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Molecular and genetic basis of sudden cardiac death

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Review Series

The abrupt cessation of effective cardiac function due to an aberrant heart rhythm can cause sudden and unexpected death at any age, a syndrome called sudden cardiac death (SCD). Annually, more than 300,000 cases of SCD occur in the United States alone, making this a major public health concern. Our current understanding of the mechanisms responsible for SCD has emerged from decades of basic science investigation into the normal electrophysiology of the heart, the molecular physiology of cardiac ion channels, fundamental cellular and tissue events associated with cardiac arrhythmias, and the molecular genetics of monogenic disorders of heart rhythm. This knowledge has helped shape the current diagnosis and treatment of inherited arrhythmia susceptibility syndromes associated with SCD and has provided a pathophysiological framework for understanding more complex conditions predisposing to this tragic event. This Review presents an overview of the molecular basis of SCD, with a focus on monogenic arrhythmia syndromes.

Molecular and genetic basis of sudden cardiac death

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The abrupt cessation of effective cardiac function due to an aberrant heart rhythm can cause sudden and unexpected death at any age, a syndrome called sudden cardiac death (SCD). Annually, more than 300,000 cases of SCD occur in the United States alone, making this a major public health concern. Our current understanding of the mechanisms responsible for SCD has emerged from decades of basic science investigation into the normal electrophysiology of the heart, the molecular physiology of cardiac ion channels, fundamental cellular and tissue events associated with cardiac arrhythmias, and the molecular genetics of monogenic disorders of heart rhythm. This knowledge has helped shape the current diagnosis and treatment of inherited arrhythmia susceptibility syndromes associated with SCD and has provided a pathophysiological framework for understanding more complex conditions predisposing to this tragic event. This Review presents an overview of the molecular basis of SCD, with a focus on monogenic arrhythmia syndromes.

Introduction

When a person dies suddenly and unexpectedly from a suspected cardiovascular cause, the term sudden cardiac death (SCD) is used to classify the mortal event. SCD is frequently caused by an abrupt change in heart rhythm (arrhythmia), most often ventricular tachycardia (VT) or ventricular fibrillation (VF), that impairs cardiac pumping, thereby depriving vital organs of oxygenated blood. A brief episode of VT or VF may cause only momentary loss of consciousness (syncope), but death is the inevitable result of sustained VF in the absence of emergent medical care. Estimates of the annual SCD incidence vary but are generally in the range of 50–100 per 100,000 persons in industrialized nations (1). In the United States, previous estimates have been as high as 450,000 deaths per year (2), representing a large fraction of total mortality due to heart disease and a substantial public health burden. These statistics largely reflect adult deaths in the setting of ischemic heart disease or heart failure, but children can also be susceptible to SCD in the context of certain genetic disorders.

Understanding the root causes of SCD has been an important research endeavor for several decades, and much progress has been made in defining the cellular, molecular, and genetic basis for ventricular arrhythmogenesis, the main pathophysiological provocateur of SCD (3). Mendelian (i.e., monogenic) syndromes predisposing to life-threatening ventricular arrhythmias in young adults and children are genetically heterogeneous, with more than 25 genes identified so far (Table 1). Molecular mechanisms related to these conditions involve membrane ion channels important for cardiomyocyte electrogenesis or regulation of intracellular Ca^{2+} homeostasis. By contrast, the genetic risk for SCD in older adults is more complex, with few if any unifying hypotheses about molecular mechanisms, although some overlap is observed with susceptibility to monogenic arrhythmia. Furthermore, the respective contributions of genetic and acquired factors to pathogenesis vary along the spectrum of age, with inborn errors having the greatest impact on SCD risk in younger subjects and acquired factors dominating risk in older subjects.

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This Review presents an overview of the molecular basis of SCD, with a focus on monogenic arrhythmia syndromes. The emerging picture of SCD risk as a complex genetic trait in older subjects has been reviewed elsewhere (4, 5). An initial brief summary of basic arrhythmia mechanisms at the cellular and tissue levels will provide a framework for presenting the molecular underpinnings.

Ventricular arrhythmia mechanisms

The normal initiation and orderly propagation of the cardiac impulse through the heart requires a tightly orchestrated sequence of changes in ionic currents that sum to produce the dynamic and phasic change in membrane potential referred to as the cardiac action potential (Figure 1). Abnormal properties of ionic currents can cause electrical disorder and lead to aberrant impulse generation or propagation. Consequently, rapid and sometimes chaotic electrical activity in the ventricles ensues, manifesting as either VT or VF that can lead to SCD. In a simplistic model, there are two major prerequisites for arrhythmic events: a vulnerable myocardial substrate and a trigger.

Myocardial conditions that increase risk for arrhythmias include structural (anatomical) and functional causes of heterogeneous conduction velocity that disrupt the normal orderly propagation of action potential waves through the ventricles (6). Heterogeneous conduction can predispose to the emergence of spiral waves, impulses that travel in a circular pattern around an anatomic barrier, as in ischemic or scarred myocardium, or around a point of reentry known as a rotor in non-ischemic and structurally normal myocardium (7). If uninterrupted, rhythmic spiral wave propagation in the ventricles will be associated with VT, but degeneration or fragmentation into smaller wavelets creates the more chaotic impulse movement associated with VF. Transmural dispersion of repolarization can also predispose to reentry. Normally, there is heterogeneity of action potential duration across the wall of the ventricles, with shorter action potentials occurring in the epicardial layer. This phenomenon arises from a more prominent epicardial transient outward current (I_{to}). Exaggeration of this transmural heterogeneity can create circumstances in which the fully repolarized epicardium can be reexcited by depolarized mid-myocardial and endocardial layers (8, 9).

