Published in final edited form as:

Epilepsy Behav. 2014 September ; 0: 172–179. doi:10.1016/j.yebeh.2013.09.019.

Genomic biomarkers of SUDEP in brain and heart

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Abstract

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of epilepsy-related mortality, but how to predict which patients are at risk and how to prevent it remains uncertain. The underlying pathomechanisms of SUDEP are still largely unknown but the general consensus is that seizures somehow disrupt normal cardiac or respiratory physiology leading to death. However, the proportion of SUDEP cases exhibiting cardiac or respiratory dysfunction as a critical factor in the terminal cascade of events remains unresolved. Although many general risk factors for SUDEP have been identified, the development of reliable patient-specific biomarkers for SUDEP is needed to provide more accurate risk prediction and personalized patient management strategies. Studies in animal models and patient groups have revealed at least nine different brain-heart genes that may contribute to a genetic susceptibility for SUDEP, making them potentially useful as genomic biomarkers. This review summarizes data on the relationship between these neurocardiac genes and SUDEP, discussing their brain-heart expression patterns and genotype-phenotype correlations in mouse models and people with epilepsy. These neurocardiac genes represent good first candidates for evaluation as genomic biomarkers of SUDEP in future studies. The development of validated reliable genomic biomarkers for SUDEP has the potential to transform the clinical treatment of epilepsy by pinpointing patients at risk of SUDEP and allowing optimized, genotype-guided therapeutic and prevention strategies.

Keywords

SUDEP; Epilepsy; Genomic biomarker; Personalized medicine; Gene profile; Brain-heart connection; Cardiac arrhythmia; Long QT syndrome

1. Introduction

Death strikes without warning in people with epilepsy at a rate up to 24 times greater than the general population [1,2]. When a person with epilepsy who is otherwise healthy dies suddenly for unknown reasons, the death is classified as Sudden Unexpected Death in

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Epilepsy (SUDEP). Such deaths are usually unwitnessed and by definition post-mortem examination fails to identify an obvious toxicological or anatomical culprit [3]. The average incidence of SUDEP is about 1 in 500, making it the leading cause of mortality in people with epilepsy accounting for about 17% of epilepsy-related deaths [4]. The exact causes of SUDEP remain mysterious but the two leading hypotheses that have emerged are that seizures disturb normal cardiac or respiratory physiology leading to death. The brain regulates heartbeat and breathing via the autonomic nervous system and seizures are known to induce cardiorespiratory changes including bradycardia, tachycardia, cardiac conduction blocks, arrhythmias, apnea, hypoventilation, and hypoxemia [5-7]. In addition, epilepsy is a risk factor for sudden cardiac arrest in the general population and several genes linked to inherited cardiac arrhythmias have now been linked to epilepsy suggesting a shared genetic basis [8,9].

Many SUDEP risk factors have been identified using descriptive cohorts and case-control studies. Consistently associated risk factors include young age (20-45 years old); generalized tonic-clonic seizures; early onset of epilepsy; male sex; subtherapeutic antiepileptic drug (AED) levels; frequent seizures; nocturnal seizures; being in bed; duration of seizure disorder; and AED polytherapy [4,9-11]. While the strength or weakness of a particular risk factor may vary between studies, the general consensus is that SUDEP is a seizure-related event affecting patients with chronic uncontrolled epilepsy [12]. Attempts have been made to quantify SUDEP risk among epilepsy patients by utilizing risk factor scoring systems. While these efforts have met a degree of success, many patients with low SUDEP risk scores still die of SUDEP while some patients with higher SUDEP risk scores do not [4]. The ability to predict with a high degree of certainty which patients will ultimately die from sudden death remains elusive.

One strategy to improve SUDEP risk assessment and prevention is the development of reliable biomarkers. The United States National Institutes of Health (NIH) defines a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [13]. In 2007, the United States National Institute of Neurological Disorders and Stroke (NINDS) published a series of epilepsy research benchmarks to guide the field of epilepsy research [14]. One of the stated benchmarks was the identification, development, and validation of biomarkers to predict individuals at-risk for epilepsy and to optimize therapies. Another benchmark urged development of strategies to prevent SUDEP and to understand its mechanisms. However, the search for biomarkers in the context of SUDEP was not explicitly stated as a benchmark goal and little progress has been made.

Identification of genomic biomarkers for SUDEP is a potential means to more accurately stratify risk assessment in epilepsy and to better inform treatment options and prevention strategies [15,16]. A genomic biomarker is a type of biological marker involving a measurable DNA and/or RNA characteristic such as single nucleotide polymorphisms (SNPs), nucleotide deletions or insertions, copy number variations, and cytogenetic rearrangements [16]. As high-throughput and large-scale genetic studies proliferate, our knowledge of epilepsy-related genetic variation continues to expand at a rapid rate [17-19]. One of the goals of the genomic era is to personalize medicine by using an individual's

genotype to provide accurate diagnosis and to tailor treatment. Toward this end, utilizing validated epilepsy gene variants to identify reliable genomic biomarkers for SUDEP could allow genotype-guided patient diagnosis and management.

