Beyond the Electrocardiogram: Mutations in Cardiac Ion Channel Genes Underlie Nonarrhythmic Phenotypes

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ABSTRACT: Cardiac ion channelopathies are an important cause of sudden death in the young and include long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, idiopathic ventricular fibrillation, and short QT syndrome. Genes that encode ion channels have been implicated in all of these conditions, leading to the widespread implementation of genetic testing for suspected channelopathies. Over the past half-century, researchers have also identified systemic pathologies that extend beyond the arrhythmic phenotype in patients with ion channel gene mutations, including deafness, epilepsy, cardiomyopathy, periodic paralysis, and congenital heart disease. A coexisting phenotype, such as cardiomyopathy, can influence evaluation and management. However, prior to recent molecular advances, our understanding and recognition of these overlapping phenotypes were poor. This review highlights the systemic and structural heart manifestations of the cardiac ion channelopathies, including their phenotypic spectrum and molecular basis.

KEYWORDS: Arrhythmia, ion channel, genetics, cardiomyopathy, sudden unexpected death

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Introduction

Our understanding of sudden unexpected death (SUD) in the young has improved substantially with the recognition of latent heart disease caused by ion channel gene mutations. The most extensively studied of these is long QT syndrome (LQTS), which was initially described as a lethal, idiopathic disease of severe QT prolongation and deafness.[1,2] In the modern era, registry data and numerous genetic breakthroughs have redefined LQTS as a heritable condition of variable severity.[3] To a lesser extent, the other channelopathies, including Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), idiopathic ventricular fibrillation, early repolarization syndrome, and short QT syndrome (SQTS), have benefited from similar molecular advancements. Some forms of familial atrial fibrillation (AF), sinoatrial node (SAN) dysfunction, sick sinus syndrome (SSS), and progressive cardiac conduction disease (PCCD) also have overlapping features of channelopathy and structural heart disease. When a pathogenic mutation in an ion channel gene is identified in the clinical setting, it can improve risk stratification, family screening and guide treatment.[3–6] In rare cases, an ion channel gene mutation may also manifest as structural heart disease,[7–12] or in noncardiac pathology, such as epilepsy.[13–15] These nonarrhythmic phenotypes can be life-threatening, and electrophysiologists need to be aware of their existence. This review describes the phenotypic spectrum and molecular basis of the nonarrhythmic phenotypes associated with ion channel gene mutations.

Ion Channel Gene Mutations in Cardiomyopathy

Many genes have been implicated in cardiovascular disease, including those associated with arrhythmia and cardiomyopathy. Among these genes, the data supporting pathogenicity are variable, in part because many cases are sporadic, and molecular mechanisms are difficult to elucidate. This section will focus on the genes for which there is reasonable and consistent evidence of a cardiac channelopathy phenotype, in addition to a potential link to cardiomyopathy (Table 1). However, even for the genes meeting this criteria (ie, *SCN5A, KCNQ1, RYR2*, and *HCN4*), disease causation may be questionable. For example, although *SCN5A* has long been associated with BrS, emerging evidence indicates that BrS may be an oligogenic disease (ie, >1 gene influences phenotype).[24] Supplementary Table 1 includes the clinical-, genetic-, and population-level evidence for disease causation for each variant. The link between many of these variants and human disease is likely to change as scientific knowledge evolves.

SCN5A

Ion influx through the voltage-gated sodium channel ($Na_v1.5$) encoded by *SCN5A* is a ubiquitous process underlying cardiomyocyte excitability and cell-to-cell conduction.[25] *SCN5A* has been implicated as a causative or modifier gene in nearly all of the channelopathies, including LQTS, BrS, CPVT, SQTS, AF, PCCD, and SSS.[8,9,26–31] The J-wave syndromes, as well as BrS, are linked to loss-of-function mutations in *SCN5A*, whereas

Table 1. Summary of genes implicated in the cardiomyopathy-channelopathy overlap syndrome.

ION CHANNEL GENES AND THEIR ASSOCIATION WITH CHANNELOPATHY AND CARDIOMYOPATHY				
	SCN5A	*KCNQ1*	*RYR2*	*HCN4*
LVNC		Nakashima et al[16]	Ohno et al[10] Campbell et al[12] Roston et al[17]	Milano et al[18]
ARVC			Tiso et al[7] Roux-Buisson et al[19]	
DCM	McNair et al[8,9] Nair et al[20] Gosselin-Badaroudine et al[21] Cheng et al[22]	Xiong et al[23]		

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; LVNC, left ventricular noncompaction.