Table 1
Genes involved in monogenic causes of SCD

Phenotype	Gene[A]	Protein	Effect of mutation	OMIM identifier[B]
LQTS	*KCNQ1* (11p15.5)	K^+ voltage-gated channel, KQT-like subfamily, member 1 ($K_V7.1$)	Loss of function, reduced I_{Ks}	607542
	KCNH2 (7q35)	K^+ voltage-gated channel, subfamily H (eag-related), member 2 ($K_V11.1$; HERG)	Loss of function, reduced I_{Kr}	152427
	SCN5A (3p21)	Na^+ channel, voltage-gated, type V, α subunit ($Na_V1.5$)	Impaired inactivation, increased persistent I_{Na}	600163
	ANK2 (4q25)	Ankyrin 2, neuronal	Aberrant localization of ion transporters	106410
	KCNE1 (21q22.1)	K^+ voltage-gated channel auxiliary subunit	Reduced I_{Ks}	176261
	KCNE2 (21q22.1)	K^+ voltage-gated channel auxiliary subunit	Reduced I_{Kr}	603796
	CAV3 (3p25)	Caveolin 3	Increased persistent I_{Na}	601253
	SCN4B (11q23)	Na^+ channel, voltage-gated, type IV, β subunit	Increased persistent I_{Na}	608256
	SNTA1 (20q11.2)	Syntrophin, α1	Increased persistent I_{Na}	601017
	AKAP9 (7q21)	A kinase (PRKA) anchor protein (*yotiao*) 9	Reduced I_{Ks}	604001
	KCNJ5 (11q24)	K^+ inwardly rectifying channel, subfamily J, member 5 (Kir3.4)	Reduced $I_{K,ACh}$	600734
Jervell and Lange-Nielson syndrome	*KCNQ1* (11p15.5)	K^+ voltage-gated channel, KQT-like subfamily, member 1 ($K_V7.1$)	Loss of function, reduced I_{Ks}	607542
	KCNE1 (21q22.1)	K^+ voltage-gated channel auxiliary subunit	Reduced I_{Ks}	176261
Andersen syndrome	*KCNJ2* (17q23.1)	K^+ inwardly rectifying channel, subfamily J, member 2 (Kir2.1)	Loss of function, reduced I_{K1}	600681
Timothy syndrome	*CACNA1C* (12p13.3)	Ca^{2+} channel, voltage-dependent, L type, α1C subunit ($Ca_V1.2$)	Gain of function, increased I_{Ca}	114205
SQTS	*KCNQ1* (11p15.5)	K^+ voltage-gated channel, KQT-like subfamily, member 1 ($K_V7.1$)	Gain of function, increased I_{Ks}	607542
	KCNH2 (7q35)	K^+ voltage-gated channel, subfamily H (eag-related),member 2 ($K_V11.1$; HERG)	Gain of function, increased I_{Kr}	152427
	KCNJ2 (17q23.1)	K^+ inwardly rectifying channel, subfamily J, member 2 (Kir2.1)	Gain of function, increased I_{K1}	600681
	CACNA1C (12p13.3)	voltage-gated Ca^{2+} channel, $Ca_V1.2$	Loss of function, reduced I_{Ca}	114205
	CACNB2 (10p12)	Ca^{2+} channel, voltage-dependent, β2 subunit	Loss of function, reduced I_{Ca}	600003
	CACNA2D1 (7q21)	Ca^{2+} channel, voltage-dependent, α2/δ subunit 1	Loss of function, reduced I_{Ca}	114204
BrS	*SCN5A* (3p21)	Na^+ channel, voltage-gated, type V, α subunit ($Na_V1.5$)	Loss of function, reduced I_{Na}	600163
	GPD1L (3q22.3)	glycerol-3-phosphate dehydrogenase 1-like	Reduced I_{Na}	611778
	SCN1B (19q13.1)	Na^+ channel, voltage-gated, type I, β subunit	Reduced I_{Na}	600235
	SCN3B (11q23.3)	Na^+ channel, voltage-gated, type III, β subunit	Reduced I_{Na}	608214
	MOG1 (17p13.1)	RAN guanine nucleotide release factor	Reduced I_{Na}	607954
	KCND3 (1p13.3)	K^+ voltage-gated channel, Shal-related subfamily, member 3 ($K_V4.3$)	Gain of function, increased I_{to}	605411
	KCNE3 (11q13)	K^+ voltage-gated channel auxiliary subunit	Increased I_{to}	604433
	KCNE5 (Xq22.3)	K^+ voltage-gated channel auxiliary subunit	Increased I_{to}	300328
	CACNA1C (12p13.3)	Ca^{2+} channel, voltage-dependent, L type, α1C subunit ($Ca_V1.2$)	Loss of function, reduced I_{Ca}	114205
	CACNB2 (10p12)	Ca^{2+} channel, voltage-dependent, β2 subunit	Loss of function, reduced I_{Ca}	60003
	KCNJ8 (12p12.1)	K^+ inwardly rectifying channel, subfamily J, member 8 (Kir6.1)	Gain of function, increased $I_{K,ATP}$	600935
CPVT	*RYR2* (1q42.1)	Ryanodine receptor 2 cardiac	Gain of function, increased SR Ca^{2+} release	180902
	CASQ2 (1p13.3)	Calsequestrin 2 cardiac muscle	Loss of function, reduced I_{Ca}	114251
	TRDN (6q22)	Triadin	Impaired regulation of SR Ca^{2+} release	603283