Several genes have been linked to SUDEP in patient and animal studies making them candidate genomic biomarkers. Since SUDEP involves some combination of abnormal brain, cardiac, and respiratory physiology, any gene with expression or phenotypes in these tissues could be a potential biomarker. This article will discuss epilepsy genes with neurocardiac expression patterns that have been implicated in SUDEP. Brain-heart dysfunction leading to SUDEP could arise from genetic variation in two main classes of neurocardiac genes based on their differing expression patterns: 1) genes with predominantly neural expression that influence the heart extrinsically via the autonomic nervous system, and 2) genes with high levels of expression in both brain and heart that can impact cardiac function either intrinsically or extrinsically. Neurorespiratory genes associated with SUDEP have been examined in-depth elsewhere and are outside the scope of this review [7]. The neurocardiac epilepsy genes discussed here represent initial candidates for consideration as genomic biomarkers in SUDEP with the hope that someday gene-based molecular profiling will improve the quality and longevity of life for epilepsy patients.

2. Candidate SUDEP biomarker genes

At least nine neurocardiac genes have been linked to SUDEP in human or animal studies. This review will highlight what is known about each of these genes with regards to their brain-heart expression pattern, epilepsy and cardiac phenotypes, and association with SUDEP (summarized in Table 1). These nine genes can be grouped generally into five “brain” and four “heart” genes depending on their predominant function and expression pattern, but all of them show some degree of neurocardiac co-expression. Furthermore, all of these genes code for ion channel proteins except for the recently described *PRRT2* gene. The predominance of ion channel genes associated with SUDEP suggests that this class of genes may be enriched for SUDEP-associated gene variants. Rare Mendelian forms of idiopathic epilepsy also primarily involve mutations in ion channels. Genetic variation in any of the SUDEP-associated neurocardiac genes discussed here deserves consideration as a potential genomic biomarker for SUDEP.

2.1. “Brain” genes

2.1.1. KCNA1—The *KCNA1* gene encodes Shaker-like voltage-gated potassium channel Kv1.1 α -subunits, which form heterotetramers with Kv1.2 and Kv1.4 α -subunits *in vivo* [20-23]. Kv1.1 channels show very strong levels of expression in brain but low levels in heart. In mouse, Kv1.1 protein is widespread throughout the brain with localization in the hippocampus, cortex, striatum, brainstem, and cerebellum [24]. In human brain, Kv1.1 subunits have been detected by immunoblot in cerebral white and gray matter, as well as spinal cord [22]. On a subcellular level, Kv1.1 channels primarily localize to axons where they act to dampen neuronal excitability by regulating action potential propagation and shape, repetitive firing properties of neurons, and neurotransmitter release [25,26]. In the heart, RT-PCR has detected *Kcna1* transcripts in mouse ventricles, atria, sinoatrial node, and atrioventricular node [27-29]. In addition, Kv1.1 protein can be detected by immunoblotting

lysates from whole mouse heart, but only at very low levels [27]. Currently, *KCNA1* expression in human heart has not been demonstrated [22]. While their role in the brain has been studied extensively, the function and relative importance of Kv1.1 channels in the heart remains unknown. One possibility is that Kv1.1 channels play a role in intrinsic cardiac pacemaking since chronic bradycardia in mice leads to compensatory upregulation of *Kcna1* mRNA expression in sinoatrial node [30].

The *KCNA1* gene has been linked to brain-driven cardiac dysfunction in a mouse model of SUDEP and to epilepsy in humans. In mice, *Kcna1* gene deletion results in severe tonic-clonic seizures that culminate in death in about 75% of animals by the age of 10 weeks [31,32]. In addition to neurological phenotypes, *Kcna1* knockout mice also exhibit cardiac abnormalities including interictal atrioventricular (AV) conduction blocks and ictal bradycardia [27]. Simultaneous *in vivo* EEG-ECG recordings captured a SUDEP event in a Kv1.1-deficient mouse in which the animal's death appeared triggered by a series of severe seizures that were coupled with profound ictal bradycardia, suggesting a lethal brain-heart mechanism [27]. *In vivo* pharmacological experiments have shown that interictal AV conduction blocks in Kv1.1-deficient mice are selectively abolished with atropine, indicating they are neurally-driven by the vagus nerve [27]. In *ex vivo* recordings of Kv1.1-deficient mouse vagus nerve, the large myelinated axons are far more susceptible to spontaneous ectopic firing in the presence of the potassium channel blocker 4-aminopyridine suggesting underlying vagal hyperexcitability [26]. In patients, *KCNA1* gene mutations have been predominantly implicated as the cause of the neurological movement disorder episodic ataxia type 1, but inherited missense mutations in *KCNA1* have also been found to underlie epilepsy in at least three different families [33-36]. However, *KCNA1* gene variants have not yet been directly linked to SUDEP or arrhythmias in patients.