LQT3 is associated with gain-of-function mutations.[9] In some channelopathies, such as CPVT and SQTS, the *SCN5A* link is limited to single families.[26,28]

A well-established nonelectrophysiological manifestation of *SCN5A* variants is dilated cardiomyopathy (DCM).[9,20–22,32] Of these, the R222Q variant is supported by the most robust data.[9,20,22,32] In a cohort of 338 genotype-elusive patients with DCM, McNair et al[9] identified 5 missense *SCN5A* variants in 15 subjects. These individuals experienced arrhythmias seemingly out of proportion to the degree of cardiac dysfunction, including supraventricular arrhythmia, SSS, AF, ventricular tachycardia (VT), and PCCD in the absence of QT prolongation or J-point elevation. These missense variants typically localized to highly conserved regions of *SCN5A*, supporting their pathogenic role, and a shared voltage-sensing mechanism underlying both DCM and arrhythmia.[9] R222Q is located in the domain I voltage sensor of *SCN5A* and leads to hyperpolarizing shifts in activation and inactivation gating.[22] This mutation reduces peak Na^+ current and incites cardiomyocyte hyperexcitability. An additional modifier in *SCN5A* (H558R) may play a role in this overlap phenotype,[22] although DCM has been reported in a second family without H558R polymorphism.[20] A distinct, but nearby, mutation (R219H) in *SCN5A* also appears to manifest in AF, VT, and DCM.[21] R219H is located in a highly conserved region of *SCN5A* and leads to excessive proton leak, suggesting that acidification of cardiomyocytes may induce DCM.[21] Additional unknown genetic modifiers may unmask *SCN5A*-linked DCM, as seen in BrS and LQTS.[4,29] It is believed that causative gene mutations involved in various cardiac phenotypes typically disrupt "final common pathways," which lead to the disease state.[33] The discovery of a *cardiomyopathy-channelopathy overlap syndrome* posed a paradigm shift in electrophysiology, namely, that electrical excitability in Na^+ channels may lead to dilatory remodeling and familial DCM.[8]

Lenegre-Lev syndrome, also known as PCCD, is defined by gradual idiopathic fibrosis of the cardiac conduction system and is usually seen in the aging population.[30] In the past, PCCD was not considered a traditional channelopathy because of its microscopic structural manifestations; however, *SCN5A* mutations have been implicated in PCCD and nonprogressive forms of conduction abnormality.[30] The mechanism linking impaired Na^+ current and PCCD is not well established, and aging likely plays a role in unmasking the phenotype.[30]

SCN5A variants can be challenging to interpret in the clinical setting. $Na_v1.5$ probably has many roles and directly interacts with other proteins, such as *PKP2*-encoded plakophilin, which underlies arrhythmogenic right ventricular cardiomyopathy (ARVC).[34] In this setting, loss of *PKP2* function leads to impaired I_{Na}, suggesting an important, shared role between desmosomes, gap junctions, and Na^+ channels in maintaining I_{Na}.[35] This discovery is supported by a large BrS cohort with coexisting Na^+ channel dysregulation and *PKP2* variants.[36] A growing number of studies also report possible subtle structural changes in patients with BrS[34] and abnormal electrograms during epicardial mapping.[37] Ablation can normalize the electrocardiogram but does not provide complete protection from arrhythmia.[38] This highlights the complex pathophysiological mechanisms of BrS, which remain elusive despite decades of research. Brugada syndrome is likely oligogenic,[24] as evidenced in stem cells which did not recapitulate an arrhythmia phenotype in vivo despite harboring *SCN5A* mutations.[39] This is highlighted by the relatively high allele frequencies of certain BrS-associated variants (Supplementary Table 1).