[A]Chromosomal location given in parentheses. [B]Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

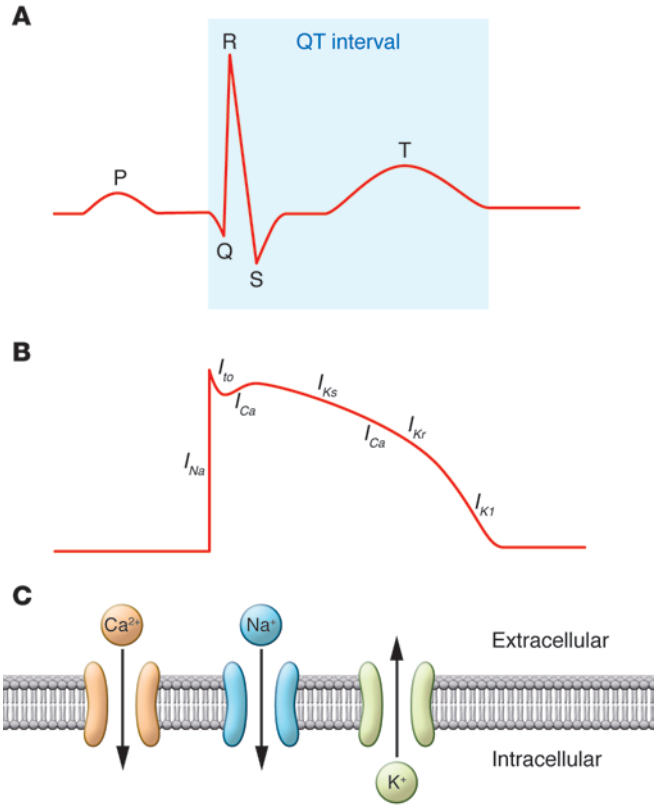

Figure 1
ECG and the cardiac action potential. Approximate temporal relationships between surface ECG (**A**) and typical ventricular action potential (**B**). Individual ionic currents responsible for different phases of the action potential are labeled and represented schematically in (**B**). In the ECG (**A**), the P wave indicates atrial depolarization, whereas the QRS complex indicates ventricular depolarization. The T wave indicates ventricular repolarization, and the Q-T interval indicates the time for the entire ventricular depolarization and repolarization sequence to occur. The ionic events underlying a cardiac action potential are illustrated in (**C**) and include the depolarizing inward Na^+ (I_{Na}) and calcium (I_{Ca}) currents, and the repolarizing transient outward current (I_{to}), and three outward potassium currents (I_{Kr}, I_{Ks}, I_{K1}).

A focal ectopic impulse generated in the ventricles can trigger the initiation of spiral waves and cause reentrant arrhythmias. At the cellular level, early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs) provide the most common mechanisms for ectopic excitation. EADs arise during the plateau phase of the cardiac action potential, whereas DADs emerge after completion of an action potential (Figure 2 and refs. 10, 11). Both events occur because of aberrant depolarizing ionic currents. In the case of EADs, increased activation of voltage-gated (L-type) Ca^{2+} channels or persistent activation of voltage-gated Na^+ channels are the usual mechanisms. By contrast, DADs arise from spontaneous intracellular Ca^{2+} release and efflux of Ca^{2+} through the electrogenic Na^+/Ca^{2+} exchanger (NCX; stoichiometry $3Na^+:1Ca^{2+}$), evoking a transient inward Na^+ (I_{Na}) current (12). Prolonged action potential duration increases the propensity of myocardial cells to exhibit EADs, whereas increased Ca^{2+} loading of the sarcoplasmic reticulum (SR) predisposes to DADs.

Cardiac action potential

The generation and propagation of action potentials in heart muscle as well as excitation-contraction coupling are physiological events dependent upon a symphony of ion channels acting in concert with many associated regulatory or interacting proteins. Ion channels are ubiquitous proteins that confer selective ionic permeability to cell membranes. Voltage-gated ion channels are opened and closed by changes in membrane potential, whereas ligand-gated ion channels require binding of intracellular or extracellular molecules to open an ionic pore. Voltage-gated ion channels with selective permeability for Na^+, K^+, and Ca^{2+} ions feature prominently in normal cardiac electrophysiology and in the molecular pathogenesis of monogenic disorders predisposing to SCD (Table 1).

Action potentials are initiated by a localized change in membrane potential that activates voltage-gated Na^+ channels, allowing rapid but transient I_{Na} and producing the typical upstroke known as phase 0 depolarization (Figure 3). In some myocytes, a rapid and transient phase 1 repolarization follows due to activation of the I_{to} conducted in part by fast-gating K^+ channels. During phases 0 and 1, Na^+ channels rapidly inactivate, while voltage-gated (L-type) Ca^{2+} channels activate and contribute to a long plateau of membrane depolarization. This plateau phase (phase 2) reflects a delicate balance between inward current, largely through L-type Ca^{2+} channels (I_{Ca}) with a small amount of residual I_{Na}, and emerging outward currents carried by K^+ channels. Activation of two types of K^+ currents (I_{Kr}, I_{Ks}) in concert with inactivation of Ca^{2+} channels tips the balance in favor of the outward current, thereby promoting phase 3 repolarization. Finally, the inward rectifying K^+ current (I_{K1}) finishes the job of repolarizing myocyte membranes. Other electrogenic transporters (NCX, Na^+/K^+ ATPase) are involved in maintaining intracellular ionic homeostasis in the face of large ion fluxes accompanying each action potential.