2.1.2. SCN1A—*SCN1A* encodes the α -subunit of brain-type tetrodotoxin (TTX)-sensitive voltage-gated Nav1.1 sodium channels, which show high levels of expression in brain and lower levels in heart [37]. Nav1.1 channels are widely distributed throughout human and rodent brain with the highest degree of clustering in neurons of the hippocampus, thalamus, cerebellum, and brainstem [38-42]. Importantly, Nav1.1 subunits exhibit selective expression in the cell bodies and axon initial segments of GABAergic interneurons [40,43,44]. Accordingly, inhibitory neurons in *Scn1a*-null mice exhibit significant reductions in sodium current density, while excitatory neurons appear relatively unaffected [40]. Thus, Nav1.1-mediated signaling is thought to be more important for regulating excitability in inhibitory neurons than in excitatory neurons. In human and mouse heart, Nav1.1 channels are expressed at both the mRNA and protein level [45-49]. The channels exhibit specific localization to the transverse tubules of the ventricles and the sinoatrial node where they are important for excitation-contraction coupling and control of heart rate, respectively [48,49].

SCN1A channelopathies are responsible for two different human epilepsies: severe myoclonic epilepsy of infancy (SMEI), also known as Dravet's syndrome, and generalized epilepsy with febrile seizures plus (GEFS+) [50,51]. In Dravet patients, upwards of 650 *SCN1A* mutations have been identified, which accounts for the majority of cases (about 85%) [52]. About 20 different *SCN1A* mutations have been linked to GEFS+, which

represents about 10% of cases [52]. About half of the Dravet mutations are nonsense or frameshifts resulting in protein truncation, whereas GEFS+ is usually associated with less severe missense mutations [53]. The prevalence of *SCN1A* mutations in these two disorders gives *SCN1A* the distinction of being the gene most commonly associated with inherited (GEFS+) and sporadic epilepsy (Dravet) [52]. *SCN1A* variants are of particular relevance to SUDEP since both Dravet syndrome and GEFS+ have been linked anecdotally to SUDEP [54,55]. Notably, SUDEP has been reported in a Dravet patient who was heterozygous for a genotyped frameshift *SCN1A* mutation [56]. Dravet syndrome is of particular importance for SUDEP since it is associated with a high mortality rate [55]. In addition, Dravet patients have been found to exhibit reduced heart rate variability and increased P wave and QT dispersion in ECG recordings, findings indicative of augmented sympathetic tone that could contribute to neurocardiac dysfunction and SUDEP in this cohort [57,58].

Several mouse strains exist with knockout or knockin mutations that model *SCN1A* channelopathies. Two different knockin mouse lines have been generated that carry human GEFS+ and Dravet *SCN1A* mutations and both exhibit spontaneous seizures and premature death [38,59]. However, most work has focused on *Scn1a* knockout models. Mice that are heterozygous *Scn1a*-nulls (*Scn1a* +/-) recapitulate many key features of Dravet syndrome, including early onset epilepsy, premature lethality, and hyperthermia-induced seizures [40]. Selective deletion of *Scn1a* in forebrain GABAergic neurons (*Scn1a* cKO) is sufficient to reproduce these neurological phenotypes, underscoring the importance of Nav1.1 channels in inhibitory interneurons [60]. *Scn1a*+/- mice begin dying prematurely at P21 and these deaths tend to occur during periods of high seizure incidence and immediately following the most severe (Racine 5) generalized tonic-clonic seizures. Similar to Kv1.1-deficient mice, both *Scn1a*+/- and *Scn1a* cKO animals exhibit an increased frequency of interictal AV blocks. When seizures are thermally induced in *Scn1a*+/- and *Scn1a* cKO animals, they exhibit cycles of ictal brady- and tachycardia indicative of brain-heart dysfunction. Blockade of central and/or peripheral muscarinic receptors with atropine or N-methyl scopolamine prevents thermal seizure-induced bradycardia and sporadic death in *Scn1a*+/- animals suggesting that lethality in this model is related to parasympathetic hyperactivation.