KCNQ1

KCNQ1, encoding the pore-forming subunit ($K_v7.1$) of the slowly activating delayed-rectifier potassium channel, underlies LQTS, SQTS,[40] and atrial arrhythmias.[40,41] Despite *KCNQ1* being an ion channel gene, cases of LQTS and SQTS complicated by cardiomyopathy have been described.[11,23] One such example is a highly arrhythmogenic cardiomyopathy observed in the setting of a loss-of-function *KCNQ1* (R397Q) mutation.[23] A hypothesized mechanism by which a mutation in *KCNQ1* propagates structural heart disease is as follows[23]: *KCNQ1* and *KCNE1* form repolarizing channels which are regulated by beta-adrenergic-mediated protein kinase

A–dependent phosphorylation. IK_s currents are also sensitive to Ca^{2+}, in part through interaction with calmodulin. Abnormal interaction between mutant $K_v7.1$ and calmodulin may lead to Ca^{2+} dysregulation and impaired cardiomyocyte contractility, thus producing a structural phenotype. Similar mechanisms have been theorized in other cardiomyopathy-channelopathy overlap syndromes,[9,42,43] including *SCN5A*-associated DCM and left ventricular noncompaction (LVNC) and *KCNQ1*-associated DCM in 3 patients with SQTS.[44] However, incomplete phenotyping and so-called tachycardia-induced cardiomyopathy may confound these reports, and mechanistic descriptions are largely speculative. Alternatively, *KCNQ1* may be a genetic modifier of structural heart disease. These dramatic but isolated observations highlight the need for further biophysical and linkage studies and detailed phenotyping.

An overlap between a channelopathy and a developmental abnormality has recently been seen in the form of LVNC.[16,42,45] Left ventricular noncompaction is an uncommon congenital cardiomyopathy defined by intertrabecular sinusoids communicating with the ventricular cavity. In 2013, Nakashima reported LVNC in a young child with cardiac arrest, QTc prolongation, and a pathogenic *KCNQ1* variant.[16] Accordingly, ion channel genes have embryological roles[46] and may also be downstream targets of transcription factors. These provide hypothetical mechanisms by which *KCNQ1* may relate to congenital heart disease. However, the channelopathy-LVNC link is ill-defined and may be attributable to the coexistence of 2 rare, unrelated pathologies.

RYR2

Catecholaminergic polymorphic ventricular tachycardia is a channelopathy that leads to polymorphic VT during exertion or emotional stress. Priori et al[47] implicated *RYR2* in CPVT, which encodes the ryanodine receptor 2 (RyR2).[47] Ryanodine receptor 2 is the largest ion channel in the human genome with a complex heterotetrameric structure, which allows it to interact with the cytosol, plasma membrane, and lumen of the sarcoplasmic reticulum.[48] As such, RyR2 may be involved in cellular processes that extend beyond the action potential. Since 2001, more than 200 gain-of-function *RYR2* variants have been described.[49] To a lesser extent, loss-of-function *RYR2* mutations exist, but instead underlie an arrhythmia syndrome distinct from CPVT.[50–52] *RYR2* variants[7,10,17,19] and abnormalities in Ca^{2+} current[53] are also associated with changes in cardiac structure.

Arrhythmogenic right ventricular cardiomyopathy came to be recognized due to its severe electrophysiological consequences (and extracardiac cutaneous phenotype). Accordingly, diagnostic criteria rely on electrical findings,[54] in addition to coexistent fibrofatty ventricular infiltration, making it the prototypical cardiomyopathy-channelopathy overlap syndrome. Arrhythmogenic right ventricular cardiomyopathy is a disorder of the intercalated disk, desmosome, and gap junction,[55,56] of which the intercalated disk is integral in forming the myocardial scaffold.[56] The intercalated disk interacts with a variety of proteins, including ion channels.[57] As Priori and colleagues were describing *RYR2*-associated CPVT, Tiso et al[7] published on 4 ARVC families with variants in *RYR2*. More recently, 6 rare missense variants in *RYR2* were identified in 64 previously genotype-elusive ARVC subjects.[19] Tiso and colleagues hypothesized that Ca^{2+} dysregulation at the sarcoplasmic reticulum, a mechanism also proposed to underlie CPVT, leads to myocardial necrosis, resulting in ARVC.[7] The role of the intercalated disk in this relationship is unclear, and data linking ion channels to the intercalated disk involve Na^{+} rather than Ca^{2+} current.[57] Further molecular work is needed to determine the mechanism of *RYR2*-related ARVC.