Many ion channels involved with the generation and propagation of cardiac action potentials are regulated by several factors, most notably β-adrenergic stimulation. In particular, during exercise or stress in which the sympathetic nervous system is activated (fight or flight response), heart rate acceleration requires shortening of the action potential duration, and this is accomplished in part by activating I_{Ks} through a cAMP-dependent mechanism. Sympathetic stimulation also enhances contractility of the heart, mainly through augmentation of Ca^{2+} influx (activation of I_{Ca}) and increased loading of the SR so that more Ca^{2+} can be released intracellularly during systole.

Monogenic causes of SCD

Two categories of monogenic heart disease predispose to SCD. These are genetic disorders of heart rhythm and familial cardiomyopathy. Cardiomyopathy is discussed in depth elsewhere in this Review series (13), and therefore the focus here will be on genetic arrhythmia susceptibility. Although rare, these syndromes have been tractable at the molecular level, and nearly two decades of research have uncovered molecular mechanisms that may be shared with more common acquired conditions. The genes responsible for congenital arrhythmia syndromes for the most part encode either ion channel subunits or proteins that interact with ion channels (Table 1).

Rare genetic conditions known to predispose to SCD in children and young adults include the congenital long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS),

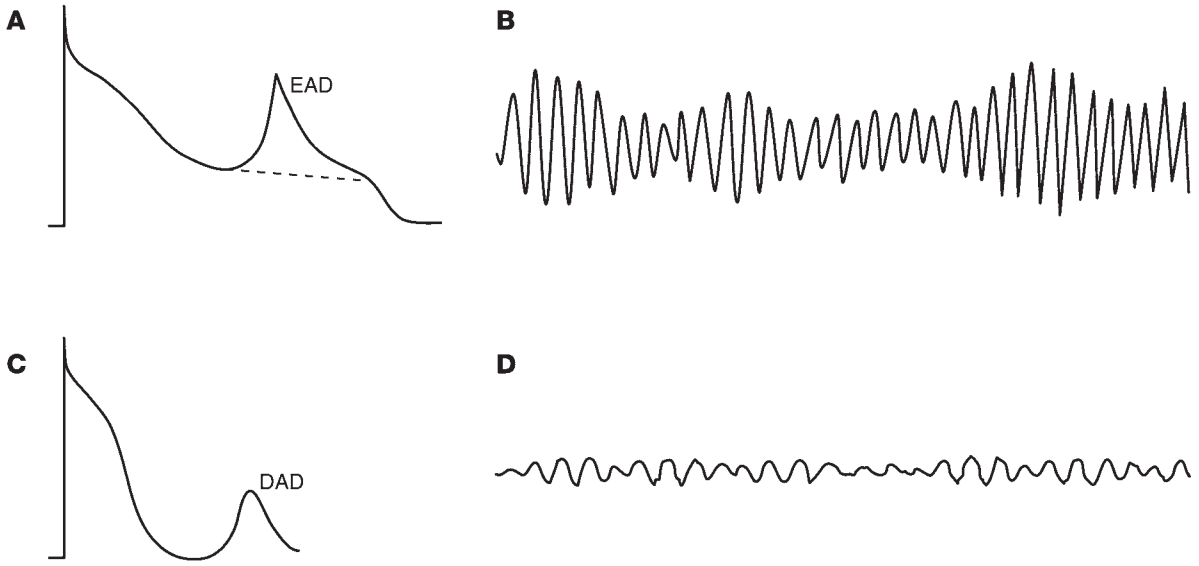

Figure 2
Afterdepolarizations and ventricular arrhythmias. EADs and DADs occur due to dysregulation of depolarizing ionic currents. (**A**) EAD illustrated in the context of prolonged action potential duration. EADs typically result from increased activation of voltage-gated (L-type) Ca^{2+} channels or persistent activation of voltage-gated Na^+ channels. (**B**) ECG from a typical polymorphic VT (also known as torsades de pointes), which is associated with EADs. (**C**) Illustration of a DAD arising after completion of action potential repolarization. DADs are commonly due to spontaneous intracellular Ca^{2+} release and efflux of Ca^{2+} through the electrogenic NCX (stoichiometry $3Na^+$:$1Ca^{2+}$), which generates a a transient I_{Na}. (**D**) ECG of VF, which is associated with DADs.

idiopathic VF, and catecholaminergic polymorphic VT (CPVT). Three general mechanisms responsible for arrhythmia susceptibility have been elucidated in these disorders: abnormal repolarization (LQTS, SQTS, BrS), slow ventricular conduction (BrS), and aberrant intracellular Ca^{2+} homeostasis (CPVT).

Congenital LQTS. The QT interval measured by standard surface ECG provides a surrogate measurement of the average ventricular action potential duration. Both a prolonged or shortened QT interval indicates an increased risk of life-threatening cardiac arrhythmia (14, 15). Congenital LQTS is characterized clinically by an increased risk of potentially fatal ventricular arrhythmias, especially torsades de pointes (16), manifesting as syncope, cardiac arrest, and SCD in otherwise healthy young adults and children. The syndrome is most often transmitted in families as an autosomal dominant trait (Romano-Ward syndrome) and less commonly as an autosomal recessive disease combined with deafness (Jervell and Lange-Nielsen syndrome). Autosomal dominant LQTS occurs in approximately 1 in 2,500 live births (17). LQTS is genetically heterogeneous and can be caused by mutations in several genes encoding voltage-gated K^+ channel subunits (*KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*) (18–23), voltage-gated Na^+ channel subunits (*SCN5A*, *SCN4B*) (24, 25), an L-type Ca^{2+} channel (*CACNA1C*) (26), inwardly rectifying K^+ channels (*KCNJ2*, *KCNJ5*) (27, 28), and various channel-interacting proteins (*ANK2*, *CAV3*, *AKAP9*, *SNTA1*) (29–32).