2.1.3. SCN8A—The *SCN8A* gene encodes the primarily neural Nav1.6 voltage-gated sodium channel α -subunits that conduct a low voltage-activated, persistent sodium current important for action potential initiation at axon initial segments [61–64]. Immunolabeling experiments performed in rats and mice show that the channels are expressed in hippocampus, cortex, and cerebellum in mammalian brain [65–68]. Nav1.6 channels are the predominant sodium channels at nodes of Ranvier of adult myelinated axons in both the CNS and PNS, replacing Nav1.2 (*SCN2A*) channels which are expressed at nodes early in development [65,69]. Nav1.6 channels are also present to a lesser degree in dendrites where they are the primary somatodendritic sodium channel that enables back-propagation of action potentials from the soma [43]. In the heart, Nav1.6 channels have been identified in mouse ventricles where they participate in excitation-contraction coupling and action potential propagation [70]. In rat heart, immunohistochemistry, western blots, and qPCR have localized Nav1.6 subunits to sinoatrial node where the channels play an important role in pacemaking [71]. In rats with induced heart failure, sinoatrial Nav1.6 channels are

downregulated, underlying their importance to nodal function [71]. The human brain-heart expression pattern of SCN8A has not yet been explored in detail.

SCN8A mutations have been linked to epilepsy in mouse models and in one human pedigree, which was also affected by SUDEP. In mice, two missense alleles (*Scn8a*^{8J} and *Scn8a*^{med-jo}) and a null allele (*Scn8a*^{med}) exhibit absence epilepsy phenotypes characterized by ethosuximide-sensitive spike-wave discharges associated with behavioral arrest [72]. In another model, mice deficient for CELF4, a neuronal RNA-binding protein, exhibit a complex seizure disorder that may be related to Nav1.6 dysregulation [73]. CELF4 binds *Scn8a* mRNA and in the absence of CELF4, Nav1.6 channels are dramatically overexpressed at axon initial segments suggesting they may play a role in seizure generation by increasing action potential initiation in this model [73]. In humans, SCN8A was linked to epilepsy and SUDEP when a *de novo* pathogenic mutation was identified by whole genome sequencing of a family quartet containing a SUDEP victim and her unaffected parents and sibling [74]. The SUDEP individual, who suffered from severe infantile epileptic encephalopathy, was found to be heterozygous for a missense SCN8A mutation that altered the biophysical properties of the channel resulting in a dominant gain-of-function phenotype [74].

2.1.4. HCN2—*HCN2* is one of a family of four genes (*HCN1-4*) that encodes a hyperpolarization-activated, cyclic nucleotide-gated cation channel, which passes a mixed Na⁺/K⁺ inward current (termed I_f in cardiac cells and I_h in neurons) that activates with hyperpolarizing steps below about −50 mV [75]. The I_f/I_h current contributes to cardiac and neuronal pacemaker activity, the setting of resting membrane potential, dendritic integration, and synaptic transmission [75,76]. In humans and mice, *HCN2* mRNA is expressed highly in brain and at a much lesser degree in heart [77,78]. *In situ* hybridization experiments reveal *HCN2* expression is nearly ubiquitous in mouse brain with the highest transcript levels observed in thalamus, hippocampus, and brainstem [79,80]. In the mammalian heart, *HCN2* mRNA is expressed at very low levels relative to other *HCN* transcripts in the cardiac conduction system, but in ventricles *HCN2* mRNA appears to be the predominant *HCN* message [81]. Immunoprecipitation and immunoblot experiments have revealed that HCN2 protein in adult mouse heart is C-terminal modified in a cardiac-specific manner and co-assembles with HCN4 subunits to form heterotetrameric channels with properties similar to endogenous myocardial I_f channels [82]. However, the role of I_f in adult atrial and ventricular tissue is unclear since it apparently makes only a minor contribution under physiological conditions [83,84].

HCN2 channelopathy has been linked to both cardiac and epilepsy phenotypes in mice and to epilepsy and SUDEP in humans. Despite the limited expression of HCN2 channels in heart, *Hcn2*-null mice exhibit cardiac sinus dysrhythmia and reduced sinoatrial HCN current [85]. In addition, they also exhibit frequent spike-wave discharges accompanied by behavioral arrest indicative of absence epilepsy [85]. Mice carrying the *apathetic* allele of *Hcn2*, a four base pair insertion resulting in protein truncation and 90% reduction in mRNA, also exhibit absence epilepsy, underscoring the importance of HCN2 channels in this neurological phenotype [86]. Notably, about 14% of *apathetic* mice die prematurely between the ages of 21-28 days with an additional 10% dying per month thereafter [86].

Although their cause of death has not been determined, the authors suggested a neurological or cardiac explanation due to the lack of findings on necropsy [86].

In humans, screening of *HCN1* and *HCN2* genes in epilepsy patients has identified a recessive loss-of-function missense mutation in the channel gating region of *HCN2* that increases neuronal excitability and underlies idiopathic generalized epilepsy [87]. In addition, a postmortem analysis of *HCN1-4* DNA variants in a group of 48 SUDEP cases found two different non-synonymous changes in *HCN2* (F738C and P802S) associated with SUDEP that were absent in controls, suggesting *HCN2* variants may underlie susceptibility to sudden death [88]. Interestingly, the study also found one unique genetic variant in *HCN4* linked to SUDEP, supporting a general role for neurocardiac HCN channels in SUDEP pathology [88].