RYR2 is also linked to LVNC.[10,45] Our group recently described a loss-of-function mutation in a family with LVNC and atypical CPVT.[17] In another family, there are 2 female CPVT probands with deletion of exon 3 in *RYR2*, exercise-induced ventricular ectopy, and LVNC.[10] Family screening identified 8 mutation carriers, of which 7 had LVNC. A structural phenotype related to *RYR2* exon 3 deletion has also been described in an unrelated patient.[12] These are some of the reports describing large exon deletions of RyR2. At present, it is not known whether larger deletions of RyR2 are likely to manifest in structural heart disease. In addition, some *RYR2* mutations may actually be benign polymorphisms,[58] and variants of unknown significance in *RYR2* are common,[59] making it difficult to link rare structural phenotypes to *RYR2*.

HCN4

Before the genetic basis of conduction disease was known, SAN dysfunction was thought to be a channelopathy, caused by impaired "funny current," I_f.[60] Using a candidate gene approach, Macri et al[61] demonstrated that *HCN4* variants cause chronotropic incompetence. *HCN4* is expressed in the SAN and encodes the hyperpolarization-activated cyclic nucleotide–gated potassium channel 4. Since their work, *HCN4* has been implicated in familial sinus bradycardia,[18,62] tachycardia-bradycardia syndrome, and AF.[62] Unlike traditional channelopathies, *HCN4* does not appear to manifest in primary ventricular arrhythmia.

In 2014, Milano and colleagues[18] showed that *HCN4* may have a structural role in a family with SAN dysfunction, LVNC, and *HCN4* mutation. There are two main mechanistic hypotheses to explain HCN4-related LVNC. The first is that although *HCN4* is expressed predominantly in the SAN, it is coexpressed in ventricular progenitor cells.[63] Under these circumstances, *HCN4* mutations could lead to congenital heart disease and then later manifest as bradycardia after birth. The second hypothesis is that trabeculation is a compensatory response to bradycardia, as seen in athletes with low resting heart rates.[64] Most recently, multiple variants in *HCN4*, including those previously implicated in LVNC,[18,65] have been shown to underlie

Table 2. Summary of genes implicated in systemic syndromes.

SYNDROME	GENE	FUNCTIONAL SIGNIFICANCE	MANIFESTATIONS	CITATION
Jervell and Lange-Nielsen syndrome	*KCNQ1/KCNE1*	LoF	QTc prolongation Deafness	Neyround et al[1]
Timothy syndrome	*CACNA1c*	GoF	QTc prolongation Congenital heart disease Syndactyly Autism Immunodeficiency Seizures/neurological deficits Hypotonia Electrolyte derangements Hypoglycemia	Splawski et al[67]
Andersen-Tawil syndrome	*KCNJ2*	LoF	QTc prolongation Micrognathia Hypertelorism Short stature Scoliosis Low-set ears Clinodactyly Periodic paralysis	Plaster et al[68]
Primary epilepsy	*KCNH2* *KCNQ1* *RYR2* *KCNJ2* *SCN5A*	LoF LoF Not listed LoF LoF	LQT2 LQT1 CPVT ATS (LQT7) BrS	Johnson et al[13] Zamorano-Leon et al[14] Goldman et al[69] Nagrani et al[70] Marquez et al[71] Sandorfi et al[72]

Abbreviations: ATS/LQT7, Andersen-Tawil syndrome/long QT syndrome type 7; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; GoF, gain of function; LoF, loss of function; LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2.

ascending aortic dilation.[66] Young patients with symptomatic, chronotropic incompetence, LVNC, and/or aortic dilation should be considered for sequencing of *HCN4*.

Extracardiac Manifestations of Ion Channel Gene Mutations

The following section discusses the channelopathies which have been classically associated with a systemic phenotype, as well as emerging theories supporting the systemic impact of these mutations. For these syndromes, a description of the systemic findings often predated the causative molecular abnormality. Table 2 summarizes these genotype-phenotype correlations.