The most common genetic subtype of LQTS, LQT1, is caused by mutations in *KCNQ1*, a gene encoding the pore-forming subunit of the voltage-gated K^+ channel ($K_V7.1$) responsible for I_{Ks} (20). Mutations in *KCNH2*, which encodes HERG ($K_V11.1$), the voltage-gated K^+ channel responsible for I_{Kr}, cause the LQT2 variant and account for the second largest proportion of LQTS cases (19, 33). Heterozygous mutations in either *KCNQ1* or *KCNH2* lead to loss of function and can exert dominant-negative effects on the wild-type (non-mutant) allele. Loss of function of either $K_V7.1$ or HERG channels will reduce I_{Ks} or I_{Kr}, respectively, causing delayed repolarization and prolonged ventricular action potential duration. During sympathetic activation, failure to augment I_{Ks} during heart rate acceleration further exposes impaired repolarization and explains why LQT1 patients are most prone to arrhythmic events during exercise and emotional stress. Mutations in *KCNE1* and *AKAP9* (encoding the A-kinase anchor protein also known as yotiao) exert similar functional effects on I_{Ks} but are much less common (31, 33). Similarly, *KCNE2* mutations associated with LQTS may disrupt HERG function and reduce I_{Kr} but sometimes only during pharmacological suppression of this current (22, 34).

In autosomal-dominant LQTS, mutations in *KCNQ1* and *KCNH2* may exert dominant-negative effects on the respective wild-type allele. Dominant-negative effects are best explained by the formation of dysfunctional tetrameric channel complexes with mixtures of wild-type and mutant subunits. Recessive *KCNQ1* and *KCNE1* mutations are responsible for Jervell and Lange-Nielsen syndrome (21, 23, 35) but do not exhibit dominant-negative effects, most likely because mutant proteins are not stable or do not form heteromultimers with wild-type subunits.

Impaired trafficking of mutant subunits is a common in vitro observation for *KCNH2* mutations (36, 37). For some *KCNH2* mutations, impaired trafficking can be corrected pharmacologically in heterologous cells (38), thus stimulating interest in this approach for therapy of LQT2. Modeling the effects of human *KCNQ1* and *KCNH2* mutations in vivo (e.g., genetically modified mice) have been challenging because of substantial differences in repolarizing currents in mouse heart. However, recent prog-

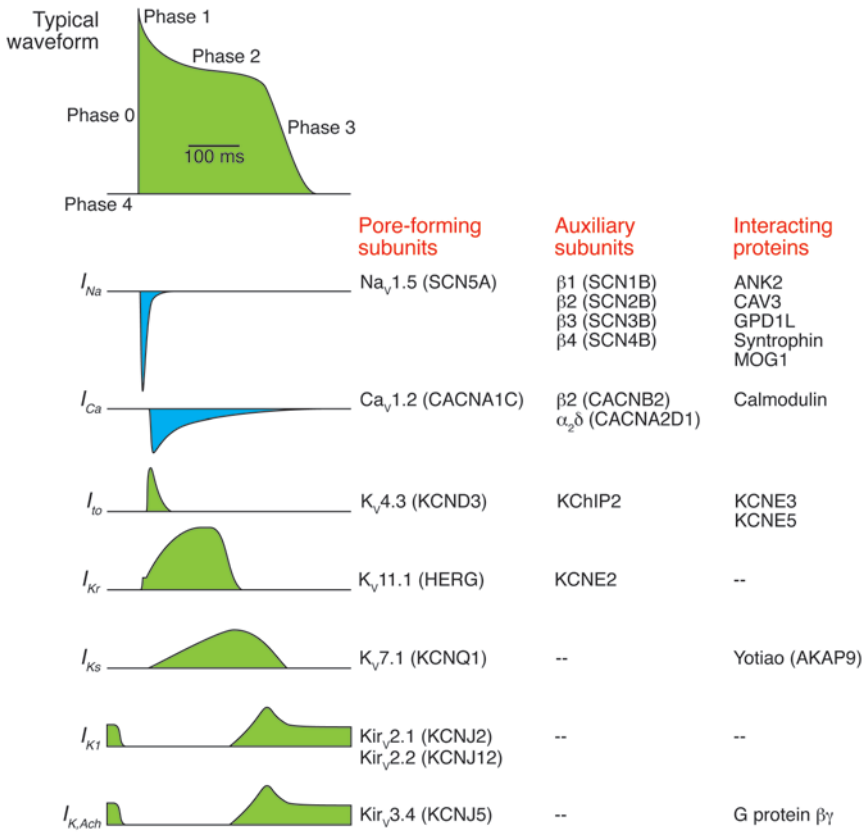

Figure 3
Ionic and molecular basis for cardiac action potential. Left: A typical ventricular action potential waveform labeled to show different phases, and representative inward (blue) or outward (green) currents aligned temporally below. Right: Molecular components of each ionic current are listed. $I_{K,Ach}$, acetylcholine-activated K^+ current.

ress has been made in generating transgenic rabbits expressing dominant-negative *KCNQ1* or *KCNH2* mutations that reproduce important features of human LQTS (39). Interestingly, loss-of-function mutations in the zebrafish homolog of *KCNH2* (zERG) cause bradycardia, AV block, and prolonged action potential duration, and this has led some investigators to propose zebrafish as a model system for testing certain functional consequences of LQT2 mutations (40).