2.1.5. PRRT2—One of the newest potential biomarkers for SUDEP is genetic variants in the *PRRT2* gene, based on its recent identification as an epilepsy gene and its association with a probable SUDEP case. The *PRRT2* gene, which encodes Proline-Rich Transmembrane protein 2, has been identified as the most frequent genetic cause of benign familial infantile epilepsy (BFIE), an early onset seizure disorder that usually begins in infancy and remits by the age of two [89]. *PRRT2* is an unusual epilepsy gene since it does not encode an ion channel protein. Sequence analysis predicts that the gene encodes a protein of unknown function composed of two C-terminal transmembrane domains following a proline-rich region [90]. Yeast two-hybrid analysis and co-immunoprecipitation experiments show that it interacts with synaptosomal associated protein 25 kDa (SNAP-25), which localizes to presynaptic terminals and is involved in neurotransmitter release as a SNARE protein [91,92]. Therefore, *PRRT2* may interact with SNAP-25 to modulate neurotransmitter release in some way yet to be determined [93].

A search of the UniGene human EST profile gene expression database reveals that *PRRT2* exhibits very strong expression in brain but low or undetectable levels in heart. Mouse *in situ* hybridization experiments, RT-PCR and immunoblots also show that *PRRT2* mRNA and protein is expressed robustly in brain, especially cerebral cortex, cerebellum, hippocampus and basal ganglia [89,90,92]. However, western blots and RT-PCR find barely detectable levels of *PRRT2* expression in mouse heart, a finding corroborated by microarray analyses which show cardiac transcripts as low or undetectable [90,92,94].

A recent case report links *PRRT2* with a death meeting the criteria for a probable SUDEP event [95]. The victim, a 14-year old boy who suffered infrequent afebrile seizures, was found dead in a supine position during his sleep but no autopsy was performed. Between the ages of 4 to 9 months old he had experienced benign familial infantile seizures consistent with *PRRT2* pathology. DNA sequencing showed that the boy carried a heterozygous duplication of a cytosine residue in the coding region of the *PRRT2* gene, which resulted in a frameshift leading to protein truncation. While the presence of this mutation in a probable SUDEP victim could be merely coincidence, the functional role of the gene in the brain and heart needs to be better understood before such a connection can be excluded.

2.2 “Heart” genes

2.2.1. Long QT syndrome genes—One of the most promising sets of SUDEP biomarkers is genetic variants in long QT syndrome (LQTS) genes. Congenital LQTS is an inherited disorder characterized by delayed cardiac repolarization resulting in abnormal pathognomonic prolongation of the QT interval on the electrocardiogram (ECG). The result of this repolarization defect is an increased propensity for a ventricular tachyarrhythmia known as torsades de pointes (TdP), which can precipitate syncope, seizures, and sudden death [96]. LQTS is linked with the inheritance of mutations in 12 different cardiac genes, which code for ion channels or channel-associated proteins [97]. Notably, all 12 genes exhibit expression in brain as well as heart. LQTS is subdivided into 12 different subtypes (LQT1-12) based on which underlying gene is found to be causative. The vast majority of genetically positive LQTS cases are caused by mutations in *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) [97]. Interestingly, each of these three genes has been associated with epilepsy and SUDEP suggesting their possible utility as genomic biomarkers for SUDEP. However, the association of LQT genes with epilepsy is not without controversy as convulsions can occur due to LQT-associated cardiac syncope and arrhythmias leading to misinterpretation as epileptic seizures [98,99]. On the other hand, undoubtedly many true epileptic seizures in LQTS patients are mislabeled as “cardiac events.”

2.2.1.1. KCNQ1: The most common form of inherited LQTS (LQT1), accounting for nearly half of cases, is caused by autosomal dominant and recessive loss-of-function mutations in the *KCNQ1* gene [97]. The *KCNQ1* gene encodes KvLQT1/Kv7.1 voltage-gated potassium channel α -subunits which conduct the slowly activating delayed-rectifier potassium current, I_{Ks} , in the heart, which is important for ventricular repolarization [100,101]. Dogma previously held that KvLQT1 channels were exclusive to the heart with no expression in brain. This paradigm shifted when two different strains of mice engineered to carry human LQT1 mutations were found to suffer spontaneous epileptic seizures in addition to displaying various cardiac rhythm disturbances, including atrial fibrillation, atrial flutter, premature ventricular contractions, and AV conduction blocks [102]. These findings led to the first demonstration of *KCNQ1* mRNA in the mouse and human brain in multiple regions including the hippocampus and cerebellum; immunoblots detected Kcnq1 protein in mouse brain as well [102]. The cardiac events in *Kcnq1* mutant mice exhibited synchronicity with epileptiform discharges suggesting they were neurally driven [102]. In one instance a rare SUDEP event in a *Kcnq1* mutant mouse was captured while recording EEG-ECG. The traces revealed spontaneous seizure activity preceding bradyarrhythmias and asystoles, which eventually evolved into electrocerebral shutdown and subsequent cardiac arrest, mirroring observations in rare cases of human SUDEP with simultaneous EEG recording [102,103]. Although *KCNQ1* mutations have not yet been definitively linked to epilepsy or SUDEP in humans, about one in five LQT1 patients exhibits a seizure phenotype suggesting *KCNQ1* mutations may increase susceptibility to epileptic seizures. The high prevalence of *KCNQ1*-associated cardiac arrhythmias combined with seizure phenotypes suggests that the neurocardiac role of this gene needs to be further examined.