Syndromic features of the long QT syndrome

The Jervell and Lange-Nielsen syndrome was described over 50 years ago as a constellation of congenital deafness, childhood SUD, and QTc prolongation.[1,2,73] We now know that this syndrome is caused by homozygous recessive mutations in *KCNE* and *KCNQ1*.[1] In the heterozygous state, enough K^+ is secreted into the endolymph to maintain the endocochlear potentials responsible for sensory conduction.[74] However, in a homozygous state, little or no functional protein is produced, resulting in deafness and a markedly prolonged QT interval.[1,73,75]

Timothy syndrome (TS) (allelic to LQT8) is an autosomal dominant type of LQTS, characterized by congenital heart disease, syndactyly, autism, and immunodeficiency.[67,76,77] Timothy syndrome is almost universally lethal by the third decade of life.[67] In 1995, the $Ca_v1.2$ Ca^{2+} channel encoded by *CACNA1c*, usually in exon 8A, was found to be causative in TS.[67] *CACNA1c* is ubiquitously expressed and has embryological importance, highlighted by the diverse congenital TS manifestations, including seizures, cognitive disability, electrolyte derangements, and hypoglycemia.[67,76,77] Polymorphisms in *CACNA1c* may also play a role in valvular heart disease[78] and psychiatric disease.[79]

Andersen-Tawil syndrome (ATS) (classified as LQT7) is an autosomal dominant syndrome classically defined by the triad of episodic flaccid paralysis, QTc prolongation, and congenital morphological anomalies.[80] In actuality, ATS is better defined by its characteristic T-U wave patterns than by QT prolongation, which is usually absent.[80] Mutations in the inward-rectifying potassium channel, *KCNJ2*, underlie ATS,[68] as well as isolated cases of SQTS[81] and CPVT.[82] In fact, the bidirectional VT characteristic of ATS is a phenocopy of CPVT, and both conditions appear to respond well to Na^+ channel antagonists,[59,83] suggesting the possibility of a shared mechanism.

The role of SCN5A in gastrointestinal motility

SCN5A-encoded $Na_v1.5$ has been identified in gastrointestinal (GI) smooth muscle cells[84] and interstitial cells of Cajal,[85] raising suspicion that the familial preponderance of certain GI