Approximately 10% of LQTS cases are caused by *SCN5A* mutations (LQT3) (33, 41). Most commonly, LQTS-associated *SCN5A* mutations confer a gain of function on the encoded cardiac Na^+ channel ($Na_V1.5$), characterized by impaired inactivation and increased persistent I_{Na} (42). A similar functional phenotype has been observed for mutations in other genes associated with LQTS including *CAV3*, *SCN4B*, and *SNTA1* that encode proteins that interact directly or indirectly with $Na_V1.5$ (25, 30, 43). Increased persistent I_{Na} disrupts the normal physiological balance of inward and outward currents flowing during the plateau phase of the cardiac action potential, causing delayed repolarization, prolonged action potential duration, and predisposition to reentrant arrhythmia triggered primarily by EADs. Genetically engineered mice carrying the first identified *SCN5A* mutation, an in-frame three-amino-acid deletion within the inactivation gate domain (delKPQ), recapitulated the cellular and molecular features of LQT3 including a propensity for ventricular arrhythmia, prolonged action potential duration with EADs, and increased persistent I_{Na} (44). Selective block of persistent I_{Na} by certain antiarrhythmic agents (e.g., mexiletine) or the anti-angina drug ranolazine may offer targeted therapy for LQT3 mutations (45–48).

Acquired LQTS is more common than congenital LQTS but shares similar pathophysiological mechanisms. Drug-induced LQTS (diLQTS), the most common form of acquired LQTS, occurs when cardiac or non-cardiac drugs block HERG channels, suppress I_{Kr}, and cause delayed repolarization (49). A genetic predisposition to diLQTS has been hypothesized, and this notion has received support from genetic association studies (50, 51). A common *KCNE1* variant (D85N) carried by 1%–2% of the general population is overrepresented among diLQTS cases (52). The variant confers a partial loss-of-function upon I_{Ks} and causes a condition referred to as reduced repolarization reserve that predisposes to overt LQTS upon collateral inhibition of I_{Kr} (53). Anecdotal evidence also suggests that latent congenital LQTS may be unmasked by HERG-blocking drugs (54, 55) or other physiological provocations such as acute myocardial infarction (56).

Syndromic LQTS: Andersen and Timothy syndromes. In addition to Jervell and Lange-Nielsen syndrome, two other LQTS subtypes have prominent extracardiac manifestations. Andersen syndrome is an autosomal dominant disorder characterized by ventricular arrhythmias, periodic paralysis, and dysmorphic facial and skeletal features (27, 57). Considerable phenotypic variability exists among people diagnosed with Andersen syndrome, with many subjects exhibiting only one or two clinical features (58, 59). Although ventricular arrhythmia can be a prominent feature, this only rarely precipitates SCD (60).

Andersen syndrome is associated with mutations in *KCNJ2* encoding the Kir2.1 inward rectifier K^+ channel (27, 61, 62) that is responsible for the main component of I_{K1}, an important current driving phase 3 repolarization (63). Dominant-negative, loss-of-function *KCNJ2* mutations reduce I_{K1} and cause prolongation of the action potential duration, with increased propensity for re-entrant arrhythmias (62, 64, 65). Some identified *KCNJ2* mutations are predicted to affect residues important for the regulation of Kir2.1 channel activity by phosphatidylinositol 4,5-bisphosphate (66). Other alleles impair trafficking of the channel to the plasma membrane (67, 68). Previous investigation of mice with homozygous deletion of *Kcnj2* demonstrated premature death secondary to cleft palate but no overt ventricular arrhythmias despite lack of measurable I_{K1} in cardiac myocytes (64, 69). By contrast, in vitro suppression of I_{K1} in isolated canine left ventricle caused delayed action potential repolarization, increased transmural dispersion of repolarization, and polymorphic VT resembling cardiac features of Andersen syndrome (70, 71).