2.2.1.2. KCNH2: The second most common form of congenital LQTS (LQT2) is caused by mutations in the *KCNH2* gene [97,104,105]. The *KCNH2* gene encodes hERG1/Kv11.1 voltage-gated potassium channel α -subunits which conduct the rapidly activating delayed-rectifier potassium current, I_{Kr} [105]. I_{Kr} and I_{Ks} (see section 2.2.1.1.) combine to generate the main delayed-rectifier currents responsible for the repolarization phase of the human cardiac action potential. Although *KCNH2* is best known for its role in the heart where it is highly expressed, it was originally identified in a human hippocampal cDNA library [104,106]. In mouse, *KCNH2* transcripts and protein show widespread expression in the brain, especially in epilepsy-relevant regions such as the hippocampus, thalamus, and cortex [107,108]. Interestingly, high expression of mErg1 (the murine homolog of ERG1) is observed in the dorsal motor nucleus of the vagus, which regulates parasympathetic control of the heart [107]. Mouse brain slice electrophysiology shows that mErg1 channels play an important role in regulating spike-frequency adaptation, threshold excitability, and discharge dynamics in neurons [109-111]. One study in rats demonstrated selective expression of Erg1 channels in hippocampal astrocytes where they apparently regulate neuronal excitability by a glial mechanism [112].

The *KCNH2* gene has been linked to epilepsy and SUDEP by a single case report and retrospective patient studies. Recently, a young woman was described who suffered both recurrent seizures as well as syncopal episodes associated with a prolonged QT interval [113]. Genetic screening identified a *de novo* *KCNH2* mutation in the patient resulting in a 296-amino acid truncation of the protein [113]. A retrospective study of 343 LQTS patients found that a personal history of seizures was far more common in LQT2 than all other subtypes (39% vs. 10%), suggesting *KCNH2* mutations confer susceptibility to epilepsy, not merely torsadogenic seizures, which are caused by prolonged cerebral hypoperfusion secondary to cardiac dysrhythmia [114]. *KCNH2* mutation was linked to SUDEP by post-mortem genetic sequencing and analysis of *KCNQ1*, *KCNH2*, and *SCN5A* in 48 SUDEP cases that occurred from 1993 to 2009 [115]. The study found a rare non-synonymous *KCNH2* single nucleotide polymorphism (R176W), previously associated with LQT, in one SUDEP case that was absent in 340 control individuals. Interestingly, this same R176W variant has also been reported in a case of sudden unexplained death [116,117]. Despite clinical evidence that *KCNH2* is likely important for epilepsy pathogenesis, no mouse model has been reported linking *KCNH2* mutations to an epilepsy phenotype. However, mutations in the *Drosophila* homolog of *KCNH2*, called *seizure*, cause temperature-induced convulsions followed by paralysis, as well as spontaneous neuronal activity [118].

2.2.1.3. SCN5A: The third most common genetic cause of LQTS is mutations in the *SCN5A* gene, which encodes the primary cardiac voltage-gated sodium channel Nav1.5 α -subunit responsible for conducting the rapid depolarizing sodium current (I_{Na}) that underlies the upstroke of the cardiac action potential [119,120]. In addition to LQT3, *SCN5A* mutations can also cause Brugada syndrome, an inherited cardiac disease associated with ventricular fibrillation and sudden cardiac death and characterized on ECG by right bundle branch block and ST-segment elevation in the right precordial leads [121]. In general, a phenotype of LQT3 or Brugada syndrome depends on the functional consequences of the underlying *SCN5A* mutations. Gain-of-function mutations that increase sodium current usually cause

LQTS, while loss-of-function alleles that decrease sodium current tend to produce Brugada syndrome [122].

