,17] The identification of etiological factors in their early stages and the fast and appropriate procedure allow the correct and early diagnosis, providing better prognosis and therapeutic outcome; more so, it can evaluate the recurrence of the disease in the family. It can be observed, in some cases, a pattern in the disturb from the discovery of genotype.[11,13,14]

The mapping of a patient's genome makes it possible to construct of a database for genetic mutations in Epilepsy, SUDEP and Dravet. It also allows the interpretation of disease etiology. It contributes to widen access to knowledge for the scientific community and to precision medicine. That's important not only to provide options and recommend the better therapeutic management based on the real genetic cause of the disease, but also to make patient's prognosis clear.[40,43]

All patient care in this process should always aim the best prognosis, even when there are serious phenotypes, which is because such conditions have consequences that are not only physiological, but also cognitive, psychologic and social, directly affecting the quality of life of the pacient.[11,13,14,34] Further studies in larger cohorts are required to define the genetic predisposition.[13]

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Conflicts of interest

The authors declare that there are no conflict of interest.

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