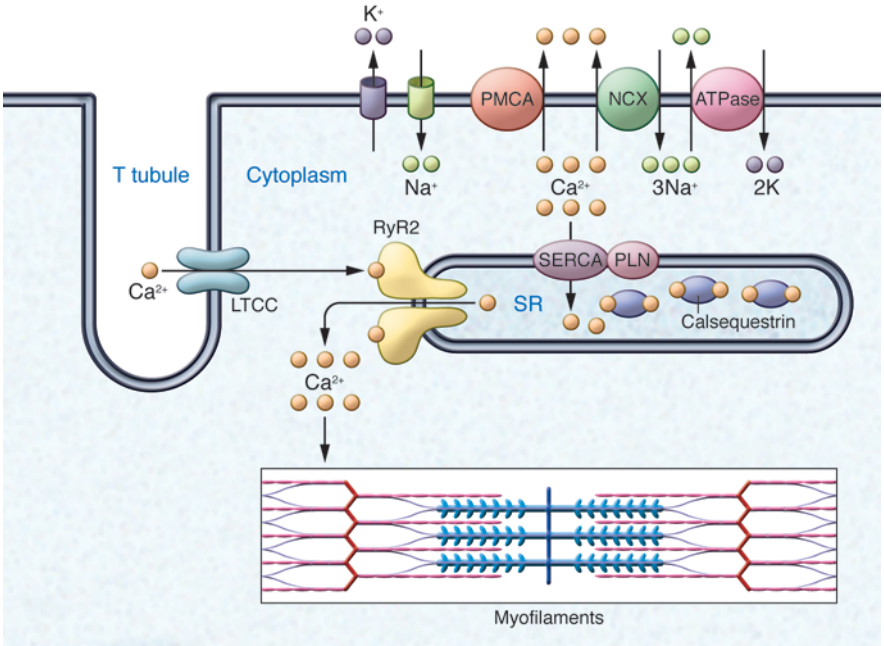

Figure 4
Molecular basis for intracellular Ca^{2+} homeostasis. Illustration of T tubule with adjacent junctional SR containing the ryanodine receptor (RYR2) Ca^{2+} release channel, calsequestrin Ca^{2+} binding protein, and Ca^{2+} pump (SERCA) with regulatory protein phospholamban (PLN). The electrogenic NCX is represented on the surface plasma membrane. Electrical impulses conducted into the T tubules trigger a wave of Ca^{2+} influx via the voltage-dependent, L-type Ca^{2+} channel (LTCC) that promotes Ca^{2+} release through RYR2. This release of Ca^{2+} from the SR promotes myocyte contraction. The subsequent removal of cytosolic Ca^{2+}, mostly by reuptake into the SR by SERCA and by pumping out of the cell by the plasma membrane Ca^{2+} ATPase (PMCA), and the exchange for extracellular Na^+ by an electrogenic NCX on the plasma membrane, terminates the contraction.

In Timothy syndrome, mutations in *CACNA1C*, which encodes the voltage-gated Ca^{2+} channel pore-forming subunit ($Ca_V1.2$), cause a complex phenotype including cardiac arrhythmia, syndactyly, and autism spectrum disorder (26). The syndrome exhibits sporadic occurrence as opposed to Mendelian inheritance, but a candidate gene survey demonstrated a common heterozygous mutation (G406R) in *CACNA1C* consistent with either de novo mutagenesis or parental mosaicism (26). A second mutation (G402S) was subsequently discovered (72). Both mutations occur within one of two mutually exclusive exons (exons 8 or 8A) present in alternatively spliced *CACNA1C* transcripts. Functionally, both mutations cause substantial impairment of channel inactivation, predicting an increased Ca^{2+} current during the plateau phase of the action potential (26, 72). Selective impairment of voltage-dependent inactivation rather than Ca^{2+}-dependent inactivation may be the main functional disturbance (73). This gain-of-function defect leads to increased Ca^{2+} entry and activation of calmodulin-dependent kinase II, stimulating a proarrhythmic cascade in isolated rabbit ventricular myocytes (74). Mice with heterozygous or homozygous expression of a Timothy syndrome mutation are not viable.

SQTS. Another disorder of repolarization, the SQTS, was described more recently and appears to be much rarer than LQTS (75). As in LQTS, subjects with SQTS can be stricken with life-threatening ventricular arrhythmias and SCD, often during childhood. Mutations in six different genes encoding either K^+ channel (*KCNQ1, KCNH2*, *KCNJ2*) (76–78) or Ca^{2+} channel (*CACNA1C*, *CACNB2*, *CACNA2D1*) (79, 80) subunits have been associated with this phenotype. Many of these SQTS genes are the same as those implicated in LQTS, but the functional consequence of mutations is opposite. Mutations in K^+ channels encoded by *KCNH2* and *KCNQ1* that cause SQTS exhibit gain-of-function effects predicted to enhance repolarizing power and shorten action potential duration (76, 77), effects that are modeled in zebrafish carrying mutant zERG channels with altered gating properties (81). By contrast, mutations in genes encoding Ca^{2+} channel subunits exhibit loss of function (79, 80). Mutations in *KCNJ2* also confer a gain of function that for some alleles stems from unique biophysical behaviors, such as loss of inward rectification (82).

BrS. Individuals with BrS have an increased risk for potentially lethal ventricular arrhythmias usually occurring during sleep, but in the absence of myocardial ischemia, electrolyte abnormalities or structural heart disease (83). Individuals with the disease may exhibit a characteristic baseline ECG pattern consisting of ST elevation in the right precordial leads, apparent right bundle branch block, but normal QT intervals. Administration of Na^+ channel blocking agents (e.g., procainamide, flecainide, ajmaline) (84) and fever (85) may unmask this ECG pattern in latent cases. A family history of unexplained sudden death is typical. The sudden unexplained death syndrome is clinically similar to BrS and causes sudden death, typically during sleep, in young and middle-aged males, with a higher prevalence in individuals from Southeast Asian countries (86–88). Inheritance is autosomal dominant with incomplete and often low penetrance and a substantial male predominance. One attractive hypothesis to explain incomplete penetrance in BrS is the existence of genetic modifiers that may be common variants in *SCN5A* or other genes (89–91).