Cardiac Nav1.5 sodium channels were originally thought to be distinguishable from the neuronal sodium channels (Nav1.1-1.3, Nav1.6, and Nav1.7) by their insensitivity to TTX blockade. However, this paradigm was revised when heart-like TTX-insensitive sodium currents were recorded in rat cortical neurons and “cardiac” *SCN5A* transcripts were identified in rat limbic brain regions [123,124]. In mouse, Nav1.5 channels localize to axons in distinct regions of the cerebral, cortex, thalamus, hypothalamus, basal ganglia, and cerebellum [125]. In humans, *SCN5A* mRNA has been detected in fetal and adult brain using RT-PCR but its regional localization and protein expression remain to be determined [126].

SCN5A has been associated with epilepsy in case reports and post-mortem DNA sequencing analyses of SUDEP cases. Recently, a pedigree was reported with three different family members exhibiting both Brugada syndrome and epilepsy apparently related to a missense *SCN5A* mutation that has been previously associated with Brugada phenotypes [127]. In another case report, post-mortem DNA sequencing of LQTS genes in a SUDEP victim identified a potentially pathogenic novel missense mutation (R523C) in a highly conserved region of the *SCN5A* gene [128]. Finally, the same post-mortem DNA analysis of SUDEP victims that associated *KCNH2* mutation with SUDEP (see section 2.2.1.2.), also identified a P1090L *SCN5A* variant in a patient that was absent in controls [115]. In addition, another SUDEP victim in that study was identified with rare variants in both *KCNH2* (R1047L) and *SCN5A* (A572D); the A572D *SCN5A* allele has been associated with sudden cardiac death and LQTS previously [115,129]. *SCN5A* has not yet been linked to epilepsy in any mouse models but this may be due to insufficient EEG screening.

In addition to associations with sudden cardiac death and SUDEP, *SCN5A* has also been linked to sudden infant death syndrome (SIDS) and sudden unexplained nocturnal death syndrome (SUNDS). Molecular screening of LQTS-associated genes was performed on a 7-week old infant who exhibited classic features of a near-SIDS event, as well as LQT [130]. DNA sequencing identified a *de novo* rare variant in *SCN5A* (S941N) that was absent in 200 control subjects. When expressed in frog oocytes, the mutation caused an increase in the late sodium current similar to that seen for other LQT3 mutations [130]. SUNDS is a disorder of Southeast Asia that causes sudden cardiac death preferentially in males as they sleep. Screening of LQTS-genes in 10 SUNDS families identified missense loss-of-function *SCN5A* mutations in three families that all resulted in reduced sodium currents [131]. The phenotype and genetics of SUNDS suggest it is an allelic disorder to Brugada syndrome or possibly the same disease. Interestingly, as has been observed in SUDEP cases, symptoms and death most commonly occur at night during sleep in LQT3, Brugada syndrome, and SUNDS, possibly due to increases in vagal tone [10,131-133].

2.2.2. Other cardiac arrhythmia genes: RYR2—The *RYR2* gene encodes the cardiac ryanodine receptor 2, which acts as an intracellular Ca^{2+} release channel that mediates excitation-contraction coupling in the heart [134]. In cardiac myocytes, extracellular Ca^{2+} enters through L-type Ca^{2+} channels and activates RYR2 channels in the sarcoplasmic reticulum generating calcium sparks (a process called Ca^{2+} -induced Ca^{2+} release) that

trigger contraction [135]. *RYR2* transcripts are widely expressed throughout the heart in both mouse and humans [29,136]. Mutations in *RYR2* are responsible for an autosomal dominant heart disease called catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1), which is characterized by stress-induced ventricular tachycardia that can lead to cardiac arrest and sudden death [137,138].

Although it is best known for its cardiac role, *RYR2* is also expressed abundantly in the brain, where the channels contribute to neuronal Ca^{2+} -induced Ca^{2+} release from intracellular stores within the endoplasmic reticulum [139]. RYR-mediated release of intracellular Ca^{2+} is important for regulating neuronal excitability, neurotransmitter release, and synaptic plasticity [139]. *In situ* hybridization and immunohistochemical experiments in rodents show that *Ryr2* message and protein is abundant in brain, with high levels in the hippocampus, cortex, and cerebellum [140-142]. *RYR2* mRNA in human brain has been detected by RT-PCR in cortex, hippocampus, basal ganglia, and cerebellum [143,144].

Mutations in the *RYR2* gene have been linked to epilepsy in mice and SUDEP in humans. When mice carry a human *RYR2* mutation that causes CPVT1 due to leaky RyR2 channels, they exhibit spontaneous generalized tonic-clonic seizures, exercise-induced ventricular arrhythmias, and sudden cardiac death [145]. However, the seizures occur in the absence of cardiac arrhythmias suggesting that leaky RyR2 channels can cause both epilepsy and cardiac phenotypes independently. In humans, postmortem molecular autopsy of long QT and CPVT genes has identified a novel sporadic missense mutation in a highly conserved region of *RYR2* in a SUDEP victim [146]. The variant allele was absent in more than 600 controls including the parents.