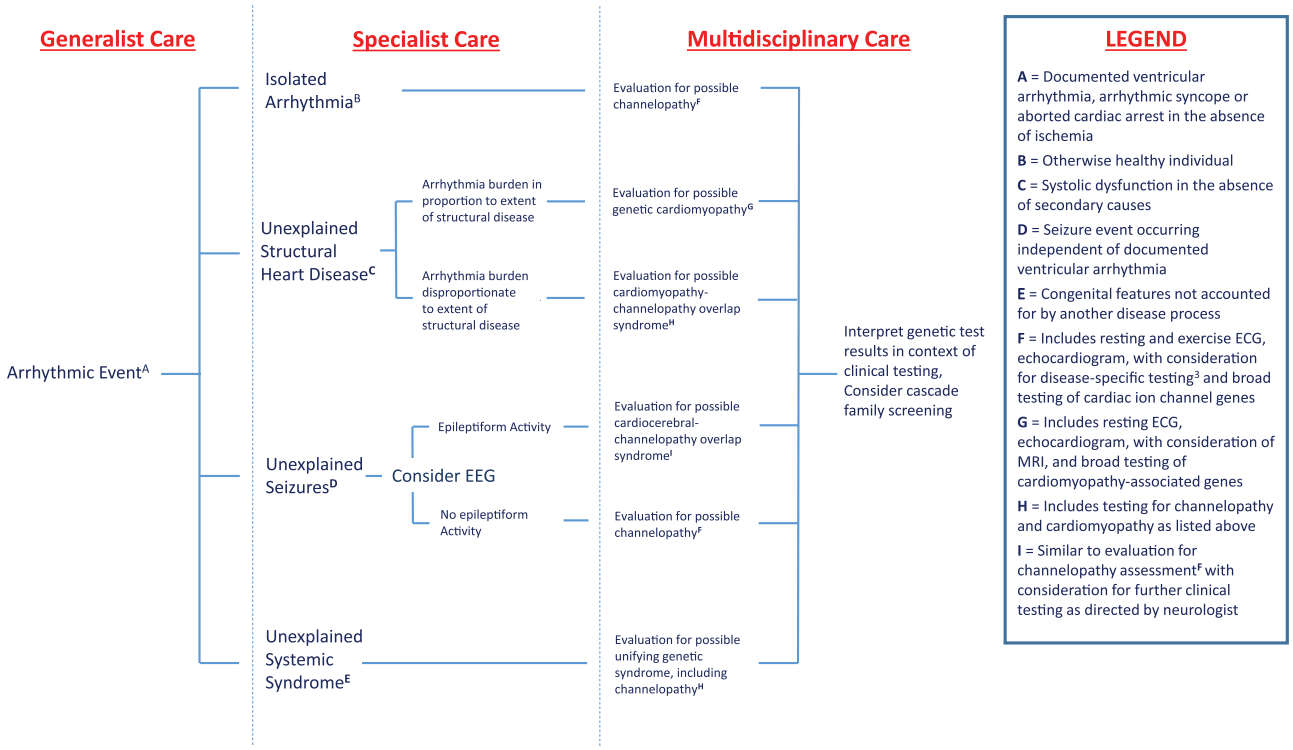

Figure 1. Simplified algorithm for the assessment of a potential ion channel overlap syndrome.

diseases could be attributable to heritable Na^+ channel defects. Subsequent functional and animal studies confirmed the importance of *SCN5A* in GI motility,[86] and *SCN5A* variants are now thought to underlie human GI syndromes,[87] including reports of overlapping GI and BrS phenotypes.[88] This example highlights the importance of pursuing comprehensive evaluations in all patients, as yet unrecognized syndromes may relate to the ion channel genes.

Glucose control in CPVT patients with RYR2 mutations

RYR2 is ubiquitously expressed in a variety of tissues, including the brain and pancreas.[89] Using oral glucose tolerance testing, Santulli et al[90] found that patients with CPVT have impaired glucose regulation, likely related to RyR2 dysfunction. They recapitulated this phenotype in CPVT mice and then rescued β-cell function in vitro using small molecules that stabilize RyR2, called "Rycals."[90] Rycals have not been studied in human CPVT but do offer hope that genotype-specific treatments are possible.[48]

Epilepsy

Ventricular arrhythmias can cause hypoxemic seizures, including reports of cardiac ion channelopathy masquerading as epilepsy.[14,91] The possibility of arrhythmic syncope must be considered in all patients with unexplained seizure, with a careful focus on the electrocardiogram and history. However, seizures can occur independent of arrhythmia in patients with channelopathy. *KCNQ1* channels are expressed in both neural and cardiac tissue,[13] and primary epilepsy and LQTS have been reported to coexist in 1 LQT1 family.[92] This relationship extends to LQT2,[14] in which seizures may be even more prevalent.[93] Recently, whole exome sequencing of SUD in epilepsy victims revealed several rare LQTS variants.[15] Animal models further support evidence of a phenotypic overlap.[69] In ATS,[71] BrS,[72] and CPVT,[70] this phenomenon may also exist, making *cardiocerebral-channelopathy overlap syndrome*[91] a suitable all-encompassing term. We recommend that cardiologists and neurologists pursue detailed phenotyping in patients with arrhythmias and seizures (Figure 1) so as not to miss this unifying syndrome.

Conclusions

Mutations in the ion channel genes underlie a variety of phenotypes that extend beyond the electrocardiogram, ranging from overt, life-threatening symptoms, to concealed, benign pathology. The most recognized overlapping manifestations include cardiomyopathy and the systemic features of LQTS, almost all of which were described before the modern molecular era. So far, no unifying mechanism exists to explain these syndromes, and a variety of additional factors may influence gene expression in ion channel diseases, such as epigenetic factors in cancer proliferation,[94] genetic compartmentalization in heart disease,[95] and posttranslational modifications in epilepsy.[96] The ion channels interact with one another, and disruption of one channel may induce dysfunction in another, as has been shown with Ca^{2+} regulation in LQTS models.[97] In many of these examples, genetic causation may be questionable,[98] and genetic testing is

probabilistic in nature.[99] We propose an assessment model (Figure 1) that emphasizes the multidisciplinary care required to evaluate these syndromes. In the future, improved clinical recognition will inform further molecular studies on the mechanistic basis of the nonarrhythmic phenotypes.

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Author Contributions

TMR conducted the literature review and wrote the manuscript. TC conducted the literature review, drafted portions of the manuscript and assisted with reference material. AL conceived the review topic and revised the manuscript. ZWL provided revisions and reference material for the manuscript. ADK conceived the review topic, and provided revisions and reference material for the manuscript. SS conceived the review topic, supervised the first author, assisted with revisions and approved of the final version of the manuscript.

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