Mutations in *SCN5A* account for less than 30% of BrS cases with known genotypes. Reduced I_{Na} is the primary pathophysiological mechanism due to loss-of-function mutations including frameshifts, splice site defects, or premature stop codons (92, 93) that are predicted to encode nonfunctional Na^+ channels. Also, some missense mutations have been demonstrated to be nonfunctional either because of impaired protein trafficking to the cell membrane or presumed disruption of ion conductance (94–96). Other missense mutations are dysfunctional, with biophysical defects predicted to reduce channel availability such as altered voltage dependence of activation, more rapid fast inactivation, and enhanced slow inactivation (97–99). Reduced I_{Na} may also be the consequence of mutations in other genes that less frequently cause BrS, including those encoding Na^+ channel β subunits (*SCN1B*, *SCN3B*) (100, 101) or glycerol-3-phosphate dehydrogenase 1-like

(*GPD1L*) (102). The latter gene defect has been suggested to cause suppression of the Na^+ current by a PKC-dependent mechanism that is linked with the redox state of the cell (103, 104). Specifically, reduced enzymatic activity of mutant GPD1L is associated with an NADH/NAD^+ imbalance that can activate protein kinase C and lead to phosphorylation of a specific serine residue (Ser1503) on $Na_V1.5$, causing reduced channel activity. Mutations in other genes have been identified in BrS that cause loss of Ca^{2+} channel function (105), increased I_{to} (106), or increased ATP-sensitive K^+ current ($I_{K,ATP}$) (107).

Two mechanisms are proposed to explain the cellular basis of BrS (108). In one mechanism, a reduction in myocardial Na^+ current is predicted to exaggerate differences in action potential duration between the inner (endocardium) and outer (epicardium) layers of ventricular muscle (8, 9). These differences occur because of an unequal distribution of I_{to}, which is more prominent in the epicardial layer and contributes to the characteristic spike and dome shape of the cardiac action potential. Reduced I_{Na} causes disproportionate shortening of epicardial action potentials because of unopposed I_{to}, leading to an exaggerated transmural dispersion of repolarization, a substrate promoting reentrant arrhythmias. This mechanism is supported by elegant work using the canine ventricular wedge model (8, 9). The second hypothesis posits that the main effect of reduced myocardial I_{Na} is slowing of impulse conduction in the right ventricle and delayed activation of the right ventricular outflow tract (RVOT) (108–111). This mechanism has gained support primarily from clinical observations including electroanatomic mapping studies (112, 113) and the observed therapeutic benefit of epicardial ablation over the RVOT (114). Heterozygous *Scn5a* knockout mice (*Scn5a*$^{+/-}$) have provided an animal model of BrS (115–117). Whether these two hypotheses are mutually exclusive or whether all cases of BrS originate by the same pathophysiological mechanism remains unclear.

CPVT. Alternations in intracellular Ca^{2+} homeostasis can also promote life-threatening ventricular arrhythmias and precipitate SCD. In the monogenic disorder CPVT, abnormal control or regulation of Ca^{2+} release from the SR can trigger DADs and cause ventricular arrhythmias (118). The condition is usually diagnosed during childhood and typically presents with syncope or SCD in the setting of exercise, emotional stress, or other circumstances associated with a surge in catecholamine release (119).

Mutations in *RYR2* encoding the cardiac ryanodine receptor/Ca^{2+} release channel are associated with autosomal dominant CPVT (120). Autosomal recessive forms of the disorder are associated with mutations in either *CASQ2,* encoding the SR Ca^{2+}-binding protein calsequestrin (121), or *TRDN*, encoding triadin, which links RYR2 with calsequestrin (122). These three proteins reside together within the terminal cisternae of the SR, where intracellular membranes lie adjacent to the transverse tubule (T tubule) region of the plasma membrane. Normally, electrical impulses conducted into the T tubules activate voltage-gated L-type Ca^{2+} channels and evoke a wave of Ca^{2+} influx sufficient to promote Ca^{2+}-induced Ca^{2+} release through RYR2. Release of Ca^{2+} from the SR promotes myocyte contraction (excitation-contraction coupling), which is then terminated by removal of cytosolic Ca^{2+} mostly by reuptake into SR by a Ca^{2+}-ATPase pump (SERCA) and through exchange for extracellular Na^+ by an electrogenic NCX on the plasma membrane (Figure 4). Spontaneous SR Ca^{2+} release during diastole can be evoked by β-adrenergic stimulation by several proposed mechanisms (123, 124).

CPVT-associated RYR2 mutations sensitize the channel to luminal Ca^{2+}, leading to exaggerated spontaneous SR Ca^{2+} release (125). The effects of *CASQ* mutations are more complex and include a loss of SR Ca^{2+} buffering, loss of RYR2 regulation by calsequestrin, and remodeling of SR ultrastructure (126–128). Loss of triadin, as in some cases of recessive CPVT (122), may also predispose to unregulated SR Ca^{2+} release by disrupting normal regulation of intracellular Ca^{2+} homeostasis. In *Trdn* knockout mice, attenuated Ca^{2+}-dependent inactivation of L-type Ca^{2+} channels appears to promote SR Ca^{2+} overload and the predisposition to aberrant SR Ca^{2+} release (129).

Summary and future directions

Fundamental molecular and genetic mechanisms of SCD have been elucidated by investigations of rare monogenic disorders of heart rhythm. Despite the identification of more than 25 causal genes, there remain many subjects with inherited arrhythmia susceptibility who do not have mutations, which suggests that other, unidentified genes exist. Newer strategies such as exome and whole genome sequencing may be valuable to uncover additional molecular etiologies. Efforts to understand mechanisms responsible for incomplete penetrance, including identification of modifier genes, will also contribute to deciphering the complex relationships between genotype and phenotype. Finally, better disease models such as cardiomyocytes derived from human-induced pluripotent stem cells created from patients with monogenic disorders predisposing to SCD, as described elsewhere in this Review series (130), may also help advance our understanding of SCD pathophysiology and inspire new therapeutic approaches.

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