3. Conclusions

Analysis of variation in neurocardiac genes related to epilepsy represents a starting point for the investigation of genomic biomarkers with clinical significance for SUDEP. The genes discussed in this review represent good first candidates for genomic biomarkers since they have all been associated with SUDEP in patients or animal models. Future work will be required to accurately assess their degree of genetic variation in the SUDEP population as a whole, their contribution to SUDEP pathomechanisms, and their relative significance for informing risk prediction and treatment. The identification of reliable genomic biomarkers for SUDEP is challenging since epilepsy is a genetically complex and heterogeneous disease [147]. As our knowledge of SUDEP gene profiles expands, developing bioinformatics and computer modeling tools to interpret this data will be imperative [148]. Part of the difficulty lies in understanding which gene variants are relevant since nearly every individual possesses many non-synonymous single nucleotide polymorphisms, even in genes known to cause epilepsy [17]. In addition, some variants may actually be beneficial serving as genomic biomarkers indicative of protection against SUDEP. For example, mutations in the P/Q-type Ca^{2+} channel gene (*Cacna1a*) or the tau microtubule-binding protein gene (*Mapt*) can dramatically improve survival and protect against SUDEP in the Kv1.1-deficiency mouse model [32,149]. Thus, genomic biomarkers will probably need to be considered as part of a comprehensive molecular profile, rather than in isolation.

The promise of the genomic era and personalized medicine is that comprehensive gene profiling will enable optimized and individualized patient diagnosis, risk assessment, treatment, and management. The identification of reliable genomic biomarkers for SUDEP could provide valuable pharmacogenetic information to indicate which antiepileptic drug (AED) treatments should be used or avoided. As an example, both carbamazepine and lamotrigine can inhibit cardiac ion channels suggesting their use in patients with variants in related “heart” epilepsy genes may be ill-advised [150]. Patient knowledge of their genomic biomarker profile might also improve adherence to AED drug regimens leading to better seizure control and decreased chance of SUDEP [150]. Genomic biomarkers would provide a valuable tool to pinpoint patients in need of special surveillance or medical intervention. For example, epilepsy patients with known deleterious variants in neurocardiac genes would benefit from prolonged Holter monitoring to determine whether they have any potentially dangerous cardiac arrhythmias that require additional attention. Doctors of patients with genomic variants related to bradyarrhythmias or vagal hyperexcitability, such as *KCNA1* mutations, may need to consider foregoing vagus nerve stimulation as an epilepsy treatment to prevent increasing vagal tone to dangerous levels. In the future, preventative implantation of cardiac pacemaker-defibrillator devices might be practical if genomic biomarker profiles become reliable enough to identify epilepsy patients at particularly high risk of lethal cardiac dysfunction [150]. The development of genomic biomarkers for SUDEP has the potential to transform the clinical treatment of epilepsy by revealing patients at risk and allowing genotype-guided life-saving intervention.

Acknowledgments

This work was supported by grants from the Citizens United for Research in Epilepsy (CURE) and the National Heart, Lung, and Blood Institute of the National Institutes of Health (R00HL107641).

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HIGHLIGHTS:

I define genomic biomarkers.

I identify nine neurocardiac genes as candidate biomarkers for SUDEP.

I discuss the brain-heart expression patterns and phenotypes of these genes.

I discuss difficulties in identifying genomic biomarkers for SUDEP.

I discuss the clinical utility of reliable SUDEP biomarkers.

Table 1

Brain-heart expression patterns and associated phenotypes of neurocardiac genes linked with SUDEP

	GENE	EXPRESSION		PHENOTYPES		
		<i>brain</i>	<i>heart</i>	<i>epilepsy</i>	<i>arrhythmias</i>	<i>SUDEP</i>
<i>“brain” genes</i>	<i>KCNA1</i>			h, m	m	m
	<i>SCN1A</i>			h, m	m	h, m
	<i>SCN8A</i>			h, m	m	h
	<i>HCN2</i>			h, m	m	h
	<i>PRRT2</i>			h		h
<i>“heart” genes</i>	<i>KCNQ1</i>			m	h, m	m
	<i>KCNH2</i>			h	h	h
	<i>SCN5A</i>			h	h, m	h
	<i>RYR2</i>			h, m	h, m	h

The circles depict approximate gene expression levels in humans (*h*) and mice (*m*) based on expressed sequence tags (ESTs) from brain and heart cDNA pools as reported by the UniGene database maintained by the National Center for Biotechnology Information (NCBI). The darkness of the fill increases with increasing expression level. Note that the levels reflected in the EST profiles may differ from data collected by other techniques such as arrays or quantitative PCR. The association of each gene with epilepsy, cardiac arrhythmias, or SUDEP in human patients or mouse models is indicated by an *h* or *m*, respectively.